Queensland Opioid Treatment Program:

Clinical Guidelines 2012

Queensland Health

Queensland Government

This report has been developed by the Drugs of Dependence Unit, Health Protection Directorate, Division of the Chief Health Officer, Queensland Health.

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Foreword

The ***Queensland Opioid Treatment Program: Clinical Guidelines 2012*** represents a revision of *Queensland Opioid Treatment Program: Clinical Guidelines 2008*. The review provides clinicians with a comprehensive, up-to-date manual covering best practice in treating opioid dependence. These guidelines are expected to be reviewed in three years by the Queensland Opioid Treatment Reference Group to ensure they continue to reflect current best practice.

For the purpose of this document, buprenorphine will refer to both buprenorphine mono (Subutex®) and buprenorphine/naloxone (Suboxone®) unless specifically stated. The term 'client' is used to include any patient, service user, consumer, person who uses drugs or person who injects drugs.

The clinical guidelines cannot provide detailed direction for managing every client in every clinical situation. In some circumstances, clinicians may need to vary their clinical practices from what is suggested in this document. It is essential that, under such circumstances, clinicians clearly document in the client's clinical file the reasons for going outside the guidelines. Individual medical practitioners, nurse practitioners and pharmacists are responsible for decisions about the safety and effectiveness of treatment for each client. The guidelines are not intended to replace professional judgment in individual cases.

This document may also be referred to as a Health Management Protocol (as required by the Drug Therapy Protocol – Opioid Treatment Program). Alcohol and Drug Services and private practitioners offering opioid treatment programs should operate in a manner that is consistent with the *Queensland Opioid Treatment Program: Clinical Guidelines 2012*. Individual services should develop workplace instructions and procedures that remain consistent with both the national and state guidelines while reflecting local needs and circumstances.

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Executive summary

The Queensland Opioid Treatment Program (QOTP) began in 1977 with the opening of the first Queensland Drug Dependence Clinic. The policy and procedures manuals and clinical guidelines have each gone through several editions, up to the current 5th edition: *Queensland Opioid Treatment Program: Clinical Guidelines 2012* (Queensland Health).

The 2012 Clinical Guidelines take into account the characteristics of high-quality guidelines in attempting to meet specific criteria for quality, ensuring clinicians work to improve the care provided for clients who are registered with the QOTP. Changes made in the 2012 Clinical Guidelines are summarised below:

- The term 'client' is used in place of patient, service user, consumer, and so on.
- The language has been changed.
- There is a new section on the use of buprenorphine/naloxone film as an additional pharmacotherapy option for treatment.
- Generic drug names are used in place of trade names where practical.
- Advice to attend emergency departments has been removed in most instances.
- The role of nurse practitioners as prescribers has been recognised throughout.
- References to support many of the statements made have been included.
- The requirement of <16 mg buprenorphine to transfer to methadone has been removed.
- More consideration is given to high-dose methadone to buprenorphine transfers.
- There is a major change for buprenorphine/naloxone unsupervised doses, increasing the differentiation from methadone unsupervised doses.
- There is an explanation of take-away dose provisions during natural disasters.
- Buprenorphine is now accepted as a standard pharmacotherapy for use during pregnancy, with promotion of breastfeeding for mothers in the opioid treatment program.
- It is stated clearly that buprenorphine mono preparation should not be offered as a take-away dose, save where the patient is on a low dose where buprenorphine/naloxone cannot be used.
- The approach to planned dose reductions is better informed.
- More attention is paid to drug-drug interactions and potential complications:
  - lists of interactions for methadone and for buprenorphine
  - QTc prolongation, methadone dose and other contributory factors
  - osteoporosis and HPA axis suppression
  - potential interaction between tobacco use and methadone metabolism
  - evidence suggesting increased risk of death on opium and other opioids.

Section 1

Principles of opioid treatment programs

In the *2010 National Drug Strategy Household Survey*, 0.8 per cent of Australians aged 14 years and older had used heroin, methadone/buprenorphine (not for maintenance treatment) or other opioid drugs in the previous 12 months. Another 3 per cent had used pharmaceutical analgesics – either prescribed (19 per cent) or over the counter (81 per cent) for non-medical purposes[1].

Approximately one in four people who use heroin will become dependent[2]. Opioid dependence can lead to a range of problems for the user, which may result in estrangement from family and non-drug-using friends, loss of desire or capacity for work, entrenchment in an illegal subculture with its attendant problems, and deterioration of physical health with a high mortality and morbidity rate. There is also a higher prevalence of psychiatric co-morbidity, for example depression, in this population.

Harm minimisation provides the basis for Australian drug policy. The concept is recognised as a positive and realistic response to the many problems associated with, or resulting from, the use of drugs in society. Minimising harm does not mean that it is possible to make drug use totally safe or without risk. Drug use always involves some potential for harm: physical, psychological, social and legal.

Opioid maintenance treatment aims to decrease the risks associated with drug use for the individual and the community at large. It is a specific treatment modality for people with dependence on opioids, in particular heroin, and also prescription opioids, where use has become problematic. Many opioid-dependent people are also dependent on a range of other drugs such as nicotine, and also benzodiazepines and alcohol, which in particular increase their risk of overdose. The appropriateness of opioid maintenance treatment needs to be determined for each individual, and the prescriber needs to carefully weigh the risks against the benefits of commencing or continuing treatment.

Treatment with methadone, buprenorphine or buprenorphine/naloxone provides a means of minimising harm to people with opioid dependence, enabling them to address appropriate areas of their lives. The pharmacological characteristics of methadone and buprenorphine enable clients to function more effectively. Opioid treatment is an open-ended intervention aimed at recovery and optimising the health of each individual in treatment. For some clients, it may be a life-long program that helps them to achieve their goals, while others will achieve a fulfilling life having completed opioid treatment.

1.1 Characteristics of opioid dependence

- Neurological adaptation to the effects of opioids (neuroadaptation) is shown by the presence of tolerance and withdrawal symptoms when opioid use ceases.
- Opioids are taken in larger amounts for longer than intended.
- There is a persistent desire, or there have been unsuccessful attempts, to cut down or control opioid use.
- A great deal of time is spent in activities necessary to obtain, use or recover from the effects of opioid use.
- Important social, occupational or recreational activities are given up or reduced because of opioid use.
- Opioid use continues despite recurrent physical or psychological problems caused or exacerbated by opioid use.

Opioid withdrawal symptoms include irritability, anxiety, restlessness, apprehension, muscular and abdominal pains, chills, nausea, diarrhoea, yawning, lacrimation, piloerection, sweating, sniffing and rhinorrhoea, sneezing, general weakness and insomnia. Signs and symptoms usually begin two to three half-lives after the last opioid dose. That is, 36 to 48 hours for long half-life opioids such as methadone, and 6 to 12 hours for short half-life opioids such as heroin and morphine.

1 Australian Institute of Health and Welfare 2011
2 Anthony et al 1994

Following cessation of short-acting opioids such as heroin or morphine, symptoms reach peak intensity within 2 to 4 days, with most of the obvious physical withdrawal signs no longer present after 7 days. The duration of methadone withdrawal is longer (5 to 21 days). This first, or acute, phase of withdrawal may then be followed by a period of protracted withdrawal, characterised by general malaise. Strong opioid cravings are likely during this time.

The opioid withdrawal syndrome is rarely life-threatening, although clients with co-existing medical or mental health disorders are at increased risk of related complications that may be serious or even fatal. Completion of withdrawal is, however, difficult for most people. Untreated methadone withdrawal symptoms may be perceived as more unpleasant than heroin withdrawal, reflecting the prolonged duration of methadone withdrawal. Issues that may influence the severity of withdrawal include the duration of opioid use, general physical health and psychological factors, such as the reasons for undertaking withdrawal and the fear of withdrawal. Buprenorphine appears to have a milder withdrawal syndrome than other opioids.

1.2 Aims of opioid treatment program

The broad aim of treatment for opioid dependence is to reduce the health, social and economic harms to individuals and the community arising from unsanctioned opioid use. Pharmacotherapies for opioid dependence should form part of a comprehensive treatment program, with access to counselling and the other ancillary services available to all clients.

These guidelines are to assist clinicians in managing people with opioid dependence, matching them to the most appropriate treatment.

Specific aims of opioid treatment are:

- significant reduction of the client's unsanctioned opioid use
- reduction in the risk of overdose
- reduction in the transmission of blood-borne diseases
- improvement in general health and social functioning, including a reduction in crime.

These objectives will not necessarily be achieved with every client, nor will they be achieved to the same degree in every opioid treatment program setting. The aim is to reduce drug-related harm as much as circumstances allow for each client. Opioid treatment benefits are highest when treatment programs are easily accessible, entry into treatment is prompt and retention in treatment is high.

The following principles are considered critical success factors and should guide the provision of opioid treatment programs in Queensland. These principles aim to maximise participation in opioid treatment and encourage client retention.

Availability: These services should be made available where a need for opioid treatment services exists.

Access: To be accessible to clients, services should be located at appropriate sites, treatment should be affordable and opening hours should optimise service use. Clients who drop out of treatment should not be denied prompt access back into treatment.

Acceptability: The operation of opioid treatment services should be acceptable to major stakeholders including clients, service providers and the local community. Opioid treatment services should develop protocols that encourage good therapeutic relationships between clinicians and clients.

Collaboration: A collaborative approach that involves the client in treatment decisions as far as possible is likely to maximise their engagement and retention in treatment. Private prescribers will usually see their clients monthly; in public clinics, the case manager often has the most regular contact with the client.

Equity: Opioid treatment services should be planned and operated to reduce inequities between target groups in terms of access to services and the quality of services offered. All clients should be treated in a non-judgmental manner and offered access to a full range of services, including medical, psychological and welfare.

Quality of care: Opioid treatment services should be planned and operated in a manner that ensures good quality services are provided that are consistent with state and national guidelines. People who manage and operate opioid treatment services should be accountable for the performance of these services, and processes should be in place to ensure accountability.

Choice: Unless there are compelling reasons (for example, a known allergy or repeated diversion) clients suitable for opioid treatment should be provided with enough information to make an informed choice between medications. Influences on choice include client experience, practical considerations around dosing and individual responses to a particular drug. When client or community safety is at particular risk, the choice of treatment may be restricted to reduce the potential for associated harm. The reasons why client choice in treatment options is restricted should be documented clearly in the client's clinical file.

Ideally, complex clients should be managed in a recognised opioid treatment clinic.

1.3 Evidence

Cochrane Reviews summarises the evidence base from randomised controlled trials (RCT) for opioid treatment, looking at outcomes such as heroin use and retention of patients in treatment. According to the rigorous standards of RCT, both methadone and buprenorphine give better outcomes than placebo. Doses of methadone from 60–100 mg/12–20 mls give better results than lower doses (‹40 mg/8 mls), and high-dose methadone (›60 mg/12 mls) gives better retention than buprenorphine[3].

National Evaluation of Pharmacotherapies in Opioid Dependence (NEPOD)[4] compared methadone, buprenorphine and naltrexone, and concluded that methadone maintenance is the most cost-effective treatment available in Australia for treating opioid dependence. Methadone was introduced into Australia in 1969; buprenorphine was made available to treat opioid dependence in 2000.

Both methadone and buprenorphine have shown to be effective treatment options for opioid-dependent clients[5]. One of the best outcome measures is the ability to retain clients in treatment, thereby protecting clients from overdose and reducing heroin use. NEPOD compared the treatment retention rates of clients assigned to opioid maintenance against those who were treated with the opioid receptor antagonist, naltrexone. Retention in treatment at six months was 44 per cent in the group treated with agonist drugs such as methadone and buprenorphine, compared to 4 per cent of those who were treated with naltrexone.

1.4 Types of opioid treatment programs in Queensland

1.4.1 Withdrawal management

Research literature suggests that, although a range of health benefits are often derived from withdrawal management, there is no evidence that it leads to lasting abstinence from opioids nor significantly improves health and functioning in the longer term for more than a small minority of those with opioid dependence. If a person relapses after withdrawal, there is also an increased overdose risk because of the loss of drug tolerance[6].

However, withdrawal management is a service that many opioid users wish to access and it may attract individuals into treatment who would not otherwise seek help. The risk of post-withdrawal overdose should be emphasised when a withdrawal program is commenced.

3 Faggiano et al 2008, Mattick et al 2008, Mattick et al 2009
4 Mattick et al 2009
5 Gibson 2008
6 Strang et al 2003

Withdrawal management should be regarded as a starting point for ongoing treatment rather than as a complete treatment in its own right. It is important that clients who have undergone withdrawal management also have access to drug treatment services such as:

- opioid maintenance treatment
- counselling
- residential therapeutic communities
- self-help programs
- naltrexone treatment.

1.4.2 Maintenance program

It is generally accepted that people with chronic medical conditions should be afforded good medical care for as long as this is required and found to be beneficial. This principle has equal application in the treatment of opioid dependence. Just as a person with insulin-dependent diabetes mellitus would not be offered time-limited treatment with insulin, the opioid-dependent person ought not to be expected to exit an opioid maintenance treatment program after an arbitrary time has elapsed and while they continue to benefit from treatment.

A maintenance program should be, therefore, of no fixed duration and the client should nominate when (and if) they are ready for withdrawal. Withdrawal from methadone or buprenorphine is encouraged when it is considered to be in the client's interest. Positive factors encouraging this choice include when the client's prospects of remaining opioid-free are good and they are confident they no longer require opioid treatment. Withdrawal from methadone or buprenorphine is best done in a gradual manner, without a fixed deadline (where possible) and with regular reviews of progress. Planned withdrawal off a 'treatment' dose of methadone may take 12–18 months to be successfully completed[7].

The philosophy behind the policy of not limiting the duration of the individual's opioid treatment is that the positive changes effected while in treatment are significant. There is nothing to gain by withdrawing a client against their wishes who has been adherent to the program.

Clients who remain in opioid maintenance programs are less likely to inject opioids or to become infected by HIV or hepatitis C[8]. They are also more likely to be able to maintain work and stabilise their important relationships. These benefits continue while the client remains in treatment.

Since use of buprenorphine has become widespread within opioid treatment programs, there has been growing understanding of how it differs from methadone. Advantages it may offer include greater flexibility with dosing, relative safety in overdose, ease and safety of induction, fewer interactions and an improved side effect profile. Both methadone and buprenorphine have earned their place in opioid treatment as each treatment modality offers benefits and each may be a valid option for a particular client.

1.5 How treatment is delivered

Public clinics (62 per cent) and private prescribers provide opioid treatment in Queensland. Public clinics are typically staffed by doctors, nurses and allied health professionals who provide a range of services including counselling and psychotherapy, general medical care, psychiatric treatment and social services. Designated opioid treatment program staff or the client's prescriber undertake clinical care. Pharmacotherapy is primarily dispensed through private pharmacies and public hospital pharmacies, but clients stabilising on treatment at a public opioid treatment clinic will normally be dosed in the clinic.

7 Nosyk et al 2012
8 Hagan et al 2011

1.6 Optimising the benefits of opioid treatment

1.6.1 Length of time in treatment

Current evidence suggests that key treatment outcomes – in particular, reduced mortality in treatment – for maintenance buprenorphine and methadone treatment are comparable under optimal treatment conditions[9]. The longer a client remains in treatment, the more likely they will do well and have improved post-treatment outcomes. People who drop out of treatment, particularly in the first year, have a very high relapse rate to opioid use. Clients should be encouraged to remain in treatment for at least 12 months to ensure enduring lifestyle changes. Opioid treatment services should routinely monitor retention rates as a quality activity and aim for retention rates of at least 40 per cent at 12 months.

1.6.2 Quality of the therapeutic relationship

Program policies, practices and staff attitudes are critical factors influencing the quality of opioid treatment programs. In more effective programs, clients have a good therapeutic relationship with at least one staff member. In addition, certain staff attitudes – notably, acceptance of the idea of indefinite maintenance rather than abstinence – are associated with better treatment outcomes. Such factors impact on the acceptability of the program to clients and its success in attracting and retaining clients in treatment. This, in turn, is the key to achieving good outcomes from both individual and public health perspectives.

1.6.3 Medical and counselling services

Some studies suggest that providing adequate medical care and counselling services for clients leads to better retention rates and outcomes. However, this is not conclusive and there is little evidence to support one particular psychosocial intervention over any other[10]. If programs do not offer these services on site, then every effort should be made to refer clients to an appropriate facility offering these ancillary services.

1.6.4 Avoiding hazards of opioid treatment

Hazards associated with opioid treatment include overdose, accidental ingestion and poisoning of a person other than the client, and diversion of methadone, buprenorphine and buprenorphine/naloxone. To minimise these hazards:

- Clinicians should be authorised to prescribe and adequately trained in providing opioid treatment services
- Opioid treatment should be voluntary and received only by those individuals assessed as suitable by an approved opioid treatment clinician
- Pharmacotherapy should generally be consumed under supervision. (*Section 10: Information for Pharmacists* outlines guidelines for supervising dosing.)
- Opioid treatment should occur in an environment that is safe for clients, staff and the community.

9 Degenhardt et al 2009
10 Amato et al 2009

Section 2

Pharmacology of opioid treatment

2.1 Methadone

Methadone is a potent synthetic opioid agonist that is absorbed well orally and has a long, although variable, plasma half-life. The effects of methadone are similar to morphine and other opioids[11].

2.1.1 Effects of methadone

Systemic effects

- Analgesia
- Sedation
- Euphoria (oral methadone causes less euphoria than intravenous heroin)
- Decreased blood pressure
- Constriction of the pupils

Respiratory effects

- Respiratory depression
- Cough suppression

Gastrointestinal effects

- Reduced gastric emptying
- Reduced gastrointestinal motility
- Elevated pyloric sphincter tone
- Elevated tone of Sphincter of Oddi can result in biliary spasm

Endocrine actions

- Reduced luteinising hormone (LH)
- Elevated prolactin
- Reduced adreno-cortico-trophic hormone (ACTH)
- Reduced testosterone (although endocrine function may return to normal after 2–10 months on methadone)
- Elevated anti-diuretic hormone (ADH)

Skin actions

- Histamine release – may cause itching[11]

2.1.2 Formulations

Two preparations are available for methadone treatment in Australia:

- Methadone syrup: This formulation contains 5 mg/1 ml methadone hydrochloride, sorbitol, glycerol, ethanol (4.75 per cent), caramel flavouring and sodium benzoate.
- Biodone Forte®: This formulation contains 5 mg/1 ml methadone hydrochloride and permicol-red colouring[11].

11 Henry-Edwards et al 2003

2.1.3 Pharmacokinetics (www.mims.hcn.net.au)

There is wide individual variability in the pharmacokinetics of methadone but, on average, blood levels rise for about 3–4 hours following ingestion of oral methadone and then begin to fall. Onset of effects occurs approximately 30 minutes after ingestion. The apparent half-life of a single first dose is 12–18 hours with a mean of 15 hours. With ongoing dosing, the half-life of methadone is extended to between 13 and 47 hours with a mean of 27 hours. This prolonged half-life contributes to the fact that methadone blood levels continue to rise during the first week of daily dosing and fall relatively slowly between doses[12].

Methadone is fat-soluble and binds to a range of body tissues including the lungs, kidneys, liver and spleen. The concentration of methadone in these organs is much higher than in blood.

Methadone is primarily broken down in the liver mainly via the cytochrome (CY) P450 3A4 and 2B6 isoenzymes, as well as 2C8, 2C19, 2D6 and 2C9 systems[13]. Approximately 10 per cent of methadone administered orally is eliminated unchanged. The rest is metabolised and the inactive metabolites are eliminated in the urine and faeces. Methadone is also secreted in sweat and saliva[12].

Methadone reaches a steady state in the body (where drug elimination equals the rate of drug administration) after a period equivalent to approximately five half-lives or 3–10 days. Once stabilisation is achieved, variations in blood concentration levels are relatively small and withdrawal symptoms are suppressed well. For some, however, fluctuations in methadone concentrations may lead to withdrawal symptoms in the latter part of the inter-dosing interval. If dose increases or split-dosing within a 24-hour period do not prevent this, other agonist replacement treatment approaches such as buprenorphine should be considered[12].

Table 1 Summary of pharmacokinetics[12]

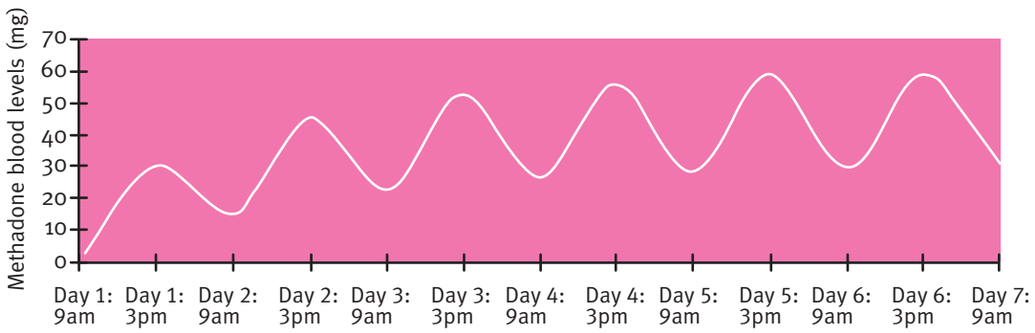
Onset of effects	30 minutes
Peak effects	Approx 3–4 hours
Half life (in MMT)	Approx 27 hours
Time to stabilise	3–10 days

2.1.4 Safety of methadone

Methadone is much less likely to cause harm than alcohol, tobacco or illicit opioid use. The major hazard associated with methadone is the risk of overdose. This risk is particularly high at the time of induction to maintenance treatment and when methadone is used in combination with other sedative drugs. The relatively slow onset of action and long half-life mean that methadone overdose can be highly deceptive and toxic effects may become life-threatening many hours after ingestion. Because methadone levels rise progressively with successive doses during induction into treatment (Table 2), most deaths in this period have occurred on the third or fourth day of treatment, and they are usually associated with benzodiazepine and/or alcohol use. Risks during induction can be minimised by adhering to the guidelines for doses and dose changes. There are concerns about findings of increased mortality in people taking opioids long term, particularly due to causes other than overdose. However, the mechanisms are not well understood[14].

12 Henry-Edwards et al 2003
13 Smith 2009
14 Dhalla 2012

Table 2 Pharmacokinetics of methadone showing the gradual increase in trough and peak levels following induction[15]



2.1.5 Side effects of methadone

Symptoms associated with methadone include:

- sleep disturbances
- nausea and vomiting
- constipation
- dry mouth and consequent dental caries (see Section 3.2)
- increased sweating
- vasodilation and itching
- menstrual irregularities in women (fertility may not be affected)
- gynaecomastia in males
- sexual dysfunction in males, including impotence
- fluid retention and weight gain
- osteoporosis.

Most people who have used heroin will experience few side effects from methadone. Once on a stable dose, tolerance develops until cognitive skills and attention are not impaired. Symptoms of constipation, sexual dysfunction and occasionally increased sweating can continue to be troubling for the duration of methadone maintenance treatment.

Loss of libido and other symptoms of hypogonadism should be investigated with serum testosterone measurement in males, as low values may warrant testosterone supplements. Prescribers should seek specialist advice in these cases.

Studies have shown high rates of osteoporosis exist in patients on methadone maintenance, particularly in males. Calcium and vitamin D supplements should be considered for at-risk clients[16]. The recommended daily intake of calcium for Australian adults ranges from 1000 mg to 1300 mg, depending on life stage and gender[17]. Vitamin D supplements (1000–2000IU daily) are indicated in cases of proven vitamin D deficiency, which may include institutionalised or house-bound people, and women who are veiled for cultural reasons[18]. Other lifestyle and nutritional risk factors for osteoporosis should also be addressed, such as smoking, physical inactivity and heavy alcohol intake[19].

15 Chapter of Addiction Medicine, RACP, 2010
16 Kim et al 2006
17 http://www.nrv.gov.au/nutrients/calcium.htm
18 Endocrinology expert group. *Therapeutic Guidelines: Endocrinology Version 3.* Melbourne: Therapeutic Guidelines Limited; 2004. p.172–3
19 Endocrinology expert group. *Therapeutic Guidelines: Endocrinology Version 3.* Melbourne: Therapeutic Guidelines Limited; 2004. p.171

Methadone may prolong the QTc interval, particulary at high doses. LAAM (Levo-Alpha Acetyl Methadol) was withdrawn from the market in Europe following cases of sudden cardiac death. In contrast, buprenorphine does not affect the QTc interval at therapeutic doses. The normal QTc interval is 450 msec in men and 470 msec in women[20]. A markedly prolonged QTc interval (>500 msec) may lead to torsade de pointes, a potentially fatal arrhythmia. The higher the methadone dose, the greater the likelihood of QTc prolongation. However, the incidence of clinically significant QTc prolongation appears to be low, although it is higher in clients on methadone than the estimated 2 per cent prevalence rate in the general population[21].

Particular caution should be exercised in clients with additional risk factors for QTc prolongation:

- stimulant use advanced age
- female gender
- bradycardia
- anti-psychotic medication
- antidepressants
- macrolide antibiotics
- anti-fungal agents
- electrolyte disturbances such as hypokalemia, hypocalcemia and hypomagnesemia
- heart disease
- pre-existing QTc prolongation (i.e. familial long QT syndromes).

Electrocardiogram (ECG) monitoring may be advisable. Ultimately, this is a matter of clinical judgment to balance risks and benefits. Regular ECG screening of all clients before and on methadone, although recommended by some (Krantz et al 2009), is probably unworkable, particularly since a normal QTc interval on treatment does not exclude QTc prolongation arising in the future. Local guidance suggests, in the absence of other risk factors, a threshold of 150 mg/30 ml methadone. Above this dosing level, clients should be monitored with ECGs every 3–6 months as part of their individual treatment plan.

2.1.6 Drug interactions with methadone

Toxicity and death have resulted from interactions between methadone and other drugs. Some psychotropic drugs may increase the actions of methadone because they have overlapping, additive effects. For example, benzodiazepines, anti-psychotic agents and alcohol may add to the respiratory depressant effects of methadone.

Other drugs interact with methadone by influencing (increasing or decreasing) metabolism *(see Appendix 8)*. CYP450-3A4 inhibitors can decrease the metabolism of methadone and cause overdose. These include some macrolides such as erythromycin, SSRIs (particularly fluvoxamine) antifungals such as ketoconazole, and drugs used to treat HIV. Drugs that induce the metabolism of methadone can cause a withdrawal syndrome if administered to clients maintained on methadone. These drugs should be avoided in methadone clients if possible. If a CYP450-inducing drug is clinically indicated for the treatment of another condition, seek specialist advice[22]. Just as levels of clozapine and olanzapine may increase dramatically with smoking cessation, concerns have been raised about methadone toxicity in such circumstances. This is due to the loss of induction of isoenzyme CYP1A2 by the tar in cigarettes[23]. Therefore, clients planning to quit smoking should be warned of this possibility. There are reports of suspected serotonin toxicity resulting in fatalities with use of MAOIs in combination with methadone[24].

A more complete list of drugs that interact with methadone appears in Appendix 10.

20 Smith, 2008
21 Mayet et al 2011
22 Henry-Edwards et al 2003
23 Wahawisan et al 2011
24 McCance-Katz E *Drug Interactions in Opioid Therapy 2012*

2.2 Buprenorphine

Buprenorphine is a derivative of an opioid alkaloid, thebaine, and is a partial opioid agonist at the mu (μ) opioid receptors in the nervous system. Buprenorphine also exhibits antagonist effects at the kappa (k) opioid receptor. The role of the kappa receptor in humans is still poorly understood[25].

2.2.1 Effects of buprenorphine

Buprenorphine is a potent μ-receptor agonist at low doses: as such, it has many of the same effects as other opioids including methadone (see section 2.1.1). However, there is a ceiling on its opioid activity. Buprenorphine diminishes cravings for heroin and reduces opioid withdrawal. Buprenorphine has a higher affinity for μ opioid receptors than full opioid agonists. Because of this, buprenorphine can block the effects of other opioid agonists in a dose-dependent fashion. By its dual effects of reducing craving and attenuating the response to administered heroin, buprenorphine reduces the self-administration of heroin.

Methadone, a full opioid agonist, also reduces the impact of additional heroin, but the effect of methadone is primarily due to the induction of cross-tolerance, which is dose-dependent. In contrast, buprenorphine achieves its effect primarily by prolonged occupancy of a high proportion of opioid receptors, blocking the action of other pure agonist opioids. Unlike methadone, the effect of buprenorphine on respiratory depression reaches a ceiling, with higher doses not increasing respiratory depression to a significant degree. However, if buprenorphine is used in combination with other central nervous system depressants, such as benzodiazepines or alcohol, the combined effect on respiration can be life-threatening.

2.2.2 Formulations

Three buprenorphine products are currently registered in Australia to treat opioid dependence within a framework of medical, social and psychological treatment:

- the mono product (Subutex®) is a sublingual tablet containing buprenorphine hydrochloride in 0.4 mg, 2 mg and 8 mg strengths
- the combination product (Suboxone®) is a sublingual tablet or film containing buprenorphine hydrochloride and naloxone hydrochloride in a ratio of 4:1 and is available in 2 mg/0.5 mg and 8 mg/2 mg strengths.

Buprenorphine is also registered in Australia as Temgesic® sublingual tablets and ampoules for intramuscular or subcutaneous injection, for the short-term relief of moderate to severe pain, including post-operative, terminal and chronic pain. A series of low-dose buprenorphine patches (Norspan®) for transdermal administration is available in Australia for pain relief.

2.2.3 Pharmacokinetics

Buprenorphine undergoes extensive first pass metabolism in the small intestine and the liver when taken orally. The use of buprenorphine by the oral route is therefore inappropriate. Peak plasma concentrations are achieved one to two hours after sublingual administration. The major metabolite, norbuprenorphine, has some opioid activity but the extent of its contribution to the effects of buprenorphine is unknown. Sublingual buprenorphine tablets have approximately 30–40 per cent of the bioavailability of intravenously injected buprenorphine. The bioavailability of sublingual buprenorphine is largely dependent on the time the drug is in contact with the oral mucosa and appears to improve as individuals practise their dosing technique[25].

Buprenorphine is principally metabolised by two hepatic pathways: conjugation with glucuronic acid and N-de-alkylation, mediated by the CYP450 3A4 isozyme. Metabolites are excreted in the biliary system, with enterohepatic cycling of buprenorphine and its metabolites. Most of the drug is excreted in the faeces with some in the urine.

25 Lintzeris et al 2006

Buprenorphine is a long-acting drug with a terminal elimination half-life of 24–37 hours. Peak clinical effects occur 1–4 hours after sublingual administration. Typically, effects will continue to be experienced for up to 12 hours at low doses (2 mg), but as long as 48–72 hours at higher doses (16 or 32 mg). The prolonged duration of effect at high doses enables double (alternate-day dosing) and even triple (third-day dosing) dispensing regimes[26].

Table 3 Onset and duration of response to buprenorphine	
Onset of effects	30–60 minutes
Peak clinical effects	1–4 hours
Duration of effects	4–12 hours at low dose (<8 mg) 24–72 hours at high dose (>16 mg)

2.2.4 Withdrawal syndrome following buprenorphine maintenance

The partial agonist properties of buprenorphine, along with its slow dissociation from opioid receptors, result in a withdrawal syndrome that is milder than that from heroin, morphine and methadone. Research evidence regarding the nature and severity of withdrawal following cessation of buprenorphine maintenance treatment remains limited. Typically, the withdrawal syndrome following the abrupt cessation of long-term buprenorphine treatment emerges within three to five days of the last dose, and mild withdrawal features continue for several weeks[26].

Treatment with opioid antagonists (such as naltrexone) can be commenced within five days of cessation of low-dose buprenorphine treatment without precipitating severe opioid withdrawal. This enables clients to transfer promptly to naltrexone treatment and avoid relapse and treatment drop-out[24]. In contrast, it is recommended that naltrexone is not started until 14 days after methadone withdrawal is completed[27].

2.2.5 Safety of buprenorphine

Buprenorphine is safer in high doses than full opioid agonists. Dose response studies show that high doses (16 mg daily or more) do not result in substantially greater peak opioid effects than lower doses (8 or 12 mg). Buprenorphine demonstrates the dose-related blockade effect of other opioids, due to the high occupancy rates of receptors. A 16 mg dose results in 85–92 per cent reduction in μ receptor availability[28]. Doses many times greater than normal therapeutic doses appear to be well tolerated in most individuals, and rarely result in clinically significant respiratory depression, except in individuals who are not opioid-tolerant.

2.2.6 Side effects of buprenorphine

The side effects of buprenorphine are similar to those of other opioids. The most common effects are:

- constipation
- disturbed sleep
- drowsiness
- sweating
- headaches
- nausea
- reduced libido[29].

26 Lintzeris et al 2006
27 Bell et al 2003
28 Greenwald et al 2003
29 Lintzeris et al 2006

Many clients report less sedation on buprenorphine than on methadone. Research evidence suggests that buprenorphine has minimal effect on psychomotor performance, and less effect than methadone or slow-release oral morphine. Any effect is likely to be greatest during the early stages of treatment or following dose increases. At such times, clients should be advised to exercise caution in driving or operating machinery. Buprenorphine appears to have minimal impact on hepatic function, although there have been case reports of acute hepatitis in clients with co-existing hepatitis C[30].

2.2.7 Drug interactions with buprenorphine

Opioid agonists

- **Precipitated withdrawal**

The initial dose of buprenorphine can precipitate opioid withdrawal in clients who have recently used an opioid drug. Buprenorphine has lower intrinsic activity and higher opioid receptor affinity than other opioids. Because of this, the first dose of buprenorphine may displace other opioids from opioid receptors and, in the short term, may not produce sufficient agonist effects to compensate for the displaced methadone or heroin. This may result in opioid withdrawal symptoms as the buprenorphine reaches its peak effects (approximately 1–4 hours after initial administration). This phenomenon, known as precipitated withdrawal, has particular clinical relevance during buprenorphine induction for people with opioid dependence[33].

- **Blockade of opioid analgesics**

Buprenorphine exerts a degree of competitive blockade to the effects of full agonist opioids, which may complicate the use of additional opioids for analgesia.

Opioid antagonists (naloxone and naltrexone)

Buprenorphine has affinity for μ opioid receptors, similar to the opioid antagonists. In the event of a buprenorphine overdose, conventional doses of naloxone may be of limited use. Very high doses of naloxone may be at least partially effective in reducing the effects of buprenorphine[31]. Because of the uncertain response to naloxone and its short half-life compared with buprenorphine, prolonged ventilatory support may be required in overdoses involving buprenorphine.

Naltrexone can precipitate a withdrawal reaction in clients on buprenorphine, although the effect may be delayed (2–4 hours, occasionally up to 8 hours).

Medications causing sedation

Buprenorphine, even at low doses, exerts additive sedative effects when used in conjunction with other sedating agents. These include other opioids, benzodiazepines, alcohol, tricyclic antidepressants, sedating antihistamines, and antipsychotics. The safety of buprenorphine mixed with high doses of other sedative drugs is still unclear: deaths from overdose have been reported[32]. However, in most fatalities reported to date involving buprenorphine and benzodiazepines, clients were injecting buprenorphine along with benzodiazepines or taking large amounts of buprenorphine outside a prescriber's care. Legitimate and appropriate prescription of these medications, coupled with responsible use by clients, is unlikely to lead to adverse consequences.

Hepatic enzyme inducers and inhibitors

Buprenorphine metabolism can be influenced by the presence of drugs and other compounds that are metabolised by or affect the activity of the cytochrome system. CYP3A4 inhibitors (such as protease inhibitors; some drugs in the class of azole antifungals such as ketoconazole; calcium channel antagonists such as nifedipine; and macrolide antibiotics such as erythromycin and clarithromycin) may increase plasma concentrations of buprenorphine[33]. CYP3A4 inducers may decrease blood concentrations of buprenorphine. However, these interactions are seldom of clinical significance (see Appendix 14).

30 Petry et al 2000, Peyriere et al 2009
31 Megarbane et al 2010
32 Pirany et al 2007
33 Lintzeris et al 2006

Serotonin toxicity

There is a case report of serotonin toxicity that may have been associated with buprenorphine in a patient on tricyclic antidepressants[34] and three reports of serotonin toxcity associated with buprenorphine in combination with MAOIs[35].

A full list of drugs that interact with buprenorphine appears at Appendix 14.

Table 4 Summary of the pharmacological and clinical properties of buprenorphine[34]

Property	Clinical implication
Buprenorphine produces opioid effects.	Buprenorphine reduces cravings for heroin and enhances treatment retention.
It prevents or alleviates heroin withdrawal symptoms.	It can be used for maintenance or withdrawal treatment.
It diminishes the effects of additional opioid use (e.g. heroin).	Buprenorphine diminishes psychological reinforcement of continued heroin use. It may complicate attempts at analgesia with opioid agonists (e.g. morphine).
Buprenorphine has a long duration of action.	Allows for once a day dosing up to three times a week.
There is a ceiling on dose response effect.	It is less sedating than full agonists (e.g. heroin, morphine or methadone). Buprenorphine doses above 12 mg/day may not increase the opioid agonist effects but will prolong the duration of action. It is safer in overdose, as high doses in isolation rarely result in fatal respiratory depression.
It is effective in a sublingual preparation.	Buprenorphine is safer in accidental overdose (e.g. in children) as it is poorly absorbed orally. However, there is more time involved in supervised dispensing.
There can be modified withdrawal precipitated by opioid antagonists.	Treatment with naltrexone can be commenced within 5–7 days of buprenorphine. However, it may complicate the management of opioid overdose, requiring high naloxone doses.
Buprenorphine has a side-effect profile similar to other opioids.	Generally, it is well tolerated, with most side effects transient.

2.2.8 Buprenorphine/naloxone combination product

The buprenorphine/naloxone combination product was developed to limit the risk of buprenorphine diversion by reducing the potential for injection, especially by opioid-dependent users who were not in treatment[36]. Queensland Needle Syringe Program data suggests that buprenorphine/naloxone injection has remained at low levels[37].

2.2.9 Formulations

Buprenorphine/naloxone sublingual tablet and sublingual film are available in two dosage strengths: 2 mg buprenorphine plus 0.5 mg naloxone, and 8 mg buprenorphine plus 2 mg naloxone. The tablet is hexagonal in shape, white in colour and has a lemon-lime flavour. The film is flat and rectangular in shape, transparent orange in colour and lime in flavour. Buprenorphine/naloxone sublingual tablets will cease to be subsidised by the Pharmaceutical Benefit Scheme (Section 100) from September 1, 2013. The sublingual film will continue to be subsidised after this date.

34 Isenberg et al 2008
35 McCance-Katz E *Drug Interactions in Opioid Therapy 2012*
36 Lintzeris et al 2006
37 Smirnov and Kemp 2012

2.2.10 Pharmacokinetics

The rationale for the combination product is the different sublingual and parenteral bioavailability of buprenorphine and naloxone. When buprenorphine is used sublingually, bioavailability is somewhere between 30 and 40 per cent while the bioavailability of naloxone via this route is less than 10 per cent. Consequently, when the combination is taken sublingually, it will act as if it was buprenorphine alone, with no apparent effect from the naloxone.

The addition of naloxone does not reduce the bioavailability of buprenorphine. Indeed, the bioavailability of chronically administered buprenorphine/naloxone may be higher than buprenorphine alone. However, if the combined preparation is injected, the naloxone will have a substantial effect and is likely to reduce the effects of the buprenorphine in the short term. It is also likely to precipitate withdrawal in opioid-dependent individuals on full opioid agonists[38].

Research shows plasma levels of buprenorphine and naloxone increase with the sublingual dose of the combination, although the increases are not directly proportional with doses. Naloxone does not appear to affect the pharmacokinetics of buprenorphine, and both mono and combination products are expected to deliver similar plasma concentrations of buprenorphine through sublingual dosing[39].

Buprenorphine/naloxone film and tablets do not meet all criteria for bioequivalence. The film may have slightly enhanced absorption of buprenorphine and naloxone compared with the tablets and studies show that the maximum plasma concentration may also be slightly higher for the film. Nevertheless, the tablets and film are considered interchangeable with comparable total plasma levels over 24 hours and studies show no significant differences in the dose effects or side effects.

Given the cessation of Pharmaceutical Benefit Scheme funding for tablets, patients should be transferred directly over to the same dose of film as they are currently receiving in tablet form. Due to the potentially greater bioavailability, clients transferring from tablets to film should be monitored for potential dose adjustments. (For buprenorphine/naloxone film product information, see Appendix 14.)

2.2.11 Side effects, safety and drug interactions

The side effects, safety and drug interaction profile of the combination product are similar enough to the mono product that, in the context of this document, they are considered the same. All opioids have misuse potential. However, as indicated in Table 5, people who are frequent users of heroin, methadone or other opioid agonists that bind less tightly to opioid receptors than buprenorphine are less likely to misuse buprenorphine. The effect of buprenorphine (taken sublingually or by intravenous injection) in people in naltrexone maintenance treatment remains unclear. Administration of buprenorphine to this population may result in a reduced agonist effect, particularly with low doses of naltrexone. This is also generally the case with implanted preparations of naltrexone[36].

38 Lintzeris et al 2006
39 eMims 2012

Table 5 Effects of mono and combination preparations of buprenorphine in various situations (Lintzeris et al 2006).

Note: There is only limited research and clinical experience in different populations of opioid users regarding the effects of buprenorphine alone and in combination with naloxone. This table summarises current expert opinion of the likely immediate effects of buprenorphine, in doses of 8–32 mg, in different situations.

Population	Combination product Sublingual (poor availability of naloxone)	Combination product IV (high availability of naloxone)	Buprenorphine mono Sublingual or IV
Dependent heroin user **Heroin: 1 hour ago**	Withdrawal precipitated by buprenorphine	Severe withdrawal due to naloxone and buprenorphine	Precipitated withdrawal
Heroin: ›12 hours ago	Agonist effects	May be mild withdrawal	Agonist effects
Non-dependent heroin user	Agonist effects	Reduced agonist effect	Agonist effects
Opioid – naive	Agonist effects (reduced if swallowed)	Agonist effect initially reduced	Agonist effects (reduced if swallowed)
Buprenorphine maintenance	Agonist effects	Agonist effect may initially be reduced	Agonist effects
Methadone maintenance **Dose: ‹24 hours ago**	Precipitated withdrawal	Severe withdrawal due to naloxone and buprenorphine	Precipitated withdrawal

The buprenorphine/naloxone combination product should not be used for people with a known allergy to naloxone. Any history or evidence of allergy to buprenorphine or naloxone should be clearly documented in the client's clinical file[40]**.**

40 Source: Approved product information for buprenorphine sublingual tablet and buprenorphine/naloxone sublingual film; Reckitt Benckiser

2.3 Naltrexone

Naltrexone hydrochloride is an orally active, long-acting opioid antagonist. It is registered in Australia for use in relapse prevention for alcohol dependence and opioid dependence[41]. However, it is not subsidised by the Pharmaceutical Benefit Scheme to treat opioid dependence. A review has highlighted the risks of overdose and death in clients treated with naltrexone due to a loss of tolerance, with a high treatment drop-out rate[42]. A position statement from the Australian National Council on Drugs (ANCD) in 2012 provides an official position on naltrexone implants for the treatment of opioid dependence: they should only be used in the context of a formal clinical trial[43].

Administration of naltrexone to a client who is physically dependent on opioids will precipitate a severe withdrawal syndrome.

Methadone maintenance clients being transferred to naltrexone should undergo methadone withdrawal (see *Section 9 – Withdrawal and Completion of Treatment*). Prescribers should seek specialist advice if it is not possible to follow this regime.

Naltrexone is subsidised on the Pharmaceutical Benefit Scheme for only one indication, which is as an authority prescription for relapse prevention in managing alcohol dependence[44]. Naltrexone is available on private prescription for relapse prevention in opioid treatment. It is not registered in Australia for use in opioid withdrawal although naltrexone is occasionally used to accelerate the process of withdrawal from opioids[44].

41 Bell et al 2003
42 Gibson and Degenhardt 2005
43 ANCD 2012
44 Bell et al 2003

Section 3
Assessment

3.1 Initial assessment

A comprehensive medical and psychosocial assessment is essential before determining a client is appropriate for opioid treatment.

Assessing a client for opioid treatment aims to:

- establish an effective therapeutic relationship with the client
- determine the client's suitability for opioid maintenance treatment
- enable the client to make an informed decision about treatment
- determine treatment goals (with harm-reduction principles in mind)
- meet the legislative requirements (e.g. documentation, gaining authority to prescribe for the client)
- document an initial treatment plan[45].

Initial assessment consists of history-taking, examination and investigations. Assessment is not a static, but a dynamic process. Assessment is the means by which the clinician gathers information to develop an understanding of the client's drug use and related behaviours and assists in developing an appropriate management plan[46].

The assessment may be conducted by practitioners from different professional backgrounds. However, all assessments must include a medical assessment by the doctor or nurse practitioner who will carry the responsibility for the decision to treat the client with methadone or buprenorphine.

The initial assessment should always cover and document medical history in detail, as outlined below in sections 3.1.1 to 3.1.10.

3.1.1 Drug use history

- age when first used drugs and relevant circumstances
- age when first used opioid(s) and relevant circumstances
- age when first dependent on opioids
- longest opioid-free period: how was it achieved?
- number of drug-free periods: how were they achieved?
- all current drug use, including alcohol, tobacco, cannabis, over-the-counter medications, caffeine and prescribed medications
- confirmation and duration, of dependence on opioids
- cues for drug use
- the perceived advantages versus disadvantages of drug use in contrast to non-drug use
- time of last use of opioids and other drugs
- route of administration (including needle-sharing and equipment-cleaning practices)
- past drug treatment history.

45 Lowinson et al 2005, Ruiz et al 2007
46 Gordon et al 2011

3.1.2 Past medical history

- history of drug-related problems (e.g. due to intoxication, withdrawal)
- history of medical conditions such as cardiac problems, epilepsy, head injury
- obstetric and gynaecological conditions (females)
- surgery
- accidents
- pain conditions
- infectious diseases especially viral hepatitis[47], HIV[48] and tuberculosis.

3.1.3 Psychological and psychiatric history

- history of psychiatric symptoms (e.g. depressive symptoms)
- prior psychiatric treatment
- past attempts at suicide or self-harm
- areas in life requiring support
- history of violence towards self or others[49].

3.1.4 Risk behaviours including infections/overdose

- use of sterile injecting equipment (e.g. needles and syringes, water for injection)
- sharing of injecting paraphernalia
- using situations and settings
- history of overdose and severity
- any other previous complications of injecting drug use.

3.1.5 Family history

- medical history, drug use and psychiatric history in family
- childhood history, and past and current relationships with family of origin
- current marriage or de facto relationships, children and quality of relationship.

3.1.6 Social history

- work history (including home duties), educational level attained, qualifications
- legal problems, previous incarceration, drug court, current charges
- interests and activities, hobbies
- relationships; extent and quality of friendships within and outside the context of drug use
- sexual relationships: sexual preference(s), sexual practices and sexual health
- accommodation: living alone, with family, with friends, type (e.g. house, flat, caravan, etc.), rental or mortgage
- current finances, levels of debt.

3.1.7 Presenting symptoms and systems review

- withdrawal symptoms and other symptoms related to any medical condition(s).

47 Hallinan et al 2007, Sylvestre 2007
48 Douglas, Bruce and Altice 2007
49 Gibbie et al 2011

3.1.8 Physical examination

- general physical examination with emphasis on organ systems that may have been affected by drug use (e.g. listen for heart murmurs and look for signs of liver disease, neurological impairment and haematological disorders)
- presence of needle track marks and signs of opioid (or other drug) intoxication or withdrawal
- psychological and psychiatric examination including mental state examination where indicated. If these skills are not available within a program, appropriate referral should be arranged.

3.1.9 Investigations

A series of routine investigations may be performed to gauge the general health status of newly registered clients, when indicated. These may include:

- full blood count
- biochemical screen (electrolytes, hepatic and renal function, C-reactive protein)
- blood-borne viruses screen
- urine drug screen
- sexual health screen
- chest X-ray
- Mantoux test
- other as indicated by history or examination (e.g. electrocardiogram).

3.1.10 Urine screening for drugs of dependence

Urine drug screens collected on the first visit may be valuable to confirm drug use history. The place of ongoing urine tests is addressed in Section 6.6 of this manual.

Medical investigations are not compulsory for entry into the Queensland Opioid Treatment Program. Rather, they should be offered in the context of facilitating good medical management.

3.2 Dental health

Drug-dependent individuals are vulnerable to dental health problems. Opioid treatment program clients have a high prevalence of decayed teeth and periodontal disease. All opioids may reduce the volume of saliva (xerostomia), which may contribute to dental decay[50]. A history of poor dental hygiene during periods of drug dependence may also contribute to the problem.

Methadone syrup contains sorbitol and glycerol, non-cariogenic sweetening agents that may counter the constipation caused by opioids. Biodone is formulated without any sweetening agent.

A few simple counter-measures may help to manage the dental health of opioid treatment program clients:

- examine the mouth and gums in the initial and subsequent physical examinations, and develop a management plan for any problems identified
- if you identify xerostomia, recommend sugar-free gum or sugar-free candy to stimulate saliva production
- recommend water diluent for take-away doses
- provide information about diet and oral hygiene when appropriate
- recommend treatment at community dental clinics for concession card holders, or by private dentists in other cases.

50 Thomson et al 2006

3.3 Pregnancy and lactation

As most opioid-dependent women are of child-bearing age when they present for opioid treatment, the following should be explored[51]:

- might they be pregnant?
- are they breastfeeding?
- if they are pregnant, what are their plans for the pregnancy?
- if they are not pregnant, what are their intentions to become pregnant?
- outline the benefits of treatment to pregnancy outcomes
- if they do not wish to become pregnant, advise regarding reliable contraception
- available support networks.

Buprenorphine/naloxone is contraindicated in pregnancy and breastfeeding. It is important that this is discussed with female clients to obtain their informed consent before commencing buprenorphine/naloxone. As set out in national guidelines, women who become pregnant while on the combination product should be switched to either methadone or buprenorphine (mono preparation). If a stable client receiving unsupervised buprenorphine/naloxone becomes pregnant, it may be appropriate to continue her on buprenorphine (mono preparation) but increase the frequency of clinical reviews in view of the change in her health status. Section 8 provides more detail on managing opioid-dependant clients who are pregnant or breastfeeding.

Note: There is less evidence about the safety of buprenorphine in pregnancy compared with methadone. Recent studies have shown that it is as safe as methadone and infants may suffer less neonatal abstinence syndrome with buprenorphine[52].

3.4 Opioid treatment and driving or operating machinery

Methadone and buprenorphine may affect the capacity of clients to drive or operate machinery, particularly during the early stages of treatment (the first 2–4 weeks), after a dose increase, or when they also take other drugs (such as benzodiazepines and/or alcohol). All clients should be warned about this effect before they enter treatment, when the dose of methadone or buprenorphine is increased, or when it appears that they may be using other drugs.

The 2012 Austroads publication *Assessing Fitness to Drive: Medical Standards for Licensing and Clinical Management Guidelines* states, "Short-acting opioids, particularly parenteral forms, may cause fluctuation in blood levels of opioids, which would be expected to be incompatible with safe driving. People using these agents should be referred for assessment by an addiction specialist. People on a stable dose of buprenorphine and methadone for their opioid dependency may not have a higher risk of a crash, providing the dose has been stabilised over some weeks and they are not abusing other impairing drugs"[53].

51 Jones et al 2008, Martin et al 2009
52 Jones et al 2010
53 www.austroads.com.au

3.5 The initial treatment plan

The treatment plan should be developed in collaboration with the client at the time of initial assessment and documented in the client's clinical file within the summary of the initial treatment plan[54].

The initial treatment plan should document:

- whether methadone or buprenorphine treatment will take place and the justification for this
- alternative management recommendations, particularly if opioid treatment is not used, including:
  - referral to a self-help group, such as Narcotics Anonymous (NA)
  - a drug-free program, either as residential (e.g. therapeutic community) or outpatient
  - continued counselling
  - referral for withdrawal management
  - treatment of physical complications
  - commencement on naltrexone
  - peer-based support organisations such as Queensland Pharmacotheraphy Advocacy Mediation and Support Service (QPAMS).

54 Strain and Stitzer 2006

Section 4
Admission or entry to program

Admission into opioid treatment should be voluntary. In general, opioid treatment is only suitable for people who are opioid dependent. The opioid dependence syndrome may appear in varying degrees in different individuals. Use the criteria for dependence in *The Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV) to determine whether a client's history indicates opioid dependence.

DSM-IV diagnostic definition of opioid dependence (APA, 1994)

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three or more of the following, occurring at any time in the same 12 month period:

1. Tolerance, as defined by either of the following:
   a) a need for markedly increased amounts of opioids to achieve intoxication or desired effect
   b) markedly diminished effect with continued use of the same amount of opioids.
2. Withdrawal, as manifested by either of the following:
   a) the characteristic withdrawal syndrome for opioids *(see Appendix 4)*
   b) opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.
3. Opioids are often taken in larger amounts or over a longer period than was intended.
4. There is a persistent desire or series of unsuccessful attempts to cut down or control opioid use.
5. A great deal of time is spent in activities necessary to obtain opioids, use opioids, or recover from their effects.
6. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
7. The opioid use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.

A person diagnosed as opioid dependent will not necessarily be physically dependent on opioids at the time of presentation. However, where there is no current neuroadaptation, careful consideration should be given to the range of treatment interventions available before determining if maintenance treatment is appropriate for the patient.

In the absence of current neuroadaptation, opioid dependence may be measured by the effort an individual – previously physically dependent on opioids – must make to refrain from relapsing to opioid use.

Those who present without physical dependence will often be younger than average and have a shorter opioid using history. These people may be among the least likely to be retained in maintenance treatment. Nevertheless, where the person has an absence of neuroadaptation, opioid maintenance should not be automatically excluded from treatment options.

This is also true of people who have been very recently released from prison, who have a history of significant opioid dependence and whose current risk of relapse has been deemed high by both themselves and a clinician. Given the high rate of death from opioid overdose in those recently released from custody, opioid treatment is often appropriate in these circumstances (see 4.1 below).

It is desirable for the client to provide proof of identity prior to treatment. However, if a client is clearly opioid dependent and cannot provide proof of identity, the prescriber should not withhold treatment on this basis. Instead, the prescriber should continue to try to establish proof of the client's identity at subsequent consultations.

4.1 Priority entry to opioid treatment

Entry into an opioid treatment program should not be delayed. If delays are unavoidable, people with certain conditions should have priority of access to opioid treatment programs. These following conditions should be given priority access to opioid treatment because of the risks that non-treatment poses to the health of the individual and the wider community:

- pregnant women and their opioid-using partners
- people with HIV and their opioid-using partners
- hepatitis B carriers (HBsAg, HBeAg positive) and their opioid-using partners
- people recently released from prison (within the previous month)
- people who commenced an opioid treatment program while a hospital inpatient. Good clinical practice should ensure effective communication between hospital and clinic occurs well before discharge
- people with serious medical and psychiatric conditions.

If a patient is considered to be at significantly higher risk than if they were not in treatment, clinical judgment should also be used to prioritise their treatment.

4.2 Contraindications to opioid treatment

In general, there are no absolute contraindications for opioid treatment. Someone should not be excluded merely on the basis of previous unsuccessful attempts at this treatment. However, certain circumstances require special consideration:

- People younger than 18 years should generally be considered for treatment other than methadone/buprenorphine. Although opioid treatment should not be precluded on the grounds of age alone, you should exercise caution in prescribing a drug of dependence for anyone aged 16–17 years[55]. Consent from the parents or legal guardian is required to treat clients under the age of 16.
- Unless they are opioid dependent, people who are poly-drug users and whose drug use includes opioids are considered inappropriate for opioid maintenance treatment.
- People who are unable to give informed consent to treatment due to acute psychosis are not considered suitable for opioid maintenance treatment. People with serious mental health problems should have these conditions stabilised before beginning treatment to ensure that informed consent can be obtained and treatment adherence can be optimised. (Appropriate arrangements should be made with mental health professionals so there can be conjoint management of co-occurring substance use and mental health problems.)
- People with severe hepatic impairment (decompensated cirrhosis), severe renal impairment or respiratory insufficiency[56] are not considered suitable.
- People who are unable to give informed consent to treatment due to acquired brain injury and/or significant cognitive impairment are also considered unsuitable for opioid maintenance treatment.

4.2.1 Precautions

- Methadone and buprenorphine should be prescribed with caution for clients with: alcohol dependence; head injury and raised intracranial pressure; ulcerative colitis; or biliary and renal tract spasm. Likewise, prescriber caution should be exercised for clients receiving monoamine oxidase inhibitors (or within 14 days of stopping such treatment). Seek specialist advice in these cases[57].
- Treatment with methadone or buprenorphine should be approached cautiously for clients who are misusing other drugs, particularly sedative drugs such as alcohol or benzodiazepines[56]. Particular emphasis should be given to assessing the level of their physical dependence on opioids, the likelihood of continued use of other sedative drugs and the risk they will overdose.

55 Henry-Edwards 2003
56 AMH 2011
57 Gillman 2005, Isenberg et al 2008

- People with a history of violent behaviour on opioid treatment (often at the clinic, surgery, dosing pharmacy or nearby) may pose a threat to both the personal safety of staff, other clients and other health professionals involved in the program, and to the program's integrity. Careful consideration should be given to the relative benefits and potential harm of providing or not providing treatment. A 'Consent to Treatment Form' signed by the client that clearly defines expected behaviours during their participation in the program can be helpful. (An example of such a form is provided in Appendix 15). In the case of co-occurring mental health problems, the involvement of mental health professionals in a shared care arrangement may also be appropriate *(see Section 8.2)*.
- People who have chronic pain may require specialist pain management *(see Section 8.4)*[58].
- Women who are pregnant, breastfeeding or planning a pregnancy are required to be assessed on the risks and benefits of treatment *(see Section 8.1)*.

4.3 Establishing an effective therapeutic relationship

Clients present for opioid treatment with a variety of attitudes and emotions. Sometimes they present in crisis, feeling out of control of their lives, vulnerable and desperate. They are often suspicious of people in positions of authority as a result of previous experiences. They may also be apprehensive about the response they will receive from the assessor.

Clients often have a clear idea of what they want, but are unsure about entering opioid treatment programs because of the restrictions involved. They may also regard opioid treatment as a last resort, so feelings of failure and inadequacy can be prominent at the initial assessment.

Clients can sometimes feel trapped on opioid treatment programs, so it is important to clearly explain the potential benefits, limitations and frustrations associated with entering opioid treatment programs. This enables potential clients to make informed decisions about entering a program that may influence their daily activities for many years.

The initial assessment is an important opportunity to begin building an effective therapeutic relationship with the client. A non-judgmental attitude, empathy, respect and willingness to listen will lay the foundations for a positive therapeutic alliance. Adequate time, education about the client's needs and encouragement of active client participation are also essential.

The importance of the first clinical contact in establishing a positive therapeutic alliance between client and clinician cannot be overstated.

4.4 Selecting maintenance pharmacotherapies

Both methadone and buprenorphine have been found to be effective in the maintenance treatment of opioid dependence[59]. Although methadone has previously been quoted to be more effective in retaining clients in treatment[60], Queensland data collected by the Drugs of Dependence Unit suggests that buprenorphine may now be a preferred treatment for some clients due to flexible dosing arrangements and increased safety.

Clients suitable for opioid treatment should be given enough information to make an informed choice between methadone and buprenorphine. The client should be presented with a balanced description of the two treatments. The choice between methadone and buprenorphine treatment should not be based on client age or the duration or severity of dependence.

58 Royal Australian College of Physicians 2009
59 Simeons et al 2005
60 Mattick et al 2008

The National Clinical Guidelines and Procedures for the Use of Buprenorphine in the Treatment of Heroin Dependence[61] recommend the following be considered when choosing maintenance pharmacotherapies:

- response to prior treatment
- previous adverse effects
- logistics of participating in treatments
- ease of withdrawal from buprenorphine maintenance treatment
- expectations of the treatment
- capacity to transfer from methadone maintenance.

Once these points have been discussed, buprenorphine should be strongly considered for those clients who have had multiple unsuccessful methadone treatment episodes or are ambivalent about maintenance treatment.

4.4.1 Relative merits of methadone and buprenorphine

More than 30 years of clinical experience and research has established that methadone in doses of 60–100 mg/12–20 ml per day is highly effective at:

- retaining people in treatment
- suppressing heroin use and its associated crime
- reducing the risk of overdose
- cutting the risk of blood-borne virus transmission[62].

Trials have suggested that buprenorphine maintenance is also effective in achieving these objectives. However, some clients prefer buprenorphine because it has different subjective effects. Choosing which treatment to offer is a matter of weighing up the pros and cons of the two drugs.

Buprenorphine is a partial opioid receptor agonist, whereas methadone is a full agonist. This means that with increasing doses, buprenorphine does not cause progressive depression of respiration and consciousness, whereas methadone does.

The clinical implications of differences in pharmacology are that:

- buprenorphine presents less risk of fatal overdose than methadone. In particular, there is less risk of overdose during induction into buprenorphine treatment[63]
- there is a risk of precipitated withdrawal during induction into buprenorphine treatment if started too soon after a dose of another opioid[64]
- buprenorphine, particularly at higher doses, has a longer duration of action than methadone. This has the advantage of making less-than-daily dosing (dosing every second or third day) effective for many clients.

Possible practical disadvantages of buprenorphine include that it is:

- more time-consuming to administer: sublingual tablets take 4–10 minutes to be absorbed. Some clients may be unable to achieve optimal absorption through this route. (This is less relevant since the introduction of the buprenorphine/naloxone film).
- more easily diverted to unsanctioned use. Without adequate supervision it can be secreted in the mouth and later removed. Injecting diverted medication that has been in the mouth increases the risk of infection by introducing oral flora into the circulation.

61 Lintzeris et al 2006
62 Connock et al 2007, Simeons et al 2006
63 White and Lopatko 2007
64 AMH 2011

Clients suitable for opioid treatment should be given enough information for them to make an informed choice between buprenorphine and methadone. It is relatively straightforward to transfer from buprenorphine to methadone, but more complex transferring from methadone to buprenorphine as this can precipitate withdrawal.

The choice between the two may be influenced by individual variations in response to a particular drug or practical consideration related to the availability of dosing.

For clients who have not done well on one treatment, the other should be considered.

Table 6 Comparison of methadone and buprenorphine

	Methadone	Buprenorphine
Classification	Full μ agonist Used for maintenance treatment	Partial μ agonist Antagonist Used for maintenance or withdrawal treatment
Substitutes for heroin	+ + + Reduces craving for heroin	+ + Reduces craving for heroin
Blocks effects of heroin	+ + At high doses (e.g. ›60 mg)	+ + + + At low doses (e.g. ≥4 mg)
Side effects	Opiate like	Less sedating Can precipitate withdrawal
Withdrawal on cessation	+ + + Described as severe and prolonged	+ + Less severe
Onset of effects	30–60 minutes	30–60 minutes
Peak effects	3–4 hours	1–4 hours
Duration of clinical effects	16–30 hours	Dose-dependent 48–72 hours at high doses
Metabolism (affected by CYP3A4 inducers/ inhibitors)	+ + + Hepatic CYP450	+/- Hepatic CYP450 and conjugation Less clinical impact on liver metabolism
Mode of administration	Oral	Sublingual
Drug interactions	Sedatives, opioid antagonists, inducers/inhibitors CYP450	Sedatives, opioid agonists and antagonists

(Methadone and buprenorphine product information – see Appendices)

4.5 Enabling the client to make an informed decision about opioid treatment

Obtain informed consent to opioid treatment in writing from the client before they enter the program.

For clients to make a fully informed decision regarding opioid treatment, staff should provide them with the following information during the initial assessment:

- an explanation of the nature of opioid treatment, including the aims, what opioid treatment can and cannot achieve, the known benefits and the drawbacks
- program policies and expectations, including frequency of picking up doses, urine testing, dosing hours, take-away doses, clinic or pharmacy schedule of appointments and the rules on violence, drug-dealing and drug use
- the expected duration of treatment
- the side effects and risks associated with taking methadone or buprenorphine
- information on the potential effect of methadone or buprenorphine on activities such as driving vehicles or operating machinery
- details of when the client will receive their first dose
- the risks of other drug use (including alcohol) while on the program
- how to obtain further information, for example contacts for local peer support organisations.

4.5.1 Written information for the client

Clients who are assessed as suitable for opioid treatment should be given written information about all aspects of the treatment program being offered, their rights, their responsibilities and the conditions under which they might be involuntarily discharged from the program.

If possible, assemble this information into a client information booklet. Clients who cannot read should have their rights and obligations explained at the time they enter the program.

Simple and clear program rules should also be displayed in the waiting area.

It is particularly important to set boundaries for client behaviour while they are on a program and that these boundaries are fully explained at the start of treatment. Experience shows that if limits are well understood, then aggressive, inappropriate or unacceptable behaviour can be minimised.

A consistent and transparent approach to client care – one that has regard to a client's wishes and uses a team-based decision-making approach to matters within the framework of the guidelines – is most likely to produce good outcomes.

Clients should:

- be given information on what they can expect from the program and staff
- be offered respect from the clinical staff
- be offered opportunities to collaborate in their treatment
- give informed consent for treatment options offered.

Staff must strictly respect clients' privacy. Staff should not pass on messages, notes, packages or goods of any kind from anyone. Staff should politely decline to answer even simple requests like 'Has X been in yet?'.

By observing these policies and explaining them, the client's privacy is protected and a commitment to privacy is demonstrated.

4.5.2 Confidentiality and security

All Queensland Health officers, employees and agents are subject to a strict statutory duty of confidentiality under the *Hospital and Health Boards Act (2011)*.

This duty, subject to certain prescribed exceptions, prohibits the release of information that could enable a person to be identified who is receiving, or has received, a public sector health service.

Disclosure of patient-identifying information to any other person, including another Queensland Health employee other than as authorised under the specific exceptions identified in the *Act*, is an offence, carrying a maximum penalty of 50 penalty units.

In addition, there are a number of specific provisions in other health legislation that relate to the confidentiality of information. These also impose penalties for improper disclosure of information.

4.6 Harm minimisation during opioid treatment

To enable goals and objectives to be agreed upon and prioritised, it is important to conduct a full assessment when the client enters treatment.

In response to information from the client, harm minimisation should begin during the assessment. For example, the medical history will include current symptoms, untreated current illnesses and any contraception used.

Following this, the client should be given information, undergo appropriate investigation and treatment, or receive an appropriate referral.

Blood-borne virus transmission risks and at-risk sexual behaviours should be assessed and brief interventions to address high-risk activities should routinely be provided, as should information about local needle and syringe programs and sexual health services.

4.6.1 HIV, hepatitis B and hepatitis C screening

Hepatic dysfunction may affect both opioid treatment and other medical treatment. All clients must be offered testing to determine their hepatitis B, C and HIV status.

To help clients to make a decision regarding testing, they should be given sufficient information to allow informed consent and to assure them that confidentiality will be maintained.

If clients choose to undergo these tests, pre- and post-test counselling is mandatory in all cases. Let the client know they can access extra support about hepatitis through the Hepatitis Council of Queensland.

All clients entering or already in an opioid treatment program who are found to have no immunity to the hepatitis B virus should be offered hepatitis B vaccination[65].

You should also consider offering vaccination to the sero-negative partners and close family contacts of clients who are hepatitis B carriers.

The hepatitis B vaccine is provided free of charge in general practice to at-risk groups, giving an option for the client when the clinic is unable to provide this service.

65 National Hepatitis B Strategy 2010

4.7 Treatment goals

The treatment goals should be discussed with the client at the time of initial assessment and documented in the client's clinical file within the summary of the initial management plan.

The initial treatment plan should document:

- whether opioid treatment will take place and the justification
- the alternative management recommendations if opioid treatment is not used.

If the client is to be admitted to an opioid treatment program, there should be documentation of:

- starting date and dose of methadone or buprenorphine
- early monitoring arrangements
- initial harm-reduction actions
- case management arrangements.

The client should be reassessed when stabilised on methadone or buprenorphine and in an improved physical and mental state that better allows them to process information and make decisions about their future. At this time, the treatment goals and management plan should be reviewed and discussed in more detail.

A desire to achieve total abstinence from drug use – including, ultimately, methadone or buprenorphine – is a legitimate goal. However long-term opioid maintenance might be more realistic in some cases.

Where abstinence is the client's desired outcome of treatment, the barriers to achieving this should be examined and the client's confidence to achieve this goal (self-efficacy) also taken into account.

4.8 Retention and motivation of clients in treatment

Some clients may present for treatment only to 'drop off' the program and return to unsanctioned drug use after a short period of time. Such presentations may be linked to fluctuating availability of 'street' heroin, and should not be regarded as unacceptable.

It is common that, after a few such visits, the client's trust in the staff increases and the client may return to stabilise on the program.

A motivation for abstinence should not be expected from clients for them to be admitted to the program. This is unrealistic as 'motivation' is a difficult enough challenge for people who are dependent on alcohol or other drugs. As such, it is not a prerequisite for treatment for either group.

The client's motivation to be abstinent from drug use may increase after a stable time on opioid treatment and after the pros and cons of drug use have shifted to make reduced and less risky drug-taking (or, indeed, a drug-free state) both more desirable and achievable.

The client's confidence and belief in their capacity to achieve and sustain progressively higher-order treatment goals (self-efficacy) also tends to grow during a stable period in opioid maintenance treatment.

It has been demonstrated that the level of self-efficacy has predictive value with respect to treatment outcome[66].

Do note that the clinician's counselling style and technique can have a positive or negative effect on a client's progress in treatment. The 'therapist effect' cannot be ignored in the effort to provide high-quality opioid treatment.

66 Kadden and Litt 2011

4.9 Client records

Clinical record-keeping within opioid treatment programs should ensure that:

- each client has a file
- each client's file is secure
- the information within the client's file is confidential
- all entries in the file are made by people authorised by the program and are signed (with designation and name printed)
- all entries in the file are legible, dated and timed
- the file contains sufficient data, including: unique record number, full name and address, date of birth, sex, language spoken, allergy to any drugs, general practitioner and person to notify in an emergency
- the file contains documentation of relevant client history, including: drug and alcohol history; present and past medical history; present and past psychiatric history; family history; social considerations; physical examination; and mental state examination
- there is evidence of a planned approach to client care
- 'alert' notations for conditions such as where allergic responses, adverse drug reactions and infection risks are present (these should be readily apparent)
- a summary sheet is completed at the time of discharge[67].

67 WHO 2009

Section 5
Commencing treatment

To encourage retention during the induction into opioid treatment, it is essential to ensure client safety while minimising signs and symptoms of withdrawal. This can be facilitated by carefully explaining the intoxicating effects and withdrawal effects during the induction and maintenance phases of treatment, establishing a therapeutic relationship and through repeated observation of clients.

It is particularly important to clearly explain that it takes time to complete induction into treatment and that clients will experience increasing drug effects over the first few days of treatment even if the dose is not increased[68].

5.1 Dosing location

Clients may be dosed with methadone or buprenorphine at an opioid treatment program clinic, a community pharmacy or a hospital pharmacy.

5.2 Role of pharmacist

Pharmacists play a key role in delivering opioid treatment services, both in terms of providing a community setting, and by maximising flexibility and convenience for clients who can be dosed near where they live or work.

The involvement of pharmacists in the program is voluntary and may be of great value in that a positive relationship can be developed between the client and pharmacist.

In general, clients receive their dose from a pharmacist at a retail pharmacy outlet. However, there are circumstances in which a client may be dosed at a clinic including:

- during the first few days of stabilisation on methadone or buprenorphine, when the client requires close observation for clinical safety reasons
- subsequently, when a client's drug-using behaviour is thought to be placing them at risk of overdose
- any time a client should not be provided with a Sunday take-away dose to ensure clinical safety or to preserve the program's integrity, and they cannot be placed with a seven-day-a-week pharmacy.

Apart from these considerations, clients are placed with pharmacies that supervise the consumption of their daily methadone or buprenorphine dose, except when the client is provided with take-away doses[69].

When a prescriber or clinic arranges for a pharmacy to commence dosing a client, the prescriber or clinic must give the client a letter of introduction (with a photograph of the client attached) to present at the pharmacy to ensure that the person presenting is the person for whom the doctor has prescribed[69]. *(An example of a letter of introduction is provided in Appendix 17.)*

Generally the pharmacist:

- develops a positive relationship with the client
- monitors the client's day-to-day level of intoxication
- dispenses the dose
- ensures that the dose has been swallowed or absorbed
- encourages the client to take the dose at approximately the same time each day
- maintains close contact with the prescriber to report signs of intoxication, other drug use, non-attendance for dosing and any problems that occur[70].

Monthly written instructions (on a specific Queensland Opioid Treatment Program Written Instruction form) are faxed or posted to the pharmacist.

Prescribers can verbally authorise the supply of methadone or buprenorphine, provided that within 24 hours of giving the verbal order, the prescriber ensures a paper written instruction for the drug is faxed to the dispenser.

68 Henry-Edwards et al 2009
69 Drug & Dependence Advisory Committee 2006, Pharmaceutical Services Branch 2004
70 Drug & Dependence Advisory Committee 2006, Pharmaceutical Services Branch 2004, Lintzeris et al 2006

Within seven days of giving the oral prescription, the prescriber must send the original written instruction, by post or by hand, to the dispenser[71].

5.3 Administering methadone or buprenorphine to clients at home

The capacity to provide methadone or buprenorphine to clients in their own home is limited by the resources available to an opioid treatment program provider. In general, if a client has a medical condition that prevents them attending the opioid treatment dosing point, the preferred options are to provide an alternative dosing point or, if it is considered safe to do so, to provide take-away doses for periods of illness or incapacity.

If these options are not available or acceptable, home dosing may be necessary in the following circumstances:

- the client has a verifiable medical condition requiring immobilisation or strict bed rest
- the client's condition has been verified by the opioid prescriber.

Prescribers should determine what resources are available in their own locality to facilitate the home delivery of methadone or buprenorphine. Resources may include local general practitioners or home delivery by the pharmacist.

5.4 Methadone – commencing methadone maintenance

Deaths during methadone induction have been related to:

- concomitant use of other drugs (particularly sedatives such as alcohol and benzodiazepines)
- inadequate assessment of tolerance
- commencement on doses that are too high for the level of tolerance
- lack of understanding of the cumulative effect of methadone
- inadequate observation and supervision of dosing
- individual variation in metabolising methadone[72].

5.5 Initial methadone dose

New clients should be dosed with caution. Initial doses should be 5–20 mg/1–4 ml. The initial dose should NEVER exceed 30 mg/6 ml.

It is mandatory to take particular care in assessing a new client’s drug use history and current clinical status before they start opioid treatment.

Base the initial dose of methadone on the assessed severity of a client’s opioid dependence, particularly on the level of a client’s tolerance to opioids.

The quantity, frequency and route of administration of opioids, findings on examination, corroborative history and urine testing together may provide some indication of a client’s opioid tolerance, but these cannot predict the client’s tolerance with certainty[73].

When deciding on the initial dose, also consider:

- where dosing is to occur
- whether staff and facilities are available to observe and assess the client before and after dosing
- who will assess withdrawal or intoxication prior to dosing
- time since last opioid use
- use of benzodiazepines or alcohol (the risk of overdose increases most markedly when other central nervous system depressants are also used)
- withholding or reducing the dose if the client shows signs of intoxication with drugs such as with benzodiazepines, alcohol or opioids.

71 Queensland Government 1996
72 White & Irvine 1999, Srivastava & Kahan 2006
73 Henry-Edwards et al 2009

The starting daily dose of methadone should be low. Usually **20 mg/4 ml or less** is sufficient to modify withdrawal greatly from even severe degrees of heroin or other opioid dependence. Occasionally higher doses may be justified, however the **maximum starting dose** should never exceed **30 mg/6 ml**.

This maximum dose should only be prescribed when there is substantial clinical evidence of a significant opioid dependence and unequivocal signs of a more severe withdrawal syndrome.

The following table should guide prescribers in determining the initial dose of methadone:

Table 7: Initial methadone doses

Situation	Initial daily dose
In general, start off low. The dose can always be increased. Prescribe this dose for people with compromised liver function, shorter opioid-use histories, or where smaller amounts of heroin are being used or use is less frequent.	5–20 mg/1–4 ml methadone
Client using opioids regularly for more than six months and in the past two weeks using twice a day or more and, in addition, they have obvious needle tracks.	20–25 mg/4–5 ml methadone
On methadone previously, has a long history of opioid dependence and is using large amounts of heroin now.	25–30 mg/5–6 ml methadone

Occasionally, a client will re-present on the first day after the administration of an initial dose of methadone still displaying signs and symptoms of severe opioid withdrawal.

Since peak serum methadone levels are attained in approximately 3–4 hours after oral administration, such persons may be considered for a supplementary dose after that period of time, following careful clinical assessment.

If the client is experiencing persistent withdrawal symptoms at 4 hours, a supplementary dose of 5 mg/1 ml can be considered. However, the maximum dose of 30 mg/6 ml on the first day of methadone treatment still applies[74].

Clients who have been using prescription opioids (for example morphine, pethidine, codeine or oxycodone) should not be commenced at doses above 25 mg/5 ml.

Comparative strengths of opioids listed in pharmacology textbooks are approximations only, and since the prescribed opioids are generally not supervised, it is impossible to be certain that the clients are in fact consuming the quantity they report. For these reasons, estimating an equivalent starting dose of methadone from these comparative tables should not be attempted.

It is very important to clearly explain to clients that it takes time to complete induction onto methadone and that they will experience increasing effects from methadone over the first few days of treatment, even if the dose is not increased[74].

The client should be seen immediately before the initial dose of methadone to determine that they are not intoxicated and ensure that it is safe to dose them.

The client is then sent directly to the pharmacist for their dose or given their dose in the clinic.

74 Henry-Edwards et al 2009

5.6 Supplementary doses

Supplementary dosing offers one alternative to help determine the appropriate starting dose.

In this alternative, the client is given an initial low dose (10–15 mg/2–3 ml), and then reviewed after four hours (when peak blood levels are reached). The client may be given a further 10–15 mg/2–3 ml if they are still experiencing opioid withdrawal symptoms, subject to the maximum first day's dose of 30 mg/6 ml. A single dose may be given on the following day.

5.7 Methadone stabilisation: Dose adjustments

Clients must be seen daily for at least the first four days in order to stabilise them on an adequate dose of methadone. Careful assessment is necessary each day and the dose titrated against the client's clinical state.

Dose increases should not exceed 5 mg/1 ml on any day except under extraordinary circumstances. The dose should not exceed 40 mg/8 ml in the first week (seven days).

The above is to safeguard the client from receiving a methadone dose that significantly overshoots their tolerance to opioids, with the attendant risks of over-sedation and toxic or even fatal consequences.

This risk is increased by the long elimination half-life of methadone and means, after a dose increase, there is a delay of approximately five days before new steady state serum levels are achieved[75].

Prescribers should refer to Section 2 for a summary of the relevant clinical pharmacology of methadone.

5.8 Regular client review

Treating prescribers or their nominees, such as clinical nurses within an opioid treatment clinic, recommend the following minimum schedule of reviews.

Review:

- daily for at least the first four days to enable the prescriber to identify the general adequacy of the client's dose
- every 2–4 days until the dose is stabilised
- every week during the following 4–6 weeks
- every 2 weeks during the following 6–8 weeks[75].

The prescriber should perform monthly reviews thereafter – although the prescriber may wish to extend review periods to up to 3 months for very stable clients.

Initially, frequent reviews by the prescriber are required to:

- titrate the individual optimal doses of methadone
- make a more comprehensive assessment of the client
- discuss treatment plans further
- assess whether the dose is preventing withdrawal symptoms and suppressing cravings
- monitor additional drug use[76].

The prescriber (or delegate) should review all clients at least once every 3 months. Individuals with continuing high-risk patterns of drug use, or concomitant medical, psychiatric or social problems, may require more frequent review.

In practice, a suitably trained nurse or opioid treatment program clinician often undertakes these reviews, with reference to the prescriber where necessary.

75 Henry-Edwards et al 2009
76 Handford 2011

5.9 Transfer from other pharmacotherapies

Prescribers may need to seek specialist advice when prescribing for clients who are transferring from pharmacotherapies with which they are unfamiliar[77]. A number of opioid conversion tables can be found in pharmacological literature. However, these tables must be treated with caution, as they are only a guide to the possible final dose of methadone. The equivalent dose of methadone cannot be known, because the prescriber cannot be sure a client has been taking all of a prescribed dose of another opioid, and because each person will respond differently to different opioids.

5.9.1 Transferring from buprenorphine

It may be appropriate to transfer a client from buprenorphine to methadone under the following circumstances:

- if the client is experiencing intolerable side-effects from buprenorphine
- if there is an inadequate response to buprenorphine treatment. Treatment with buprenorphine should be considered unsuccessful if it has not resulted in marked improvements in the client's drug use, injecting risk practices or other outcomes identified by the client and clinician as treatment goals
- if the client is transferring to a program where buprenorphine is not available. As buprenorphine may be unavailable overseas, clients may need to transfer to methadone in such circumstances. To facilitate the subsequent return to buprenorphine treatment (if planned), the lowest effective methadone dose should be used[77].

Methadone can be commenced 24 hours after the last dose of buprenorphine. The initial methadone dose should not exceed 30 mg/6 ml and clients transferring from lower doses of buprenorphine (4 mg or less) should be commenced on lower doses of methadone (20 mg/4 ml or less). Care should be taken not to increase the dose of methadone too quickly[77].

5.9.2 Transferring from naltrexone

Transferring a client from naltrexone tablets to methadone will generally be considered if they relapse to opioid use after ceasing naltrexone. Because of the loss of tolerance on naltrexone, clients transferring to agonist treatment should be treated as opioid-naive and non-tolerant unless the clinical circumstances clearly indicate there has been a return to regular, significant heroin use.

Do not administer methadone until at least 72 hours after the last dose of naltrexone. This is in order to reduce the blockage from residual naltrexone. Extreme caution should be exercised with commencing doses of methadone. No commencing dose should be greater than 20 mg/4 ml[77].

Despite being unregistered with the Therapeutic Goods Administration, naltrexone implants are being used in the treatment of opioid dependence. If a client with an implant in situ seeks to be registered for opioid replacement, advice should be sought from an addiction specialist.

77 Henry-Edwards et al 2009

5.10 Buprenorphine – commencing maintenance treatment

All new and re-admitted clients assessed as suitable for buprenorphine treatment should be commenced on buprenorphine/naloxone film. Once stabilised, clients may receive combination film on alternate-day or three times weekly dosing, not exceeding the maximum daily dose of 32 mg.

5.10.1 Commencing buprenorphine from heroin use

The aim is to stabilise clients on an effective dose of buprenorphine as soon as possible. More rapid induction (such as 12–16 mg by day three) is associated with better retention in treatment. However, this needs to be weighed against individual reactions to initial dosing and safety considerations[78].

Rapid dose induction is most easily achieved with an initial dose in the range of 4–8 mg. Higher initial doses will facilitate rapid dose induction but increase the risk of precipitated withdrawal (if the client has recently used opioids) or sedation (if the client has a lower level of opioid dependence or also consumes other sedatives, such as benzodiazepines). An additional safeguard against precipitated withdrawal, particularly when there are limited objective features of opioid withdrawal, is to administer a test dose of 2–4 mg of buprenorphine. This can be followed after 2 hours by the balance of desired dose (up to 8 mg total) on the first day, that is, an additional 6 or 4 mg. The test dose significantly reduces the risk of severe precipitated withdrawal, while at the same time allowing an effective total dose of buprenorphine to be given on the day of induction[78].

An appropriate dose to reach on the first day is 8 mg. The initial dose should not be greater than 8 mg.

The following factors must be taken into consideration when considering the initial dose of buprenorphine:

- the time since last opioid use, and whether long-acting opioids such as methadone have been taken in the last 1–2 days
- that clients experiencing considerable opioid withdrawal at the time of the first dose require higher doses of buprenorphine to alleviate withdrawal symptoms. Clients with little or no indication of opioid withdrawal at the time of the first dose should be prescribed a lower dose or be asked to represent at a later time (see rationale below)
- the perceived likelihood of concurrent drug use, including alcohol consumption, unauthorised use of prescription sedative drugs (particularly benzodiazepines), or illicit drug use. In such instances, lower doses of buprenorphine should be prescribed, with frequent reviews
- that concurrent medical conditions (particularly impaired hepatic function and interactions with other medications) warrant the use of lower initial doses of buprenorphine with regular monitoring *(see Section 2 Pharmacology of opioid treatment)*[79].

The first dose of buprenorphine should be administered when the client has clear objective features of withdrawal: at least 6, and preferably 12, hours after last heroin use.

While it is common for clients to report withdrawal symptoms 6–8 hours after last heroin use and 24–36 hours after the last methadone dose, there are a number of factors that influence opioid metabolism[80].

Obtaining a client's withdrawal history can be a useful adjunct to determining when to administer the first dose of buprenorphine, but best clinical practice is to rely on physical examination targeting objective opioid withdrawal signs rather than a specific time frame of last reported use. For more information on the use of withdrawal scales, see the *Queensland Alcohol and Drug Withdrawal Clinical Practice Guidelines*.

78 Lintzeris et al 2009
79 Handford 2011
80 White and Irvine 1999

Recording a thorough drug history immediately prior to the first dose of buprenorphine is essential. Clients may be unaware of the opioid content of some drugs or may not consider some opioid drugs (such as codeine-based medications) as opioids at all. Therefore, it is important to prompt clients regarding other opioid use, including mentioning specific opiates, when taking a drug use history.

Prescribers, pharmacists and nursing staff should take care not to administer the first dose to a client within 6 hours of heroin use, and especially not to clients intoxicated on opioids. If they do, the client is likely to experience opioid withdrawal, as the buprenorphine displaces heroin from the opioid receptors. Buprenorphine-precipitated withdrawal typically begins 1–4 hours after the first buprenorphine dose, is generally mild to moderate in severity, and lasts for up to 12 hours. If this happens, clients may require symptomatic withdrawal medication, and should be directed to see their prescriber[81].

Subsequent doses of buprenorphine (taken the following day) should result in light or minimal withdrawal discomfort if the client has not used heroin during the intervening period. Clients who continue to use heroin between their first and second doses of buprenorphine may have difficulty stabilising on the treatment and experience ongoing symptoms of opioid withdrawal. They should be advised to cease heroin use at least 6 hours prior to the next dose of buprenorphine[82].

5.11 Transferring from methadone maintenance treatment

Buprenorphine has a higher affinity for μ opioid receptors than methadone, but a weaker action (lower intrinsic activity) at these receptors. When methadone clients take a dose of buprenorphine, the methadone is displaced from the opioid receptors by buprenorphine. Clients on low doses of methadone (for example, less than 30 mg/6 ml) generally tolerate this transition with minimal discomfort. However, clients on higher doses of methadone may find the replacement of methadone with buprenorphine precipitates transient opioid withdrawal[82].

This has a number of clinical implications. Wherever possible, clients in methadone treatment should have their methadone dose reduced and should be stabilised on this low dose prior to transferring to buprenorphine, in order to minimise any opioid withdrawal 'features'. Table 8 describes key factors in the development of precipitated withdrawal[82].

5.11.1 Commencing buprenorphine from other opioids

A growing proportion of people entering opioid treatment have been misusing pharmaceutical opioids, generally over-the-counter codeine containing compound analgesics or slow-release preparations of morphine, oxycodone, etc. Before starting buprenorphine, the half life of these preparations needs to be considered, though in most cases any slow-release properties will have been disrupted to gain a rapid onset of action. It is still recommended that a client has clear signs of withdrawal prior to the first dose of buprenorphine to avoid precipitated withdrawal, the risks of which may be further reduced with an initial test dose of 2–4 mg *(see Table 8)*.

81 Lintzeris et al 2009; Handford 2011
82 Lintzeris et al 2009

Table 8: Key factors affecting precipitated withdrawal

Factor	Discussion	Recommended strategy
Dose of methadone	Doses greater than 30 mg/6 ml of methadone are more often associated with precipitated withdrawal. In general, the higher the methadone dose, the more severe the withdrawal experienced.	Attempt to transfer from less than 30 mg/6 ml where possible. Clients on >40 mg/8 ml methadone should not attempt transfer without specialist advice and support.
Time between last methadone dose and first buprenorphine dose	Buprenorphine should not be taken within 24 hours of the last methadone dose. Increasing the interval between the last dose of methadone and the first dose of buprenorphine reduces the incidence and severity of precipitated withdrawal.	Cease methadone and delay the first dose of buprenorphine until the client is showing features of methadone withdrawal.
Dose of buprenorphine	Low doses of buprenorphine (e.g. 2 mg) are generally inadequate as a substitute for methadone (unless the methadone dose is very low). High first doses of buprenorphine (e.g. 8 mg or more) are more likely to precipitate withdrawal, as there is greater displacement of methadone from the receptors. This is a common mistake by inexperienced prescribers.	First does of buprenorphine should generally be 4 mg, with review of the client 2–4 hours later (or early the following day).
Client expectation	Clients who are not prepared for the possibility of precipitated withdrawal are more likely to be distressed and confused by its onset, with potential negative consequences (e.g. treatment dropout, misuse of other medications).	Inform clients fully (and carers, where relevant). Provide written information. Prepare a contingency management plan for severe symptoms.
Use of other medications	Symptomatic medication (e.g. clonidine) may help relieve any precipitated withdrawal.	Prescribe and dispense in accordance with a management plan.

5.11.2 Transferring to buprenorphine from doses of methadone of 40 mg/8 ml or less

Wherever possible, clients should be on a methadone dose of less than 40 mg/8 ml for at least one week prior to receiving their first dose of buprenorphine. Preferably, clients should experience a mild degree of methadone withdrawal prior to converting to buprenorphine. The optimal methadone dose prior to transferring to buprenorphine may be below 30 mg/6 ml of methadone[83].

The following conversion rates should be used as a guide when changing from low-dose methadone to buprenorphine.

Table 9: Guide for conversion rates when transfering from methodone to buprenorphine

Last oral methadone dose	Initial buprenorphine dose	Day 2 buprenorphine dose
20–40 mg/4–8 ml	4 mg–8 mg	8–12 mg
10–20 mg/2–4 ml	4 mg–6 mg	4–10 mg
5–10 mg/1–2 ml	2 mg	2–6 mg

The first dose of buprenorphine should only be administered in the presence of objective opioid withdrawal symptoms.

83 Lintzeris et al 2009, Handford 2011

The likelihood of precipitating withdrawal on commencing buprenorphine is reduced as the time interval between the last methadone dose and the first buprenorphine dose increases. A precipitated withdrawal may be avoided by ensuring the last dose of methadone is taken early in the morning, and the first dose of buprenorphine is taken late the following day[84].

5.11.3 Transferring to buprenorphine from doses of methadone greater than 40 mg/8 ml

Most clients in methadone treatment require maintenance doses of greater than 40 mg/8 ml of methadone to achieve abstinence from heroin, and are unable to reduce their dose of methadone below 40 mg/8 ml without considerable discomfort or relapsing to heroin use. In these cases, transferring to buprenorphine may need to be considered at higher methadone doses, with the inherent risks associated with such a procedure explained fully to the client[84].

It is possible to transfer to buprenorphine from methadone doses of 40–60 mg/8–12 ml for those clients who choose to do so. The general principles are:

- Provide information to patients on potential risks.
- Accomplish the transfer in an ambulatory setting, although consider providing inpatient care in the case of unstable drug use or co-morbidities or if the patient is transferring from very high doses of methadone (>100 mg/20 ml).
- Reduce the methadone dose gradually until the dose no longer holds the patient for 24 hours, aiming for less than 40 mg/8 ml if possible.
- Initiate buprenorphine at least 24 hours after the last methadone dose or when the client has significant, objective features of opioid withdrawal. This sometimes means that buprenorphine is not commenced until 48–96 hours after the last dose of methadone. The client is encouraged to wait as long as possible between the last dose of methadone and the first dose of buprenorphine to minimise the risk of precipitated withdrawal.
- Begin with a small test dose of buprenorphine (2–4 mg) to reduce the risk of precipitated withdrawal. Ensure a total of at least 8 mg is given on the first day. Often 12 mg or more is required to manage withdrawal symptoms.
- Review frequently, titrate buprenorphine and give reassurance; 20–30 per cent of patients are likely to return to methadone within two months of transfer[85].

5.12 Buprenorphine stabilisation: Dose adjustments

The optimal maintenance dose needs to be matched to the client's response to buprenorphine. Typically, a maintenance dose will be in the range of 8–24 mg/day. People's responses vary considerably, according to the following factors:

- absorption and metabolism of buprenorphine. The duration of contact with the oral mucosa is a significant factor in absorption rates of buprenorphine. Instructing clients in the technique of administering buprenorphine is important
- experience of side effects
- continued use of other drugs[84].

These variations require the clinician to titrate the buprenorphine dose to optimise treatment objectives[84].

Stability with buprenorphine is achieved quickly, and the effects of a dose-change should become apparent within 2–3 days. Consequently, dose levels of buprenorphine can be more rapidly titrated than methadone, according to client response.

84 Lintzeris et al 2009
85 Lintzeris and Batey 2010

5.13 Regular client review

Clients will be seen daily for at least the first four days and then every 2–4 days in order to stabilise them on an adequate dose of buprenorphine. After this time, dosing may be continued at the clinic under certain circumstances. In any event, careful assessment is necessary and the dose must be titrated against the client's clinical state[86].

Maintenance buprenorphine doses can generally be achieved well within the first week of treatment, subject to adherence to the treatment plan by the client.

The following minimal schedule of reviews is recommended by treating prescribers or their nominees:

- daily for at least the first four days. This enables the prescriber to identify the onset of any precipitated withdrawal and the general adequacy of the client's dose
- every 2–4 days until the dose is stabilised
- every week during the following 4–6 weeks
- every two weeks during the following 6–8 weeks
- monthly reviews thereafter, although the prescriber may wish to extend reviews to up to three months for very stable clients.

The maximum interval between client reviews should be three months.

5.13.1 Stop dose

Requests for clients to present to the program are often delivered by the pharmacist at the request of program staff or the prescriber. If a client ignores such requests, the pharmacist may be instructed to withhold the dose ('stop dose') on a particular day in order to persuade the client to attend as requested.

However, the stop dose should not be regarded as a routine measure to ensure clients attend their appointments. Less draconian steps should be used first. For example, if a client has failed to attend two appointments, their take-away doses should be reviewed and, as a final measure, the stop dose may be instituted.

Regular reviews by the prescriber are required to:

- titrate the individual optimal doses of buprenorphine
- make a more comprehensive assessment of the client
- further discuss treatment plans
- assess whether the dose is preventing withdrawals and suppressing cravings
- monitor additional drug use.

Dose increases should be made only after the prescriber or delegate reviews the client.

Individuals with continuing high-risk patterns of drug use or concomitant medical, psychiatric or social problems may require more frequent review[87]. The buprenorphine dose may be decreased where there are concerns regarding the client's safety (for example, where there are reports of intoxication or overdose).

86 Lintzeris et al 2009
87 Lintzeris et al 2009, Handford 2011

5.14 Changes in buprenorphine dose

The dose response curve of buprenorphine indicates that small increments have a greater impact at low doses, whereas at higher doses, larger changes are required for a substantial change of effect[88].

The following increments are proposed:

- below 16 mg buprenorphine: dose changes of 2–4 mg
- above 16 mg buprenorphine: dose changes of 4–8 mg[88].

At each review, the buprenorphine dose should be titrated according to the following parameters:

- features of intoxication or withdrawal over the preceding 24 hours (self-report, examination)
- cravings for heroin use
- additional drug use (heroin and other drugs), and the reason stated by the client for using
- side-effects or other adverse events (including intoxicated presentations, overdoses)
- adherence to dosing regime (attendance for dosing, route of administration)
- client satisfaction with buprenorphine dose and treatment[89].

The following should guide prescribers in determining the buprenorphine dose:

Table 10: Guide for determining buprenorphine dose

Decrease buprenorphine dose	Maintain buprenorphine dose	Increase buprenorphine dose
Features of intoxication from buprenorphine (e.g. sedation) particularly at peak effect times (1–4 hours after dosing) Severe or intolerable side-effects	No features of withdrawal or intoxication Low cravings for heroin or other drugs Nil or mild and tolerable side-effects	Features of withdrawal over preceding 24 hours, increasing in the period immediately prior to the next dose No features of intoxication particularly at peak effect times (1–4 hours after dosing) Intense cravings for heroin in past 24 hours or heroin use to avert withdrawal Nil or mild and tolerable side-effects

88 Lintzeris et al 2009
89 Lintzeris et al 2009, Handford 2011

Section 6
Maintenance

6.1 Methadone maintenance

6.1.1 Dose levels

Individual methadone doses should be determined for each client. Generally, a higher dose is required for maintenance than is required for initial stabilisation. Client input into treatment decisions – including determining dose levels – promotes a good therapeutic relationship by enhancing trust and responsibility, so the methadone dose should be tailored in negotiation with the client.

The research evidence suggests that methadone maintenance doses greater than 60 mg/12 ml per day are associated with better treatment outcomes in terms of reducing illicit opioid use, retention in treatment[90] and HIV risk-taking behaviour[91].

Maintenance doses for effective methadone maintenance treatment are typically 60–100 mg/12–20 ml per day[90]. However, some clients may respond well to lower doses. Of greatest importance to the client is satisfaction: if they are to refrain from using illicit opioids, the dose of methadone chosen must satisfy them.

Broadly, the upper limit in Queensland for a methadone maintenance dose is 150 mg/30 ml per day. Some clients may benefit from a daily dose greater than 150 mg/30 ml, but a prescriber should carefully consider any decision to increase the dose beyond 150 mg. Seek and document a review by the clinical team – in the case of a clinic – or a second opinion from an addiction specialist when doses are to be raised above 150 mg/30 ml. ECG monitoring is recommended at doses equal to or greater than 150 mg/30 ml. While available evidence is limited,[90] it does not show doses greater than 100 mg/20 ml are of benefit.

6.1.2 Changes in methadone dose

When deciding about dose changes, the following should be taken into consideration:

- concurrent use of illicit opioids and continued injecting use may indicate the need for a higher dose
- individual variation in methadone metabolism
- use of other medications
- pregnancy
- polydrug use.

Dose increases should be made only after the prescriber (or delegate) reviews the client.

6.2 Agreement or adherence to treatment objectives

Daily administration of methadone is recommended to maintain plasma methadone levels and to avoid withdrawal symptoms. If plasma levels are not maintained, cross-tolerance to heroin will lessen, reducing the capacity of methadone maintenance treatment to moderate the effect of heroin. Reduced treatment adherence is therefore associated with an increased risk of relapse to heroin use.

6.3 Dose reductions

Dose reductions are usually made in consultation with the client. The exceptions to this are for considerations of safety, such as if the client presents in an intoxicated state.

Where there is concern about the dysfunctional use of alcohol or other unsanctioned drugs, clinicians should review the client's clinical status expeditiously. The methadone dose may be decreased or withheld where there are concerns regarding the client's safety, for example, where there are reports of intoxication or overdose.

90 Faggiano et al 2008
91 Mattick et al 2008; Gowing et al 2011

6.4 Transfer to other pharmacotherapies

6.4.1 Buprenorphine

Buprenorphine has a higher affinity for μ receptors than methadone but has a weaker intrinsic action at these receptors[92]. Consequently, when methadone clients take a dose of buprenorphine, methadone is displaced from the μ receptors.

Clients on low doses of methadone (‹30 mg/‹6 ml) generally tolerate this transfer with minimal discomfort[93].

Clients on higher doses of methadone may find replacing methadone with buprenorphine precipitates transient opioid withdrawal.

Very low doses of buprenorphine (for example, 2 mg) are generally not adequate to substitute for methadone while high doses (8 mg or more) are more likely to precipitate withdrawal.

Buprenorphine should not be administered within 24 hours of the last methadone dose. The first dose of buprenorphine should be delayed as long as possible and ideally until there are objective signs of withdrawal. Increasing the interval between the last dose of methadone and the first dose of buprenorphine reduces the incidence and severity of precipitated withdrawal. It is important the client is aware of the reason for the delay in dosing and does not supplement the buprenorphine dose with other opioids, especially heroin, as this will further exacerbate withdrawal.

6.5 Buprenorphine maintenance

6.5.1 Dose levels

Buprenorphine doses need to be individually titrated according to the client's response to treatment. Effective maintenance doses, resulting in reduced heroin use and retention in treatment, are achieved with buprenorphine doses in the range of 8–24 mg per day. Doses of 6 mg/day or less have not been shown to be significantly different from placebo in reducing heroin use, though they do help clients to stay in treatment[94].

Some clients may be satisfactorily maintained on daily doses of 4–12 mg, while doses of ‹4 mg are less effective in retaining clients in treatment or reducing heroin use (not significantly different to placebo)[95]. There is little evidence surrounding daily doses higher than 24 mg or regarding adverse events at maintenance daily doses greater than 32 mg. The maximum daily dose of buprenorphine recommended in product information sheets is 32 mg.

Effective maintenance doses, which reduce heroin use and improve treatment retention, are achieved with buprenorphine doses in the range of 8–24 mg per day. The maximum recommended daily buprenorphine dose is 32 mg.

Increasing doses of buprenorphine can reduce a client's use of heroin or other opioids[95]. This provides higher levels of receptor occupation, blocking the effects of additional heroin use. However, this only succeeds up to a point. Continued heroin use, despite adequate doses of buprenorphine, may indicate that the client needs more intensive psychosocial interventions, alternative opioid substitution (such as methadone), or both. Methadone taken at moderate to high doses (above 80 mg/16 ml per day) and through flexible regimes offers higher retention rates than buprehenorphine at any dose and comparable regimes[95].

92 Marquet 2002
93 Lintzeris, Clark, Winstock, Dunlop, Muhleisen, Gowing, Ali, Ritter, Bell, Quigley, Mattick, Monheit, White 2006
94 Mattick et al 2008, Mattick, Kimber, Breen, Davoli 2008
95 Mattick et al 2008

6.5.2 Dose reductions

Buprenorphine should be prescribed in increments of 2 mg so that whole film or tablets can be used. Some clients on maintenance may request to undertake a prolonged and gradual withdrawal from buprenorphine, as if they were tapering off methadone. However, the pharmacology of buprenorphine – which differs significantly to methadone – means dose changes of 2 mg buprenorphine should not cause any significant symptoms for clients. Clients should be educated about the differences between buprenorphine and methadone and adhere to 2 mg dose changes, at least until the daily dose is 4 mg or less. Optimum final tapering rates for buprenorphine have not been established, although some clients do appear to benefit from tapered treatment with doses less than 2 mg.

6.5.3 Frequency of buprenorphine dosing: double (alternate-day) and triple (third daily) dosing regimes

Buprenorphine dosing begins on a daily basis. Many clients who are stabilised on buprenorphine can be maintained on double-dosing, some even on triple-dosing, without experiencing features of intoxication or withdrawal[96].

Reduced frequency dosing offers clients greater convenience, and all clients should be encouraged to try double- or triple-dosing if they meet these conditions:

- They are on a stable dose of buprenorphine.
- They do not engage in high-risk drug use (such as frequent misuse of other sedatives including alcohol, benzodiazepines, heroin or other opioids, or indicated by intoxicated presentations to the pharmacy, clinic or medical practitioner, or a recent history of overdose).

However, not all clients will be suited to double- or triple-dosing regimes, as some will experience increased cravings or features of withdrawal on the non-dosing days.

A minority of clients are more comfortable and more effectively maintained on daily, rather than double- or triple-dosing regimes.

It is recommended that suitable clients initially be trialled for two weeks on a double-dosing regime of buprenorphine. If this is successful, the client can then be trialled on a triple-dosing regime. If a client does not stabilise due to the onset of withdrawal, cravings, side-effects or features of intoxication, they should be returned to a more frequent dosing regime.

6.5.4 Double-dosing

This involves attending the pharmacy for dosing on alternate days (that is, a dose every 48 hours) or attending four times a week (with three 48-hour doses and one 24-hour dose each week). An example could be attending on Monday, Tuesday, Thursday and Saturday. The advantage of the latter approach is the client is on a regular attendance each week, with less likelihood of attendance errors on the client's part and dosing errors by the pharmacist.

The dose dispensed for a 48-hour period is initially double the normal daily (24-hour) buprenorphine dose (to a maximum of 32 mg dosed at a time). The client may be reviewed (by phone if appropriate) following the first or second 48-hour dose, and the dose titrated according to the response:

- If the client reports features of intoxication from the buprenorphine during its peak effects (within the first 24 hours), the 48-hour dose should be reduced.
- If the client reports the dose does not prevent the onset of opioid withdrawal or cravings over a 48-hour period, then the 48-hour buprenorphine dose should be increased.

Once the 48-hour dose is established, use half this dose as the 24-hour dose both for documentation on the script and for single, daily dosing if required.

96 Schottenfeld et al 2000

6.5.5 Triple-dosing

Some clients may tolerate triple-dosing with buprenorphine, reducing the inconvenience of further treatment. This regime should not be attempted until a two-week trial on double-dosing has been successful.

The recommended regime for triple-dosing is:

- 3-day dose = 3 times the normal 24-hour dose if the 24-hour buprenorphine dose is less than 12 mg
- 3-day dose = 32 mg when the 24-hour buprenorphine dose is greater than 12 mg.

The client should be reviewed in the week following the first 72-hour dose, and the dose titrated accordingly. If a client cannot be stabilised on a triple-dosing regime, they can return to a double-dosing regime.

Table 11: Double- and triple-dosing with buprenorphine

Daily dose (24 hours)	Two-day dose (48 hours)	Three-day dose (72 hours)
4 mg	8 mg	12 mg
6 mg	12 mg	18 mg
8 mg	16 mg	24 mg
10 mg	20 mg	30 mg
12 mg	24 mg	32 mg
14 mg	28 mg	Not advised
16 mg	32 mg	Not advised
18 mg and over	32 mg	Not advised

Some clients attempting double-dosing may benefit from doses greater than 32 mg. However, there is limited evidence regarding the safety of higher doses, and buprenorphine is registered in Australia with a maximum recommended dose of 32 mg. Practitioners should be aware of the medico-legal implications of off-label prescribing before they prescribe doses greater than 32 mg. In these cases, frequent clinical and hepatic monitoring should be undertaken because of the increased potential for adverse consequences.

6.5.6 Take-away doses

Supervised dosing is an essential component of methadone and buprenorphine treatment and, in general, doses should be consumed under direct supervision[97]. Research shows supervision significantly improves retention and outcomes with buprenorphine[98]. However, there are circumstances where the prescriber may appropriately authorise either a one-off dose or regular take-away doses. Because of the safety risks associated with providing take-away doses, restriction and monitoring are necessary. Risks include:

- accidental overdose or death of the client or another person (the risk of an accidental overdose is much greater for children or opioid-naive adults)
- dose diversion
- self-administration by injection, resulting in toxicity, bacterial infection or the spread of blood-borne viruses. It is estimated that at least 0.1 per cent of methadone and buprenorphine/naloxone doses in Queensland are injected. This rises to more than 1 per cent for buprenorphine mono[99].

97 Lintzeris et al 2006
98 Auriacombe, Franque, Daulouède, Brisseau-Gimenez, Tignol 2002
99 Smirnov and Kemp 2012

Despite the dangers of their inappropriate use, giving select clients controlled access to take-away doses can provide benefits. Take-away doses can reinforce adherence to program goals and objectives. Take-away doses can also encourage and empower clients to take responsibility for their drug use and to play an active role in their treatment. Providing take-away doses can promote a trusting relationship between staff and clients, and free the client from the need to attend the pharmacy or clinic daily. The increased normalisation of the client's education, training, employment and home duties improves the chances of recovery.

6.5.7 Authorising take-away doses

The decision to provide a client with take-away doses requires clinicians to consider each case individually, taking into account the client's stability, reliability and progress, as well as the quantity of methadone or buprenorphine to be dispensed.

Factors demonstrating stability include:

- evidence the client is not engaging in continuing hazardous or unsanctioned concurrent substance use. (Evidence of hazardous use should be based on history, self-report, examination of injection sites for evidence of recent drug injection, urine testing, observation for signs of intoxication or withdrawal, and feedback from others involved in the client's care)
- regular presentation for dosing as prescribed
- no evidence of diversion of administered doses or take-away doses
- adherence to any care plan in place
- living in stable and secure accommodation
- regular and reliable contact with the prescriber or case manager
- history of responsible use of take-away doses.

Instability or unreliability in a client who is receiving take-away doses should prompt a review of take-away dosing arrangements. The prescriber must be satisfied that reduced dosing supervision will not encourage unsanctioned opioid use.

Clients should be able to provide adequate and safe storage arrangements for their take-away doses and should understand the potential risks of accidental ingestion by children before they are considered sufficiently reliable to receive take-away doses. Clients should also show they understand the dangers that ingestion of take-away doses poses to non-tolerant adults.

Providing take-away doses is a clinical decision and it is paramount that reasons for providing take-away doses be clearly documented in the client's clinical file. The factors that demonstrate stability should be recorded. Comprehensive and accurate documentation is critical to delivering safe and effective treatment to clients on the opioid treatment program. Documentation informs other clinicians involved in the clientcare, satisfies medico-legal proof requirements and allows monitoring through audits.

6.5.8 Clients receiving buprenorphine

All clients on buprenorphine mono suitable for take-away privileges should receive their take-away dose in the form of buprenorphine/naloxone. Using the combination product for take-away doses reduces non-conformity in taking the mono product and the harms that may follow.

- Stable clients may receive buprenorphine mono if they are not receiving any take-away doses.
- Clients on buprenorphine mono, who are assessed as suitable for regular take-away doses, can receive similar numbers of combination product take-away doses. The number of take-away doses can be increased over time if stability continues. If the client remains on the mono product, the prescriber should clearly document on the written instruction whether take-away doses are to be buprenorphine mono (for pregnant clients or people who are allergic to naloxone) or the combination.

6.5.9 Contraindications to providing take-away doses

The following should be considered absolute contraindications to providing take-away doses:

- repeated intoxication on presentation for dosing or treatment reviews
- being intoxicated on presentation to collect take-away doses.

Other contraindications to providing take-away doses are:

- diversion of methadone or buprenorphine within the past two months
- habitual injection of methadone or buprenorphine
- chaotic and unpredictable behaviour at present
- current hazardous use of drugs (including alcohol)
- risk to child safety. That is, the client cannot demonstrate or guarantee that their storage and handling of take-away doses meets safety standards.

In assessing whether the use of alcohol or other drugs is hazardous, consider whether the client's alcohol or drug use presents a danger of overdose. If take-away doses are to be provided, the prescriber must be satisfied the combination of drugs consumed does not represent a hazard to the client. The prescriber must also be satisfied the ongoing consumption of drugs other than methadone or buprenorphine does not reflect client instability.

6.5.10 When to stop providing take-away doses

Once a client is receiving take-away doses, they may become very distressed at any suggestion that their continued access to take-away doses will be curtailed. This is one of the most difficult issues for the prescriber or clinician to manage. Clinicians usually have good relationships with their clients and may be unwilling to cause distress and conflict. There is often considerable pressure on clinicians to overlook a client's instability and continue to authorise take-away doses. This is not good clinical practice.

It is common for drug-dependent clients to do well in treatment for a time, and then, due to changes in life circumstances or unknown reasons, relapse to periods of drug use. This does not necessarily mean a return to opioid use, but may involve other drugs such as stimulants, benzodiazepines or alcohol. While it is not possible to control the behaviour of others, it is possible to intervene to reduce the risks associated with destructive drug use, and supervised daily dosing is an important measure to reduce risk. Clients exhibiting instability are not suitable for regular take-away doses, and if a person receiving take-away doses develops, for example, an alcohol problem or another indicator of instability, they may need to return to supervised dosing.

Issues showing a client may need to return to supervised dosing include:

- self-report or clinical evidence of relapse to opioid or other dependent drug use
- evidence of diversion
- recent injection marks
- deterioration in psychological, physical or social wellbeing.

Re-introduction of take-away doses should only occur after at least 12 weeks of evident stability and any re-introduction should be gradual.

6.5.11 A stepped approach to providing take-away doses

The majority of opioid treatment programs in Queensland use community pharmacies to dispense methadone and buprenorphine doses. Apart from seven-day trading pharmacies, most pharmacies are closed on Sundays and public holidays. It is, therefore, necessary for clients to receive a take-away dose for these days, providing the client is considered to be sufficiently stable and likely to adhere to the prescribed treatment. New clients undergoing induction onto opioid treatment who do not meet criteria for take-away doses and clients who require supervised dosing should either be placed with a seven-day pharmacy or required to attend an opioid treatment clinic (when available) for dosing on Sundays and public holidays.

As an alternative to take-away doses, clients on buprenorphine may be double-dosed on Saturdays. If a client is using other substances, such as cannabis or benzodiazepines, even at doses and in a manner that suggests they are not at obvious risk of overdose, double-dosing remains the preferred treatment approach. In circumstances where double-dosing is not possible – for example, when the daily dose exceeds 16 mg or when the dose is too low for double-dosing to be effective – a Sunday take-away dose of the combination product may be allowed when there is no accessible Sunday dosing option.

If a pharmacy is closed on both Saturday and Sunday, alternative arrangements must be made. For example, double- or triple-dosing should be considered for clients on buprenorphine.

In the following areas, stability should be judged according the criteria laid down in 6.5.7.

6.5.12 Methadone take-away doses

New clients – of the clinic or prescriber – during the first 3 months

There should be no access to additional take-away doses, except in the most exceptional circumstances. Prescribers will need to consider when each newly admitted client is stable enough to receive take-away doses for Sundays or public holidays. The 3 month limit below does not apply to Sunday or public holiday doses.

After a minimum period of 3 months in treatment: 2 take-away doses

After a minimum of 3 months' continuous stability in treatment, the client may receive 2 take-away doses per week as long as they continue to meet the criteria for stability.

After a minimum period of 6 months in treatment: 3 take-away doses

If the client remains stable while receiving 2 take-away doses per week and they have been in treatment for more than 6 months, they can be considered for 3 take-away doses per week. Again, this can continue for as long as the client meets stability criteria.

After a minimum period of 9 months in treatment: 4 take-away doses

If the client remains stable while receiving 3 take-away doses per week and they have been in treatment for more than 9 months, they can be considered for 4 take-away doses each week. This can continue for as long as the client meets stability criteria.

6.5.13 Buprenorphine/naloxone take-away doses

Reflecting the greater safety offered by the combination product, an accelerated stepped approach applies to buprenorphine/naloxone take-away doses.

New clients – of the clinic or prescriber – during the first 2 months

There should be no access to additional take-away doses, except in the most exceptional circumstances, during the first 2 months. Prescribers will need to consider when each newly admitted client is stable enough to receive take-away doses for Sundays or public holidays. The 2 month limit does not apply to Sunday or public holiday doses.

After a minimum period of 2 months in treatment: 2 take-away doses

After a minimum of 2 months' continuous stability in treatment, the client may receive 2 take-away doses each week as long as they continue to meet the criteria for stability.

After a minimum period of 3 months in treatment: 3 take-away doses

If the client remains stable while receiving 2 take-away doses per week and they have been in treatment for more than 3 months, their take-away doses can be extended to three per week. Again, this can continue for as long as the client meets stability criteria.

After a minimum period of 4 months in treatment: 4 take-away doses

If the client remains stable while receiving 3 take-away doses per week and they have been in treatment for more than 4 months, they can be considered for 4 take-away doses each week. This can continue for as long as the client meets stability criteria.

After a minimum period of 5 months in treatment: 5 take-away doses

If the client remains stable while receiving 4 take-away doses per week and they have been in treatment for more than 5 months, they can be considered for 5 take-away doses each week. This can continue for as long as the client meets stability criteria.

After a minimum period of 6 months in treatment: 6 take-away doses

If the client remains stable while receiving 5 take-away doses per week and they have been in treatment for more than 6 months, they can be considered for 6 take-away doses each week. This can continue for as long as the client meets stability criteria.

After a minimum period of 12 months in treatment: 7–31 take-away doses

If the client remains stable during another 6 months of treatment while receiving 6 take-away doses per week, the prescriber may decide to allow the client a month's worth of doses (that is, up to 31 take-away doses). The amount of take-away doses depends on the individual's circumstances but, in such a case, there is no longer a requirement for a supervised dose when take-away doses are collected. If moving from 6 to 31 take-away doses in one step seems too large a change, fortnightly dosing with 13 take-away doses for 3 months is suggested to allow a suitable transition for stable clients. It is important to highlight the importance of safely and securely storing multiple take-away doses with the client, since it is unlikely that such doses will be replaced if they are lost or stolen.

The maximum number of buprenorphine/naloxone take-away doses should not exceed 31 consecutive doses.

The maximum methadone take-away doses should never exceed four in a week.

6.5.14 Unsupervised buprenorphine/naloxone dosing procedures

Clients should only be transferred to unsupervised dosing following a thorough review of stability and discussion about the ongoing goals of therapy. The pharmacist must be advised by telephone and in writing of any changes.

6.5.15 Current clients transferring from methadone to buprenorphine/naloxone

People who have been on long-term, stable methadone treatment may seek to transfer to buprenorphine in order to receive unsupervised dosing with buprenorphine/naloxone. Such clients should be warned that there is a small risk of their being destabilised by transferring. Previously stable clients on methadone may be eligible to receive unsupervised doses of buprenorphine/naloxone after demonstrating a month of maintained stability on buprenorphine.

6.5.16 Dosing schedule

Many clients change their dosing schedule when they receive buprenorphine/naloxone take-away doses. Clients on second-daily supervised dosing often return to daily dosing with take-away doses. Clients should be advised to take the prescribed dose at the same time each day. A regular dosing routine is likely to foster better clinical outcomes than the widely varying troughs and peaks associated with an irregular dosing pattern.

Most clients will stabilise on doses between 8–24 mg/day. Prescribers should be aware that requests for higher doses may reflect poor absorption of the drug or the possibility of non-compliance with the program. If clients complain that doses of 16 mg/day are inadequate, it is recommended that a test dose be administered under supervision (checking for technique). The client should then be reviewed after 24 hours.

Assessment of suitability for take-away methadone or buprenorphine/naloxone doses must be clearly recorded in the client's clinical notes. Notes should include:

- **details of any indicators of stability that are present**
- **documentation of the absence of contraindications**
- **details of any other psychoactive drugs being used.**

Any indication of instability or unreliability in a client who is receiving take-away doses should prompt a review of take-away dosing arrangements.

6.5.17 Short-term take-away doses

Take-away doses can be provided for specific short periods in response to unforeseen circumstances. Short-term take-away dosing may be appropriate in times of crisis, for example when there has been a death or serious illness in the family, when clients have an illness that prevents them from attending their pharmacy or clinic daily, or when other unforeseen urgent situations arise. In these instances, prescribers must consider that the potentially destabilising effects of the event may mean take-away doses are not the safest option. Alternatively, providing take-away doses could be beneficial to the client's emotional and psychological wellbeing. Always explore all alternatives available, such as providing doses at a more conveniently located pharmacy or clinic.

The long-acting nature of buprenorphine means that some clients only need to be dosed every second or third day. Interval dosing options should be used as an alternative to providing one-off take-away doses. Make regular take-away doses only necessary for buprenorphine clients who can't tolerate interval-dosing schedules.

6.5.18 Take-away doses for declared emergencies

Where a State Emergency declaration is in place or is expected imminently – such as a cyclone or a flood – take-away doses can be issued for the expected duration of the emergency. This would normally be in the range of 3 to 5 days. In this case, these take-away doses may be issued without regard for current client stability.

6.5.19 Floating take-away dose

Clients who are working or studying may have difficulty determining the best days during the week for their take-away dose because of the nature of their work or study.

Provided the prescriber is satisfied the client meets all requirements for stability and the pharmacist is in agreement, the client can be authorised to have a floating take-away dose. This enables the pharmacist and the client to determine which day is best suited for the take-away dose on a weekly basis, according to work and study commitments. For example, this could be recorded on the written instruction form as 'take-away doses for Saturday and Sunday and one extra for the week' for those clients on three take-away doses per week.

Floating take-away doses should be discussed with the pharmacist to ensure they are happy with the arrangement. If the pharmacist finds the arrangement unsatisfactory, the prescriber should be notified.

6.5.20 Rural and remote areas

In rural and remote areas where access to methadone and buprenorphine administration is difficult, opioid treatment programs may have to develop a policy on take-away doses that acknowledges the impracticality of seven-day-a-week supervised dosing for some clients. Such a policy must address the needs of the individual client while maintaining program objectives, and should define the degree of geographical inaccessibility that will exempt a rural client from the standard restrictions on take-away doses.

6.5.21 Transfer from another prescribing doctor

Take-away dose arrangements are not automatically transferred when clients change prescriber or clinic, but they should not be changed without good reason. The new prescriber is responsible for reassessing the client's suitability for take-away doses and the appropriateness of the previous take-away dose regimen. The new prescriber should contact the previous prescriber for information to help assess the client's suitability for take-away doses. If the new prescriber makes changes to the client's take-away doses, they should explain their reasons to the client.

To adequately assess the client's stability and reliability, the number of take-away doses provided by the new prescribing doctor during the first month should not exceed the number provided previously.

6.5.22 Authorisation, preparation and supply of take-away doses

While take-away doses can only be authorised by the prescriber, they should be discussed with the clinicians or pharmacist with whom the client has more regular contact. Where there is good reason for concern about clinical safety, diversion or other misuse, take-away doses should not be provided.

Under current legislation, take-away doses may be prepared only by a prescriber or pharmacist, or under a pharmacist's direct personal supervision.

The majority of opioid treatment clients in Queensland attend public sector clinics where medical officers, nurses and allied health professionals provide services. It is acceptable practice for any opioid treatment program clinician to notify the client's pharmacist of the authorised take-away dose or doses.

The take-away dose must be given to the client on the day before the scheduled days of absence from the usual dispensing location. At that time, the client is to be told that methadone and buprenorphine are for oral consumption only and advised of the dangers of misuse, the hazards of using methadone or buprenorphine in combination with other drugs, and the toxic potential if taken by children or a person not tolerant of opioids.

The pharmacist or dosing location must be notified on every occasion a take-away dose is authorised. All take-away dose authorisations and pharmacy notifications must be clearly recorded in the client's clinical file. When regular take-away doses are provided, the current written instruction must specify the days of the week on which the client is to receive take-away doses. If the client receives floating take-away doses, the number of take-away doses per week should be specified and the prescriber should define the days that the week commences and finishes (for example, the week runs from Monday to Sunday).

Clients are responsible for the care and proper consumption of each take-away dose once they have taken possession of it. Clients should be encouraged to have a locked receptacle (e.g. cash box) in which to store take-away doses. These may be taken to the pharmacy to minimise the risk of accidental ingestion by another person.

To avoid risk of consumption by children or other unauthorised people, the client should be advised that take-away doses should be stored in a place that is not easily accessible by people other than themselves. To further reduce the risk of overdose by children, take-away doses of methadone or buprenorphine should not be stored in the refrigerator.

Take-away doses should only be collected from the pharmacy by the client for whom the dose is prescribed, on the day prior to the prescribed take-away dose. No other person is able to collect this medication on behalf of the client.

In the event that a client reports that take-away doses have been lost, stolen or damaged, they should not be replaced unless there is a medical indication to do so (such as to prevent withdrawal symptoms in pregnant clients).

If medically indicated, replacement doses should be carefully titrated against the clinical condition of the client. Replacement doses are not usually full doses. Careful assessment and monitoring are required to ensure that the client is not overdosed.

6.6 Urine drug testing

While urine drug screening can be a tool to maximise the safety and efficacy of treatment, physical examination of the client remains the most reliable means of detecting whether it is unsafe to dose a client at their current methadone or buprenorphine dose.

Urine drug screening may be useful in the following circumstances:

- as part of the initial assessment, especially where opioid use is uncertain
- to gain further information about the drug use of clients
- to provide objective evidence of progress toward treatment goals
- as one method of monitoring extraneous drug use or diversion of methadone.

However, its utility is limited for several reasons:

- urine samples may not be a reliable indication of drug use if sample collection is not observed, but many clients find supervised collection demeaning
- false positive and false negative results do occur
- there are significant costs associated with urine drug testing
- retention in treatment is a critical outcome for reducing drug-associated harms, more so than short-term abstinence from opioids or other drugs.

Clinicians should not order urine drug screens for legal purposes. Doing so may confuse the therapeutic role of the clinician with the forensic role of the legal and child safety systems and it introduces disincentives to accurate drug use reporting.

Buprenorphine may not be detected in some routine urine toxicology screens. Gas chromatography, gas mass spectrometry or specific antibody tests can detect buprenorphine in urine. Instant urine tests for buprenorphine are commercially available.

The value of urine screening is enhanced when the tests are conducted on an irregular and random basis.

6.6.1 Urine drug testing frequency

Prescribers should endorse the urine drug screen request to the effect that the client is undertaking a drug rehabilitation program. Medicare Australia rebates a maximum of 21 urine drug tests per client in their first year of treatment, and no more than 15 in each subsequent year.

6.7 Ancillary services

Opioid treatment service providers are directly responsible for assessing and reviewing clients with respect to their opioid treatment and for managing any other drug and alcohol use problems.

However, opioid treatment clients often have complex psychosocial and health problems. This means they should also have prompt access to medical assessment, psychiatric assessment and social assessment, and appropriate subsequent management.

A case management approach is the best way to ensure opioid treatment clients receive ancillary services.

Ancillary services should be provided either by the opioid treatment service providers or by referral. The different services are outlined below.

6.7.1 Withdrawal management

Managing drug withdrawal in dependent clients aims to reduce the severity of symptoms. Although opioid withdrawal can be very uncomfortable, it is not normally life-threatening. There is a variety of approaches to withdrawal for opioid dependence. They include inpatient or outpatient, and either with or without medication.

6.7.2 Outpatient and day patient drug-free programs

There is a range of outpatient and day patient drug-free programs offered in the private and public health sectors. The interventions vary widely. There has been little evaluation of counselling interventions for opioid dependence, but many drug users report that they find value in counselling.

6.7.3 Residential rehabilitation services

Residential rehabilitation programs vary in their structure and the interventions they offer. Some are staffed by program graduates, although many employ qualified clinicians. Therapeutic communities have been found to attract and retain a relatively small proportion of opioid users. Those who remain in treatment longer have better outcomes than those in treatment for shorter periods and those not receiving treatment.

6.7.4 Self-help groups

Support organisations in the community are generally confidential, accessible and provide continuing assistance. Alcohol and Drug Information Service and the local Alcohol, Tobacco and Other Drug Service can provide information on peer-based groups in the local area.

6.7.5 Crisis intervention

Clients commonly present with urgent problems that can be managed by a range of staff (depending upon their skills) or by assessment and referral.

6.7.6 Medical services (preventive, early intervention and treatment)

Compared with the general population, opioid dependent people have greater health risks and morbidity. Access to a range of medical services appears to improve treatment outcome in this population.

6.7.7 Psychiatric services

Opioid treatment clients have higher than average rates of mental health disorders[100]. Specific psychiatric treatment for people with such disorders appears to improve the outcomes of opioid treatment. Available evidence, while limited, suggests that psychological support (such as cognitive-behavioural therapy) may be a useful adjunct to opioid treatment for clients with amenable psychiatric disorders. Therefore, access to psychological support should be given to people with specific indications – including anxiety and depressive disorders. There is no evidence to support psychosocial interventions in treating opioid maintenance clients without psychiatric disorders[101].

6.7.8 Counselling (brief, supportive and problem-oriented)

Counselling should not be mandated in opioid treatment programs, although it can add to the effectiveness of opioid maintenance treatment for clients with current life problems. Cognitive-behavioural therapies (such as motivational interviewing), relapse-prevention counselling and social skills training are some of the counselling approaches often employed.

Ancillary services should only be provided if the client wants to be involved.

6.8 Specific clinical situations

6.8.1 Missed methadone or buprenorphine doses

A missed dose does not always signify the use of illicit or prescribed drugs, although clients may use other drugs to alleviate discomfort. At times, close clinical supervision is required with certain clients, particularly when recent history suggests the client frequently uses other intoxicating substances which, when taken in combination with methadone or buprenorphine, place them at risk.

When clients miss dosing on any day, the pharmacist will notify the prescriber. The prescriber must then decide whether the client needs to be reviewed prior to the re-commencement of dosing. The primary consideration is the client's current clinical safety. If this is not at risk, the prescriber may

100 Pani, Vacca, Trogu, Amato and Davoli 2010
101 Amato, Minozzi, Davoli and Vecchi 2011

authorise the re-commencement of dosing without requiring the client to attend for clinical review. However, where there is reason for concern or where the clinician believes that it may be beneficial for the client to receive active intervention, the prescriber may direct the pharmacist to withhold the methadone or buprenorphine dose prior to such a review.

To ensure their safety, clients who miss three or more days of methadone or buprenorphine should be reviewed by their prescriber (or delegate) prior to receiving a further dose.

6.8.2 Missed methadone dose

A review of fatalities associated with methadone treatment suggests that clients who miss three or more consecutive doses are at risk of overdose. This reflects some loss of tolerance and possibly use of other depressant drugs.

The overriding principle is if a client is intoxicated, no dose should be given.

In general, the following schedule can be viewed as safe and effective.

Missed 1 or 2 consecutive methadone doses

The pharmacist should notify the prescriber or case manager, and the prescriber or case manager will decide whether the client needs to be reviewed prior to dosing. In most circumstances, the client can receive their usual dose. A pharmacist's notification may present a particular problem on Fridays or weekends when the prescriber is not contactable. In these cases, it would be expected that local arrangements between pharmacy and prescriber or clinic would operate.

Missed 3 consecutive methadone doses

A review by the prescriber – or, in public clinics, the case manager – is needed.

- Record withdrawal symptoms and assess for intoxication or withdrawal.
- Enquire about any drug use since the last dose.
- Note the reason for missed doses and the response (if appropriate).
- If the normal dose of methadone is ›80 mg / ›16 ml, give half the normal dose. Between 40–80 mg or 8–16 ml, give 40 mg/8 ml. Below 40 mg / 8 ml, give the normal dose.
- With daily monitoring, the methadone dose can generally be increased back to the previous normal dose over three to four days, rather than following the cautious approach stipulated during induction. That is because, in this case, there is a much better understanding of the client's opioid tolerance.

Missed 4–5 consecutive methadone doses

A review by the prescriber is mandated, as outlined above.

- The client may be restarted at 40 mg/8 ml or half their normal dose, whichever is lower.
- The client can be brought up to their normal dose over a few days with regular review by the prescriber.

Missed ›5 consecutive doses

In this case, the prescriber needs to treat the client as a new induction into treatment when reinstating the client back onto a stable dose.

6.8.3 Missed buprenorphine dose or doses

Missed doses are more common with buprenorphine. The longer half-life allows some clients to attend erratically with minimal withdrawal discomfort. This may lead to suboptimal dosing and instability, and should be discouraged.

In general, the following schedule can be viewed as safe and effective.

Missed 1 or 2 consecutive buprenorphine doses

The pharmacist will notify the prescriber or case manager, and the prescriber will decide whether the client needs to be reviewed prior to dosing. In most circumstances, the client can receive their usual dose. This may present a particular problem on Fridays or weekends when the prescriber is not contactable. In this situation, local arrangements put in place between the pharmacy and prescriber or clinic would operate.

Missed 3–5 consecutive buprenorphine doses

A review by the prescriber or case manager is needed.

- Record any withdrawal symptoms, and assess for intoxication or withdrawal.
- Enquire about any drug use since the last dose, particularly opioid use.
- Note the reason for missed doses and the response (if appropriate).
- If the client has no contraindications, and has clear signs of withdrawal, resume normal daily dosing, up to 24 mg.

Missed >5 consecutive buprenorphine doses

- Treat client as a new induction into treatment when reinstating the client back onto a stable dose.

6.8.4 Vomited methadone dose

Clients may vomit shortly after having their methadone dose. This creates uncertainty about the amount of methadone that has been absorbed. As vomiting does not necessarily empty the stomach contents entirely, some or even most of the methadone dose may still be absorbed. The time elapsed is also significant, as it takes 20–30 minutes for the entire dose to be absorbed.

Uncertainty regarding the amount of methadone absorbed dictates that no extra methadone should be given without review of the client by their prescriber. Review the client 4–6 hours after consumption of their dose when plasma levels will be at their peak. If at this time the client is in opioid withdrawal, a supplementary dose of no more than half the client's usual methadone dose can be given. If a client reports vomiting their dose more than 20–30 minutes after consumption, reassurance that their dose has been absorbed is all that is required.

If a pregnant client has vomited within five minutes of receiving her methadone dose and the vomiting has been observed, she may be given a supplementary dose of half her usual dose (up to a maximum of 40 mg/8 ml). If a pregnant client cannot be reviewed 4–6 hours after vomiting, a supplementary dose should be considered because withdrawal symptoms can produce foetal distress. If the prescriber is unavailable, pregnant women should be directed to their nearest public clinic.

6.8.5 Vomiting after buprenorphine dose

There is no need to replace buprenorphine if a client vomits after dosing, as buprenorphine is absorbed sublingually.

6.8.6 Concurrent drug use

The use of drugs other than prescribed methadone or buprenorphine (including alcohol and tobacco) may be detected by self-report, by regular urine drug testing or by observing changes in a client's clinical condition or behaviour. Usually the therapeutic relationship with clients on the program is such that they report the problematic use of other drugs. The response should take into account the client's safety, the client's wishes and the severity of the problems (actual or potential) resulting from concurrent drug use.

It is usually in the client's interest to persist with opioid treatment. The risk arising from other drug use needs to be balanced against the potential risk of increased hazardous drug use if treatment is withdrawn. Every effort should be made to engage clients who continue with poly-drug use.

While maintaining a good relationship with the client, boundaries may need to be placed on dosing arrangements, take-away doses may need to be reviewed, and a treatment plan may need to be prepared between the client and the clinician to manage poly-drug use.

6.8.6.1 Client safety – concurrent drug use

The use of benzodiazepines, alcohol, illicit opioids, tricyclic antidepressants and antipsychotics in combination with methadone or buprenorphine is common among opioid users, and can result in toxicity and life-threatening overdose.

Do not dose a client with a blood alcohol content above 0.05 per cent. Wait until their blood alcohol content has dropped (the rate of fall is approximately 0.01 per cent every hour).

Clients who use any of these drugs should be reminded about interactions with their opioid treatment and the risks of concurrent drug use. Review any authorisation for take-away doses and, if intoxication prior to dosing cannot be adequately assessed at the client's dosing point, consider an alternative. Clients who are using other opioids, benzodiazepines, alcohol, tricyclic antidepressants or antipsychotics in large doses should not have take-away doses authorised and should generally be dosed by persons trained and experienced in identifying drug intoxication. Dosing at a clinic may be preferable for a period to allow the client to be observed for intoxication. These clients may also require more comprehensive and intensive treatment approaches.

Concurrent drug use may result in a range of client problems that are not directly related to client safety. Regular, or even intermittent, other drug use can affect client stability and treatment progress. It can also place clients at risk of involvement in crime – such as due to disinhibition associated with benzodiazepine use – blood-borne viruses, and relationship, social and employment problems.

6.8.6.2 Client wishes – concurrent drug use

Discuss how a client wishes to address their drug use once the safety considerations have been addressed. Clients not wishing to alter their concurrent drug use and those who are unsure if they want to change should be given information about the harmful consequences of drug use. Motivational interviewing can be used effectively with these clients[102]: frequently review the pros and cons of opioid treatment and weigh the risks of combining opioid treatment with other drug use against the benefits in reducing harms, improving health and improving social functioning. Drug use during opioid treatment, particularly during the first 3 months, is common. If a client's safety is not at risk from ongoing drug use, it will usually be in the client's interest to persist with treatment.

The clinic or prescriber who registered the client is best suited to manage any concurrent drug use. Collaborate with clients who do want to change their concurrent drug use to develop a treatment plan. This may include:

- help with selective withdrawal management (inpatient or outpatient). Guidance on appropriate withdrawal procedures can be accessed through the *Queensland Alcohol and Drug Withdrawal Clinical Practice Guidelines 2012*
- strategies to help withdrawal from other drugs
- training in relapse prevention
- other skills that will help to reduce or abstain from other drug use (such as relaxation techniques and social skills training)
- alterations to methadone or buprenorphine doses
- shared agreement on opioid treatment program objectives and incentives (for example, offering a regular take-away dose after one month's abstinence from alcohol)
- shared agreement on how frequently progress will be monitored.

Clearly document this plan in the client's clinical file.

102 Miller and Rollnick 2002

Section 7
Managing treatment-related issues

Opioid-dependent clients embarking on pharmacotherapy programs are committing themselves to enormous life changes in order to face the challenges of leading a drug-free lifestyle and adhering to the rules of the program. People who depend on unsanctioned drugs frequently experience stigma and discrimination from members of the community and from health care workers because of their drug-using status. This often creates a climate of distrust, and clients may find it difficult to adjust to the therapeutic relationship that the program involves.

It is important to remember that regular dosing – which helps the client to maintain stable plasma levels of methadone or buprenorphine – can assume a very central role in their lives. Clinicians need to be aware that a power imbalance can exist between them and the client, and this requires monitoring to ensure fair treatment for all clients. Power imbalance can cause client insecurity and tension, responses that clinicians should take into consideration as they build respectful and non-judgmental therapeutic relationships. Clients should expect a high level of professionalism from the clinicians involved in their treatment plan.

7.1 Behaviour

The behaviour of clients attending opioid treatment programs and pharmacies is important because the sustainability of a program relies on the tolerance of individuals and businesses living or working nearby. The continuation of opioid treatment programs also depends on the goodwill of the many pharmacists who participate in the program and provide a most valuable service.

Clients should be informed and reminded by the prescriber and clinic staff that aggressive behaviour in opioid treatment programs is unacceptable and that violence or threatened violence will not be tolerated. Clients need to know inappropriate behaviour in or near dosing locations is also unacceptable, and that this may cause pharmacists to withdraw their services. This, in turn, would impact on the program's ability to function. *(Examples of expected behaviour standards in opioid treatment programs are contained within Appendix 15 and Appendix 16.)*

7.2 Intoxication

Intoxication can result from a methadone or buprenorphine dose that is too high but may also result from other drug use (including alcohol). Extreme caution should be taken if a decision is made to prescribe benzodiazepines in combination with methadone or buprenorphine, particularly during the first two weeks of treatment. Generally benzodiazepine prescribing is discouraged outside the context of an agreed withdrawal plan[103].

Clients with chronic liver disease may be at greater risk of overdose due to their decreased ability to metabolise drugs. Dose increases should be cautious, particularly with methadone.

If a client presents intoxicated with other drugs, the risks associated with overdose must be considered. Do not increase the client's dose. If significantly intoxicated, withhold the dose or reduce it to a very low level in order to ensure the client's safety. Alternatively, ask the client to return when they have sobered up to be reassessed for when it is safe to dose them. It is important to explain your rationale to the client so they understand the change in treatment plan.

When intoxication occurs, clinicians or clinic staff should adopt a general strategy of supporting the client to decrease their extra drug use rather than decreasing the methadone or buprenorphine dose. The overriding priority, though, is reducing the potential for harm to the client. Every effort should be made to keep the client in treatment. Dose reduction in these circumstances may:

- result in an increase of illicit drug use
- inhibit the client's self-disclosure and compromise trust between the clinician and the client
- result in voluntary withdrawal from treatment.

Non-opioid drug use (for example, the use of benzodiazepines, alcohol or amphetamines) does not in general respond to increases in methadone or buprenorphine doses during an opioid treatment program.

103 Queensland Health 2012

7.3 Use of other opioids

Two strategies are useful to consider when clients are using other opioid drugs.

In instances where clients are regularly using other opioids and are not intoxicated, a dose increase of 5–10 mg/1–2 ml methadone or 4–8 mg buprenorphine may help to decrease extra opioid use and ultimately achieve abstinence. The client should always be reviewed after each dose increase to ensure they are not showing symptoms of intoxication. It is important to explain to the client that it may take 4 to 5 days to experience the full effects of the increase.

In other instances, a client may plan to stop using other opioids but may feel unable to cope with the expected withdrawal symptoms. In this situation, it may be useful to increase the dose of methadone or buprenorphine to coincide with their planned cessation of other opioids.

In either situation, if significant use continues despite high-dose methadone (100–150 mg/20–30 ml per day) or buprenorphine (24–32 mg/day), the prescriber must consider the relative merits of continuing the prescription of such high doses compared with a lower dose. In doing so, the prescriber must endeavour to negotiate with the client so a joint decision can be made that balances the potential benefits and harms to the individual's health and social functioning.

7.4 Use of benzodiazepines

Many clients who use opioids may, at times, use benzodiazepines to relieve symptoms when their primary drug of choice is unavailable. Some clients may be dependent on benzodiazepines. Others may binge opportunistically on benzodiazepines or other drugs, seeking intoxication.

7.4.1 Occasional use of benzodiazepines when opioids are unavailable

For these individuals, opioids are the drug of choice but they may seek additional drugs in the initial stage of methadone or buprenorphine treatment in order to help relieve the discomfort of stabilisation when methadone or buprenorphine levels are still relatively low. It is vital to explain the importance of not mixing sedative drugs and using simple measures such as hot baths, rest and paracetamol in the knowledge that, over time, the effect of methadone or buprenorphine will increase to relieve symptoms. It may be tempting to help relieve symptoms by using benzodiazepines. However, it is preferable – and much safer – to encourage the client to wait and to learn to tolerate the temporary discomfort.

7.4.2 Benzodiazepine dependence

While methadone or buprenorphine maintenance is used to treat opioid dependence, there are a number of individuals who have a substantial dependence on both opioids and benzodiazepines. Where benzodiazepine dependence exists, it is important not to cease benzodiazepines abruptly because of the risk of withdrawal seizures. However, it is equally important to reduce the risks associated with prescribing the potentially fatal combination of methadone or buprenorphine and benzodiazepines by educating the client about the risks of overdose and death and agreeing on a benzodiazepine withdrawal care plan[104].

Clinicians should exercise caution in prescribing benzodiazepines in opioid maintenance treatment because of the increased risk of respiratory depression, coma and death[105]. However, since clients on opioid treatment may continue to seek and misuse benzodiazepines, prescribers and clinics should recognise their central role in managing benzodiazepine dependence.

7.4.2.1 Managing benzodiazepine dependence

In seeking to manage these clients, there is a trade-off between the risk of trying to stabilise the client by prescribing benzodiazepines and the risk of not intervening and putting the client in withdrawal or seeking non-prescribed drugs. The following are recommendations for prescribing to this group of clients:

- Obtain a careful history of benzodiazepine use, recognising that estimates of use may be very inexact.

104 Queensland Health 2012
105 Lintzeris et al 2006 and 2007

- Corroborate any history of major withdrawal, for example hospital admission with seizures.
- Collect a urine drug screen to look for the presence of benzodiazepines, if necessary.
- With the client, plan and document a care plan – for example, withdrawal or gradual reduction or, on occasion, low-dose maintenance.
- Benzodiazepines should ideally be dispensed daily with the client's opioid treatment.
- If low-dose maintenance is being considered, the client should be referred to a specialist, such as an addiction specialist or psychiatrist, for their opinion.

Although the client's permission is not required by law, it is good practice for clients to be made aware that their history of obtaining benzodiazepines will be monitored through the Medicare Prescription Shopping Program. Inform the client that periodic checks will be made with the program to confirm the client is not receiving benzodiazepines from other doctors. Prescribers must register for the program (a form can be downloaded from the Medicare website). Once registered, doctors can access information 24 hours a day, seven days a week. The program phone number is 1800 631 181.

7.4.3 Intoxication seeking

People who use benzodiazepines may be difficult to manage at times in general practice. The combination of drugs frequently results in unpredictable effects. The risk of death from intoxication is high in this group, particularly during stabilisation on opioid treatment. It is advisable for general practitioners to refer this group to an opioid treatment clinic since assessing the degree of opioid dependence versus benzodiazepine dependence is difficult and the complex needs of these clients – and their suitability for opioid maintenance – are often better dealt within a multidisciplinary setting.

7.5 Use of alcohol

Hazardous levels of alcohol consumption by opioid treatment program clients are relatively common and a significant cause for concern[106]. Alcohol consumption and its effects should be monitored by client interview and, where appropriate, blood alcohol level (BAL) per cent readings and liver function tests. A client with a blood alcohol concentration greater than 0.05 per cent should not be dosed. Opioid treatment clients who consume alcohol in a harmful way should be closely monitored to reduce harm, and appropriate interventions (counselling, acamprosate or disulfiram, or selective withdrawal management) should be provided.

7.6 Use of psychostimulants

In the 1990s, many amphetamine users switched to heroin as cheap supplies became readily available, illustrating the relationship between stimulant and opioid use[107]. The *National Drug Strategy Household Survey Report 2010* showed 51 per cent of heroin users had also used amphetamines in the previous year. At the same time, 80 per cent of heroin users had also used cannabis, the most commonly used illicit substance.

Many clients appear to use heroin to help 'come down' after a period of amphetamine use. The major concerns about amphetamine use in clients on opioid treatment are the increase in risk-taking behaviour, ongoing injection drug use and association with the related subculture.

Stimulant use in a client on methadone may lead to hazardous, prolonged QTc intervals[108]. Amphetamine users should be closely monitored to minimise harm from methadone or buprenorphine administration. Cocaine may reduce the pharmacological efficacy of methadone (that is, drug–drug pharmacokinetic interaction), although it is also reported that entry into opioid treatment appears to reduce cocaine use in addition to heroin use and is generally stabilising for many people who are dually dependent on heroin and cocaine[109].

106 Haber et al 2009
107 McKetin et al 2005
108 Mayet et al 2011
109 McCance-Katz et al 2009 and 2010

7.7 Administering methadone or buprenorphine when clients present appearing intoxicated

The person dosing – the nurse or pharmacist – should always assess the client before administering a dose. This assessment should ensure the client is not showing evidence of intoxication due to opioids or other drugs, including alcohol.

Clients who appear to be intoxicated should not be dosed or given a take-away dose at that time *(see assessment of acute intoxication in Appendix 4)*. They should be asked to return later when they are no longer intoxicated. In some instances, when intoxication is evident but not pronounced, a reduced dose may be given after review by the prescriber or delegate such as a clinical nurse[110].

7.8 Overdose at the administration point

Medical emergency procedures should be available for clients who demonstrate signs of drug overdose at the administration point. Such procedures will depend upon the setting, severity and urgency of the situation. Procedures may include cardio-pulmonary resuscitation, calling for an ambulance (or the resuscitation team if associated with a hospital), calling for urgent medical assistance and closely monitoring the client. If indicated and possible, management may include administering oxygen, gaining venous access and administering naloxone[111].

In Australia, more than 90 per cent of deaths during stabilisation on methadone involve other drugs, in particular alcohol, benzodiazepines and antidepressants[110]. The use of other drugs in combination with opioids, particularly sedatives, significantly increases the risk of respiratory depression and death[111].

The long half-life of methadone means methadone overdose can be deceptive. Clients who are thought to have taken a methadone overdose require prolonged observation as toxic effects may become life-threatening many hours after ingestion, including during sleep. Clients and their relatives should be warned that deep snoring during induction to methadone treatment could be a sign of dangerous respiratory depression and relatives should be encouraged to seek urgent medical attention. Heavy snoring during maintenance treatment may be associated with sleep apnoea and should also be reported[110].

Naloxone (Narcan), which promptly reverses methadone-induced stupor or coma, should be administered in the form of a prolonged infusion to treat methadone overdose. A single dose of naloxone may wear off within an hour and clients can then lapse back into a coma due to the long-lasting effects of methadone reported[110]. The half-life of naloxone is less than 1.1 hours (+/- 0.6 hours) compared with 27 hours (+/- 12 hours) for methadone[112].

Due to the ceiling dose response of buprenorphine, the risk of lethal overdose in an individual is less than that associated with methadone. While overdose on buprenorphine is relatively uncommon, there is greater risk in combination with other sedative drugs, such as alcohol, benzodiazepines, barbiturates, tricyclic antidepressants and antipsychotics. Several such deaths have been reported[113].

Buprenorphine has a high affinity for μ opioid receptors and is not easily displaced by naloxone. Doses of 10 to 30 times the normal naloxone doses used to reverse heroin overdose (up to 10–35 mg/70 kg) may be required to reverse the effects of buprenorphine toxicity[111].

At the time of admission to an opioid treatment program, encourage the client to nominate a contact person who can be notified in the event of an overdose or emergency.

110 Henry-Edwards et al 2003
111 NSW Health 2006
112 Brunton et al 2011
113 Lintzeris et al 2006

7.8.1 Child overdose

Young children may inadvertently ingest methadone and buprenorphine take-away doses. A client or another person may also deliberately administer methadone or buprenorphine to a child. Ingestion of methadone can be particularly dangerous for children and is a potentially life-threatening situation. Buprenorphine, while safer in adults, can also pose a significant risk to children if consumed.

In the case of a child ingesting methadone or buprenorphine, recommended procedures are:

- Assess the level of consciousness and monitor this continuously until the child is in the care of ambulance or other qualified staff.
- Refer the child to a hospital emergency department without delay, providing the information available about the amount taken and the time.
- Administer oxygen if available.
- Consider naloxone administration if the child is showing signs of respiratory depression. Document any treatment given.
- Notify the prescriber of the incident.

If a child has ingested methadone or buprenorphine by any means, the child has been placed at risk of harm and the appropriate authorities – such as Department of Communities (Child Safety Services) and police – should be notified[114].

7.9 Administering an incorrect methadone or buprenorphine dose

To minimise the possibility of dosing errors:

- Attach a photograph to every client's record from which they can be easily and accurately identified.
- If there is more than one client with the same surname, make a note on the client's record alerting the staff to this (for example, 'Caution: other client has similar surname').
- Put a cautionary note on the record of new clients who are unfamiliar to staff (e.g. 'Caution – new client').

7.9.1 Incorrect methadone dose administered

A client who receives a methadone dose in excess of that prescribed is at risk of overdose. Clients should be informed of the risks and signs and symptoms of overdose[115].

Clients who in the first two weeks of induction receive an overdose of any magnitude require observation for four hours, when the effects of peak serum levels are seen. If signs of intoxication develop, more prolonged observation is required. This may require sending the client to a hospital emergency department[115].

Clients who have been on a dose of methadone >40 mg/8 ml per day consistently for two months will generally tolerate a dose that is double their usual dose without significant symptoms. For an overdose that is greater than double the usual daily dose, the client will require observation for at least four hours. If signs of intoxication are observed, prolonged observation must be maintained[115].

If clients are receiving regular take-away doses, or if they do not attend daily, it cannot safely be assumed that they have been taking their daily dose and have a known level of tolerance. Therefore, such clients require observation in the event of overdose of >50 per cent of their usual dose[115].

If a client's level of tolerance is uncertain (their dose is less than 40 mg/8 ml per day or they have been in treatment for less than 2 months), they require observation for at least four hours if they are given a dose that is 50 per cent or more than their usual dose[115].

114 NSW Health 2006
115 Henry-Edwards et al 2003

A client who receives a methadone dose in excess of that prescribed is at risk of overdose. The critical issues that determine how clinicians should respond to an accidental overdose are the client's level of tolerance and the amount of methadone given in error.

Signs and symptoms of methadone overdose include:

- pinpoint pupils
- nausea
- dizziness
- feeling intoxicated
- sedation or nodding off
- unsteady gait
- slurred speech
- snoring
- hypotension
- slow pulse (bradycardia)
- shallow breathing (hypoventilation)
- frothing at the mouth
- coma.[116]

The effect of the overdose will depend on:

- the size of the overdose as a proportion of the usual dose
- the length of time the client has been in treatment at the current dose
- other individual characteristics, including impaired liver or kidney function
- whether the client has recently consumed other drugs.

The appropriate course of action, therefore, will depend on these variables.

7.9.2 Methadone overdoses up to 50 per cent of the normal dose

The dispensing pharmacist (or nursing staff) should:

- Notify the prescriber (or a registered nurse if the client is registered with a public clinic). If the prescriber cannot be contacted, a drug and alcohol medical specialist should be consulted.
- Advise the client of the mistake, carefully explain the consequences and warn against any additional drug use, and against driving or operating machinery.
- Advise the client to go to the nearest hospital emergency department should any symptoms of an overdose develop.
- If possible, a contact person nominated by the client should be informed and advised of the event.
- Document the event[116].

The client should be reviewed by the prescriber prior to the next dose of methadone.

7.9.3 Methadone overdoses greater than 50 per cent of the normal dose

The dispensing pharmacist (or nursing staff) should:

- Advise the client of the mistake. The possible seriousness of the overdose should be carefully explained.
- Contact the client's prescriber immediately for consultation. If the prescriber cannot be contacted, an addiction specialist should be consulted[116].

116 Henry-Edwards et al 2003

Emesis after the first 10 minutes is not enough to prevent a methadone overdose. Because it is impossible to determine whether the stomach has been emptied, it is impossible to determine if the risks of overdose and possible death have been eliminated.

Inducing emesis may be dangerous and is contraindicated, particularly if the client has respiratory depression, an obstructed airway, is drowsy, or has other signs or symptoms of central nervous system depression. If there is concern about the amount of methadone consumed, it is best to be cautious and have the client present to an emergency department without delay.

If it is decided by the prescriber that the client requires hospitalisation, explain this to the client and escort the client to the emergency department. The situation should be explained to the triage nurse. If a client refuses to present to the emergency department – despite being advised of the potential lethality of the dose consumed – try to ensure they understand the concerns of the prescriber and remain with another responsible adult over the next six hours. Give the client information regarding methadone overdose and urge him or her to seek medical attention if symptoms of overdose appear. Additionally, warn the client against any additional drug use, and against driving or operating machinery.

If the client leaves before the mistake is realised, the prescriber and, in a clinic, the senior registered nurse need to be informed and, depending on the advice of the prescriber, all efforts must be made to contact the client or anybody who may know their whereabouts. In attempting to locate a client, their confidentiality should be maintained at all times[117]. The prescriber should review the client before the next dose of methadone.

7.9.4 Excess buprenorphine dose administered

The risks associated with an incorrect dose of buprenorphine are less severe than with other opioid medications. In the event of an incorrect (excess) dose being administered:

- the dispensing pharmacist (or nursing staff) should immediately notify the client and prescriber of the error
- the client should be warned of the likely consequences (including increased sedation or drowsiness that may occur for several hours afterwards), warned against any additional drug use, and against driving or operating machinery for the rest of the day
- the client should be monitored for at least six hours by a clinician or in a hospital emergency department, if any of the following circumstances apply:
  - the client is sedated following the dose (for any reason)
  - the client is new to substitution treatment (within the first two weeks of treatment)
  - the regular daily buprenorphine dose is ≤4 mg and the client was incorrectly administered a dose of ≥ 16 mg[118]
  - a buprenorphine dose ≥ 64 mg was incorrectly administered (regardless of routine daily dose)[119].

The prescriber should review the client before the next dose of buprenorphine.

It may be that a lower dose, or no dose, is required the following day (in effect, a two-day dose may have been administered).

7.10 Selective withdrawal management

Clients on opioid treatment with co-existing dependence on other drugs – in particular benzodiazepines, alcohol or psychostimulants – may require assistance to withdraw from those drugs while continuing opioid treatment[120].

117 Hospital and Health Boards Act 2011
118 NSW Health 2006
119 Lintzeris et al 2006
120 Queensland Health 2012

Unless the client requires hospital admission, the client's opioid treatment prescriber should support and encourage the client by offering to manage selective withdrawal treatment.

The prescribing doctor should:

- review the client frequently
- monitor the client closely for evidence of intoxication with sedative drugs in combination with methadone or buprenorphine
- provide only small quantities of withdrawal medication at a time (preferably daily pick-up of withdrawal medication).

The *Queensland Alcohol and Drug Withdrawal Clinical Practice Guidelines 2012* will be of assistance in managing the client's withdrawal regime.

Consultation with an addiction specialist should be undertaken in more complicated cases, or if the prescribing doctor is unfamiliar with the accepted treatment approach.

7.11 Managing inpatients

If an opioid-dependent person is admitted to hospital, the prescribing of methadone, buprenorphine or other opioid drugs may need to be reviewed, either as a continuation of an opioid treatment program, as treatment of opioid withdrawal, or for the relief of pain.

7.11.1 Treatment of an inpatient currently on an opioid treatment program

In general, a client on an opioid treatment program should continue methadone or buprenorphine treatment in hospital. The client has one authorised opioid treatment prescriber who has received specific authorisation to prescribe for that client. When clients are admitted to hospital, the hospital resident medical officer can take over prescribing the client's opioid treatment. In all cases of clients being hospitalised, the admitting team should liaise with the client's prescriber or clinic about their current treatment plan.

When a client on opioid treatment is admitted, the hospital pharmacist or, preferably, the medical officer should:

- Verify the client's identity.
- Contact the Drugs of Dependence Unit (07 3328 9890) to identify the prescriber or clinic. Alternatively, the client may identify the prescriber or clinic and pharmacy.
- Contact the client's prescriber or clinic to confirm:
  - the current dose of methadone or buprenorphine
  - the date and time of the last dose
  - whether the client has been given any take-away doses.

The dosing information must be established to avoid administering an overdose. Use the following steps:

- Provided that there is no medical contraindication, dose methadone once a day in liquid form or buprenorphine (sublingually), with the usual frequency for that client (e.g. daily, alternate days, every third day), according to the dosage regime of the client's authorised prescriber.
- Advise the client's prescriber of the approximate length of stay in hospital to prevent the client being removed from the program through non-attendance.
- When a client is discharged from hospital, inform the prescriber or clinic in advance to ensure that appropriate arrangements are made for the client to continue the opioid treatment program without interruption.

Hospitals should not normally dispense any take-away doses without first consulting the authorised prescriber or clinic.

Most stable clients taking methadone or buprenorphine will not exhibit withdrawal symptoms and signs until more than 24 hours after the last dose was administered. If contact cannot be made with the client's prescriber or clinic, or the Drugs of Dependence Unit, an addiction specialist should be consulted for advice on dosing.

7.11.2 Clients with take-away doses who are admitted to hospital

Clients are on rare occasions prescribed take-away doses for the days they are in hospital. In such cases, clients should be requested to hand the take-away doses to the ward staff and have their doses dispensed through the hospital pharmacy. This allows closer monitoring of their clinical condition and certainty about the dose an inpatient is receiving. If a client declines to hand over their take-away doses, they should not be administered methadone or buprenorphine, and the client's clinical condition should be monitored for intoxication or withdrawal and treated appropriately.

If a client is admitted unexpectedly to hospital and does not have with them the take-away doses they have already been supplied, the admitting team should consult the prescriber or clinic, and then dose the client following a team decision.

An addiction specialist should be consulted if there are concerns about the client's clinical condition.

7.11.3 Acute pain management in hospital for clients on an opioid treatment program

Clients on opioid treatment who are experiencing pain in hospital often have their pain under-treated. It is as important to provide analgesia (including parenteral analgesia) for clients who are on an opioid treatment program as for any other patient. Opioid analgesia should not be withheld for fear of creating problems of dependency when clients have acute severe pain in the hospital setting. In this situation, opioids in addition to the client's usual methadone or buprenorphine dose may be prescribed to relieve pain[121].

7.11.4 Acute pain management of inpatients currently on methadone

Because of their tolerance to opioids, clients taking methadone may require larger doses of analgesia for adequate pain relief, but the initial dose and route of administration should be the same as normally prescribed for pain relief in similar circumstances[121]. If analgesia is not achieved, urgently consult practitioners with appropriate expertise in pain management. Consulting an addiction specialist may also be helpful.

Methadone clients with a painful condition that would normally be treated with oral opioid analgesics may be treated instead with an increased methadone dose for a time.

If analgesia is required for more than two days, orally administered analgesics are preferred, and short-term increases in the methadone dose are useful to provide pain relief.

Concerns about creating problems related to opioid dependence arise when clients take opioid analgesics for a protracted period (longer than normally expected for the condition being treated). Clearly document the management plan for clients requiring ongoing analgesia in the client's medical records, and include plans for reducing analgesia dose frequency and amount. The authorised prescriber or clinic must be informed before their client's discharge to ensure appropriate arrangements are made to continue treatment without disruption.

7.11.5 Acute pain management of inpatients currently on buprenorphine

The strong affinity of buprenorphine for μ opioid receptors and its partial agonist properties reduce the response of clients on buprenorphine to opioid agonists. Consequently, clients on buprenorphine who suffer severe or acute pain will require alternatives to opioids where indicated, or higher doses of opioid analgesia than individuals not in buprenorphine treatment.

If acute or subacute analgesia is required, the current buprenorphine dose should be maintained. A temporary increase in the buprenorphine dose for a time may provide additional analgesic cover, as may dividing the daily dose into a three times daily regime[121].

121 Alford et al 2006

Where additional opioid analgesia is required, the dose of opioid (e.g. morphine) should be titrated according to clinical response. The dose of analgesic should be closely monitored if buprenorphine is reduced or stopped. The concern is that high morphine doses may be required while buprenorphine is exerting 'blockade' effects. Then, as the buprenorphine levels reduce (with a corresponding reduction in the 'blocking' effects of buprenorphine), this may lead to the potential for over-sedation – or even overdose – from high morphine doses. If buprenorphine treatment stops completely (e.g. due to the hospital pharmacy not having the drug, doctor uncertainty or inexperience, or client non-cooperation), the dose of morphine needs to be closely monitored daily for at least 4–5 days after the last buprenorphine dose. It will likely be reduced over time to avoid overdose.

7.11.6 Responsibilities of the opioid treatment program administration point or prescriber

When a prescriber is contacted regarding inpatient treatment of an opioid treatment program client, they must ensure the administration point has been notified.

When a prescriber or staff member at an administration point is contacted regarding inpatient treatment of an opioid treatment program client, they should recognise the hospital doctor may be inexperienced in treating opioid-dependent people. Therefore, they should take all possible steps to provide assistance. This includes, but is not limited to, giving the following information:

- the necessary steps to be taken to conform with legal requirements regarding opioid treatment, including steps to be taken on discharge
- the history and progress of the client – in particular, information regarding their stability, methadone or buprenorphine dose and likely pain relief needs.

Hospital staff may be unfamiliar with methadone or buprenorphine doses and the significance of dose changes (for example, is it high or low? What is the range?). If possible, these details should be documented in the client's hospital notes.

To avoid double-dosing, the prescriber or clinic staff member should confirm the client has been discharged and confirm the date on which the client last received a methadone or buprenorphine dose before recommencing dosing in the community. When a prescriber or clinic is contacted regarding treatment, they must ensure the administration point has been notified.

7.11.7 Treatment of an opioid-dependent inpatient not currently on an opioid treatment program

Adequate treatment of opioid withdrawal in hospital is important to minimise client discomfort and assist clients to successfully complete withdrawal. Some clients leave hospital against advice because they are not coping with the discomfort of withdrawal. Alternatively, they may self-medicate with unsanctioned drugs that can confuse assessment and treatment in hospital.

Buprenorphine is effective in reducing opioid withdrawal symptoms and increases the likelihood that a client will remain in hospital for treatment of the primary condition for which they were admitted. As a partial agonist, it can also facilitate transition to other treatments such as buprenorphine or methadone maintenance, or naltrexone.

The use of buprenorphine in hospital should, however, not be commenced until consideration has been given to the impact on analgesia. The partial agonist properties and strong binding to the opioid receptors complicate analgesic use where clients have a condition requiring potent analgesia. Alternatives for these clients include methadone or medications to treat withdrawal symptoms such as clonidine, anti-emetics and anti-diarrhoeal agents[122].

122 Queensland Health 2012

The treatment of opioid withdrawal using buprenorphine or methadone in the hospital setting should be consistent with *The Queensland Alcohol and Drug Withdrawal Clinical Practice Guidelines*.

Advice regarding the nearest approved opioid treatment provider can be obtained from the Drugs of Dependence Unit in Queensland Health *(Appendix 6)*. Input from local alcohol and drug consultation liaison services, where available, should be sought.

On occasion it may be in the best interests of an inpatient to commence opioid treatment while in hospital. One example is where a patient has an infective complication of injection opioid use, such as bacterial endocarditis. In such a case, early consultation with a clinic or prescriber is recommended. If a timely appointment for opioid treatment after discharge cannot be arranged, interim approval may be given by the Drugs of Dependence Unit to the patient's GP to continue prescribing until the appointment date.

7.12 Opioid treatment program clients who present to hospitals or general practice clinics out of hours

It is not uncommon for clients who are on an opioid treatment program to present to hospitals or general practice clinics outside opioid treatment program hours with complaints that they have missed, lost, broken, stolen or vomited their methadone or buprenorphine dose and are in severe withdrawal. Such clients may be seeking replacement or additional methadone or buprenorphine. In these situations the following advice is offered:

- contact the client's prescriber if possible. Drugs of Dependence Unit will have information on prescriber contact details
- ADIS (the Alcohol and Drug Information Service) can provide information after-hours about a client's registration status (phone 07 3837 5989 or 1800 177 833)
- lost, broken, missed, vomited or stolen doses cannot be replaced in most circumstances
- if confirmation can be made that doses have been legitimately lost, then doses may be replaced at the prescriber's discretion.

It must be acknowledged that statements about missed, lost, broken, stolen or vomited doses may be true. However, this policy has been developed in order to protect the clinical safety of clients who may be drug-seeking, to encourage treatment adherence and to encourage self-responsibility in safeguarding take-away doses. Given the long half-life of methadone and buprenorphine, it is unlikely that missing one day's dose will cause significant physical discomfort, particularly in a client who has been stabilised on their dose.

Section 8
Clients with particular needs

8.1 Opioid-dependent pregnant women

Pregnant women who are dependent on opioids are at particularly high risk of complications during pregnancy because of a variety of factors. These may include:

- inadequate antenatal care
- biological issues, such as inadequate nutrition, blood-borne virus exposure and overdose
- psychological issues, such as depression and other mental health problems
- social problems, including domestic violence, and financial, accommodation, relationship and legal problems
- other substance use, including tobacco, cannabis and other drug use
- repeated cycles of opioid intoxication and withdrawal due to heroin dependence that are dangerous to the foetus.[123]

There may be a range of obstetric complications including:

- premature labour
- intrauterine growth retardation and low birth weight
- miscarriage
- intrauterine infection
- antepartum and postpartum haemorrhage
- intrauterine hypoxia or anoxia
- pre-eclampsia.

Opioid dependence during pregnancy is associated with risks for the newborn infant such as:

- neonatal abstinence syndrome
- sudden infant death syndrome.

Good antenatal care, even in women who continue substance use, will improve outcomes for the mother and infant. Therefore, it is important to support the pregnant woman through early referral for antenatal care and then closely liaise with the obstetric team regarding her opioid treatment[124]. Pregnant women dependent on opioids require treatment to minimise harm to the foetus and improve maternal health. Benefits to the mother and child in the short and long term will be provided through early involvement of multidisciplinary care, induction onto a stable dose of opioid replacement therapy and regular monitoring[125].

8.1.1 Opioid withdrawal in pregnancy

Acute opioid withdrawal during pregnancy carries particular risks including miscarriage, premature labour and foetal hypoxia and distress. Specialist care by an obstetrics team in combination with alcohol and drug specialists is required to manage opioid withdrawal in pregnancy[126].

Withdrawal during pregnancy can result in:

- miscarriage during the first trimester
- premature labour during the third trimester
- high risk of return to illicit opioid use with associated harms.

Antenatal and postnatal care should be managed in collaboration with a specialist obstetric service experienced in managing drug dependency during pregnancy.

123 Finnegan LP 1988 and 1991
124 Wilbourne, Wallerstedt, Dorato & Curet 2001
125 Winklbaur et al 2008
126 Young 2007

8.1.2 Opioid treatment in pregnancy

Pregnancy may be accompanied by the risks of exposing the foetus to unsanctioned short-acting opioids, or to methadone or buprenorphine[127]. The Australian Drug Evaluation Committee (ADEC) states opioids have "caused, or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible". The aims of treatment for pregnant women are the same as for all pregnant women:

- to minimise the likelihood of complications
- to provide comprehensive antenatal and postnatal care.

Since its introduction for treating opioid dependence in the past decade[128], buprenorphine is now considered an acceptable form of treatment for opioid dependence in pregnancy[129]. Treatment of opioid-dependent women during pregnancy with methadone or buprenorphine improves antenatal care and reduces exposure to the risks associated with illicit drug use[128].

Antenatal care should be managed, if possible, in collaboration with obstetric services that specialise in managing drug dependence during pregnancy. Some women may be initially reluctant to advise other health practitioners if they are on an opioid treatment program. This may reflect past experience with negative attitudes and values expressed about being drug-dependent. Clients should be counselled about the importance of a partnership approach between alcohol and drug services, specialist obstetric services and other relevant services in the care of their pregnancy[130].

Treatment providers often manage opioid-dependent women who additionally receive medication such as antidepressants. Evidence confirms the relative safety of selective serotonin reuptake inhibitors (SSRIs) during pregnancy. However, anxiety persists about possible teratogenic effects and postnatal behavioural disorders as part of neonatal withdrawal[131].

8.1.3 Issues to be addressed during the initial assessment

As most opioid-dependent women are in their child-bearing years when they present for opioid treatment, the following should be explored during assessment:

- Are they pregnant?
- Are they breastfeeding?
- If they are pregnant, what are their plans for the pregnancy?
- If they are not pregnant, are they planning to become pregnant?
- What positive effect does treatment have on a safe pregnancy and birth?

If the client does not wish or plan to become pregnant, the clinician should provide advice about reliable contraception.

Methadone and buprenorphine are the treatments of choice for women assessed as appropriate for opioid treatment during pregnancy.

Methadone has long been regarded as the gold standard treatment to the client and provides safe and more stable conditions for the pregnancy in comparison to no treatment[132]. However, buprenorphine is now proven as an alternative safe medication to use in opioid treatment[133]. If a pregnant woman uses opioids fewer than 3 times per week, has been using opioids for less than 3 months or has been using very small quantities of opioids, she is unlikely to be dependent and treatment options should be explored with her[134].

127 Young 2007
128 Kakko 2008
129 Jones, Kaltenbach, Heil, Stine, Coyle, Arria, O'Grady, Selby, Martin and Fischer, 2010 and Dunlop et al 2003
130 Wilbourne et al 2001
131 Winklbaur et al 2008
132 Jones et al 2010
133 Winklbaur, Jung et al 2008
134 Young 2007

Ultimately, the decision to start any opioid treatment for a pregnant woman involves careful assessment of the risks associated with continuing drug use and, when there is some uncertainty about the level of opioid dependence, the risks associated with treating her with a dependence-forming opioid.

If a pregnant woman is assessed as suitable for opioid replacement therapy, early stabilisation on a program is of paramount importance. The general principle is to individually titrate the dose of opioid treatment to prevent withdrawal symptoms and prevent ongoing opioid use. If the partner of the pregnant woman is also opioid-dependent, they should be given priority registration to the program to reduce exposure to unsanctioned opioid use in the woman's immediate environment[135].

8.1.4 Methadone treatment during pregnancy

National clinical guidelines advise it is preferable for a woman to be maintained on a dose of methadone or buprenorphine at delivery than to continue intermittent opioid and other drug use. However, some pregnant women are determined to withdraw off their opioid treatment. In this situation, any dose reductions should be undertaken only if the pregnancy is stable and only in the second trimester, which is considered the least harmful time[136].

Methadone dose reductions of 5 mg per fortnight are safe for doses above 40 mg/day and reductions of 2.5 mg per fortnight are safe when the dose is 40 mg or less. Most importantly, the approach to dose adjustments, in terms of their magnitude and rate, needs to be flexible and undertaken in consultation with the woman. It may be possible to undertake more frequent dose reductions, but the severity of opioid withdrawal symptoms and the woman's capacity to cope must guide clinical decision-making[136]. Withdrawal symptoms should be avoided as far as possible as they may cause considerable distress to the foetus[137].

If the prescriber decides with the client that dose reductions should occur, the second trimester is considered the least harmful period for an adverse obstetric event.

Physiological changes in the later stages of pregnancy (e.g. expanded plasma volume; an increase in plasma proteins which bind methadone; and placental metabolism of methadone) may reduce the bioavailability of methadone, making treatment at a given dose potentially less effective. It is often necessary to titrate the woman's methadone dose upwards to avoid withdrawal symptoms[135]. Occasionally, split doses may prevent withdrawal effects in a pregnant woman, and they are sometimes used to avoid increasing dosages as the pregnancy progresses[135]. Split-dosing may normalise foetal activity on ultrasound, since peak methadone doses may affect foetal heart rate and motor activity.

8.1.5 Buprenorphine treatment during pregnancy

Buprenorphine/naloxone is contraindicated in pregnancy and breastfeeding.

Buprenorphine treatment during pregnancy has now been shown to be safe and efficacious for the mother and foetus, and is an alternative treatment for opioid-dependent pregnant women[135].

The recommended treatment is buprenorphine mono, rather than the combined buprenorphine/naloxone product. If a stable client receiving buprenorphine/naloxone becomes pregnant, it is appropriate to change to buprenorphine[138]. Support should also be offered to link the woman in with specialist antenatal care as discussed above.

For all pregnant women on opioid treatment, clinical review by the treating prescriber and multi-disciplinary team should occur on a frequent and regular basis. Review alcohol and drug use regularly, particularly in the third trimester when dose increases may be needed to promote stability.

135 Wilbourne et al 2001
136 Henry-Edwards et al 2003
137 Winklbaur, Jung et al 2008
138 Dunlop et al 2003

Usual maintenance doses associated with significant reduction in heroin use are 8–24 mg buprenorphine. The available data for opioid replacement dose and incidence of neonatal abstinence syndrome (NAS) suggests no significant correlation. A proportion of clients on buprenorphine will experience opioid withdrawal when buprenorphine dosing occurs less frequently than daily (e.g. alternate day dosing)[139].

Withdrawal symptoms should be avoided as much as possible as they may cause foetal distress leading to preterm labour and foetal loss. If the prescriber decides with the client that dose reductions should occur, the second trimester is considered the least harmful period for an adverse obstetric event[140].

It is recommended that all pregnant women on buprenorphine be placed on a daily dosing schedule during pregnancy.

General principles of opioid maintenance should be followed during pregnancy. Dose increases may be required throughout the pregnancy, especially during the third trimester[141].

8.1.6 Dose review after giving birth

The maintenance dose should be reviewed in the early days following birth and regularly as indicated thereafter. The focus in reviewing the dose should be on supporting and enhancing the woman's stability, taking into account:

- signs of withdrawal or intoxication
- risk of reverting to unsanctioned drug use.

Effective liaison between relevant services including midwifery and obstetric, neonatal, child protection and drug treatment services is crucial in the postnatal period. The case manager can facilitate this.

8.1.7 Use of other substances during pregnancy

Other substances, licit and illicit – including nicotine, alcohol, cannabis, benzodiazepines, amphetamines and cocaine – pose potential risks to pregnant women and their babies. Use of these substances during pregnancy should be addressed[142].

Women who are pregnant or who may become pregnant are therefore a high priority for interventions to reduce drug use. In addition to midwifery and obstetric care, research suggests pregnant women with problematic substance use benefit from:

- referral to specialist alcohol and drug assessment
- appointment of a consistent case manager and care team who communicate effectively
- specific treatment for drug use, including counselling, pharmacotherapies and relapse prevention strategies[143].

8.1.8 Management of neonatal care

Neonates born to mothers who have been on opioid treatment programs or women who have been regularly taking other opioids (e.g. heroin) during their pregnancies, are at risk of developing a neonatal abstinence syndrome from opioids[144].

139 Dunlop et al 2003
140 Winklebaur, Jung et al 2008, Dunlop et al 2003
141 Winklebaur et al 2008, Jung et al 2008
142 O'Grady et al 2009, Winklbaur et al 2008
143 Commonwealth of Australia 2006
144 O'Grady et al 2009

The use of opioid antagonists (e.g. naltrexone) is strictly contraindicated for neonates born to opioid-dependent mothers due to the risk of seizures in the neonate.

8.1.9 Neonatal abstinence syndrome

Data suggests neonatal abstinence syndrome (NAS) is likely to occur in babies born to opioid-dependent women and may sometimes require pharmacological treatment. NAS includes the signs and symptoms related to the central nervous system, the gastrointestinal system and the respiratory system of opioid-exposed infants[145]. The incidence of NAS may be less severe in women stabilised on buprenorphine rather than methadone[146]. In keeping with current management strategies for neonates experiencing withdrawal, the infant should ideally remain with the mother where possible.

Experienced staff should observe all babies born to opioid-dependent mothers for developing signs of withdrawal. A validated scale should be used to assess the presence and severity of NAS, for example the Finnegan scale[147]. Withdrawal symptoms can start at any time during the first 24 hours following delivery, and up to 10 days post-natally, depending on the substance or substances the baby was exposed in utero. Withdrawal from additional substances (for example benzodiazepines) used with methadone or buprenorphine may delay the onset of symptoms and also prolong and complicate the withdrawal process[148].

8.1.10 Breastfeeding while on methadone or buprenorphine

Breastfeeding promotes mother-child bonding and may decrease NAS severity[148]. Recent data shows no significant differences between opioid-dependent mothers who are being treated with methadone or buprenorphine and safety in breastfeeding. Concentrations of methadone and buprenorphine in breast milk are low and remain stable over time. Women on methadone or buprenorphine should be strongly encouraged to breastfeed. The benefits of breastfeeding greatly outweigh minimal risks of low concentrations of methadone or buprenorphine present in breast milk[149]. Two notable exceptions are if the mother has cracked or bleeding nipples and is HIV positive or hepatitis C RNA positive. Nipple shields and expressing milk are suggestions that can allay concerns about cracked nipples[150].

The delay between delivery and appearance of NAS reflects similar concentrations of methadone or buprenorphine in the mother and neonate at birth, following which levels then gradually decline in the neonate. It is unclear if the effect of breastfeeding on NAS is due to the beneficial effects of breastfeeding itself or because the low concentrations of methadone or buprenorphine present in breast milk mitigate withdrawal[151].

8.2 Clients with co-existing mental health problems

Depression and anxiety, personality disorders and alcohol misuse and dependence are more common among opioid users than in the general population. Some mental health problems will abate with the general stabilisation produced by opioid treatment. The severity of remaining psychiatric problems tends to predict the response to opioid treatment[148]. After stabilising a client on opioid treatment, screen again for psychiatric disorders. A careful and detailed mental state examination will usually suffice. There are many widely available tools that can also be used.

145 Wilbourne et al 2001
146 Jansson et al 2011, Jones et al 2010 and Kakko et al 2008
147 Finnegan, 1988 and 1991
148 Winklbaur et al 2008
149 Glatstein, Garcia-Bournissen, Finkelstein and Koren 2008
150 O'Grady, Hopewell and White 2009
151 Glatstein et al 2008, Malpas, Horwood and Darlow 1997, and Malpas T 1999

8.3 Clients with hepatitis C, hepatitis B and HIV

When assessing an individual for opioid treatment, it is important to obtain a detailed history of HIV and viral hepatitis transmission risk behaviours. The drug history should include information about unsafe injecting practices and the personal history should cover sexual relationships and at-risk sexual behaviours. Universal infection control precautions should be in place regardless of the HIV or hepatitis status of individual clients[152].

Education regarding HIV and viral hepatitis should be provided to all clients at the initial assessment because there are people who subsequently do not return for further treatment. Even for this group, such a brief intervention may have significant individual and public health benefits[152].

More detailed information should also be provided at a later date, when the client has stabilised on methadone or buprenorphine.

Education for clients should include the following components:

- information regarding safer injection practices (including the availability of sterile injecting equipment)
- information regarding safer sexual practices
- access to health and alcohol and drug services
- prevention, testing and treatment of other sexually transmitted infections
- pregnancy advice for women
- assertion and negotiation skills (especially for women)
- discussion of sexuality issues
- desirability of testing
- pre- and post-test counselling.

8.3.1 Hepatitis C

This blood-borne virus is a major public health concern. Hepatitis C virus (HCV) is spread primarily through injecting drug use. The majority of individuals entering opioid treatment programs will be hepatitis C reactive. Hepatitis C reactive individuals should have their hepatitis B status checked, since hepatitis B co-infection may cause their illness to be more aggressive[153].

Education and counselling should provide detailed information about hepatitis C infection, and aimed at reducing risk behaviours and minimising transmission. Information should include advice on reducing hazardous use of all drugs (particularly alcohol, cannabis and tobacco) and managing ill health due to hepatitis C. Clients should be advised against sharing injecting equipment (including tourniquets, spoons and solvents), as well as razors, toothbrushes and other items that may be vehicles for the exchange of blood[153]. Referral to the Hepatitis Council of Queensland is recommended for professional peer support for people living with hepatitis C.

No changes are recommended to manage pregnancy or labour in women who have HCV, nor managing neonates, within Australia[153]. Despite HCV RNA being detectable in breast milk, breastfeeding has not been directly linked to HCV. Specialist assessment and follow-up of infants born to HCV RNA positive mothers should be encouraged[153].

8.3.2 Hepatitis B

Hepatitis B vaccination is recommended to all clients on the opioid treatment program who are found to have no immunity to the hepatitis B virus[153]. It is recommended that vaccination should be offered to sero-negative partners and close family contacts of clients who are hepatitis B sero-positive and potentially infectious. Chronic hepatitis B carriers (HBsAg or eAg positive) should be referred to a liver clinic or gastroenterologist for assessment. The hepatitis B vaccination is free for at-risk groups including intravenous drug users[152], and should be made available in all opioid treatment clinics.

152 ASHM 2008
153 ASHM 2009

8.3.4 HIV

Clients who are HIV-positive should, if possible, be managed in collaboration with specialist services and community-based support services. These clients may have a range of conditions, such as depression or tuberculosis, and may be treated with pharmacological agents that interact with methadone or buprenorphine[154].

8.4 Therapeutic opioid dependence

Therapeutic opioid dependence may be defined as opioid dependence that has developed in the context of opioid treatment of a painful (non-malignant) medical condition. The dependence is on prescribed opioids – and in a significant proportion of clients with chronic pain, dependence on opioid medication could become a more significant problem than the original underlying medical condition which may have resolved or diminished in importance. This is a growing area of concern, with the number of people in Australia dependent on opioids for chronic non-malignant pain outnumbering clients with heroin dependence by perhaps 4:1[155].

Ideally, a multidisciplinary treatment team should manage clients with therapeutic opioid dependence. This group of clients is often complex and challenging, and can benefit from the contribution of medical, nursing and allied health specialties. The team members will vary according to circumstances, and may include some or all of the following:

- General practitioner: to take a central role in managing and coordinating the treatment plan, prescribing pain relief and participating in managing the therapeutic opioid dependence.
- Specialist practitioner: in the appropriate discipline (for example, an orthopaedic specialist for back pain or a neurologist for headache). The role of these specialists is to confirm the cause of the pain, to offer or advise on the appropriate treatment, and to assess any exacerbation of previously stable pain.
- Pain clinic: the role of the pain clinic is essentially to advise on and, when indicated, administer appropriate pain relief. The client may need to be admitted for inpatient assessment, opioid medication withdrawal and other methods of pain relief substituted, in association with psychosocial support.
- Psychiatrist: to manage pre-existing or concomitant psychopathology, if such exists.
- Addiction specialist: experienced in treating drug dependence.
- Social worker or psychologist: to play a special role in assisting with coordinating the team, providing support for the clients, and helping them develop coping skills to prevent relapse.
- Physical therapists, physiotherapists and occupational therapists: have important roles in maximising the value of physical therapies and in relaxation training. Their contribution is important both in managing clients with non-malignant pain and in clients with cancer.
- The Drugs of Dependence Unit is responsible for enforcing the legislation governing the prescription of controlled drugs and restricted drugs of dependence. The relevant legislation is the *Health (Drugs and Poisons) Regulation 1996*[156].

At the outset, organic pathology requires adequate assessment. A pain clinic or an appropriate medical specialist is the most appropriate avenue for conducting the initial assessment.

If organic pathology resulting in chronic pain is judged to be the predominant problem – and the client is not associated with unsanctioned drug use – the client is usually best treated by his or her general practitioner (the appropriate prescriber to treat pain). A long-acting oral or transdermal opioid is appropriate for pain relief as part of a comprehensive pain management program. Parenteral opioids (particularly self-administered) are not appropriate for chronic pain management outside of specialised pain units.

154 ASHM 2008
155 Lintzeris 2010
156 Queensland Government 1996

Medical practitioners may refer patients receiving opioid medications for pain conditions to an alcohol and drug service for assessment. A recommendation to refer is usually made by the Drugs of Dependence Unit or the Therapeutic Opioid Drug Dependence Committee. Clients may also self-refer with problems associated with their use of opioids for non-malignant pain management.

It is the responsibility of alcohol and drug service clinicians to provide a comprehensive assessment of the person and to provide advice to the client's general practitioner on the most appropriate way to manage the client's opioid use. The assessment or review should include the following:

- a full alcohol and drug history
- any signs or evidence of injecting drug use
- any signs or evidence of illicit drug use, including misuse of prescribed medication
- urine drug screen
- a recommendation about whether the person should be registered on the Queensland Opioid Treatment Program.

This will ensure clients receive the most effective treatment for their condition. However, it does not necessarily mean they will be admitted to an opioid treatment program.

Therapeutic opioid dependence is best managed by negotiating a realistic goal, whether this is ceasing opioid use or opioid maintenance. The latter may be the only realistic option for people using large quantities of opioids for a number of years. In such instances, the opioid medication should be orally administered and long acting (such as physeptone tablets) and supplies must be issued frequently and in small quantities to aid concordance. The treatment regime must be closely monitored and run within strict limits. These include that the maximum dose should not be increased and that lost or broken doses should not be replaced.

If opioid dependence is judged to be the predominant problem – and if those patients treated by general practitioners become non-concordant with the treatment regime (such as 'doctor shopping', injecting medication, escalating their dose or beginning to procure unsanctioned opioids) they will generally need to be transferred to an opioid treatment program.

8.4.1 Therapeutic Opioid Drug Dependence Committee

The role of the Therapeutic Opioid Drug Dependence Committee is to advise Queensland Health on appropriate ways to manage clients receiving long-term Schedule 8 medications outside an opioid treatment program. The committee meets every three months to review the clinical management of all notified clients and other people as a result of their opioid drug-seeking behaviour. This committee does not see clients, but reviews the files made available to them from the Drugs of Dependence Unit. The committee also provides advice to general practitioners about opioid management.

Section 9
Withdrawal and completion of treatment

9.1 Length of treatment

The longer clients remain in treatment, the more likely they are to have a positive outcome afterwards.

There is no optimal duration of opioid treatment, but removing people from treatment before the client and treating staff believe that they are ready to reduce their methadone or buprenorphine use results in very poor outcomes, including high rates of relapse into opioid use[157].

Clients should be encouraged to consider the benefits and consequences of reducing their methadone or buprenorphine dose throughout their treatment program.

Treatment staff should regularly focus with clients on the changes the client needs to have in place to successfully reduce their methadone or buprenorphine dose, and explore strategies with clients that are likely to help them to successfully reduce.

The characteristics that suggest a client may be ready to reduce their methadone or buprenorphine dose include stable employment, stable accommodation, stability in relationships, no illicit drug use and the absence of prominent psychiatric symptoms[158].

Aftercare and easy access back into treatment are needed and are important elements of the services that should be provided within opioid treatment programs[158].

9.2 Completing opioid maintenance treatment

Methadone or buprenorphine treatment should not be seen as being time limited, and clients should be encouraged to remain in treatment for as long as they perceive that continued benefit is being achieved. There is considerable evidence indicating that the benefits to the client and the community are maximised when clients are retained in treatment for at least 12 months[159]. Advising clients about the risk of relapse may reduce premature withdrawal from treatment.

9.3 Planned withdrawal from methadone or buprenorphine

Clients who complete their opioid treatment program after a gradual withdrawal from methadone or buprenorphine are least likely to relapse into illicit opioid use[160]. The decision to withdraw voluntarily from methadone or buprenorphine should ideally be made collaboratively between the client, the prescriber and the case manager[158]. When all parties agree about the timing and method of withdrawal, clients tend to be more successful in their reduction. It remains, however, the client's right to withdraw from methadone or buprenorphine at any time.

Take a flexible approach to dose reduction in voluntary withdrawal. The aim is to maximise the client's chances of completing the opioid treatment program in a manner that minimises the risks of relapse into opioid use. Individuals vary greatly and it is best to allow clients to control the frequency and amounts by which their dose is reduced during voluntary reduction. Even at slow rates of reduction, it is common for clients to experience some withdrawal discomfort at times. It may be appropriate to maintain a client at a constant dose at times during the reduction, until the client is better prepared to reduce further[161]. If relapse is likely or has occurred, further reductions in methadone or buprenorphine dose may need to be suspended or an increase in dose considered.

During the withdrawal period, clients will usually benefit from increased psychosocial support. Throughout the reduction phase, provide accurate information about what the client is experiencing along with supportive counselling (orientated towards preventing relapse) to enhance the likelihood of a successful outcome.

157 Hallinan et al 2006
158 Henry-Edwards et al 2009
159 White et al 2007
160 Nosyk et al 2012
161 Nosyk et al 2012; Henry-Edwards et al 2009

9.4 Methadone reduction rates

In general, the following rate of methadone reduction is well tolerated by clients:

- Clients on doses greater than 80 mg/16 ml will usually tolerate reductions of 5 mg/1 ml per fortnight or month until they reduce to about 70–80 mg/14–16 ml.
- Individuals whose daily methadone dose is between 40 mg and 80 mg will generally tolerate a reduction of 2.5–5 mg per fortnight or month.
- When the dose falls below 40 mg/8 ml, the likelihood of a client experiencing withdrawal symptoms becomes greater. It is preferable, therefore, to slow the rate of reduction to 2.5 mg/0.5 ml per fortnight or month[162].
- It is also suggested that reductions should be interspersed with periods of a stable dose so that time spent reducing should be 25–50 per cent of the total period from when reductions began.

9.5 Buprenorphine reduction rates

Withdrawal from buprenorphine appears to be less prolonged and less severe than methadone withdrawal. Withdrawal symptoms appear to be milder during buprenorphine dose reductions, and the rate of buprenorphine dose reduction may be more rapid than with methadone, though each client should be closely monitored during reductions to ensure that they are able to manage any withdrawal symptoms. The symptoms and signs of withdrawal from buprenorphine are qualitatively similar to withdrawal from other opioids:

- Those on doses above 16 mg will usually tolerate reductions of 4 mg per fortnight or month.
- Individuals whose daily buprenorphine dose is between 8 mg and 16 mg will generally tolerate a reduction of 2–4 mg per fortnight or month.
- When the dose falls below 8 mg, it is preferable to reduce the dose by 2 mg per fortnight or month.
- Above 2–4 mg, reductions should be in multiples of 2 mg, contrasting with the approach used for methadone.

9.6 Adjunctive pharmacotherapy during withdrawal phase

Sleep disturbance is common among people who withdraw from almost any psychoactive drug, including methadone and buprenorphine[163]. Explain this to clients, provide information about withdrawal-related symptoms and offer training in non-pharmacological sleep hygiene strategies to help them cope with disturbed sleep.

Other psychotropic medication (in particular, hypnotics and sedatives) is not recommended for clients during monitored withdrawal, except when indicated for clients with diagnosed psychiatric co-morbidity. If it is considered appropriate to prescribe sedative or hypnotic medication, it should be at a low dose for a specified short duration (3–5 days). The client should be made aware of the reason for its prescription, the associated risks of taking such medication and the intended short duration of this treatment. Provide ongoing supervision in all cases and, for safety, restrict the quantity of tablets to 1–2 days' worth.

9.7 Avoiding secondary alcohol and sedative or hypnotic problems

During and after withdrawal from opioids, over-indulgence in alcohol and the inappropriate use of sedative or hypnotic medication is common. This should not necessarily be construed as indicating a long-term shift to alcohol and other drug dependence, but the clinician should remain vigilant to the possibility that alcohol consumption or other drug use may be increasing to hazardous or harmful levels and provide appropriate interventions.

162 Nosyk et al 2012
163 Beswick et al 2003

9.8 Readmission to treatment

When relapse occurs some time after leaving treatment and the client seeks readmission to an opioid treatment program, this should be offered expeditiously and without recrimination.

Provided that the person is clinically suitable for opioid treatment, there should be no barriers to readmission for at least one month after leaving the program.

9.9 Involuntary termination of opioid treatment

It is occasionally necessary to discharge a client from treatment for the safety or wellbeing of the client, other clients or staff[164]. At the beginning of opioid maintenance treatment, clients should be provided in writing with the conditions under which they may be involuntarily discharged.

Situations that may warrant this action include:

- violence or threat of violence against staff or other clients
- property damage or theft from the opioid treatment program or pharmacy
- repeated drug dealing near the opioid treatment program premises or pharmacy
- repeated diversion of methadone or buprenorphine.

It is preferable, where possible, to transfer the client to another program instead of withdrawing them entirely from opioid treatment.

If the client is to be involuntarily withdrawn from opioid treatment, reduction in dosage should be gradual. Rapid dose reduction or abrupt cessation of treatment is warranted only in cases of violence, assault or threatened assault[164]. Clients who are to be discharged should be advised of other treatment options, including withdrawal management. They should be warned that their tolerance to other opioids may be reduced, reminded of the risks associated with resuming drug use, and offered relapse prevention strategies. A management plan for subsequent readmission should be documented in the case record of each client involuntarily withdrawn from the program.

9.10 Failure to attend for treatment

A client who has not presented to pick up their methadone or buprenorphine dose for three or more consecutive days should not receive methadone or buprenorphine without review by the prescriber or delegate in consultation with the prescriber.

A client who fails to attend for 14 consecutive days should be discharged from opioid treatment. Although it may be useful to extend this period to facilitate re-engagement to treatment, it may effectively create a barrier to new clients accessing treatment.

9.11 Appeals

Clients should have access to procedures intended to resolve conflicts between themselves and those responsible for their treatment.

All opioid treatment programs must have documented policy and procedures in relation to an appeals mechanism. If clients wish to register a complaint about their treatment, they can do so through the Health Quality and Complaints Commission. Another peer-based organisation in Queensland that is available to offer advocacy and support to clients on opioid treatment programs is Queensland Pharmacotheapy Advocacy Mediation and Support Service *(see Appendix 6 for contact details of these agencies)*.

164 Henry-Edwards et al 2009

The following principles apply to the issue of appeals:

- Clients should be informed in writing of their rights to register a complaint and the procedures for doing so at the time of their admission into opioid treatment.
- Clients who cannot read should be read their rights and obligations at the time they enter treatment.
- If possible, clients should be retained in the current treatment program pending the resolution of the complaint.

9.12 Aftercare

Aftercare refers to structured interventions that assist clients who have completed treatment to continue their recovery, remain drug-free and improve their psychosocial functioning. Clinicians working in opioid treatment programs should, whenever acceptable to the client, offer support services themselves or by referral.

Such services might include skills training (such as relapse prevention, problem-solving skills or vocational skills training), social support services (including peer-based community organisations), or motivational counselling sessions. Providing such aftercare to motivated clients will enhance the overall efficacy and cost effectiveness of treatment.

9.13 Transfer of opioid treatment

Good communication between transferring and receiving prescribers and pharmacists is important. It is also important that clients give adequate notice of their need or desire to be transferred to another prescriber. Transfers may be intrastate (within Queensland), interstate or international.

9.13.1 Procedures for arranging transfers

Permanent intrastate transfer (within Queensland)

1. The transferring prescriber contacts the receiving prescriber to ascertain if the transfer will be accepted.
2. The transferring prescriber must fax or mail to the receiving prescriber details including the client's name, address and date of birth, relevant clinical details (dose, clinical progress, and past and current medical and psychiatric problems), expected dates of temporary or permanent transfer with the new prescriber, and a photograph of the client. These details and the photograph should reach the receiving prescriber before the first visit of the client.
3. To avoid the potential for double-dosing, the transferring prescriber should notify the client's dosing site and cancel all written instructions and prescriptions.
4. The transferring prescriber must complete the Queensland Opioid Treatment Program discharge form and forward it to the Drugs of Dependence Unit within 72 hours of the client's treatment exit. In completing the discharge form, the transferring prescriber must indicate in the space provided that the discharge is for reasons of transfer.
5. The receiving prescriber will admit the client in the usual way, indicating on the admission form in the space provided as well as by telephone that the admission is a result of a transfer.

Transfer between dosing sites in Queensland

Clients may request transfer to other dispensing locations, on a temporary or permanent basis, for work, holiday or other reasons. To avoid the risk of dual dosing on the same day, good communication between prescribers and pharmacists is important.

Both pharmacists must be notified by telephone of the transfer of a client. The former pharmacist should be notified first so the date of the last collected dose is confirmed prior to cancellation of that written instruction. Please note that the client should not transfer between pharmacies if they hold outstanding debts at the former pharmacy.

It should be established that the receiving pharmacy has been authorised by the Drugs of Dependence Unit to administer opioid treatment pharmacotherapies.

Interstate transfer

The prescriber or clinic should make arrangements for temporary interstate dosing. The prescriber must first contact the destination state's equivalent Drugs of Dependence Unit to ensure they comply with the state or territory regulations *(see Appendix 5)*.

For permanent interstate transfers, processes vary across states and territories, but in every case the Queensland prescriber is required to provide the information necessary for safe transfer to the receiving prescriber. Under usual circumstances, at least three weeks' notice of intention to transfer should be provided.

- The transferring prescriber must fax or mail to the receiving prescriber details including the client's name, address and date of birth, relevant clinical details (dose, clinical progress, and past and current medical and psychiatric problems), expected dates of temporary or permanent transfer with the new prescriber and photographs of the client. The receiving prescriber will need these details prior to the client's arrival.
- To avoid the potential for double-dosing, the transferring prescriber should notify the client's dosing site and cancel all written instructions and prescriptions.
- The transferring prescriber must complete the discharge form and forward it to the Drugs of Dependence Unit within 72 hours of the client's treatment exit if the transfer is permanent. In completing the discharge form, the transferring prescriber must indicate in the space provided that the discharge is for reasons of transfer.

(See Appendix 6 for a list of jurisdictional telephone numbers for arranging interstate transfers.)

International travel

If clients are travelling overseas, the prescriber should undertake the following steps before the client confirms their travel plans.

- Find out details about the possibility of travel to different countries for clients on the opioid treatment program at: www.indro-online.de/travel.htm.
- Confirm whether the client is able to leave the country carrying the required amount of medication with the Department of Foreign Affairs and Trade.
- Ensure it is legal to arrive with, transit through, travel with and consume the medication with the embassy or consulate of the transit and destination countries.
- Prepare a letter confirming that the client is legally prescribed the medication for personal use under the laws of Australia. The client should keep this letter secure with their medication during travel. In some instances, it may be an additional requirement for the letter to be translated into the language of the destination country.

Provision of take-away doses to enable travel is at the discretion of the prescriber.

- If the client is registered on buprenorphine, then the number of take-away doses provided for travel is at the discretion of the prescriber.
- If the client is registered on methadone, then the prescriber should seek written approval from the Drugs of Dependence Unit to provide take-away doses for travel in the form of physeptone tablets. Providing physeptone tablets for travel will avoid the risk of breakage or spilling methadone syrup or liquid doses.

International transfer

In the case of clients seeking to travel abroad permanently, find out details about coordinating an international transfer for clients on the opioid treatment program at: www.indro-online.de/travel.htm.

Arrangements for an international transfer should be made well in advance (at least one month before travel arrangements are made). International transfers are not always possible due to laws in other countries.

Generally, take-away physeptone or buprenorphine doses will only be provided for the shortest period necessary for the client to reach their destination.

Contact the Drugs of Dependence Unit for further information.

Section 10
Information for pharmacists

This section gives pharmacists advice on supplying and administering methadone syrup or liquid and buprenorphine to clients on the Queensland Opioid Treatment Program. In circumstances not specifically addressed by these guidelines, please contact the client's prescriber or the Drugs of Dependence Unit.

It is important all participating pharmacists familiarise themselves with the complete *Queensland Opioid Treatment Program Clinical Guidelines and Drug Therapy Protocols 2008* as well as this section of the document.

Pharmacists who want to participate in the Queensland Opioid Treatment Program should contact the Drugs of Dependence Unit.

10.1 Role of pharmacists

Pharmacists have a key role in delivering opioid treatment services. Community pharmacy dosing greatly assists in the process of normalising the lifestyle of clients in the longer term. The involvement of pharmacists in the Queensland Opioid Treatment Program is voluntary and enables clients to dose near where they live or work. Many clients develop healthy relationships with their pharmacist.

Generally the pharmacist:

- monitors the client's day-to-day level of intoxication
- dispenses the dose
- converses with the client after consumption to ensure the dose has been swallowed or absorbed
- encourages the client to dose at a similar time each day
- maintains close contact with the prescriber to report signs of intoxication, other drug use, non-attendance for dosing, and any problems or crises that present.

10.2 Harm minimisation

Harm minimisation is the basis for Australian drug policy[165]. The concept is recognised as a positive and realistic response to dealing with the many problems associated with, or resulting from, the use of drugs in society[166].

Minimising harm does not mean it is possible for drug use to be totally safe or without risk. Drug use always involves potential for harm – physical, psychological, social or legal[165].

10.3 Opioid maintenance treatment

Opioid dependence is often a chronic relapsing condition[167]. Opioid maintenance treatment aims to decrease the risks of drug use for the individual and the community at large. It is a specific treatment modality for people who have problems related to dependence on opioids – heroin in particular.

Methadone and buprenorphine may be prescribed to opioid-dependent people to allow them to improve their health and lifestyle. Because of their pharmacological characteristics, both drugs allow the person to become more stable and to function more normally[166].

Opioid treatment programs allow people to receive appropriate ancillary treatment and help, so that if they subsequently wish to withdraw from their opioid treatment program they have a realistic chance of maintaining abstinence[166].

Specifically, opioid treatment is provided to:

- bring to an end or significantly reduce the client's unsanctioned opioid use
- reduce the risk of overdose and death associated with opioid use

165 Ministerial Council on Drug Strategy 2011
166 Drugs of Dependence Advisory Committee 2006
167 Mental Health and Drug and Alcohol Office 2006

- reduce the transmission of blood-borne diseases
- improve general health and social functioning, including reduce crime[168].

These objectives will not necessarily be achieved with each client, nor to the same degree in each opioid treatment program setting. The aim is to reduce drug-related harm as much as circumstances allow for each client and for the community.

While a client continues to benefit from opioid maintenance treatment, such treatment should continue to be made available to that person without an expectation or pressure on them to exit treatment prematurely[169].

10.4 Opioid treatment program structure

People who want treatment may be referred to an opioid treatment program by a medical practitioner or other health professional, or may present at a program because they have made a decision to seek treatment for their opioid (usually heroin) dependence. Most people presenting at programs self-refer.

All new admissions undergo a comprehensive medical and psychosocial assessment where treatment options are explored[170]. Once in the program, the person attends a pharmacy and consumes an oral dose of methadone syrup or liquid or sublingual dose of buprenorphine. Initially, the person is assessed daily, then as regularly as the prescriber deems appropriate, until their methadone or buprenorphine dose is stable.

All clients, including those who appear to be doing well, have a periodic review in which recent drug use, social functioning, and psychological and physical health are assessed. This review aims to make sure the treatment is meeting the client's specific needs, to make sure clinical safety is not being compromised, and to let the client and clinician discuss the client's progress and treatment[171].

The prescriber or case manager may contact the pharmacist or dosing location in order to pass a message to the client regarding review appointments.

There is no optimal duration of opioid treatment, but removing people from treatment before the client and treating staff believe they are ready to reduce their methadone or buprenorphine dose results in very poor outcomes, including high rates of relapse into opioid use[168].

10.5 Formulations

Two preparations are available for methadone maintenance in Australia:

- Methadone Syrup®: This formulation contains 5 mg/ml methadone hydrochloride. It also contains sorbitol, glycerol, ethanol (4.75 per cent), caramel, flavouring and sodium benzoate.
- Biodone Forte®: This formulation contains 5 mg/ml methadone hydrochloride. It also contains permicol-red colouring[172].

Three buprenorphine products are currently registered in Australia to treat opioid dependence within a framework of medical, social and psychological treatment:

- the mono product Subutex® is a sublingual tablet containing buprenorphine hydrochloride in 0.4 mg, 2 mg and 8 mg strengths
- the combination product Suboxone® is a sublingual tablet or film containing buprenorphine hydrochloride and naloxone hydrochloride in a ratio of 4:1 and is available in 2 mg/0.5 mg and 8 mg/2 mg strengths[170].

168 Mental Health and Drug and Alcohol Office 2006
169 Drug of Dependence Advisory Committee 2006
170 Henry-Edwards et al 2003 and Lintzeris et al 2006
171 Lintzeris et al 2006
172 Henry-Edwards et al 2003

In the context of this document, the general chemical name 'buprenorphine' is used for information that applies to either preparation. Where it is necessary to distinguish between the preparations, either Subutex® (buprenorphine mono) or Suboxone® (buprenorphine/naloxone) will be specified.

10.6 Dosing procedures

Each of the following factors must be confirmed when dosing any opioid treatment program client.

- **Identification of the client**: Check the client's photograph attached to a letter of introduction provided by the prescriber or clinic. Refer to the photograph regularly and ask for a new one when required. Confirm the name and date of birth of the client.
- **Current dose**: Check the dose with the written instructions before every dose and ensure the written instructions are current.
- **Safety to dose**: If there are any signs of intoxication or the client misses any doses of methadone or buprenorphine, the pharmacist should contact the prescriber to discuss the situation and obtain a direction regarding the dose.
- **Unacceptable behaviour or condition**: If the client exhibits unacceptable behaviours or declines in their physical or mental health or appearance, the prescriber or clinic should be contacted.
- **Documentation**: Ensure opioid treatment program guidelines, client records and photographs, written instructions and all communications with prescribers or case managers are documented and easily accessible by all pharmacists – especially locums[173].

10.7 Dose preparation

Each methadone or buprenorphine dose should be prepared at the time the client presents at the pharmacy. Preparing doses in advance carries a high risk of providing an incorrect dose to the client when they present later.

If it is absolutely necessary to pre-prepare doses, the following procedures should be followed in order to minimise any risk of error:

- doses are only to be prepared on the day of dosing
- measure the dose into a container with secure closure and clearly label with the client's full name and dose (methadone doses should be labelled in both milligrams and millilitres). If preparing methadone take-away doses, closures must be child-proof[174].
- store prepared doses (including take-away doses) securely, in a Controlled Drugs safe, until the client presents to the pharmacy for their medication
- the identity of both the pharmacist who prepares the dose and the pharmacist who administers the dose should be clearly documented
- do not dilute or crush doses until the client presents for dosing. This will enable the administering pharmacist to verify the accuracy of the dose.

Please note: Traditional pharmacy measures, (for example conical flasks), are not generally accurate enough for measuring methadone syrup or liquid. It is recommended that a syringe or displacement pump be used instead.

173 Drugs of Dependence Advisory Committee 2006, Pharmaceutical Services Branch 2004, Lintzeris et al 2006
174 Drugs of Dependence Advisory Committee 2006

10.8 Administration of dose

When administering methadone or buprenorphine, the following should occur:

- The client's identity and current dose should be verified with the current written instruction and photograph.
- Regular doses of methadone or buprenorphine should be administered using disposable cups or bottles.
- To protect the client's privacy, a discreet area of the pharmacy should be used when dosing, if possible.
- Do not let the client access the dispensary at any time.[175]

A third party may not collect any doses unless specifically authorised by the prescriber or clinic.

10.8.1 Administering methadone doses

The procedure for administering methadone syrup or liquid should be as follows:

Administering the dose: Supervised dose of methadone should be presented to the client undiluted. The client may dilute with water themselves, if desired.

Observing: Clients are required to drink their methadone in front of the pharmacist and they may follow that with a drink of water if desired. Ensure they are drinking out of a cup and not a bottle. Clients may attempt to divert their dose into the bottle. Take part in a short conversation with the client to ensure the dose has been swallowed.[176]

10.8.2 Administering buprenorphine sublingual tablets

The procedure for administering buprenorphine tablets should be as follows:

Before administering: Buprenorphine tablets should be rough-crushed (coarsely crumbled) and placed in a dry, disposable dosing cup by the pharmacist. It is not advisable to crush into a fine powder as this tends to increase saliva, making it unpleasant for the client and may prolong the dissolving process.

Administering the dose: Each client is expected to tip the tablets directly from the cup under their tongue and show the pharmacist that they are in place.

Observing: Observe the correct placement of crushed tablets. Advise the client not to chew or swallow until the tablets have fully dissolved.

Supervision time: Clients must wait in sight of the pharmacy staff for up to five minutes or until their medication has been absorbed. No food or drink should be consumed until the film is completely dissolved.[177]

10.8.3 Administering buprenorphine sublingual film

The procedure for administering buprenorphine sublingual film should be as follows:

- **Before administering:** Advise the client not to eat immediately before dosing, as it may interfere with absorption. Offer a sip of water to moisten mouth. Ensure the client's hands are clean and dry, as the film may stick to wet fingers and make correct placement in the client's mouth difficult. Collect films needed to make up the dose and check these against the written instruction. Films should not be cut to manipulate the dose (e.g. half a 2/0.5 mg film to achieve a 1/0.25 mg dose). Clarify with the prescriber in such an event.
- **Administering the dose:** Open all packages (bend along the dotted line and tear at the perforation or cut open with scissors) and offer the open packages to client, who removes the films from the packages one at a time to place in their mouth. Alternatively, the pharmacist removes all the films from the packages and places them into an appropriate container (e.g. a 20 ml transparent plastic medication cup) and offers the container of films to the client to place in their mouth one at a time.

175 Pharmaceutical Services Branch 2004, Drugs of Dependence Advisory Committee 2006
176 Pharmaceutical Services Branch 2004
177 Lintzeris et al 2006, Pharmaceutical Services Branch 2004

- **Observing:** Observe the correct placement of films. Clients should hold the films by their edges, and place them sublingually one at a time. If multiple films are needed, the first two are placed under the tongue, either side of the frenulum, and the rest are placed onto the inside of the cheeks. (Although buccal administration is an off-license method of use, the bioavailability of sublingual and buccal administration is similar.) Advise the client not to attempt to move the films once they have been placed in the mouth, nor to chew or swallow until the films have fully dissolved (generally 2–5 minutes). If films accidentally become stuck on top of the tongue or to the teeth, reassure the client that buprenorphine will still be absorbed and to keep their mouth closed with the mucous membranes in contact with the films as they dissolve.
- **Supervision time**: Films adhere to mucous membranes within seconds and are difficult to remove within 30 to 60 seconds. Thus, under normal circumstances, post-dose supervision does not need to exceed 1 minute. Discourage the client from overlapping films when placing them in their mouth. This impairs adherence to the mucosa and prolongs the time required for supervision[178].

10.8.3.1 Multiple buprenorphine doses

Because of the long half-life of buprenorphine, many clients who are stabilised on buprenorphine can be maintained on alternate days, some even on third-daily dosing, without experiencing features of intoxication or withdrawal[179].

These are referred to as 'double dosing' or 'triple dosing', and, when prescribed, should be recorded on the written instruction as '2D' or '3D' with a cross or line in the following day/s when the client doesn't attend the pharmacy. The maximum dose administered on one day should not exceed 32 mg[179].

10.8.3.2 Double dosing

Double dosing involves attending the pharmacy for dosing on alternate days – that is, a dose every 48 hours – or attending four times a week – with 3 x 48-hour doses and 1 x 24-hour dose each week. In the latter, for example, dosing would occur on Monday, Tuesday, Thursday and Saturday.

The advantage of the latter approach is that the client attends regularly each week, reducing the risk of attendance errors on the client's part and dosing errors by the pharmacist[179].

10.8.3.3 Triple dosing

Some clients may tolerate triple dosing with buprenorphine, reducing the inconvenience of treatment further. This regime should be attempted once a 2-week trial on double dosing has been successful.

The recommended regime for triple dosing is:

- 3-day dose = 3 times the normal 24-hour dose if the 24-hour buprenorphine dose is ‹12 mg
- 3-day dose = 32 mg when the 24-hour buprenorphine dose is ›12 mg[179]. *(Refer to Sections 6.5.3, 6.5.4 and 6.5.5 for more information)*

10.9 Take-away doses

Supervised dosing is an essential component of methadone and buprenorphine treatment and, in general, doses should be consumed under direct supervision. However, there are circumstances where the prescriber may appropriately authorise either a one-off or regular take-away doses.

Take-away doses can only be authorised by the prescriber, but should be discussed with the clinicians and pharmacists with whom the client has more regular contact. It is acceptable practice for any opioid treatment program clinician to notify the client's pharmacist of the authorised take-away doses.

When regular take-away doses are provided, the prescriber must specify the days of the week on which the client is authorised to receive take-away doses on the current written instruction *(see Section 6.5.21)*. The take-away doses must be given to the client on the day before the scheduled days of absence from the usual dispensing location.[180]

178 Drugs of Dependence Unit 2012
179 Lintzeris et al 2006
180 Mental Health and Drug and Alcohol Office 2006

At that time, the client is to be informed that methadone and buprenorphine are for oral and sublingual consumption respectively only and advised of the dangers of misuse, the hazards of using methadone and buprenorphine in combination with other drugs, and the toxic potential if taken by children or a person not tolerant of opioids[181].

To avoid risk of consumption by children or other unauthorised people, the client should be advised that take-away doses must be stored in a place that is not easily accessible by people other than themselves[182]. It is recommended that take-away doses be stored in a locked box or secure lockable cupboard or safe. Take-away doses do not need to be refrigerated.

Clients are responsible for the care and proper consumption of each take-away dose once they have taken possession of it[183].

In the event a client reports their take-away doses have been lost, stolen or damaged, they should not be replaced without the prescriber's authorisation.

10.9.1 Floating take-away dose

Clients who are working or studying may have difficulty determining the best days during the week for their take-away dose because of the nature of these activities.

Provided the prescriber is satisfied the client meets all requirements for stability and the pharmacist agrees, the client can be authorised to have a 'floating take-away dose'. This enables the pharmacist and the client to determine which day is best suited for the take-away dose on a weekly basis according to work or study commitments.

For example, for those clients on 3 take-away doses per week this can be recorded on the written instruction form as 'take-away doses for Saturday and Sunday and one extra for the week'.

Floating take-away doses should be discussed with the pharmacist to make sure they agree with the arrangement. If the pharmacist finds the arrangement unsatisfactory, the prescriber should be notified.

10.9.2 Preparing and labelling take-away doses

10.9.2.1 Preparation of methadone take-away doses

Each take-away dose of methadone syrup or liquid must be packaged in separate bottles and labelled to reflect the daily dose on the written instruction.

Methadone take-away doses should be diluted and supplied in clean 200 ml amber bottles (glass or plastic) fitted with a child-resistant closure. Each individual take-away dose must be labelled.

Dilution of methadone to 200 ml is a strategy to reduce the likelihood of injection and to deter small children from consuming sufficient drug to cause overdose[181]. The diluent recommended is purified water. The use of fruit juice or cordial is no longer recommended.

Prepared take-away doses should be packed in clean, new bottles on each occasion. It is not acceptable to recycle used bottles because of the risks associated with microbial contamination[184].

181 Mental Health and Drug and Alcohol Office 2006
182 Drugs of Dependence Advisory Committee 2006
183 Mental Health and Drug and Alcohol Office 2006, Drugs of Dependence Advisory Committee 2006
184 Pharmaceutical Services Branch 2004

Methadone take-away doses should be packaged as one daily dose per bottle and be labelled with the:

- name, strength and quantity of the drug
- client's name
- date on which the take-away dose was dispensed
- adequate directions, including the date on which the take-away dose is to be taken
- the 'Keep out of reach of children' warning in red font on a white background
- name, address and telephone number of the pharmacy or dosing site
- dispenser's initials
- medication expiry date.

The appropriate legislated mandatory driving hazard warning label (ancillary label 1) **must** be affixed to the container[185].

When labelling methadone take-away doses, they should be labelled in milligrams unless you have been notified that the client is undergoing blind dose reductions.

It is advisable to use your prescription dispensing software (for example WiniFRED) to dispense take-away doses, as it will give a detailed label and keep an accurate record of the doses dispensed.

For example:

Methadone Liquid 5 mg/ml (60 mg/12 ml, diluted) 60 mg take-away dose for Tuesday 14.02.12 Mr John Citizen 13.02.12 Expiry date: June 2012 IC KEEP OUT OF REACH OF CHILDREN SMITHTOWN PHARMACY 22 Browns Rd SMITHTOWN 4123 PH: 1234 5678	Also attach ancillary label #1: 'This medication may cause drowsiness and may increase the effects of alcohol. If affected, do not drive a motor vehicle or operate machinery.'

10.9.2.2 Preparation of buprenorphine take-away doses

Buprenorphine/naloxone take-away doses should be supplied in the original blister packs or sealed pouches. Daily doses of buprenorphine/naloxone do **not** need to be **individually** packaged and labelled. Each strength may be dispensed in its own envelope or box and labelled to reflect the daily dose on the written instruction.

Buprenorphine/naloxone films of the same strength should be supplied in the original sealed pouch within an envelope or box.

Buprenorphine sublingual tablets of the same strength should be supplied in the blister packs within an envelope or box.

Buprenorphine/naloxone take-away doses should be labelled with the:

- name, strength and quantity of the drug
- client's name
- date on which the take-away dose was dispensed
- adequate daily dose directions (including the date range within which the take-away doses are to be taken, as per the written instruction.)
- The 'Keep out of reach of children' warning in red font on a white background
- name, address and telephone number of the pharmacy or dosing site
- dispenser's initials
- medication expiry date.

185 Queensland Government 1996, Pharmaceutical Services Branch 2004

The appropriate legislated mandatory driving hazard warning label (ancillary label 1) **must** be affixed to the container[186].

As the medication should be dispensed in original packaging, blind reductions of buprenorphine are not possible. Therefore, take-away doses should be labelled in milligrams. It is advisable to use your prescription dispensing software (for example WiniFRED) to dispense take-away doses as it will provide a detailed label and keep an accurate record of the doses dispensed.

For example: A client on a daily dose of Suboxone Film 18 mg who receives 31 take-away doses at a time should get two boxes or envelopes of films labelled as follows:

Suboxone Sublingual Film 2 mg/0.5 mg (qty 31 films) Take ONE film daily from 01/03/2012 to 31/03/2012, inclusive. (To be taken in conjunction with Suboxone 8 mg/2 mg films to make up a total daily dose of 18 mg.) Mr John Citizen 13.02.12 Expiry date: June 2012 IC KEEP OUT OF REACH OF CHILDREN SMITHTOWN PHARMACY 22 Browns Rd SMITHTOWN 4123 PH: 1234 5678	Also attach ancillary label #1: 'This medication may cause drowsiness and may increase the effects of alcohol. If affected, do not drive a motor vehicle or operate machinery.'

Suboxone Sublingual Film 8 mg/0.5 mg (qty 62 films) Take TWO films daily from 01/02/2012 to 31/02/2012, inclusive. (To be taken in conjunction with Suboxone 2 mg/0.5 mg films to make up a total daily dose of 18 mg) Mr John Citizen 13.02.12 Expiry date: June 2012 IC KEEP OUT OF REACH OF CHILDREN SMITHTOWN PHARMACY 22 Browns Rd SMITHTOWN 4123 PH: 1234 5678	Also attach a ancillary label #1: 'This medication may cause drowsiness and may increase the effects of alcohol. If affected, do not drive a motor vehicle or operate machinery.'

It is advisable to count out the take-away doses in front of the client on pick-up so that both parties are satisfied that the correct number of tablets or films have been dispensed for the given take-away period.

10.10 Storage of methadone and buprenorphine

Methadone and buprenorphine are Schedule 8 drugs and must be stored in a Controlled Drugs safe as specified by the *Health (Drugs and Poisons) Regulation 1996*[187].

Ensure that methadone and buprenorphine products are never accessible to clients except at the time of dosing, and even then they should remain under the strict supervision of the pharmacist. After preparation of a dose, any prepared doses or take-away doses should be returned to the safe immediately[188].

186 Queensland Government 1996, Pharmaceutical Services Branch 2004
187 Queensland Government 1996
188 Drugs of Dependence Advisory Committee 2006

10.11 Written instructions

Written instructions must not be given to clients under any circumstances.

A specialised written instruction form that assists with monitoring the use of methadone and buprenorphine has been designed for use in the Queensland Opioid Treatment Program.

It should be noted the date of the written instruction cannot be later than the date of the first dose administered or supplied. The written instruction must include the name and address of the dosing pharmacy and **is not transferrable between pharmacies**.

If a client asks for their written instruction to be sent to another pharmacy, always direct the client back to their prescriber, as a new written instruction needs to be arranged for the new pharmacy.

In the interests of good clinical care, prescribers can verbally authorise the supply of methadone or buprenorphine, provided that within 24 hours of giving the verbal order, the prescriber ensures a copy of the written instruction is faxed to the dispenser. Within seven days of giving the verbal order and faxed copy of the written instruction, the prescriber must send the original written instruction, by post or by hand, to the dispenser. If a client presents and there is no written instruction for dosing, the pharmacist must ring the clinic or prescriber to confirm the order, and cannot administer or supply a dose until they have received a copy of the written instruction.

The left side of the written instruction is for the prescriber's instructions. The pharmacist shall not make any changes, additions or deletions to this information under any circumstances.

Notes can be made by the pharmacist on the written instruction in the 'Dispenser Notes' box on the bottom right corner. Each day's regular supervised dose (R) should be recorded and initialled legibly by the dosing pharmacist on the right side of the written instruction as it is administered or supplied to the client.

Methadone doses should be recorded in milligrams. The pharmacist refers to the 'Dose Type Codes' (bottom left side of the written instruction) to record the daily dose types. Other dose type codes – for example, take-away dose (T), not picked up (NP), dose withheld (DW), double dose/two-day dose (2D) – should be recorded as described on the written instruction.

The prescriber may alter dosing arrangements during the month, so it is essential the most current written instruction is referred to when dosing clients. Any outdated written instructions should be clearly marked. At the end of each month, the top (white) copy of the written instruction/s must be forwarded to the Drugs of Dependence Unit. The bottom (green) copy is kept at the pharmacy.

Queensland Health uses a computer-based system (ATODS-IS vII) when creating written instructions. One printed copy of this printed with prescriber signature is sent to the pharmacist. At the end of the month, the original completed Queensland Health written instruction is to be forwarded to the Drugs of Dependency Unit and a photocopy or scan of the completed document kept for the pharmacy record. There is no minimum time specified for keeping these records, but it is recommended that they be retained for two years[189].

Methadone syrup, Biodone solution, Subutex tablets and Suboxone tablets and film may only be dispensed from a written instruction. A regular PBS prescription is not valid, even with the changes to interstate prescribing of controlled drugs.

There can be circumstances where interstate clients transfer temporarily to a Queensland pharmacy, for a maximum of 4 weeks. The interstate prescriber must first apply to the Drugs of Dependence Unit for a temporary interstate transfer and will subsequently be sent a Queensland Opioid Treatment Program written instruction form that is to be completed and forwarded to the dosing point.

189 Queensland Government 1996

10.12 Record maintenance

All records relating to opioid treatment program clients must be kept up to date and accurate. Doing so will help with the frequent enquiries made by prescribers, case managers and clients regarding take-away doses, missed doses, transfers, hospitalisation and other issues[190].

Individual client records should be kept separately, for example in a folder with clear document holders or dividers. The current written instruction and a photograph of each client should be readily accessible at the front of each client's record[190]. *(Refer to Appendix 18 for more information.)*

10.13 Controlled drugs record

The *Health (Drugs and Poisons) Regulation 1996* requires the pharmacist who makes a transaction in a controlled drug to record the transaction on the same day in a record book known as the *Controlled Drugs Book*.

Written instructions issued for people on the opioid treatment program have provision for the details of daily administration or supply to be included. This is considered an adequate record on the day-to-day use of methadone and buprenorphine.

On completion of the written instruction, the total amount dispensed should be entered into the *Controlled Drugs Book*[191].

10.14 Confidentiality

The Queensland Opioid Treatment Program advocates a strict policy of confidentiality for clients on the program. Pharmacists may have to deal with difficult scenarios, for example clients purchasing needles and syringes. In the interest of harm reduction, it is not considered necessary for pharmacists to report such behaviour. However, the prescriber or clinic should be notified if there are any concerns regarding poly-drug use, diversion of doses or intoxication with any substance.

The prescriber or clinic should also be notified if a client presents with a medical prescription for opioids, sedatives or other psychoactive drugs[192].

10.15 Intoxication

Intoxication results from excessive use of one drug – including alcohol – or a combination of drugs.

Clients should always be assessed by the dosing pharmacist before a dose of methadone or buprenorphine dose is administered[193]. This assessment should quickly ensure the client is not showing evidence of intoxication from opioids or other drugs.

Common signs of intoxication include:

- slurred speech
- unsteady gait
- drowsiness and nodding off
- pupil constriction
- shallow breathing
- smell of alcohol[194].

Deaths due to methadone alone are rare. Deaths involving methadone almost always involve other central nervous system depressant drugs such as benzodiazepines, alcohol, antidepressants and antipsychotics.

190 Pharmaceutical Services Branch 2004, Drug of Dependence Advisory Committee 2006
191 Queensland Government 1996
192 *Hospital and Health Boards Act (2011)*
193 Drugs of Dependence Advisory Committee 2006, Henry-Edwards et al 2003
194 Henry-Edwards et al 2003

The risk of lethal overdose on buprenorphine in an opioid-tolerant individual is less than that associated with the use of other medications, such as methadone. This is due to the ceiling dose-response effects of buprenorphine.

However, while overdose on buprenorphine is relatively uncommon, there is greater risk when it is used in combination with other sedative drugs, such as alcohol, benzodiazepines, antidepressants and antipsychotics. Several such deaths have been reported[195].

Clients who appear to be intoxicated with depressant drugs should not be given their dose, nor given a take-away dose at that time[196]. If you suspect a client is intoxicated, contact the prescriber for instructions[197]. If you are unable to contact the prescriber, the client should be referred to the nearest hospital emergency department.

10.16 Diversion

Diversion refers to methadone or buprenorphine doses being used other than as intended, for example being removed from the dosing point. Some clients may spit out supervised doses (or use take-away doses) to either inject or sell. If you suspect a client of diverting his or her dose, the prescriber or case manager should be notified as soon as possible.[198]

10.17 Administration of incorrect methadone or buprenorphine dose

To minimise dosing mishaps, you must follow the procedures outlined in Sections 7.9 and 10.8.

If the client is given an incorrect dose and is still at the dosing point, the client should be informed and asked to wait while the prescriber is notified. If the client has left the dosing point before the mistake is realised, the pharmacist should try to contact the client as well as informing the prescriber of the situation.

The client should be reviewed by the prescriber before receiving their next dose of methadone or buprenorphine[199].

10.18 Vomited doses

10.18.1 Vomiting after methadone dose

Clients may vomit shortly after having their methadone dose. This creates uncertainty about the amount of methadone that has been absorbed.

If vomiting occurs within 20–30 minutes of ingesting their dose, the prescriber should be contacted and advised of the incident. If vomiting occurs more than 20–30 minutes after ingestion, the dose is likely to have been absorbed[200].

10.18.2 Vomiting after buprenorphine dose

As buprenorphine is absorbed sublingually, there is no need for replacement of buprenorphine if a client vomits after dosing. However, the prescriber should be notified of the incident.[201]

195 Lintzeris et al 2006
196 Henry-Edwards et al 2003, Lintzeris et al 2006, and Drug of Dependence Advisory Committee 2006
197 Drug of Dependence Advisory Committee 2006, Pharmaceutical Services Branch 2004
198 Drugs of Dependence Advisory Committee 2006
199 Henry-Edwards et al 2003, Lintzeris et al 2006
200 Drugs of Dependence Advisory Committee 2006, Mental Health and Drug and Alcohol Office 2006
201 Drug of Dependence Advisory Committee 2006

10.19 Missed doses

When clients miss picking up their dose on any day, the prescriber should be notified of this by the pharmacist. The prescriber then must decide whether the client needs to be reviewed before recommencing dosing. Where there is reason for concern, the prescriber may direct the pharmacist to withhold the dose.

If a client has not collected their dose for 3 consecutive days, the dose should be withheld until the prescriber reviews the client.

The prescriber may decide to decrease the client's recommencing dose, as their opioid tolerance may be reduced[202].

10.20 Hospitalisation

Never dose a client on their report of the last dose alone. All doses must be confirmed with the prescriber, clinic or dosing pharmacy.

In general, a client on an opioid treatment program should continue methadone or buprenorphine treatment in hospital. When such clients are admitted to hospital, the hospital medical officer can take over prescribing the client's methadone or buprenorphine.

When a client on opioid treatment is admitted, the hospital pharmacist or, preferably, the medical officer should:

- verify the client's identity
- contact the Drugs of Dependence Unit (07 3328 9890) to identify the prescriber or clinic. Alternatively, the client may identify the prescriber or clinic and pharmacy
- contact the client's prescriber or clinic to confirm:
  - the current dose of methadone or buprenorphine
  - the date and time of the last dose
  - whether the client has been given any take-away doses.

Most stable clients taking methadone or buprenorphine will not exhibit withdrawal symptoms and signs until more than 24 hours after the last dose was administered. If contact cannot be made with the client's prescriber or clinic or the Drugs of Dependence Unit, an addiction specialist should be consulted for advice on dosing.

Due to the long half-life of methadone and buprenorphine, it is possible to delay or withhold the dose until it can be confirmed without the client experiencing any severe side effects.

Clients may be prescribed take-away doses for the days they are in hospital. In such cases, clients should be requested to hand the take-away doses to the ward staff and have their doses dispensed through the hospital pharmacy to allow closer monitoring of their clinical condition and certainty about the dose they are receiving as an inpatient.

If a client declines to hand over their take-away doses, they should not be administered methadone or buprenorphine, and the client's clinical condition should be monitored for intoxication or withdrawal. This then should be treated appropriately.

An addiction specialist should be consulted if there are concerns about the client's clinical condition. In the circumstance of unexpected hospitalisation where the client is admitted without any take-away doses that may have already been supplied, the admitting team should consult the prescriber or clinic and then dose the client following a team decision.

202 Henry-Edwards et al 2003, Lintzeris et al 2006

The dosing information must be established to avoid administering an overdose. Use the following steps:

- Provided there is no medical contraindication, dose methadone once a day in liquid form or buprenorphine (sublingually), with the usual frequency for that client (for example daily, alternate days, every third day) according to the dosage regime of the client's authorised prescriber.
- Advise the client's prescriber of their approximate length of stay in hospital to prevent the client being removed from the program through non-attendance.
- When a client is discharged from hospital, inform the prescriber or clinic in advance to ensure appropriate arrangements are made for the client to continue the opioid treatment program without interruption.

There is a risk that clients who are dosed prior to discharge from hospital may present to the pharmacy and be dosed twice in one day[203]. *(Also refer to section 7.11 – Managing Inpatients.)*

It is essential to contact the prescriber before re-commencing dosing to confirm that the client has been discharged. Hospitals should not normally dispense any take-away doses without first consulting the authorised prescriber or clinic.

10.21 Payment of dispensing fee

The Commonwealth Government funds methadone and buprenorphine to treat opioid-dependent persons under Section 100 of the *Pharmaceutical Benefits Scheme*.

Pharmacists participating in the opioid treatment program are required to supervise the consumption of this medication on a daily basis and also attend to substantial paperwork associated with this dispensing. For this reason, most pharmacies charge a dispensing fee. Each pharmacy sets its own fee according to the costs involved[204].

Opioid treatment program clients may demonstrate varying levels of stability in their work, accommodation and lifestyle. Some clients are consistent in paying this fee, while others can have problems maintaining regular payments. When accepting a client for dosing at your pharmacy, it is important to explain clearly what is expected and the consequences of non-payment[205].

Some pharmacies allow several days' credit; others offer no credit. If credit is allowed, strict limits should be enforced – for example, a maximum of 2 weeks dosing with no payment, then a no-pay, no-dose policy. It may be helpful to use a written agreement *(see Appendix 16)* that is negotiated when the client first attends the pharmacy to manage this and other issues[204].

To avoid any disagreement regarding payment, it is strongly recommended that accurate payment records are maintained and that clients are issued receipts.

Payment of a dispensing fee is between the client and the dosing pharmacy. Other than avoiding transferring a client to another pharmacy when dispensing fees are outstanding at the previous, prescribers or clinics do not become involved in issues regarding payment of dispensing fees[206].

10.22 Pharmacy opening hours

Some pharmacies close on weekends, public holidays and other times. It is important to clarify instructions with the prescriber before dosing on these days, as some clients may be unsuitable for extra take-away doses.

If a client has not presented for dosing prior to the pharmacy closing for the day, they must miss that day's dose. The prescriber or clinic should be informed in the event of any missed dose.

It is not appropriate for the dose to be taken out of the pharmacy to be given at another location, for example at the home of the client or pharmacist.

203 Mental Health and Drug and Alcohol Office 2006
204 Drug of Dependence Advisory Committee 2006
205 ACT Health 2009
206 Pharmaceutical Services Branch, 2004, ACT Health 2009

10.23 Client behaviour

Although many clients experience varying stages of stability during their time in treatment and this can affect their behaviour in the pharmacy, they are expected to be courteous and considerate of pharmacy staff and other customers at all times. Rude, aggressive or offensive behaviour and shoplifting should not be tolerated.

Pharmacists are not expected to place themselves, their staff or their pharmacy at risk at any time. If any client demonstrates inappropriate behaviour, the pharmacist should contact the prescriber or clinic.[207]

10.24 Written agreements

It may be helpful to implement a formal written agreement between the pharmacist and the client[208]. Some pharmacists use such agreements for every client when dosing commences, others may only use the agreement for clients who exhibit inappropriate behaviour[209]. *(See Appendix 16 for a sample agreement)*.

10.25 Additional drug use

It is not uncommon for opioid treatment program clients to use other drugs, often against medical advice.

10.26 Other medications

10.26.1 Prescribed medicines

Some clients require treatment with prescribed medications for physical or psychiatric conditions or other legitimate purposes. In these circumstances, it is appropriate for the dosing pharmacy to dispense the associated prescriptions.

However, some clients might also obtain prescriptions for opioids medications, sedatives or other psychoactive drugs by illegitimate means. The prescriber should be notified if a client presents with a prescription for these classes of drugs.

10.26.2 Over-the-counter medicines

Clients may need Pharmacy Only or Pharmacist Only products at certain times. Pharmacists should exercise the usual care in these circumstances. If there is any suspicion of inappropriate use, the prescriber or clinic should be notified. Products containing codeine should be avoided unless specifically authorised by the opioid treatment prescriber, as these may destabilise the client's opioid treatment[210].

10.26.3 Unsanctioned drug use

If you suspect any client is using unsanctioned drugs, the opioid treatment prescriber or clinic should be notified.

207 Mental Health and Drug and Alcohol Office 2006
208 ACT Health 2009
209 Drug of Dependence Advisory Committee 2006, Pharmaceutical Services Branch 2004
210 Henry-Edwards et al 2003

10.27 Treatment of opioid withdrawal

Clients can experience opioid withdrawal symptoms when they are stabilising on a new treatment program, reducing their dose or missing daily doses.

Signs and symptoms of opioid withdrawal include irritability, anxiety, restlessness, apprehension, muscular pains, abdominal pains, chills, nausea, diarrhoea, yawning, lacrimation, piloerection, sweating, sniffing, sneezing, rhinorrhoea, general weakness and insomnia[211].

Pharmacists may provide treatments such as paracetamol, ibuprofen, loperamide, hyoscine butylbromide, vitamin and mineral supplements as required. Sedating antihistamines – especially doxylamine and diphenhydramine – may be misused and should not be used without approval by the opioid treatment prescriber.

Other advice, such as sleep hygiene, smoking cessation and guidelines on low-risk alcohol intake, may also be provided by the dosing pharmacist.

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Section 11
Legal and operational issues

The *Health (Drugs and Poisons) Regulation 1996* (the Regulation) is the legal instrument underpinning the prescribing of methadone, buprenorphine and other controlled drugs of dependency in Queensland. Enquiries about the Regulation and its application can be directed to the Queensland Health Drugs of Dependence Unit.

11.1 Definition of a drug-dependent person

A drug-dependent person is defined by Part 1 Section 5 of the *Health Act 1937* as a person who demonstrates impaired control, or exhibits drug-seeking behaviour that suggests impaired control over the person's continued use of controlled or restricted drugs or poisons; and who, when the administration to the person of controlled or restricted drugs or poisons ceases, suffers or is likely to suffer mental or physical distress or disorder.

11.2 Section 120 – Reports

Section 120 of the Regulation requires all prescribers to notify the Chief Executive, Queensland Health, if they have prescribed a controlled drug for a period for more than two months to a person who is not drug-dependent. Further, if a prescriber reasonably suspects a person has been treated with a controlled drug by another prescriber for more than two months, and they intend to administer, dispense, prescribe or supply a controlled drug to that person, the prescriber should notify the Chief Executive, Queensland Health as soon as possible.

11.3 Section 122 – Approvals

Section 122 of the Regulation requires a prescriber to get treatment approval from the Drugs of Dependence Unit prior to administering, dispensing, prescribing or supplying a controlled drug to a person the prescriber reasonably believes could be drug dependent.

In the context of pain management, each situation should be assessed individually. Approval is generally not required for hospital inpatients or emergency treatments, such as the acute treatment of a myocardial infarction, or a broken limb pending hospital admission. However, an approval is required for outpatient treatment or for ongoing treatment of an injury with controlled drugs.

Where treatment is provided outside of business hours or prior to the prescriber seeking approval from the Drugs of Dependency Unit, the prescriber must provide a written report to the Chief Executive detailing the circumstances of the client's treatment as soon as possible.

The requirement to obtain an approval to treat a painful medical condition should not be seen as a reason to provide less than appropriate analgesia. Rather, it should be seen as a requirement to ensure any necessary medications are prescribed from a single source, with appropriate management and supervision, and that those medications are prescribed without compromising the duty of care to the client while minimising the risks of diversion of the medication.

11.4 The DDU enquiry service

If a prescriber is unfamiliar with a client or reasonably suspects a client could be drug dependent, the prescriber should ideally contact the Drugs of Dependence Unit (07 3328 9890) to establish the status of the client before prescribing. The Drugs of Dependence Unit enquiry service is available 24 hours a day, 7 days a week.

11.5 Section 25 – Suspension or cancellation of endorsement

If a prescriber treats a client with a controlled drug (Schedule 8) or with restricted drugs of dependence (Schedule 4) without the approval of the Chief Executive, the prescriber could face prosecution. Further, if this type of prescribing persists, section 25 of the Regulation permits the Chief Executive to revoke a prescriber's right to prescribe controlled or restricted drugs.

11.6 Requirements of the Regulation on a person

- Section 121 of the Regulation requires a person to inform a prescriber of all controlled or restricted drugs of dependence received from other prescribers in the preceding two months.
- A person must use their correct name and address.

The compliance of opioid treatment prescribers with the Regulation is monitored by District Environmental Health Officers and Officers of the Queensland Health Drugs of Dependence Unit.

11.7 Approval to prescribe for opioid dependent people

In Queensland, any prescriber who wants to treat an opioid dependent person with methadone or buprenorphine must be approved by the Chief Executive of Queensland Health or their delegate. Authorised prescribers are usually:

- attached to an opioid treatment clinic
- general practitioners
- psychiatrists
- hospital superintendents and, in country areas, other full-time hospital medical staff.

To be an approved Queensland opioid treatment provider, the prescriber must successfully complete the Queensland Opioid Treatment Program Prescriber's Accreditation Course to demonstrate their clinical competence in opioid treatment.

The completion of the course involves a formal training program, achieving a satisfactory score on a knowledge test, and completing a supervised clinical attachment within two months of completing the training.

Provision of the formal training, supervision of the test and coordination of the clinical attachment is facilitated by the Queensland Health Drugs of Dependence Unit. When a prescriber is approved to provide opioid pharmacotherapies for the treatment of drug-dependent people, the Chief Executive or their delegate issues an approval to this effect. This approval has individual conditions and is valid for a 12-month period.

The Drugs of Dependence Unit actively encourages prescribers to become more involved with dependence issues. For more information on the training course, contact the Drugs of Dependence Unit on 07 3328 9890.

11.8 Section 213 – Approval to prescribe restricted drugs

Section 213 of the Regulation requires prescribers to obtain approval to treat clients on an opioid treatment program with certain restricted drugs of dependency (S4 medications). As with other approvals, the prescriber must contact the Drugs of Dependence Unit to obtain an approval to prescribe for drug-dependent people who are also dependent on benzodiazepines. These approvals are based on protocols treating benzodiazepine dependence and are valid for 12 months.

11.9 Confidentiality

The Queensland Opioid Treatment Program advocates a strict policy of confidentiality for program clients. It is important to make clients aware their cases will be discussed at case conferences and team meetings within the clinic and that their information will not be passed on to another party unless the client has given permission.

The exception to this is if the holder of the information is legally compelled to provide information. For example, the Department of Child Safety has the power to request information and medical records. As such, medical practitioners and registered nurses are legally required to report suspected abuse or neglect of children to the Department of Child Safety.

It is also important clients are aware other agencies may subpoena medical records at any time (*Health Services Act*).

11.10 Admission and discharge procedures

(see Appendices 1 and 2)

When clients are admitted to the program, the Queensland Opioid Treatment Program – Admission Form must be completed. This form is required for all new clients, re-admissions, changes of drug name (for clients being maintained on the new drug) and transfers from another prescriber.

This form must be dated on the day the client is first assessed, and the date of the first dose must also be documented on the form. The date of the first dose can be after the date of the first assessment. This form – including a photograph of the client – is then forwarded to the Drugs of Dependence Unit (DDU) and a copy is kept for the client's record.

On completion of treatment or transfer to another prescriber, the prescriber must complete a Queensland Opioid Treatment Program – Discharge Form. However, this form is not required if a client has merely changed their treatment drug.

The discharge form should then be either faxed or posted to the Drugs of Dependence Unit as soon as possible after the client's last dose. This form must be completed for any client who has not received a dose for 14 days.

11.10.1 Queensland Health system for admissions and discharges

Queensland Health ATODS–IS vII – the client case-management software used by Queensland Health – has business rules on admission and discharge processes. These business rules are outlined in Section 10 of the ATODS–IS vII, *User Manual 2011*.

11.11 Written instructions

(see Appendix 3)

Written instructions must not be given to clients under any circumstances.

A special written instruction form that helps with monitoring the use of methadone and buprenorphine has been designed for the Queensland Opioid Treatment Program.

The date of the written instruction cannot be later than the date of the first dose administered or supplied. The written instruction must also include the name and address of the dosing pharmacy and **is not transferrable between pharmacies**. If a client asks for their written instruction to be sent to another pharmacy, always direct the client back to their prescriber, as a new written instruction needs to be arranged for the new pharmacy.

The written instruction can be faxed to the pharmacy or dosing location prior to the original being mailed. If a client presents and there is no written instruction for dosing, the pharmacist must ring the clinic or prescriber to confirm the order, and cannot administer or supply a dose until a copy of the written instruction has been received.

The left side of the written instruction is for the prescriber's instructions and the pharmacist shall not make any changes, additions or deletions to this information under any circumstances. The pharmacist can, however, make notes on the written instruction in the 'Dispenser Notes' box on the bottom right corner.

When it is administered or supplied to the client, each day's regular supervised dose (R) should be recorded and initialled legibly by the dosing pharmacist on the right side of the written instruction. Methadone doses should be recorded in milligrams and millilitres.

Pharmacists shall refer to the 'Dose Type Codes' on the bottom left side of the written instruction to record the daily dose types. Other dose type codes – for example, take-away dose (T), not picked up (NP), dose withheld (DW), double dose/two-day dose (2D) – should be recorded as described on the written instruction.

Dosing arrangements might be altered by the prescriber during the month, so it is essential the most current written instruction is referred to when dosing clients. Any outdated written instructions must be clearly marked.

At the end of each month, the top (white) copy of the written instruction must be forwarded to the Drugs of Dependence Unit, while the bottom (green) copy is kept at the pharmacy.

11.11.1 Queensland Health system for written instructions

Queensland Health uses the computer-based system ATODS–IS vII when creating written instructions. One printed copy of this printed written instruction (with prescriber signature) is sent to the pharmacist.

At the end of the month, the original, completed Queensland Health Written Instruction must be forwarded to the Drugs of Dependency Unit and a photocopy or scan of the completed document kept for the pharmacy record. There is no minimum time specified for keeping these records, however, it is recommended that they be retained for two years[212].

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Section 12
Appendices

Appendix 1

Guidelines for completing of the Queensland Opioid Treatment Program admission form

Amendment to existing admission

For change from detoxification to maintenance, check 'Change of treatment type' box. For change from buprenorphine to methadone or vice versa, check 'Change of treatment drug' box.

Patient details

Name, address (includes PO Box mailing addresses), date of birth, any aliases, height (cm), weight (kg).

Distinguishing marks (scars, features) or tattoos

This should include descriptions such as size, content of tattoos, colour/s, and physical location. Provide specific details that could readily identify the client from the description provided. Preferably provide a detailed description of tattoos, scars and so forth that may help differentiate between two clients with the same name. This information can be very helpful for Drugs of Dependence Unit when dealing with phone enquiries from general practitioners.

Indigenous status

Check the box by which the client identifies him or herself.

South Sea Islander status

Check appropriate box.

Drug use and treatment history

This box gives some indication of the client's history.

Age of first use of narcotics

Self-reported age at which the client first used opioid/opiate drugs.

Age of first dependence on narcotics

Self-reported age at which the client first considered themselves to be dependent on opioids.

Age at first admission on opioid treatment

Self-reported age at which the client was first admitted to an authorised opioid substitution treatment program (in any state or overseas).

Last discharge from opioid treatment

Date on which the client was last discharged from an authorised opioid substitution treatment program. Information is available from the Drugs of Dependence Unit if the patient was last treated in Queensland or an approximate date is satisfactory if the patient cannot remember.

Australian state of discharge

Australian state or territory where the client was last admitted to an opioid substitution program.

Primary drug of dependence

The main drug, as assessed by the clinician, that has led a person to seek treatment from the service. When completing an admission form for a transfer, the primary drug of dependence should be recorded as the drug that led them to seek treatment initially and not the medication (methadone, buprenorphine or buprenorphine/naloxone) they are presently taking.

Mode of use for primary drug of dependence

The client's usual method of administering the primary drug of dependence, as assessed by the clinician.

Other drugs of use

A drug apart from the primary drug of dependence that the clinician assesses as being of concern. This section should include all other drugs that the patient uses, whether on a regular or spasmodic basis.

Drug dependence status

Non-therapeutic dependence refers to clients whose dependence results from use of mainly illicit or 'street' drugs (e.g. heroin) or illicit, black-market therapeutic drugs. Therapeutic dependence refers to clients that have been initiated on analgesia by a medical practitioner for treatment of a medical condition that was not primarily drug dependence. Dependence might have then ensued from long-term treatment with therapeutic narcotic drugs. The underlying condition should be confirmed by supporting medical evidence.

Main opioid treatment

Maintenance refers to those clients who plan to remain on a program for a length of time >28 days.

Withdrawal refers to a planned withdrawal program of 5 to 28 days (for example, prior to entry into a residential rehabilitation centre).

Opioid treatment drug

Choose Subutex®, Suboxone® or methadone syrup/liquid.

Initial dose

Refers to the starting dose given on day 1.

Maximum daily dose

The maximum daily dose for both Subutex® and Suboxone® is 32 mg. The maximum daily dose for methadone is 150 mg.

Comments

This space can be used for any information you feel could be relevant. This could include information about where a patient has transferred from or who their previous prescriber was. The prescriber's name and address should be completed and the form should be signed and dated by the prescriber before being faxed immediately to the Drugs of Dependence Unit.

Photograph

A photograph of the patient should be attached to the original admission form and posted to the Drugs of Dependence Unit.

Queensland Government

QUEENSLAND OPIOID TREATMENT PROGRAM (QOTP) - ADMISSION

Drugs of Dependence Unit
Locked Bag 21
FORTITUDE VALLEY BC Q 4006

Phone: (07) 3328 9815
Fax: (07) 3328 9435
Email: ddu@health.qld.gov.au

Forward original to Drugs of Dependence Unit

Retain copy for doctor/clinic records

This form to be completed on commencement of Opioid Treatment and faxed immediately to the Drugs of Dependence Unit, or phone to advise if you don't have a fax.
Please ensure all details are completed.

Please forward a photo with this form

☐ Amendment to existing admission? Reason: Change of ☐ Treatment type; ☐ Treatment drug

PATIENT DETAILS

Surname: _____ Given Name(s): _____

Alias: _____ Date of Birth: ____/____/____ Sex: ☐ M ☐ F

Address: : _____ Postcode: _____

Height(cm): _____ Weight(kg): _____ Distinguishing mark(s) tattoo(s): _____

_____

Indigenous Status	South Sea Islander Status	Drug use & treatment history
☐ Neither Aboriginal nor Torres Strait Islander origin ☐ Aboriginal but not Torres Strait Islander origin ☐ Torres Strait Islander but not Aboriginal origin ☐ Aboriginal and Torres Strait Islander ☐ Not Stated	☐ No ☐ Yes ☐ Not stated/unknown	Age of first use of narcotics: _____ Age of first dependence on narcotics: _____ Age of first admission on Opioid Treatment: _____ Last discharge from Opioid Treatment: ____/____/____ Australian state of last discharge _____

Primary Drug of Dependence (One selection only)	Mode of Use for Primary Drug of Dependence (one selection only)		Other drugs of use (up to 5 selections)	
☐ Heroin 1202 ☐ Morphine 1102 ☐ Pethidine 1306 ☐ Methadone (syrup/liq.) 1305 ☐ Physeptone 1307 ☐ Buprenorphine 1201 ☐ Oxycodone 1203 ☐ Other Narcotic (Specify) _____	☐ Ingests ☐ Smokes ☑ Injects - intravenous ☐ Injects - intramuscular ☐ Injects - subcutaneous ☐ Injects – other ☐ Sniffs (powder) ☐ Inhales (vapour) ☐ Sublingual	☐ Rectal ☐ Dermal ☐ Other (please specify) _____	☐ Nil ☐ Heroin 1202 ☐ Morphine 1102 ☐ Pethidine 1306 ☐ Methadone (syrup/liq.) 1305 ☐ Physeptone 1307 ☐ Buprenorphine 1201 ☐ Oxycodone 1203	☐ Amphetamines 3100 (incl methylamphetamine) ☐ Benzodiazepines 2400 ☐ Alcohol 2101 ☐ Cannabis 3201 ☐ Nicotine 3906 ☐ Anti-depressants 5000 ☐ Other/s (Specify) _____

Drug dependence status: ☐ Therapeutic ☐ Non-therapeutic

Main opioid treatment: ☐ Maintenance ☐ Withdrawal

Opioid treatment drug: ☐ Suboxone - Buprenorphine/Naloxone ☐ Subutex - Buprenorphine ☐ Methadone syrup/liquid

Date of first dose: ____/____/____ Initial Dose (mg): _____ Maximum Daily Dose (mg): _____

* Please advise Drugs of Dependence Unit, Tel: (07) 3328 9815 of daily doses exceeding 32 mg buprenorphine or 150mg methadone.

Comments: _____

_____

_____

Doctor/Clinic Name: _____

Address: _____

_____ Postcode: _____

Doctor's signature: _____ Date: ____/____/____

OFFICE USE ONLY

CLINIC NUMBER:	PATIENT RECORD NUMBER:	DATE RECEIVED:	ENTERED (DATE/STAFF)	CHECKED (DATE/STAFF)
COMMENTS: _____				

Appendix 2

Guidelines for completing the Opioid Treatment Program discharge form

Date of last dose

This should be confirmed with the patient's pharmacy, particularly if the patient is transferring to another prescriber, to ensure they are not double-dosed.

Opioid treatment drug

Choose Subutex®, Suboxone® or methadone syrup/liquid.

Patient details

Ensure all fields are completed with the same patient details as contained in the admission form.

Reason for cessation of opioid treatment program

Please choose the most relevant option.

Comments

Use this space to make any comments you feel would be helpful for tracking patients, for example the name of the prescriber/clinic that a patient may be transferring to.

The prescribing doctor's name and address should be completed and the form should be signed and dated by the prescribing doctor before being faxed and posted to the Drugs of Dependence Unit.

QUEENSLAND OPIOID TREATMENT PROGRAM (QOTP) - DISCHARGE

Queensland Government

Drugs of Dependence Unit
Locked Bag 21
FORTITUDE VALLEY BC Q 4006

Phone: (07) 3328 9815
Fax: (07) 3328 9435
Email: ddu@health.qld.gov.au

Forward original to Drugs of Dependence Unit

Retain copy for doctor/clinic records

This form to be completed on cessation of Opioid Treatment and faxed immediately to the Drugs of Dependence Unit, or phone to advise if you don't have a fax.
Please ensure all details are completed.

Date of last dose: _____ / _____ / _____

Opioid treatment drug: ☐ Suboxone-Buprenorphine/Naloxone ☐ Subutex-Buprenorphine ☐ Methadone syrup/liquid

PATIENT DETAILS

Surname: _____ Given Name(s): _____

Address: : _____ Postcode: _____

Date of Birth: _____ / _____ / _____ Sex: ☐ M ☐ F

REASON FOR CESSATION OF OTP TREATMENT: (Indicate one answer only)

- ☐ Treatment completed
- ☐ Change in main treatment type
- ☐ Change in the delivery setting
- ☐ Change in the principal drug of concern
- ☐ Transferred to another service provider
- ☐ Ceased to participate against advice
- ☐ Ceased to participate without notice (failed to pick up)
- ☐ Ceased to participate involuntarily (non-compliance)
- ☐ Ceased to participate at expiation
- ☐ Ceased to participate by mutual agreement
- ☐ Drug court and/or sanctioned by court diversion service
- ☐ Imprisoned, other than drug court sanctioned
- ☐ Died
- ☐ Other
- ☐ Not stated/ inadequately described

Comments: _____

Doctor/Clinic Name: _____

Address: _____

_____ Postcode: _____

Doctor's signature: _____ Date: _____ / _____ / _____

OFFICE USE ONLY

CLINIC NUMBER:	PATIENT RECORD NUMBER:	DATE RECEIVED:	ENTERED (DATE/STAFF)	CHECKED (DATE/STAFF)
COMMENTS:				

Appendix 3

Guidelines for completing the Queensland Opioid Treatment Program Written Instruction forms

It is important the written instruction is written clearly to avoid mistakes in dosing.

Name of the drug

For buprenorphine, state either Subutex® or Suboxone® (tablets or film). For methadone, state either methadone syrup or biodone. The prescriber's name, address and prescriber number should be completed and the written instruction dated.

Patient details

The patient's name, address and date of birth should be fully completed.

For month and year of

The month and year that the written instruction is for.

For supply/administration at

Name and address of the pharmacy/clinic.

Dose

Buprenorphine (Subutex® or Suboxone® – tablets or film) doses should be recorded in milligrams (mg) and methadone should have both the milligrams and millilitres recorded (mg/ml).

Prescriber instructions

Should include instructions for dosing, including take-away doses and double or triple dosing – for example, 'Double-dose Mondays and Wednesdays, triple-dose Fridays'). If doses are supplied in the clinic setting, they should be recorded on the right-hand side of the written instruction and indicate the date, quantity, what type of dose it was (for example, regular supervised dose is recorded as 'R') and the signature of the supplier.

Queensland Opioid Treatment Program (QOTP) – Written Instruction

Queensland Government
Queensland Health

Name of Drug:.....

Doctor.....

Address.....

.....

Qld. Reg. No. ..... Date .....

Telephone No. ..... Fax No. .....

Patient Details:

(Surname)

(Given Names) (Date of Birth)

Address:

(Number) (Street)

(Suburb) (Postcode)

For month & year of:

For supply/administration at:

Address:

Dose:

Give.....mg (.....mls) on dates.....to.....inclusive

Give.....mg (.....mls) on dates.....to.....inclusive

Give.....mg (.....mls) on dates.....to.....inclusive

Give.....mg (.....mls) on dates.....to.....inclusive

Give.....mg (.....mls) on dates.....to.....inclusive

Total Quantity to be given on this instruction.....mg

Prescriber Instructions:

Doctor's Signature .....

Dose Type Codes			
METHADONE AND BUPRENORPHINE:		C	Cancelled (at request of prescriber)
R	Regular (Supervised dose)	P	Replacement Dose (Prescriber approved only)
T	Take Away dose		
NP	Not Picked Up	**BUPRENORPHINE ONLY:**	
S	Supplementary Dose (Top-up)	2D	Double Dose/ two day dose
DW	Dose Withheld (for clinical reasons)	3D	Triple dose/ three day dose

This written instruction must be forwarded to the Chief Executive in accordance with the Health (Drugs & Poisons) Regulation – 1996 within 14 days of completion of supply/administration.

Record of Supply/Administration

Please complete dose type column as indicated below. (e.g. if client picks up 2 doses on a Saturday, 1 being for Sunday, then T is marked on Sunday column).

	Methadone	**Subutex**			**Suboxone**			
Date	Quantity mg	0.4mg tablets	2mg tablets	8mg tablets	2mg	8mg	Dose type	Supplier's Signature
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								
17								
18								
19								
20								
21								
22								
23								
24								
25								
26								
27								
28								
29								
30								
31								
								Total

Dispenser Notes:

OFFICE USE ONLY

Version: Jan 2008

Date Received/Processing Number	Entered	Checked	Comments

Appendix 4

Assessment of acute intoxication

Class of drug	Intoxication	Overdose
Opioids e.g. methadone, heroin, morphine	Constriction of pupils, itching/ scratching, sedation/somnolence, lowered blood pressure, slowed pulse, hypoventilation	Loss of consciousness, respiratory depression, pinpoint pupils, hypotension, bradycardia, pulmonary oedema
Alcohol	Relaxation, disinhibition, impaired co-ordination, impaired judgment, decreased concentration, slurred speech, ataxia, vomiting	Disorientation/confusion, respiratory depression, loss of consciousness, loss of bladder control
Benzodiazepines: e.g. diazepam, oxazepam, flunitrazepam	Disinhibition, sedation, drooling, inco-ordination, slurred speech, lowered blood pressure, dizziness	Stupor/coma, ataxia, confusion, respiratory depression
Stimulants e.g. amphetamines, cocaine	Hyperactivity, restlessness, agitation, anxiety, great dilation of pupils, elevated blood pressure, increased pulse, raised temperature, sweating, tremor	Acute paranoid psychosis, panic attacks, seizures, cardiac arrhythmias, myocardial ischaemia, hypertensive crisis, stroke, hyperpyrexia, dehydration
Cannabis	Relaxation, decreased concentration, decreased psychomotor performance, impaired balance, conjunctival infection	Paranoid psychosis, confusion, agitation, anxiety/panic, hallucinations

Appendix 5

Interstate contact list

For patient information and opioid program patient transfers – as of March 2012

NEW SOUTH WALES – 02 9879 3214

Pharmaceutical Services
New South Wales Ministry of Health
PO Box 103
Gladesville NSW 1675

Non-program enquiries	Phone: 02 9879 5239
Opioid program transfers	Phone: 02 9879 3214
General advice (e.g. legislation, policies)	Phone: 02 9879 3214 Fax: 02 9859 5165

AUSTRALIAN CAPITAL TERRITORY – 02 6244 2191

Opiate Treatment Service
Alcohol and Other Drugs Program
Building 7
The Canberra Hospital
Palmer Street
Garran ACT 2605

General enquiries	Phone: 02 6244 2191 Fax: 02 6244 4622

VICTORIA – 1300 364 545

Drugs and Poisons Unit
Victorian Department of Health Services
PO Box 1670N
Melbourne VIC 3001

General enquiries	Phone: 1300 364 545 Fax: 1300 360 830
Opioid program transfers	Phone: 1800 888 236

TASMANIA – 03 6233 2064

Pharmaceutical Services Branch
Department of Community Health Services
GPO Box 125
Hobart TAS 7000

General enquiries	Phone: 03 6233 2064 Fax: 03 6233 3904
Opioid program transfers	Phone: 03 6230 7972

SOUTH AUSTRALIA – 1300 652 584

Drugs of Dependence Unit
South Australia Department of Health
PO Box 6
Rundle Mall
Adelaide SA 5000

General enquiries and opioid program transfers	Phone: 1300 652 584 Fax: 1300 658 447 E-mail: onlineservices@health.sa.gov.au

NORTHERN TERRITORY – 08 8922 7341

Chief Poisons Officer
Poisons Branch
Territory Health Services
PO Box 40596
Casaurina NT 0811

General enquiries and opioid program transfers	Phone: 08 8922 7341 Fax: 08 8922 7200

WESTERN AUSTRALIA – 08 9222 4424

Pharmaceutical Services
Health Department of Western Australia
PO Box 8172
Perth BC WA 6849

General enquiries	Phone: 08 9222 4424
Opioid program transfers	Phone: 08 9222 6812

Appendix 6

Contact numbers for Queensland

Drugs of Dependence Unit (DDU)

Locked Bag 21

Fortitude Valley BC Qld 4006

QOTP phone: 07 3328 9815

Enquiries: 07 3328 9890

QOTP admissions and discharges fax: 07 3328 9435

Enquiries fax: 07 3328 9821

E-mail: ddu@health.qld.gov.au

Enquiry service is available 7 days a week and 24 hours a day – enquiry service transfers to ADIS after hours (see below).

Alcohol and Drug Information Service (ADIS)

Phone: 07 3837 5989

Or free call: 1800 177 833

24 hours, 7 days a week from anywhere in Queensland

Hospital Alcohol and Drug Service (HADS)

Inpatient detoxification service for advice about/or referral to detoxification services

Royal Brisbane and Women's Hospital

PO Box 4029

Herston Qld 4006

Phone 24 hours, 7 days a week: 07 3646 8704

Fax: 07 3646 7772

Consultation liaison available 8.30am to 4.30pm, Monday to Friday

Phone: 07 3646 8710 or 07 3646 3581

Hepatitis B vaccination

General information – contact your local public health unit

Provision of vaccines – Queensland Health Immunisation Program

PO Box 2368

Fortitude Valley BC Qld 4006

Phone: 07 3328 9888

Facsimile: 07 3328 9720

Health Quality and Complaints Commission

GPO Box 3089

Brisbane Qld 4001

Street: Level 17, 53 Albert Street, Brisbane Qld 4000

Phone: 07 3120 5999

Free call outside Brisbane: 1800 077 308

E-mail: info@hqcc.qld.gov.au

Web: www.hqcc.qld.gov.au

Hepatitis Queensland

PO Box 3490

South Brisbane Qld 4101

Street: Suite 2, 12 Cordelia Street

South Brisbane Qld 4101

Phone: 07 3846 0020

Infoline: 1800 648 491

Fax: 07 3844 8065

Web: www.hepqld.asn.au

Queensland Pharmacotherapy Advocacy Mediation and Support Service (QPAMS)

Queensland Injectors Voice for Advocacy and Action (QuIVAA)

PO Box 2470 Fortitude Valley BC Qld 4006

Street: 1 Hamilton Place, Bowen Hills Qld 4006

Phone: 07 3620 8160

Or free call: 1800 175 889

Fax: 07 3854 1070

Web: www.quivaa.org

Appendix 7

Example of assessment of suitability for unsupervised medication doses in the treatment of opioid dependency

(based on the Royal Australasian College of Physicians – Australasian Chapter of Addiction Medicine, *Clinical Guidelines*).

The following checklist was developed by the Chapter of Addiction Medicine to help clinicians determine stability prior to allowing clients to have take-away doses. This was developed specifically for buprenorphine/naloxone take-away doses, but could also be used to determine stability for methadone take-away doses.

As with all medical records, documentation is important for prescribers to demonstrate their decision-making process. The decision-making process is based on individual cases rather than the strict application of guidelines.

Strong contraindications (recent behaviour in the past 4 to 8 weeks).

If any of these items present below mean that take-away doses should not be provided:

- recent diversion
- regular injecting drug use
- erratic/threatening behaviours
- irregular attendance for pick-up
- episodes for refused dosing
- risky substance use/presenting intoxicated
- recent attempts of self-harm
- recent overdose
- unstable accommodation/homelessness
- steady dose ‹4 weeks
- significant mental health problems
- significant physical health problems
- child risk/protection issues.

Indications for consideration of take-away doses

(at least 2 of the items below are required to support the provision of take-away doses)

- a stable dose ›4 weeks
- regular pick-up, good presentation
- stable accommodation
- employment/education commitments
- difficulty accessing clinic for example, money or transport reasons
- no injecting drug use or recent diversion or risky substance use.

To support the initiation or continuation of take-away doses, the above factors should be clearly documented in the client's notes each time the client is reviewed.

Appendix 8

MIMS Full Prescribing Information

Methadone Syrup

Company Sigma

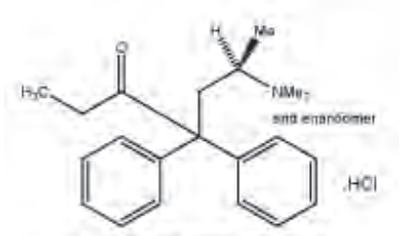
Primary Section: Poisoning, Toxicity and Drug Dependence - Agents used in drug dependence

ARTG Registered medicine

MIMS revision date: 01 Nov 2008

Composition ***Active.*** Methadone hydrochloride.

Inactive. Caramel, ethanol, glycerol, sodium benzoate, sorbitol solution 70% (noncrystallising), purified water and flavour pharmaceutical 503978A.



Methadone hydrochloride

Description Chemical name: (6*RS*)6-(dimethylamino)-4,4- diphenylheptan-3-one hydrochloride. Molecular formula: $C_{21}H_{27}NO.HCl$. MW: 345.9. CAS: 1095-90-5. Methadone is a racemic mixture and levo-methadone is the active isomer. It occurs as odourless, colourless crystals or a white crystalline powder. It is soluble in water, freely soluble in alcohol and chloroform; practically insoluble in ether and in glycerol.

Actions Synthetic opioid analgesic with the general properties of morphine.

Pharmacology. The pharmacological actions of methadone are qualitatively similar to those of morphine. Significant quantitative differences are its effective analgesic activity after administration by the oral route and its tendency to show persistent effects with repeated administration.

Pharmacodynamic effects. The combination of opioid agonism and N-methyl-D-aspartate (NMDA) antagonism by methadone produces an additive analgesic response while limiting opioid tolerance.

Pharmacokinetics.*Absorption.* Methadone hydrochloride is readily absorbed after administration by mouth and has high oral bioavailability. Peak plasma concentrations have been reported one to five hours after oral administration of a single dose in tablet form.

Distribution. Methadone undergoes considerable tissue distribution and protein binding is reported to be 60 to 90% with $alpha_1$-acid glycoprotein being the main binding protein in plasma.

Metabolism. Methadone undergoes N-demethylation to 2-ethylidene-1,5-dimethyl- 3,3-diphenylpyrrilidine (EDDP) with CYP3A4 being the main enzyme responsible. However, other CYP450 enzymes, including CYP2D6, are also likely to be involved in methadone's metabolism.

Excretion. Elimination of methadone occurs principally by metabolism, followed by urinary and faecal excretion of the metabolites, though there is some renal excretion of unchanged methadone. Marked interindividual variations in kinetics have been observed with methadone. Elimination half-lives vary considerably (a range of 15 to 60 hours has been reported) and careful adjustment of dosage is necessary with repeated administration.

Plasma concentrations have been found to vary widely during methadone maintenance therapy with large differences between patients and wide fluctuations in individual patients. Declining concentrations have been reported during methadone maintenance suggesting that tolerance occurs, possibly as a result of autoinduction of hepatic microsomal enzymes.

Special patient populations.*Elderly.* Methadone clearance does not appear to be markedly affected by age, though a slight decrease has been observed over age 65.

Renal impairment. Although methadone is mostly eliminated by metabolism, a significant proportion of the dose is excreted via the kidney.

Indications Treatment of dependence on opioid drugs.

Treatment of severe pain.

Contraindications Hypersensitivity to methadone or other components of Methadone Syrup.

Like other opioids, methadone is contraindicated in patients with respiratory depression, especially in the presence of cyanosis and excessive bronchial secretions.
An attack of bronchial asthma.
Acute alcoholism, head injury and raised intracranial pressure.
Individuals receiving monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping such treatment.
As with other opioids, methadone is contraindicated in patients with ulcerative colitis, since it may precipitate toxic dilatation or spasm of the colon.
As with all narcotic analgesics, methadone should not be administered to patients with severe hepatic impairment as it may precipitate hepatic encephalopathy (see Precautions).
Biliary and renal tract spasm.
Individuals with existing QT prolongation, including those with congenital long QT syndrome (see Precautions).

Precautions Deaths due to cardiac arrhythmias and respiratory depression may occur, particularly in patients receiving methadone for analgesia during treatment initiation or conversion from other opioids.

Respiratory depression. Respiratory depression is the major hazard associated with methadone treatment. The peak depressive effects persist longer than peak analgesic effects, especially during the initial dosing period. Particular care should be taken during the dose initiation and adjustment period to minimise the risk of dose accumulation (see Dosage and Administration).

Cardiac repolarisation. *In vivo* and *in vitro* studies have demonstrated that methadone inhibits cardiac potassium channels and prolongs cardiac repolarisation (i.e. prolongs the QT interval). QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone and appear to be more common with higher doses. Particular caution and careful monitoring is recommended in patients at risk of prolonged QT interval (e.g. cardiac hypertrophy, concomitant diuretic use, hypokalaemia, hypomagnesaemia), patients with a previous history of cardiac repolarisation prolongation, those taking medications affecting cardiac repolarisation or methadone metabolism, and in patients with an increased risk of arrhythmia (see Contraindications and Interactions). Patients developing QT prolongation while on methadone treatment should be evaluated for modifiable risk factors, such as concomitant medications with cardiac effects, drugs which might cause electrolyte abnormalities and drugs which might act as inhibitors of methadone metabolism.

Dependence. In common with all opioids, prolonged use of methadone has the potential to produce dependence of the morphine type. The possibility of addiction cannot be excluded and patients should be reminded of the necessity of adhering to the prescribed dosage. However, when used for pain relief in terminal care, the risk of dependence is of limited concern. Discontinuation of therapy with methadone should be carried out gradually in patients who may have developed physical dependence, to avoid precipitating withdrawal symptoms (see Adverse Reactions).

Phaeochromocytoma. Extreme caution should be exercised when administering methadone to patients with phaeochromocytoma, since aggravated hypertension has been reported in association with diamorphine.
Methadone should be used with caution in the presence of hypothyroidism, adrenocortical insufficiency, hypopituitarism, prostatic hypertrophy, shock and diabetes mellitus.
Methadone Syrup is not suitable for administration by injection.
Methadone Syrup is for oral use only.

Impaired renal function. Methadone should be used with caution in patients with renal dysfunction. The dosage interval should be increased to a minimum of eight hourly when the glomerular filtration rate (GFR) is 10 to 50 mL/minute and to a minimum of 12 hourly when the GFR is below 10 mL/minute.

Impaired hepatic function. Particular care should be taken when methadone is to be used in patients with hepatic impairment as these patients metabolise methadone more slowly than normal patients. Where not contraindicated methadone should be given at less than the normal recommended dose and the patient's response used as a guide to further dosage requirements (see Contraindications).

Use in the elderly. Methadone has a long plasma half-life which may lead to accumulation, particularly if renal function is impaired (see Impaired renal function).
In common with other opioids, methadone may cause confusion in this age group, therefore, careful monitoring is advised.

Carcinogenesis, mutagenesis, impairment of fertility. ***Mutagenic potential.*** Methadone did not exhibit demonstrable mutagenic activity in a wide range of standard *in vitro* and *in vivo* mutagenicity assays. However, in a Dominant Lethal assay in mice, treatment with methadone at doses between 1 and 6 mg/kg was associated with increased preimplantation deaths and chromosomal aberrations of sperm cells when compared with controls.
Carcinogenic potential. Long-term carcinogenicity tests in rodents did not reveal any evidence of methadone related neoplasia.
Teratogenic potential. No teratogenic effects have been observed in standard teratogenicity studies in rats and

rabbits given methadone at doses from 10 to 50 times the average daily human maintenance dose. Developmental abnormalities of the central nervous system (CNS) have been reported in hamsters and mice given high doses in early pregnancy.

Impairment of fertility. Methadone does not appear to impair human female fertility.

Studies in men on methadone maintenance programs have shown that methadone reduces serum testosterone and markedly depresses the ejaculate volume and sperm motility. The sperm counts of methadone subjects were twice that of controls but this reflected the lack of dilution from seminal secretions. A reduction in libido has been reported as well as impotence, delayed and/or failed ejaculation.

Use in pregnancy. (Category C)

There is insufficient evidence on which to determine the safety profile of methadone in pregnancy, therefore, it should only be used if the potential benefit outweighs the potential risk.

Narcotic analgesics may cause respiratory depression in the newborn infant. During the last two to three hours before expected delivery narcotic analgesics should therefore only be used after weighing the needs of the mother against the risk to the fetus. Methadone is not recommended for use during labour because its prolonged duration of action increases the risk of respiratory depression in the neonate.

Like other opiates, methadone crosses the placenta during pregnancy, and most neonates born to mothers on methadone maintenance will suffer from withdrawal if left untreated.

Withdrawal symptoms may be observed in infants born to mothers receiving methadone maintenance consisting of CNS, gastrointestinal and respiratory disturbances. Abstinence syndrome may not occur in the neonate for some days after birth. Therefore, in addition to initial monitoring of respiratory depression, neonates should undergo prolonged monitoring for signs and symptoms of withdrawal.

Infants born to mothers on methadone maintenance have been reported to have smaller birthweights when compared to infants of nondrug exposed mothers. The infants born to mothers on methadone maintenance were not small for gestational age, and by 6 months of age, these infants did not exhibit any general development sequelae.

Use in lactation. Methadone is distributed into breast milk, with a mean ratio of milk to plasma concentration of 0.44. However, doses of methadone to the infant via breast milk are low, estimated at 3% of maternal doses on average, and insufficient to prevent neonatal abstinence syndrome in infants born to mothers on methadone maintenance.

Breastfeeding is permissible in mothers receiving methadone for maintenance therapy but the baby should be monitored to avoid sedation.

Use in children. Methadone is not recommended for use in children less than 18 years of age since documented clinical experience has been insufficient to establish a suitable dosage regimen; furthermore, children are particularly sensitive to the respiratory and CNS effects of methadone.

Effect on ability to drive or operate machinery. In common with other opioids, methadone may produce orthostatic hypotension and drowsiness in ambulatory patients. They should be cautioned, therefore, against driving vehicles, operating machinery or other activities requiring vigilance.

Interactions Methadone is metabolised by various cytochrome P450 (CYP450) enzymes. Therefore, coadministration of drugs known to interfere with CYP450 enzymes may affect its clinical activity (see Actions, Pharmacokinetics).

Some compounds may increase the metabolism of methadone, e.g. rifampicin, phenytoin, carbamazepine, St John's wort and antiretroviral agents used in the treatment of human immunodeficiency virus (HIV) infection (particularly nevirapine, efavirenz and some protease inhibitors). This has the potential to result in withdrawal symptoms.

Patients on methadone maintenance who are also taking enzyme inducers, such as carbamazepine, may require higher than typical doses of methadone.

Some compounds may decrease the metabolism of methadone, e.g. fluconazole and some selective serotonin reuptake inhibitors (SSRIs), particularly fluvoxamine. This may increase the likelihood of methadone toxicity.

In addition to compounds that may decrease the metabolism of methadone, extreme caution is necessary when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone (see Precautions). Interactions may occur with methadone and potentially arrhythmogenic agents such as class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants and calcium channel blockers. Caution should also be exercised when prescribing concomitant drugs capable of inducing electrolyte disturbances that may prolong the QT interval (hypomagnesaemia, hypokalaemia). These include diuretics, laxatives and, in rare cases, mineralocorticoid hormones.

Methadone can also affect the metabolism of other drugs. Plasma concentrations of some drugs may be increased, e.g. nelfinavir, zidovudine, fluconazole and desipramine, whereas concentrations of others may be decreased, e.g. abacavir and amprenavir.

MAOIs may prolong and enhance the respiratory depressant effects of methadone. Opioids and MAOIs used together may cause fatal hypotension and coma.
Central nervous system depressants. The general depressant effects of methadone may be enhanced by other centrally acting agents such as alcohol, barbiturates, neuromuscular blocking agents, phenothiazines and tranquillizers. Some psychotropic drugs, however, may potentiate the analgesic effects of methadone.
Propranolol has been reported to enhance the lethality of toxic doses of opioids in animals. Although the significance of this finding is not known for humans, caution should be exercised when such drugs are coadministered.

Adverse Reactions

Respiratory. The major side effect of methadone is respiratory depression.
Gastrointestinal. Reported events include nausea*, vomiting*, dry mouth* and constipation. Methadone, in common with other opioids may cause spasm of the biliary tract (see Contraindications).
Neurological. Reported events include dizziness*, drowsiness*, lightheadedness*, sweating* and confusion*. Euphoria has been reported at higher doses in tolerant patients.
Cardiovascular. Hypotension, collapse and generalised oedema have occasionally been reported.
Electrocardiogram (ECG) changes including QT prolongation and torsades de pointes have occurred very rarely, usually in patients with risk factors or receiving high doses of methadone (see Precautions).
Renal. Methadone, in common with other opioids, may cause spasm of the renal tract (see Contraindications). It also possesses antidiuretic properties, and urinary retention or hesitancy has been reported.
Endocrine. Prolonged use of methadone in men has been reported to be associated with the development of gynaecomastia.
Withdrawal (abstinence) syndrome. Chronic use of opioid analgesics may be associated with the development of physical dependence. An abstinence syndrome may be precipitated when opioid administration is suddenly discontinued or opioid antagonists administered. Withdrawal symptoms that may be observed after discontinuation of opioid use include body aches, diarrhoea, piloerection, anorexia, nervousness or restlessness, rhinorrhoea, sneezing, tremors or shivering, abdominal colic, nausea, sleep disturbance, unusual increase in sweating and yawning, weakness, tachycardia and unexplained fever. With appropriate dose adjustments and gradual withdrawal these symptoms are usually mild.
In known drug addicts, methadone has produced withdrawal symptoms but these are mild. Tolerance and dependence of the morphine type may occur.
*These adverse reactions appear to be more common in ambulatory patients and in those receiving oral therapy.

Dosage and Administration

Methadone Syrup must not be used parenterally.
Dose initiation, titration and duration should be individualised, taking into account the pharmacodynamic and pharmacokinetic properties of methadone and the need for close observation of the patient for cumulative toxicity. This should be based on a careful evaluation of subjective and objective patient data, bearing in mind clinical status, including hepatic or renal function of the patient.
Care needs to be taken with methadone to avoid toxicity because the time to reach steady-state concentrations following a change in dosage may be up to 12 days. Dose conversion ratios from other opioids are not static, but are a function of previous opioid exposure. Incomplete cross tolerance between micro-opioid agonists makes determination of dosing during opioid conversion complex.
It is recommended that use of this drug should only be undertaken by prescribers familiar with its use.
Treatment of dependence on opioid drugs. A dose of 10 to 20 mg by mouth may be given initially and increased as necessary by 5 to 10 mg daily. The dose must not be increased by more than 5 to 10 mg daily, and by no more than 30 mg in any seven day period. After stabilisation, which can often be achieved with a daily dose of 30 to 50 mg daily (up to a maximum of 80 mg daily), the dose of methadone is gradually decreased until total withdrawal is achieved. Some treatment schedules for opioid dependence involve prolonged maintenance therapy with methadone where the daily dose is adjusted carefully for the individual.
Treatment of severe pain.*Adults.* Usual single dose 5 to 10 mg by mouth.
Owing to its long plasma half-life, caution with repeated dosage should be observed in all patients, particularly in the very ill or elderly. The usual initial dose should be 5 to 10 mg six to eight hourly, later adjusted to the degree of pain relief obtained. Doses administered more frequently than six to eight hourly are liable to cause accumulation with increasing sedation and respiratory depression. In chronic use, methadone should not be administered more than twice daily.
Methadone may be used in combination with non-narcotic analgesics to provide additive analgesia.
Where the drug is given orally for longer duration, it is wise to restrict the dose to the smallest amount which controls the symptoms.
Children and adolescents aged less than 18 years. Methadone is not recommended for use in this age group, since documented clinical experience has been insufficient to establish a suitable dosage regimen;

furthermore, children are particularly sensitive to the respiratory and CNS depressant effects of methadone.

Elderly. Methadone has a long plasma half-life which may lead to accumulation, particularly if renal function is impaired (see Precautions and Actions, Pharmacokinetics).

In common with other opioids, methadone may cause confusion in this age group; therefore, careful monitoring is advised.

Renal impairment. Methadone should be used with caution in patients with renal dysfunction; the dosage interval should be increased to a minimum of eight hourly when the GFR is 10 to 50 mL/minute and to a minimum of 12 hourly when the GFR is below 10 mL/minute.

Hepatic impairment. Particular care should be taken when methadone is to be used in patients with hepatic impairment as these patients metabolise methadone more slowly than normal patients. Where not contraindicated, methadone should be given at less than the normal recommended dose and the patient's response used as a guide to further dosage requirements (see Contraindications).

Cardiac repolarisation disorders. Methadone should be administered with particular caution to patients at risk of development of prolonged QT interval (see Contraindications and Precautions).

Overdosage

Symptoms. The symptoms and signs of overdosage with methadone parallel those for other opioids, namely profound respiratory depression, pinpoint pupils, hypotension, circulatory failure, pulmonary oedema, coma and death.

Mydriasis may replace miosis as asphyxia intervenes. Drowsiness, floppiness, pinpoint pupils and apnoea have been reported in children.

Treatment. General supportive measures, including ECG monitoring, should be employed as required. Lavage, dialysis and CNS stimulation are contraindicated. The specific opioid antagonist naloxone can be used for the reversal of coma and the restoration of spontaneous respiration. Intravenous infusion is the preferred route of administration in the management of methadone overdose because of the short half-life of naloxone relative to the long half-life of methadone, continuous infusion reduces the possibility of prolonged respiratory depression and the risk of relapse, which can occur suddenly. It should be noted that QT prolongation will not be reversed by naloxone.

In opioid dependent patients the administration of the usual dose of an opioid antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of the antagonist administered. The use of an opioid antagonist in such a person should be avoided if possible. If it must be used to treat serious respiratory depression in the physically dependent person the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.

Patients should be monitored closely for at least 48 hours after apparent recovery in case of relapse, since the duration of action of the antagonist may be substantially shorter than that of methadone.

The use of other respiratory or central stimulants is not recommended.

Acidification of the urine will enhance urinary excretion of methadone.

Methadone is not dialysable by either peritoneal dialysis or haemodialysis.

Contact the Poisons Information Centre (telephone 131 126) for advice on overdose management.

Presentation

Oral liquid, 5 mg/mL: 200 mL, 1 L.

Storage

Store below 25 deg. C. Protect from light.

Poisons Schedule

S8.

Date of TGA approval or last amendment

22/02/2007

Appendix 9

MIMS Full Prescribing Information

Biodone Forte

Company Biomed

Primary Section: Poisoning, Toxicity and Drug Dependence - Agents used in drug dependence

MIMS revision date: 01 Feb 2006

Composition ***Active.*** Methadone hydrochloride.

Inactive. Permicol red.

Description Chemical name: (6-dimethylamino-4,4-diphenyl- 3-heptanone hydrochloride). Molecular formula: $C_{21}H_{27}NO.HCl$. MW: 345.9. CAS: 1095-90-5.

Methadone is a racemic mixture of two enantiomers. The l-enantiomer is more potent with respect to analgesic activity, respiratory depression and addiction liability.

It occurs as odourless, colourless crystals or white crystalline powder. It is soluble in water, freely soluble in alcohol and chloroform, particularly insoluble in ether and in glycerol.

Biodone Forte is a solution of methadone hydrochloride in water.

Actions Methadone hydrochloride is a synthetic opioid analgesic with the general properties of morphine.

Pharmacology. The pharmacological actions of methadone are qualitatively similar to those of morphine.

Significant quantitative differences are its effective analgesic activity after administration by the oral route and its tendency to show persistent effects with repeated administration.

Pharmacokinetics. Methadone hydrochloride is readily absorbed after administration by mouth and has high oral bioavailability. Peak plasma concentrations have been reported one to five hours after oral administration of a single dose in tablet form. It undergoes considerable tissue distribution and protein binding is reported to be 60 to 90% with $alpha_1$-acid glycoprotein being the main binding protein in the plasma. Metabolism to the major metabolite 2-ethylidine-1,5-dimethyl, 3,3-diphenylpyrrolidine and the minor metabolite 2-ethyl-3,3- diphenyl-5- methylpyrrolidine, both of them inactive, occurs in the liver. These metabolites are excreted in the faeces and urine together with unchanged methadone. Other metabolites, including methadol and normethadol (reported to be pharmacologically active), have also been described but account for a small proportion of the dose. The liver may also serve as a major storage site of unchanged methadone which is taken up, bound non-specifically by the liver and released again mainly unchanged.

Marked interindividual variations in kinetics have been observed with methadone. Elimination half-lives vary considerably (a range of 15 to 60 hours has been reported) and careful adjustment of dosage is necessary with repeated administration, after which there is a gradual accumulation in the tissues.

Plasma concentrations have been found to vary widely during methadone maintenance therapy with large differences between patients and wide fluctuations in individual patients. Declining concentrations have been reported during methadone maintenance suggesting that tolerance occurs, possibly as a result of autoinduction of hepatic microsomal enzymes.

Indications Detoxification and maintenance treatment of dependence on opioid drugs.

Contraindications Hypersensitivity to methadone or permicol red, which are the only components in the formulation.

Like other opioids, methadone is contraindicated in patients with respiratory depression, especially in the presence of cyanosis and excessive bronchial secretions.

Methadone should not be given during an attack of bronchial asthma.

Methadone is contraindicated in the presence of acute alcoholism, head injury and raised intracranial pressure.

Methadone is contraindicated in individuals receiving monoamine oxidase inhibitors or within 14 days of stopping such treatment.

As with other opioids, methadone is contraindicated in patients with ulcerative colitis, since it may precipitate toxic dilation or spasm of the colon.

As with all opioid analgesics, methadone should not be administered to patients with severe hepatic impairment as it may precipitate hepatic encephalopathy (see Precautions, Impaired hepatic function).

Methadone is contraindicated in biliary and renal tract spasm.

Methadone is contraindicated in individuals with existing QT prolongation, including those with congenital long QT syndrome (see Precautions).

Precautions In common with all opioids, prolonged use of methadone has the potential to produce dependence of the morphine type. The withdrawal symptoms are less intense but more prolonged than those produced by

morphine or diamorphine. They develop more slowly and do not usually appear until 24 to 48 hours after the last dose. Discontinuation of methadone therapy should be carried out gradually in patients who may have developed physical dependence on the medicine so as to avoid precipitating withdrawal symptoms (see Adverse Reactions).
Methadone should be used with caution in the presence of hypothyroidism, adrenocortical insufficiency, hypopituitarism, prostatic hypertrophy, shock and diabetes mellitus.
Extreme caution should be exercised when administering methadone to patients with phaeochromocytoma, since aggravated hypertension has been reported in association with diamorphine.
In vivo and *in vitro* studies have demonstrated that methadone inhibits cardiac potassium channels and prolongs cardiac repolarisation (i.e. prolongs the QT interval). QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone and appear to be more common with higher doses.
Particular caution and careful monitoring are recommended in patients at risk of prolonged QT interval (e.g. cardiac hypertrophy, concomitant diuretic use, hypokalaemia, hypomagnesaemia), patients with a previous history of cardiac repolarisation prolongation, those taking medications affecting cardiac repolarisation or methadone metabolism and in patients with an increased risk of arrhythmia (see Contraindications and Interactions). Patients developing QT prolongation while on methadone treatment should be evaluated for modifiable risk factors, such as concomitant medications with cardiac effects, drugs which might cause electrolyte abnormalities and drugs which might act as inhibitors of methadone metabolism.
Biodone Forte is not intended for administration by injection.
Biodone Forte is for oral use only.

Cardiac repolarisation disorders. Methadone should be administered with particular caution to patients at risk for development of prolonged QT interval (see Precautions and Contraindications).

Impaired renal function. Methadone should be used with caution in patients with renal dysfunction.

Impaired hepatic function. Particular care should be taken when methadone is to be used in patients with hepatic impairment as these patients metabolise methadone more slowly than normal patients. Where not contraindicated methadone should be given at less than the normal recommended dose and the patient's response used as a guide to further dosage requirements (see Contraindications).

Use in the elderly. Methadone has a long plasma half-life, which may lead to accumulation, particularly if renal function is impaired (see Impaired renal function).
In common with other opioids, methadone may cause confusion in this age group, therefore careful monitoring is advised.

Carcinogenesis, mutagenesis, impairment of fertility. Methadone did not exhibit demonstrable mutagenic activity in a wide range of standard *in vitro* and *in vivo* mutagenicity assays. However in a dominant lethal assay in mice treatment with methadone at doses between 1 and 6 mg/kg was associated with increased preimplantation deaths and chromosomal aberrations of sperm cells when compared with controls.
Long-term carcinogenicity tests in rodents did not reveal any evidence of methadone related neoplasia.
Methadone does not appear to impair human female fertility.
Studies in men on methadone maintenance programs have shown that methadone reduces serum testosterone and markedly depresses the ejaculate volume and sperm motility. The sperm counts of methadone subjects were twice that of controls but this reflected the lack of dilution from seminal secretions. A reduction in libido has been reported as well as impotence, delayed and/or failed ejaculation.

Use in pregnancy. (Category C)
There is insufficient evidence on which to determine the safety profile of methadone in pregnancy, therefore it should only be used if the potential benefit outweighs the potential risk.
No teratogenic effects have been observed in standard teratogenicity studies in rats and rabbits given methadone at doses from 10 to 50 times the average daily human maintenance dose. Developmental abnormalities of the central nervous system have been reported in hamsters and mice given high doses in early pregnancy.
Opioid analgesics may cause respiratory depression in the newborn infant. During the last two to three hours before expected delivery, opioid analgesics should therefore only be used after weighing the needs of the mother against the risk to the fetus. Methadone is not recommended for use during labour because its prolonged duration of action increases the risk of respiratory depression in the neonate.
Like other opioids, methadone crosses the placenta during pregnancy, and most neonates born to mothers on methadone maintenance will suffer from withdrawal if left untreated.
Withdrawal symptoms pertaining to the central nervous system, gastrointestinal system and respiratory system may be observed in infants born to mothers receiving methadone maintenance. Neonatal abstinence syndrome may not occur until some days after birth. Therefore, in addition to initial monitoring of respiratory depression, neonates should undergo prolonged monitoring for signs and symptoms of methadone withdrawal.
Infants born to mothers on methadone maintenance have been reported to have smaller birthweights when compared

to infants of non-drug exposed mothers. The infants born to mothers on methadone were not small for gestational age and, by six months of age, these infants did not exhibit any general development sequelae.

Use in lactation. Methadone is distributed into breast milk with a mean ratio of milk to plasma concentration of 0.44. However, doses of methadone to the infant by breast milk are low, estimated at 3% of maternal dose, on average, and insufficient to prevent neonatal abstinence syndrome in infants born to mothers on methadone maintenance.

Breastfeeding is permissible in mothers receiving methadone for maintenance therapy but the baby should be monitored to avoid sedation.

Use in children. Methadone is not recommended for use in children less than 18 years of age since documented clinical experience has been insufficient to establish a suitable dosage regimen. Furthermore, children are particularly sensitive to the respiratory and central nervous system effects of methadone.

Effect on ability to drive or operate machinery. In common with other opioids methadone may produce orthostatic hypotension and drowsiness in ambulatory patients. They should be cautioned, therefore, against driving vehicles, operating machinery or other activities requiring vigilance.

Interactions Methadone is metabolised by various cytochrome P450 (CYP450) enzymes. Therefore coadministration of drugs known to interfere with the CYP450 enzymes may affect its clinical activity.

Some compounds may increase the metabolism of methadone, e.g. rifampicin, phenytoin, carbamazepine, St John's wort and antiretroviral agents used in the treatment of HIV infection (particularly nevirapine, efavirenz and some protease inhibitors). This has the potential to result in withdrawal symptoms.

Patients on methadone maintenance who are also taking enzyme inducers such as carbamazepine, may require higher than typical doses of methadone.

Some compounds may decrease the metabolism of methadone, e.g. fluconazole and some serotonin reuptake inhibitors (SSRIs), particularly fluvoxamine. This may increase the likelihood of toxicity.

In addition to compounds that may decrease the metabolism of methadone, extreme caution is necessary when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone (see Precautions). Interactions may occur with methadone and potentially arrhythmogenic agents such as class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants and calcium channel blockers. Caution should also be exercised when prescribing concomitant drugs capable of inducing electrolyte disturbances that may prolong the QT interval (hypokalaemia, hypomagnesaemia). These include diuretics, laxatives and in rare cases mineralocorticoid hormones.

Methadone can also affect the metabolism of other drugs. Plasma concentrations of some drugs may be increased, e.g. nelfinavir, zidovudine, fluconazole and desipramine, whereas concentrations of other drugs may be decreased, e.g. abacavir and amprenavir.

Monoamine oxidase inhibitors (MAOIs) may prolong and enhance the respiratory depressant effects of methadone. Opioids and MAOIs used together may cause fatal hypotension and coma.

The general depressant effects of methadone may be enhanced by other centrally acting agents such as alcohol, barbiturates, neuromuscular blocking agents, phenothiazines and tranquillizers. Some psychotropic drugs, however, may potentiate the analgesic effects of methadone. The intestinal effects of methadone may delay the absorption of mexiletine.

Propranolol has been reported to enhance the lethality of toxic doses of opioids in animals. Although the significance of this finding is not known for humans, caution should be exercised when such drugs are coadministered.

Opioid analgesics may antagonise the effects of agents that stimulate gastrointestinal motility (metoclopramide, domperidone, cisapride).

Anticholinergics increase the risk of constipation, urinary retention and so on. Antihypertensives may aggravate the hypotensive effects of opioid analgesics.

Laboratory tests. The serum BSP retention test may be increased (hepatotoxic effect or spasm of sphincter of Oddi). Plasma cortisol may be increased in response to cold to an extent not seen in controls. An increase in the serum albumin, prolactin and immunoglobulin (IgG) levels may be seen as a response to chronic administration. A significant decrease in serum indocyanine green level has been observed in a small series of patients with normal liver function tests. PCO_2 may be increased due to decreased pulmonary ventilation. False positive urine pregnancy tests have occurred, mainly with the Gravindex test. Physiological changes in thyroid hormones may be seen, including a decrease in serum thyroxine (T4), a decrease in free thyroxine and an increase in tri-iodothyronine (T3).

Adverse Reactions The major side effect of methadone is respiratory depression.

Other reported events include nausea, vomiting, constipation, dizziness, drowsiness, lightheadedness, dry mouth, sweating and confusion. These effects appear to be more common in ambulatory patients and in those receiving oral therapy. Less common reactions include bradycardia, tachycardia, palpitations, blurred vision, stomach cramps or

pain.
Euphoria has been reported at higher doses in tolerant patients.
Hypotension, collapse and generalised oedema have occasionally been reported. ECG changes including QT prolongation and torsades de pointes have occurred very rarely, usually in patients with risk factors or receiving high doses of methadone (see Precautions).
Chronic use of opioid analgesics may be associated with the development of physical dependence. A withdrawal (abstinence) syndrome may be precipitated when opioid administration is suddenly discontinued or opioid antagonists administered. Withdrawal symptoms that may be observed after discontinuation of opioid use include body aches, diarrhoea, piloerection, anorexia, nervousness or restlessness, rhinorrhoea, sneezing, tremors or shivering, abdominal colic, nausea, sleep disturbance, unusual increase in sweating or yawning, weakness, tachycardia and unexplained fever. With appropriate dose adjustment and gradual withdrawal these symptoms are usually mild.
Methadone, in common with other opioids, may cause spasm of the biliary and renal tracts (see Contraindications). It also possesses antidiuretic properties.
Prolonged use of methadone in men has been reported to be associated with the development of gynaecomastia.

Dosage and Administration Dosage and duration of treatment should be individualised.
A dose of 10 to 20 mg by mouth may be given initially and increased as necessary by 5 to 10 mg daily. The dose must not be increased by more than 5 to 10 mg daily and by no more than 30 mg in any seven day period. After stabilisation, which can often be achieved with a daily dose of 30 to 50 mg daily (up to a maximum of 80 mg daily), the dose of methadone is gradually decreased until total withdrawal is achieved. Some treatment schedules for opioid dependence involved prolonged maintenance therapy with methadone where the daily dose is adjusted carefully for the individual.
The dose of Biodone Forte required is to be measured accurately, using a calibrated dropper or other appropriate method.
Dilution may be required by local protocols and this dilution should be made with distilled water if the solution is for immediate consumption, or with a solution containing 0.1% sodium benzoate for take away doses, which should be used within five days of preparation. Dilution of take away doses, usually to 200 mL, is a strategy intended to reduce the likelihood of injection and of small children consuming sufficient of the drug to cause overdose. Take away solutions should be packaged in registered Quinex containers and sealed with a childproof cap.

Overdosage **Symptoms.** The symptoms and signs of overdosage with methadone parallel these for other opioids, namely profound respiratory depression, pinpoint pupils, hypotension, circulatory failure and pulmonary oedema and coma.
Mydriasis may replace miosis as asphyxia intervenes. Drowsiness, floppiness, pinpoint pupils and apnoea have been reported in children.
Treatment. General supportive measures, including ECG monitoring, should be employed as required. The specific opioid antagonist naloxone can be used for the reversal of coma and the restoration of spontaneous respiration. Intravenous infusion is the preferred route of administration in the management of methadone overdose because of the short half-life of naloxone relative to the longer half-life of methadone. Continuous infusion reduces the possibility of prolonged respiratory depression and the risk of relapse, which can occur suddenly. It should be noted that QT prolongation will not be reversed by naloxone.
In opioid dependent patients the administration of the usual dose of an opioid antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of the antagonist administered. The use of an opioid antagonist should be avoided if possible. If it must be used to treat respiratory depression in the physically dependent person the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.
Patients should be monitored closely for at least 48 hours after apparent recovery in case of relapse, since the duration of action of the antagonist may be substantially shorter than that of methadone.
The use of respiratory or central stimulants is not recommended.
Acidification of the urine will enhance urinary excretion of methadone.
Methadone is not dialysable by either peritoneal dialysis or haemodialysis.

Presentation Oral liquid, 5 mg/mL: 200 mL and 1,000 mL (glass bottles).

Storage Store below 25 deg. C. Protect from light. Do not freeze.

Poisons Schedule S8.

Date of TGA approval or last amendment 01/02/2005

Appendix 10

Possible drug interactions with methadone hydrochloride

Drug	Status of interaction	Effect	Mechanism
Abacavir	Clinically important	Reduced methadone levels	Increased methadone metabolism
Alcohol	Clinically important	Increased sedation, increased respiratory depression. Combination may also have increased hepatotoxic potential	Additive central nervous system depression
Barbiturates	Clinically important	Reduced methadone levels, increased sedation. Additive central nervous system (CNS) depression	Barbiturates stimulate hepatic enzymes involved in methadone maintenance
Benzodiazepines	Clinically important	Enhanced sedative effect	Additive CNS depression
Buprenorphine	Clinically important	Antagonist effect or enhanced sedative and respiratory depression	Buprenorphine is a partial agonist of opiate receptors
Carbamazapine	Clinically important	Reduced methadone levels	Carbamazapine stimulates hepatic enzymes involved in methadone metabolism
Chloral hydrate	Clinically important	Enhanced sedative effect	Additive CNS depression
Chlormethiazole	Clinically important	Enhanced sedative effect	Additive CNS depression
Cimetidine	Two cases have been shown in patients taking methadone as analgesia	Possible increase in methadone plasma levels	Cimetidine inhibits hepatic enzymes involved in methadone metabolism
Ciprofloxacin	Case in a patient taking methadone	Enhanced sedative effect and respiratory depression requiring naloxone	Probably by inhibiting hepatic enzymes involved in methadone metabolism
Cisapride Domperidone Metoclopramide	Theoretical	Theoretically might increase the speed of onset of methadone absorption but not the extent of such	Possibly by reversing the delayed gastric emptying associated with opioids
Cyclizine and other sedating antihistamines (cyclizine is not available in Australia)	Clinically important	Anecdotal reports of injection of cyclizine with opioids causing hallucinations. Reports of injections of high doses of diphenhydramine to achieve 'buzz'	Additive psychoactive effects. Antimuscarinic effects at high doses
Delavirdine	Theoretical	Theoretically might raise plasma methadone levels	
Desipramine	Clinically important	Raised desipramine levels by up to a factor of two	Unknown mechanism not seen with other tricyclic antidepressants
Efavirenz	Clinically important	Reduced plasma levels of methadone	Increased methadone metabolism
Other tricyclic antidepressants	Theoretical	Enhanced sedative effect that is dose-dependent	Additive CNS depression
Didanosine	Clinically important	Reduced plasma levels of stavudine. No effect on methadone	Increased didanosine metabolism
Disulfiram	Avoid in combination with methadone formulations containing alcohol (check with manufacturer)	Very unpleasant reaction to alcohol which can be dangerous	Disulfiram inhibits metabolism of alcohol, allowing metabolites to build up

Drug	Status of interaction	Effect	Mechanism
Erythromycin	In theory, should interact, but combination has not been studied	Increase in methadone levels	Decreased methadone metabolism
Fluconazole	In theory, the same as ketoconazole	Raised methadone levels	Decreased methadone metabolism
Fluoxetine/ Sertraline	Clinically important, but not as significant as for fluvoxamine	Raised methadone levels	Decreased methadone metabolism
Fluvoxamine	Clinically important	Raised plasma methadone levels	Decreased methadone metabolism
Other selective serotonin reuptake inhibitors (SSRIs)	Theoretical	Raised plasma methadone levels	Decreased methadone metabolism
Grapefruit juice	Should interact in theory and there have been several anecdotal reports	Raised methadone levels	Decreased methadone metabolism
Indinavir	Clinically important	Raised methadone levels	Decreased methadone metabolism
Ketoconazole	Clinically important	Raised methadone levels	Decreased methadone metabolism
MAOI (including selegiline and moclobemide)	Severe with pethidine described with methadone	CNS excitation, delirium, hyperpyrexia, convulsions, hypotension or respiratory depression	Unclear, avoid the combination if possible
Naltrexone	Clinically important	Blocks effect of methadone (long-acting)	Opioid antagonist – competes for opiate receptors
Naloxone	Clinically important	Blocks effects of methadone (short-acting) but may be needed if overdose suspected	Opioid antagonist – competes for opiate receptors
Nelfinavir		Decreased methadone levels	Increased methadone metabolism
Nevirapine	Clinically important	Decreased methadone levels	Increased methadone metabolism
Nifedipine	Has only been demonstrated in vitro	Increased nifedipine level. No effect on methadone levels	Methadone increases metabolism of nifedipine
Omeprazole	To date, only demonstrated in animals	Increased methadone levels	Possibly an effect on methadone absorption from the gut
Pentazocine		Antagonist effect or enhanced sedative and respiratory depression	Pentazocine is a partial agonist of opiate receptors that have a weak antagonist effect
Phenobarbitone	See barbiturates above	As for barbiturates	As for barbiturates
Phenytoin	Clinically important	Reduced methadone levels	Stimulates hepatic enzymes involved in methadone metabolism
Propanolol	To date, only demonstrated in animals. Significance in humans is not known. Exercise caution when co-administering	Enhanced lethality of toxic doses of opioids	Promotes bradycardia
Rifampicin	Very important. Most patients are likely to be affected	Reduced methadone levels	Stimulates hepatic enzymes involved in methadone metabolism
Rifabutin	Occasionally clinically important	Decreased methadone levels	Increased methadone metabolism

Drug	Status of interaction	Effect	Mechanism
Ritonavir	Clinically important	Ritonavir may decrease plasma methadone levels	Increased methadone metabolism
Stavudine	Clinically important	Reduced plasma levels of stavudine. No effect on methadone	Increased stavudine metabolism
Thioridazine	Clinically important	Enhanced sedative effect that is dose-dependent	Enhanced CNS depression
Tobacco smoke	Uncertain	Increased plasma methadone levels	Loss of CYP 1A2 induction
Other protease inhibitors	Theoretical	May raise or lower methadone plasma levels	Inhibits methadone metabolism
Urine acidifiers (e.g. ascorbic acid/ vitamin C)	Clinically important	Increased plasma methadone levels	Increased urinary excretion of methadone
Urine alkalisers (e.g. sodium bicarbonate)	Clinically important	Increased plasma methadone levels	Reduced urinary excretion of methadone
Zidovudine	Clinically important	Raised plasma levels of zidovudine. No effects on methadone levels	Unknown
Zopiclone	Clinically important	Enhanced sedative and respiratory depressant effect	Additive CNS depression
Other opioid agonists	Clinically important	Enhanced sedative effect. Enhanced respiratory depression	Additive CNS depression
Other CNS depressant drugs (e.g. neuroleptics, hyoscine)	Clinically important	Enhanced sedative effect that is dose-dependent	Additive CNS depression

This table is based on the table published in the *Clinical Guidelines and Procedures for the Use of Methadone in the Maintenance Treatment of Opioid Dependence* (National Drug Strategy, Australian Government Department of Health and Ageing, 2003), which in turn was based on a table in *Drug Misuse and Dependence – Guidelines on Clinical Management* (Department of Health, The Scottish Office Department of Health, Welsh Office, Department of Health and Social Service Northern Ireland, 1999). Additional information has been added from *Methadone Interactions with HIV Antiviral Drugs: All the Meds Together in One Big Chart*. Harm Reduction Coalition, New York.

Appendix 11

MIMS Full Prescribing Information

Suboxone Sublingual Film

Company Reckitt Benckiser

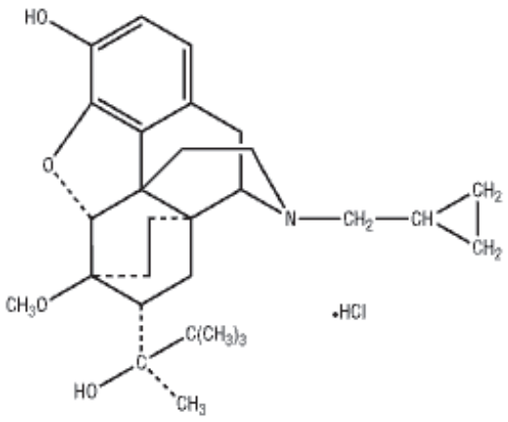
Primary Section: Poisoning, Toxicity and Drug Dependence - Agents used in drug dependence

ARTG Registered medicine

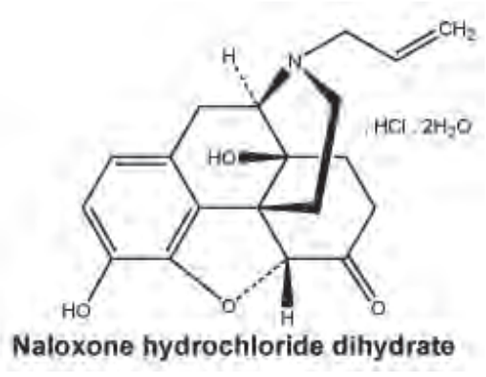
MIMS revision date: 01 Sep 2011

Composition Buprenorphine hydrochloride and naloxone hydrochloride at a ratio of 4:1 buprenorphine:naloxone.

Excipients Acesulfame potassium, anhydrous citric acid, maltitol solution, hypromellose, polyethylene oxide, anhydrous sodium citrate, lime flavour, Sunset Yellow FCF and a white printing ink.



Buprenorphine hydrochloride



Naloxone hydrochloride dihydrate

Description ***Buprenorphine hydrochloride.*** Chemical name: 21- cyclopropyl-7alpha-[(S)- 1-hydroxy- 1, 2, 2-trimethylpropyl]-6, 14-endo-ethano-6, 7, 8, 14-tetrahydrooripavine hydrochloride. Molecular formula: $C_{29}H_{41}NO_4HCl$. MW: 504.09. CAS: 53152-21-9. Buprenorphine hydrochloride is a white powder, weakly acidic with limited solubility in water (19.5 mg/mL at 37deg. C, pH 4.1).

Naloxone hydrochloride dihydrate. Chemical name: (-)-17-allyl-4, 5alpha-epoxy-3, 14-dihydroxymorphinan- 6-one hydrochloride dihydrate. Molecular formula: $C_{19}H_{21}NO_4HCl.2H_2O$. MW: 399.87. CAS: 51481-60-8. Naloxone hydrochloride is a white to slightly off white powder that exists as the dihydrate and is soluble in water, in dilute acids and in strong alkali.

Suboxone Sublingual Film is a soluble film intended for sublingual administration.

Actions **Pharmacology.Pharmacodynamic properties.** Buprenorphine is a mu opioid receptor partial agonist, kappa (kappa) opioid receptor antagonist. Its activity in opioid maintenance treatment is attributed to its slow dissociation from the mu receptors in the brain which reduces craving for opioids and opioid withdrawal symptoms. This minimises the need of the addicted patient for illicit opiate drugs.

During clinical pharmacology studies in opiate dependent subjects, buprenorphine demonstrated a ceiling effect on a number of parameters, including positive mood, 'good effect', and respiratory depression.

Naloxone is an antagonist at mu opioid receptors. Because of its almost complete first pass metabolism, naloxone administered orally or sublingually has no detectable pharmacological activity. However, when administered intravenously to opiate dependent persons, the presence of naloxone in Suboxone Sublingual Film produces marked opiate antagonist effects and opiate withdrawal, thereby deterring intravenous abuse.

Pharmacokinetic properties*Absorption.* When taken orally, buprenorphine undergoes first-pass metabolism with N-dealkylation and glucuronidation in the small intestine and the liver. The use of Suboxone Sublingual Film by the oral route is therefore inappropriate. Suboxone Sublingual Films are for sublingual administration.

Table 1 shows the pharmacokinetic parameters of buprenorphine, norbuprenorphine, and naloxone after administration of Suboxone Sublingual Film in randomised, crossover studies. For the 2/0.5 mg soluble film (Study 20-250-SA), the film to tablet ratio of geometric means are ln Cmax 121.66 % (90% CI 112.62-131.43), ln AUClast 116.40% (90% CI 108.70-124.63), and ln AUCinf 114.22% (90% CI 106.65-122.32). For the 8/2 mg soluble film, (Study 20-273-SA), the film to tablet ratios are ln Cmax 127.80 (90% CI 116.11-140.66), ln AUClast 120.15 (90% CI 110.24-130.96), and ln AUCinf 119.51 (90% CI 110.28-129.51). Overall, there was wide variability in the sublingual absorption of buprenorphine and naloxone. Suboxone Sublingual Film and Suboxone Sublingual Tablet do not meet all criteria for bioequivalence. Patients being switched between tablets and soluble films may therefore require dosage adjustment (see Dosage and Administration).

Suboxone Sublingual Film

Pharmacokinetic parameters of buprenorphine, norbuprenorphine and naloxone after sublingual administration of Suboxone

Dose	Analyte	Study	Cmax (nanogram/mL) mean (CV%)	Tmax (h) median (min-max)
2 mg/0.5 mg	Buprenorphine	250-SA	0.947 (40%)	1.53 (0.75-1.53)
	Norbuprenorphine	250-SA	0.312 (45%)	1.38 (0.5-8.0)
	Naloxone[a]	250-SA	54.1 (42%)	0.75 (0.5-2.0)
8 mg/2 mg	Buprenorphine	273-SA	3.37 (53%)	1.25 (0.75-4.0)
	Norbuprenorphine	273-SA	1.40 (78%)	1.25 (0.75-12.0)
	Naloxone[a]	273-SA	193 (47%)	0.75 (0.5-1.25)

[a] Naloxone Cmax expressed as picogram/mL. Naloxone AUCinf expressed as h*picogram/mL.

Distribution. The absorption of buprenorphine is followed by a rapid distribution phase (distribution half-life of 2 to 5 hours). Following intravenous administration, naloxone is rapidly distributed (distribution half-life of around 4 minutes).

Buprenorphine is highly lipophilic which leads to rapid penetration of the blood brain barrier. The drug is around 96% protein bound primarily to alpha and beta globulin. Naloxone is approximately 45% protein bound, primarily to albumin.

Metabolism and elimination. In animals and man buprenorphine is metabolised by phase 1 (oxidative) and phase 2 (conjugation) reactions. It is oxidatively metabolised by N-dealkylation to norbuprenorphine by CYP 3A4. In *in vitro* metabolic studies, addition of specific inhibitors of CYP 3A4 (e.g. ketoconazole, gestodene, nifedipine, norfluoxetine, ritonavir) inhibited formation of norbuprenorphine (see also Precautions and Interactions with Other Medicines). There was no indication of the involvement of CYP 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 in the N-dealkylation of buprenorphine. Buprenorphine was a weak competitive inhibitor of CYP 2D6 and CYP 3A4.

Norbuprenorphine is a mu agonist with weak intrinsic activity and is considered to be an inactive metabolite.

Naloxone undergoes direct glucuroconjugation to naloxone-3-glucuronide as well as N-dealkylation and reduction of the 6-oxo group.

Elimination of buprenorphine is biexponential or triexponential, with a long terminal elimination phase (mean half-life of 34.6 hours, range 20.4-72.9 hours), due in part to re-absorption of buprenorphine after intestinal hydrolysis of the conjugated metabolite, and in part to the highly lipophilic nature of the molecule. Naloxone has a short elimination half-life (mean 1.1 hours, range 0.63-1.94 hours).

Buprenorphine is essentially eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites (70%), the rest being eliminated in the urine. Naloxone is excreted in the urine.

Elderly. No pharmacokinetic data in elderly patients are available.

Clinical trials. Efficacy of buprenorphine in combination with naloxone was demonstrated with Suboxone Tablets. No clinical efficacy studies have been conducted with Suboxone Sublingual Film.

All trials used buprenorphine in conjunction with psychosocial counselling as part of a comprehensive addiction treatment program. There have been no clinical studies conducted to assess the efficacy of buprenorphine as the only component of treatment.

Clinical pharmacology studies on Suboxone tablets demonstrate an aversive effect if Suboxone tablets are misused by the injection route by opioid dependent patients.

Indications Treatment of opiate dependence within a framework of medical, social and psychological treatment.

Contraindications Hypersensitivity to buprenorphine or naloxone or any other component of the soluble film.
Children less than 16 years of age.
Severe respiratory or hepatic insufficiency (Child-Pugh B or C).
Acute intoxication with alcohol or other CNS depressant.
Pregnancy.
Breastfeeding.

Precautions **General.** Suboxone Sublingual Film should be administered with caution in elderly or debilitated patients and those with impairment of hepatic, pulmonary, or renal function; myxoedema or hypothyroidism, adrenal cortical insufficiency (e.g. Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.
Buprenorphine increases intracholedochal pressure as do other opiates. Therefore, caution should be exercised when Suboxone Sublingual Film is to be administered to patients with dysfunction of the biliary tract.
As with other opioids, caution is advised in patients using buprenorphine and having: hypotension, prostatic hypertrophy and urethral stenosis.
As with other mu opiate receptor agonists, the administration of Suboxone Sublingual Film may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Respiratory depression. Suboxone Sublingual Film is intended for sublingual use only. Significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. A number of deaths have occurred when individuals have intravenously misused buprenorphine, usually with benzodiazepines concomitantly. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other opioids. Patients should be warned of the potential danger of the self administration of benzodiazepines or other CNS depressants at the same time as receiving Suboxone Sublingual Film.
In the event of depression of respiratory or cardiac function, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. High doses of naloxone hydrochloride 10-35 mg/70 kg may be of limited value in the management of buprenorphine overdose.
Suboxone Sublingual Film should be used with caution in patients with compromised respiratory function (e.g. chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression).

CNS depression. Patients receiving Suboxone Sublingual Film in the presence of other narcotic analgesics, general anaesthetics, benzodiazepines, phenothiazines, other tranquillisers, sedatives/ hypnotics, or other CNS depressants (including alcohol) may exhibit increased CNS depression. When such combined therapy is contemplated, reduction of the dose of one or both agents should be considered. Suboxone Sublingual Film should be used cautiously with MAOIs, based on experience with morphine.

Hepatitis, hepatic events. Hepatic necrosis and hepatitis with jaundice have been reported with buprenorphine use. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. Serious cases of acute hepatic injury have also been reported in a context of misuse, especially by the intravenous route. These hepatic injuries were dose related, and could be due to mitochondrial toxicity. Pre-existing or acquired mitochondrial impairment (genetic diseases, viral infections particularly chronic hepatitis C, alcohol abuse, anorexia, associated mitochondrial toxins, e.g. aspirin, isoniazid, valproate, amiodarone, antiviral nucleoside analogues) could promote the occurrence of such hepatic injuries. These cofactors must be taken into account before prescribing Suboxone Sublingual Film and during treatment monitoring. Measurement of liver function prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function tests during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending upon the findings, the medicinal product may be discontinued cautiously so as to prevent withdrawal syndrome and to prevent a return to drug addiction. If the drug treatment is continued, hepatic function should be monitored closely.

Hepatic disease. Because buprenorphine is metabolised by the liver, its activity may be increased and/or extended in those individuals with impaired hepatic function. Naloxone metabolism may also be impaired in hepatic failure patients. Because hepatic elimination plays a relatively large role (~70%) in the overall clearance of Suboxone Sublingual Film, lower initial doses and cautious titration of dosage may be required in patients with hepatic dysfunction.

CYP3A4 inhibitors. Because CYP3A4 inhibitors may increase concentrations of buprenorphine, patients already

treated with CYP3A4 inhibitors should have their dose of Suboxone Sublingual Film titrated carefully since a reduced dose may be required in these patients (see Interactions with Other Medicines).

Renal disease. Renal elimination plays a relatively small role (~30%) in the overall clearance of buprenorphine. Therefore no dose modification based on renal function is required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment (ClCr < 30 mL/min).

Use in ambulatory patients. Suboxone Sublingual Film may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Patients should be cautioned accordingly. Like other opiates, Suboxone Sublingual Film may produce orthostatic hypotension in ambulatory patients.

Head injury and increased intracranial pressure. Suboxone Sublingual Film, like other potent opiates may itself elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased. Suboxone Sublingual Film can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

Opiate withdrawal effects. Because Suboxone Sublingual Film contains naloxone, it is highly likely to produce marked and intense opiate withdrawal symptoms if injected.

Suboxone Sublingual Film may produce withdrawal symptoms in opiate dependent subjects if it is administered too soon after another opiate. Discontinuation of treatment may result in a withdrawal syndrome that may be delayed. Studies in animals, as well as clinical experience, have showed that buprenorphine may produce dependence but at a lower level than morphine. Consequently, it is important to follow the Dosage and Administration recommendations.

Neonatal abstinence syndrome. Neonatal withdrawal has been reported in the infants of women treated with buprenorphine during pregnancy. Time to onset of withdrawal symptoms ranged from day 1 to day 8 of life with most (69%) occurring on day 1. Adverse events associated with neonatal withdrawal syndrome included hypertonia, neonatal tremor, neonatal agitation, and myoclonus. There have been rare reports of convulsions and in one case, apnoea and bradycardia were also reported. In many cases the withdrawal was serious and required treatment (See Use in pregnancy).

Allergic reactions. Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the postmarketing experience. The most common signs and symptoms include rashes, hives, and pruritus. Cases of bronchospasm, angioneurotic oedema, and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine or naloxone is a contraindication to Suboxone Sublingual Film use.

Effects on fertility. There were no effects on mating performance or fertility in rats following buprenorphine treatment at oral doses ca 20 times the maximum clinical dose of 32 mg/day (based on mg/m^2). Dietary administration of Suboxone tablets to rats at doses of 47 mg/kg/day or greater (estimated respective buprenorphine and naloxone exposures 14 and 24 times the anticipated clinical exposure, based on plasma AUC) resulted in reduced female conception rates. A dietary dose of 9.4 mg/kg/day (twice the anticipated clinical exposure for both buprenorphine (based on AUC) and naloxone (based on mg/m^2) had no adverse effect on fertility.

Use in pregnancy (Category C)

In rats, oral administration of buprenorphine at doses up to 20 times the maximum clinical dose of 32 mg/day (based on mg/m^2) prior to and during gestation and lactation resulted in reduced implantation, fewer live births, and reduced pup weight gain and survival. There was no evidence of teratogenicity in rats and rabbits following parenteral administration of buprenorphine during the period of organogenesis, although there was embryofoetal toxicity, and reduced pup viability and developmental delays in rats. There was no evidence of teratogenicity in rats and rabbits following oral or intramuscular administration of maternally toxic doses of combinations of buprenorphine + naloxone during the period of organogenesis, although post-implantation losses were increased. In rats, oral (20 times maximum clinical dose, based on mg/m^2) or intramuscular administration of buprenorphine from late gestation to weaning was associated with increased stillbirths, reduced postnatal survival, and delayed postnatal development including weight gain and some neurological functions (surface righting reflex and startle response).

There are no adequate or well controlled studies of Suboxone Sublingual Film in pregnant women. Buprenorphine readily crosses the placental barrier, and may cause respiratory depression in neonates. During the last three months of pregnancy, chronic use of buprenorphine may be responsible for a withdrawal syndrome in neonates. Suboxone Sublingual Film is contraindicated in pregnancy (see Contraindications). Continued use of heroin during pregnancy is associated with significant risk to the mother and the foetus and neonate.

Use in lactation. Animal studies indicate buprenorphine has the potential to inhibit lactation or milk production. In rats, oral (20 times maximum clinical dose, based on mg/m^2) or intramuscular administration of buprenorphine from late gestation to weaning was associated with increased stillbirths, reduced postnatal survival, and delayed

postnatal development including weight gain and some neurological functions (surface righting reflex and startle response). The no effect level for developmental effects was twice the maximum clinical dose, based on mg/m^2.
Because buprenorphine is excreted into human milk, Suboxone Sublingual Film should not be used by breastfeeding women.

Paediatric use. Suboxone Sublingual Film is not recommended for use in children. The safety and effectiveness of Suboxone Sublingual Film in subjects below the age of 16 has not been established.

Carcinogenicity. In mice, no evidence for carcinogenicity due to buprenorphine was noted in life-time studies at dietary doses of up to 100 mg/kg/day, which equates to ca 14-fold human exposure at the maximum recommended clinical dose of 32 mg based on body surface area.
In rats, statistically significant (trend test adjusted for survival) dose related increases in testicular interstitial (Leydig) cell tumours occurred at a dietary buprenorphine dose of 55 mg/kg/day (16-fold the maximal recommended human sublingual dose of 32 mg, on a mg/m^2 basis); the no effect dose was 5.4 mg/kg/day (twice the maximal human dose, on a mg/m^2 basis).
The carcinogenic potential of naloxone alone has not been investigated in long-term animal studies.
In a 2 year dietary study with Suboxone tablets in rats, Leydig cell adenomas were found at doses of 6-115 mg/kg/day, associated with respective exposures (plasma AUC) to buprenorphine and naloxone of 2 to 21-fold, and up to 58-fold, anticipated human exposure. A NOEL was not established in the study.

Genotoxicity. In genotoxicity studies using buprenorphine and naloxone (9:2), assays for bacterial gene mutations and chromosomal damage (human lymphocytes *in vitro* and rat micronucleus test *in vivo*) were negative.

Interactions

Benzodiazepines. A number of deaths and cases of coma have occurred when individuals have intravenously misused buprenorphine and benzodiazepines concomitantly. Patients should be warned of the potential danger of the intravenous self administration of benzodiazepines or other CNS depressants at the same time as receiving Suboxone Sublingual Film (see Precautions).

CYP3A4 inhibitors. An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased Cmax and AUC of buprenorphine (approximately 50% and 70% respectively) and, to a lesser extent, of norbuprenorphine. Patients receiving Suboxone Sublingual Film should be closely monitored, and may require dose reduction if combined with potent CYP3A4 inhibitors e.g. protease inhibitors like ritonavir, nelfinavir or indinavir, azole antifungals like ketoconazole or itraconazole, calcium channel antagonists, and macrolide antibiotics (see Precautions).

CYP3A4 inducers. The interaction of buprenorphine with CYP3A4 inducers has not been investigated; therefore it is recommended that patients receiving Suboxone Sublingual Film should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are coadministered.

Effects on laboratory tests. Athletes should be aware that this medicine may cause a positive reaction to antidoping tests.

Adverse Reactions

Safety study of Suboxone Sublingual Film. The clinical safety of Suboxone Sublingual Film was evaluated in a trial (RB-US-07-0001) of 382 patients stabilised on Suboxone sublingual tablets for at least 30 days and then switched to Suboxone Sublingual Film for maintenance treatment. Two hundred and forty nine (249) patients completed at least 12 weeks of dosing with the Suboxone Sublingual Film. Patients received Suboxone Sublingual Film sublingually or buccally in a 1:1 ratio (N = 194 sublingually, N = 188 buccally). Adjunctive treatment was treatment as usual with varying levels of counselling and behavioural treatment. Treatment was conducted on an outpatient basis. Among all patients who received Suboxone Sublingual Film either sublingually or buccally, the most common treatment emergent adverse events were oral mucosal erythema, sinusitis, toothache, and upper respiratory infection. The most common treatment emergent adverse event for the patients administered Suboxone Sublingual Film sublingually were vomiting (4 patients, 2.1%) and upper respiratory tract infection (4 patients, 2.1%). All other adverse events were reported in 3 (1.5%) or fewer patients.
Adverse events reported to occur in at least 1% of patients being treated with Suboxone Sublingual Film in this trial are shown in Table 2.

Suboxone Sublingual Film **Table 2**

Adverse events (≥ 1%) by body system and treatment group in study RB-US-07-0001, sublingual administration

System organ class Preferred term	Sublingual N = 194
Infections and infestations	
Sinusitis	3 (1.5%)
Upper respiratory tract infection	4 (2.1%)
Pharyngitis streptococcal	3 (1.5%)
Urinary tract infection	3 (1.5%)
Influenza	2 (1.0%)
Tooth abscess	3 (1.5%)
Gastrointestinal disorders	
Glossodynia	3 (1.5%)
Hypoaesthesia oral	2 (1.0%)
Nausea	3 (1.5%)
Oral mucosal erythema	2 (1.0%)
Toothache	3 (1.5%)
Vomiting	4 (2.1%)
Musculoskeletal and connective tissues disorders	
Back pain	3 (1.5%)
Arthralgia	3 (1.5%)
Musculoskeletal pain	2 (1.0%)
Psychiatric disorders	
Insomnia	2 (1.0%)
Stress	2 (1.0%)
Injury, poisoning and procedural complications	
Skin laceration	2 (1.0%)
General disorders and administration site conditions	
Pain	3 (1.5%)
Nervous system disorders	
Headache	2 (1.0%)
Renal and urinary disorders	
Nephrolithiasis	2 (1.0%)
Skin and subcutaneous tissue disorders	
Dermatitis contact	2 (1.0%)
Pregnancy, puerperium and perinatal conditions	
Pregnancy	2 (1.0%)

* AEs are coded using medical dictionary for regulatory activities (MedDRA) version 11.0 terminology.

Clinical trials of Suboxone tablets. Adverse events reported to occur to at least 5% of patients being treated in clinical trials of Suboxone tablets (CR96/013 + CR96/014) are shown in Tables 3 and 4.

Suboxone Sublingual Film **Table 3**

Adverse events (≥ 1%) by body system and treatment group in study CR96/013

Body system/ adverse event (COSTART terminology)	Suboxone (buprenorphine/ naloxone) sublingual tablets 16/4 mg/day N = 107 n (%)	Subutex (buprenorphine) sublingual tablets 16 mg/day N = 103 n (%)	Placebo N = 107 n (%)	All subjects (N = 317) n (%)
Body as a whole				
Abscess	2 (1.9%)	1 (1.0%)	1 (0.9%)	4 (1.3%)
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)	19 (6.0%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)	24 (7.6%)
Fever	3 (2.8%)	3 (2.9%)	4 (3.7%)	10 (3.2%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)	93 (29.3%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)	25 (7.9%)
Accidental injury	2 (1.9%)	5 (4.9%)	5 (4.7%)	12 (3.8%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)	63 (19.9%)
Pain abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)	31 (9.8%)
Pain back	4 (3.7%)	8 (7.8%)	12 (11.2%)	24 (7.6%)
Withdrawal syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)	86 (27.1%)
Cardiovascular system				
Vasodilation	10 (9.3%)	4 (3.9%)	7 (6.5%)	21 (6.6%)
Digestive system				
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)	24 (7.6%)
Diarrhea	4 (3.7%)	5 (4.9%)	16 (15.0%)	25 (7.9%)
Dyspepsia	4 (3.7%)	5 (4.9%)	5 (4.7%)	14 (4.4%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)	42 (13.2%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)	21 (6.6%)
Metabolic/nutritional disorders				
Peripheral edema	1 (0.9%)	1 (1.0%)	2 (1.9%)	4 (1.3%)
Musculoskeletal system				
Myalgia	4 (3.7%)	1 (1.0%)	1 (0.9%)	6 (1.9%)
Nervous system				
Agitation	3 (2.8%)	2 (1.9%)	0	5 (1.6%)
Anxiety	3 (2.8%)	5 (4.9%)	4 (3.7%)	12 (3.8%)
Dizziness	5 (4.7%)	3 (2.9%)	4 (3.7%)	12 (3.8%)
Hyperkinesia	3 (2.8%)	2 (1.9%)	0	5 (1.6%)
Hypertonia	2 (1.9%)	0	2 (1.9%)	4 (1.3%)
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)	54 (17.0%)
Nervousness	5 (4.7%)	6 (5.8%)	4 (3.7%)	15 (4.7%)
Paresthesia	3 (2.8%)	3 (2.9%)	0	6 (1.9%)
Somnolence	8 (7.5%)	4 (3.9%)	2 (1.9%)	14 (4.4%)
Thinking abnormal	2 (1.9%)	1 (1.0%)	1 (0.9%)	4 (1.3%)
Tremor	2 (1.9%)	1 (1.0%)	2 (1.9%)	5 (1.6%)

Respiratory system				
Cough increased	1 (0.9%)	2 (1.9%)	2 (1.9%)	5 (1.6%)
Pharyngitis	2 (1.9%)	4 (3.9%)	1 (0.9%)	7 (2.2%)
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)	29 (9.1%)
Skin and appendages				
Sweating	15 (14.0%)	13 (12.6%)	11 (10.3%)	39 (12.3%)
Special senses				
Amblyopia				
Lacrimation disorder				
Urogenital system				
Dysmenorrhea				
Urinary tract infection				

Abbreviations: COSTART = coding symbols for thesaurus of adverse reaction terms

Suboxone Sublingual Film **Table 4**

Adverse events (≥ 1%) by body system and treatment group in study CR96/014

Body system/ adverse event (COSTART terminology)	All Suboxone sublingual tablet subjects N = 472 n (%)
Body as a whole	
Abscess	17 (3.6%)
Allergic reaction	8 (1.7%)
Asthenia	48 (10.2%)
Chills	44 (9.3%)
Cyst	7 (1.5%)
Edema, face	8 (1.7%)
Fever	36 (7.6%)
Flu syndrome	89 (18.9%)
Headache	202 (42.8%)
Infection	5 (1.1%)
Infection, viral	5 (1.1%)
Accidental injury	72 (15.3%)
Malaise	9 (1.9%)
Neck rigid	5 (1.1%)
Pain	197 (41.7%)
Pain, abdomen	77 (16.3%)
Pain, back	132 (28.0%)
Pain, chest	23 (4.9%)
Pain, neck	12 (2.5%)
Withdrawal syndrome	194 (41.1%)
Cardiovascular system	
Hypertension	17 (3.6%)
Migraine	13 (2.8%)
Vasodilation	29 (6.1%)
Digestive system	
Abscess, periodontal	10 (2.1%)
Anorexia	16 (3.4%)
Constipation	115 (24.4%)
Diarrhea	50 (10.6%)
Dyspepsia	45 (9.5%)
Flatulence	11 (2.3%)
Gastrointestinal disorder	
Liver function abnormal	18 (3.8%)
Nausea	76 (16.1%)
Stomatitis	5 (1.1%)
Tooth disorder	37 (7.8%)
Ulcer, mouth	6 (1.3%)
Vomiting	61 (12.9%)
Hemic/lympatic system	

Anemia	7 (1.5%)
Ecchymosis	6 (1.3%)
Lymphadenopathy	5 (1.1%)
Metabolic/nutritional disorders	
Peripheral edema	24 (5.1%)
Hyperglycemia	5 (1.1%)
Weight decreased	15 (3.2%)
Musculoskeletal system	
Arthralgia	20 (4.2%)
Arthritis	5 (1.1%)
Leg cramps	13 (2.8%)
Joint disorder	9 (1.9%)
Myalgia	31 (6.6%)
Nervous system	
Agitation	10 (2.1%)
Anxiety	65 (13.8%)
Depression	70 (14.8%)
Dizziness	33 (7.0%)
Dream abnormalities	9 (1.9%)
Drug dependence	9 (1.9%)
Hypertonia	9 (1.9%)
Insomnia	138 (29.2%)
Libido decreased	9 (1.9%)
Nervousness	42 (8.9%)
Paresthesia	28 (5.9%)
Somnolence	40 (8.5%)
Thinking abnormal	6 (1.3%)
Tremor	7 (1.5%)
Respiratory system	
Asthma	21 (4.4%)
Bronchitis	9 (1.9%)
Cough increased	36 (7.6%)
Dyspnea	9 (1.9%)
Lung disorder	10 (2.1%)
Pharyngitis	64 (13.6%)
Pneumonia	12 (2.5%)
Respiratory disorder	7 (1.5%)
Rhinitis	75 (15.9%)
Sinusitis	7 (1.5%)
Sputum increased	5 (1.1%)
Yawn	6 (1.3%)
Skin and appendages	
Acne	5 (1.1%)
Dermatological contact	5 (1.1%)
Herpes simplex	6 (1.3%)

Nodule, skin	6 (1.3%)
Pruritus	11 (2.3%)
Skin dry	6 (1.3%)
Sweat	74 (15.7%)
Urticaria	6 (1.3%)
Special senses	
Amblyopia	5 (1.1%)
Conjunctivitis	14 (3.0%)
Eye disorder	8 (1.7%)
Lacrimation disorder	14 (3.0%)
Pain, ear	8 (1.7%)
Urogenital system	
Dysmenorrhea	19 (4.0%)
Dysuria	9 (1.9%)
Hematuria	8 (1.7%)
Impotence	11 (2.3%)
Urinary tract infection	19 (4.0%)
Urine abnormality	12 (2.5%)
Vaginitis	11 (2.3%)

The most common adverse events reported were those related to withdrawal symptoms (e.g. abdominal pain, diarrhoea, muscle aches, anxiety, sweating). In patients with marked drug dependence, initial administration of buprenorphine can produce a withdrawal effect similar to that associated with naloxone.

Note. Patients enrolled in study RB-US-07-0001 on the soluble film were on a stable buprenorphine treatment prior to study initiation, while patients enrolled in studies CR96/013 and CR96/014 were buprenorphine naive individuals. As a result, the number of AEs observed in study RB-US-07-0001 are likely to be fewer than those observed in studies CR96/013 and CR96/014.

As with other opiates, orthostatic hypotension can occur (see Precautions).

Postmarketing experience with buprenorphine alone. Postmarketing experience with buprenorphine alone for treatment of opiate dependence has been associated with the following rare side effects: respiratory depression and coma, hallucinations, neonatal withdrawal syndrome, neonatal tremor, neonatal feeding disorder, foetal disorders, convulsions, confusion, miosis, weight decrease, asphyxia, hypoventilation, pruritus, angioedema, heart rate and rhythm disorders, and deaths.

Very rare (< 0.01%) side effects: loss of consciousness, cognitive disorders, psychosis, hallucinations, suicidal ideation, disorders of pregnancy (such as miscarriage and termination of pregnancy, premature birth, placental abruption, prolonged labour), foetal and neonatal complications (such as foetal disorders, foetal malformation, foetal growth retardation, foetal cystic hygroma, micrognathia, decreased oxygen saturation, developmental speech disorder, foetal dwarfism, foetal asphyxia, foetal cardiac rhythm disorder, cleft palate, Klinefelter's syndrome, intersexual genitalia, neonatal withdrawal syndrome, neonatal tremor, neonatal feeding disorder, infant respiratory distress syndrome and subarachnoid bleeding), heart murmur, convulsions, confusion, miosis, weight decrease, asphyxia, hypoventilation, pruritus, angioedema, heart rate and rhythm disorders, pulmonary oedema, septic shock, infections (including sepsis, septic arthritis and septic embolus, staphylococcal sacroileitis, brain abscess, pneumonia and endocarditis and amniotic fluid infection) events associated with intravenous misuse (such as cutaneous ulceration, eschar, lividoid and necrotic lesions and penile and scrotal lesion), aphasia, aphonia, slurred speech, diplopia, facial palsy, ascites and lympodoema, pulmonary oedema, pulmonary artery thrombosis, pericardial effusion, shock, cerebrovascular accident, Popeye syndrome, intracranial haemorrhage, nephropathy, colic, denutrition splenic infarction, electrolyte imbalance (such as hyperkalaemia, hyponatraemia and hypoglycaemia), deaths (including death from suicide and sudden infant death syndrome) and unusual reactions. The actual incidence of all cases is extremely low and must be taken in consideration with the comorbidities, lifestyle, environmental factors, and concomitant illicit and licit drug use of the population under treatment.

Postmarketing experience with Suboxone tablets. A postmarketing study looking at injecting practices in Australia suggested that the combination of buprenorphine and naloxone is less commonly injected than

buprenorphine alone.
Additionally, postmarketing experience with Suboxone tablets for treatment of opiate dependence has been associated rarely with the following side effects: insomnia, reduced feeling, anorexia (see also Tables 3 and 4 above), amnesia, convulsions, blood in vomit, fatigue, jaundice, swollen joints, miscarriage, shortness of breath, and suicide ideation.
Cases of hepatitis with jaundice, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy, and asymptomatic elevations in hepatic transaminases have been reported with buprenorphine use (see Precautions).
In cases of intravenous misuse of buprenorphine, local reactions, sometimes septic, and potentially serious acute hepatitis have been reported.
Cases of acute or chronic hypersensitivity have been reported with buprenorphine with symptoms including rashes, hives, pruritus and reported cases of bronchospasm, angioneurotic oedema, and anaphylactic shock (see Precautions and Contraindications).
Additionally, postmarketing experience with Suboxone tablets for treatment of opiate dependence has been associated very rarely (< 0.01%) with the following side effects: attempted suicide, disorders of pregnancy (such as premature birth), foetal and neonatal complications (such as foetal disorders, foetal malformation, foetal growth retardation, foetal cystic hygroma, micrognathia, macrocephaly, meconium staining and aspiration, decreased oxygen saturation, neonatal aspiration, asphyxia, developmental speech disorder, foetal dwarfism, foetal asphyxia, foetal cardiac rhythm disorder, low birthweight, Klinefelter's syndrome, mitochondrial disease, abnormal behaviour, developmental delay, developmental speech disorder intersexual genitalia, neonatal withdrawal syndrome, neonatal tremor, neonatal feeding disorder, subarachnoid bleeding and sudden infant death syndrome), pancreatitis, loss of consciousness, depression of consciousness, coordination disturbance, hallucinations, psychosis, mental disturbance and altered mental state, cerebral oedema, heart rate and rhythm disorders, septic shock, infections (including sepsis, pneumonia, chorioamniotitis and amniotic fluid infection), events associated with intravenous misuse (such as cellulitis), blurred vision, papilloedema, ascites and peripheral oedema, renal failure, adrenal insufficiency, electrolyte imbalance (such as hyperkalaemia, hypocalcaemia, hypomagnesaemia, hyponatraemia and hypoglycaemia) and deaths (including death from suicide and sudden infant death syndrome). The actual incidence of all cases is extremely low and must be taken in consideration with the comorbidities, lifestyle, environmental factors, and concomitant illicit and licit drug use of the population under treatment.

Dosage and Administration Treatment with Suboxone Sublingual Film is intended for adults and children aged 16 years or over who have agreed to be treated for addiction. When initiating buprenorphine treatment, the physician should be aware that it can precipitate withdrawal in opioid dependent patients if given too soon after the administration of heroin, methadone or another opiate.
Suboxone Sublingual Film and Suboxone Sublingual Tablet do not meet all criteria for bioequivalence (see section Pharmacokinetics). Patients being switched between tablets and soluble films may therefore require dosage adjustment.
The route of administration of Suboxone Sublingual Film is sublingual. Suboxone Sublingual Films should not be swallowed whole as this reduces the bioavailability of the medicine. Physicians must advise patients that the sublingual route is the only effective and safe route of administration for this medicine.
Please note. The following instructions refer to the buprenorphine content of each dose. Suboxone Sublingual Film 8 mg/2 mg (buprenorphine/naloxone) is referred to as the 8 mg dose and Suboxone Sublingual Film 2 mg/0.5 mg (buprenorphine/ naloxone) is referred to as the 2 mg dose.
Method of administration. Place Suboxone Sublingual Film under the tongue. If an additional Suboxone Sublingual Film is necessary to achieve the prescribed dose, place it sublingually on the opposite side from the first film, and in a manner to minimise overlapping as much as possible. If more than two films are required, place the next film or films after the first two have dissolved. The soluble film must be kept under the tongue until it is completely dissolved, which takes on average between 4 and 8 minutes. No food or drink should be consumed until the film is completely dissolved. Suboxone Sublingual Films should not be chewed, swallowed, or moved from placement.
Starting Suboxone Sublingual Film. An adequate maintenance dose, titrated to clinical effectiveness, should be achieved as rapidly as possible to prevent undue opiate withdrawal symptoms due to inadequate dosage.
Prior to induction, consideration should be given to the type of opiate dependence (i.e. long or short acting opiate), the time since last opiate use and the degree or level of opiate dependence.
Induction onto Subutex (buprenorphine tablets) is recommended when there is doubt about the level of dependence or previous drug use, to avoid precipitating opiate withdrawal. Patients can be switched to Suboxone Sublingual Film on the third day.
Patients taking street heroin (or other short acting opiates). When treatment starts the dose of Suboxone

Sublingual Film should be taken at least 6 hours after the patient last used opiates or when the early signs of withdrawal appear. The recommended starting dose is 4 mg Suboxone Sublingual Film on day one, with a possible additional 4 mg depending on the individual patient's requirement.

Patients on methadone. Before starting treatment with Suboxone Sublingual Film, the maintenance dose of methadone should be reduced to a maximum of 30 mg per day. The first dose of Suboxone Sublingual Film should be taken at least 24 hours after the patient last used methadone. The initial 4 mg Suboxone Sublingual Film induction dose should ideally be administered when early signs of withdrawal are evident.

Dosage adjustment and maintenance. The dose of Suboxone Sublingual Film should be adjusted progressively according to the clinical effect in the individual patient and should not exceed a maximum daily dose of 32 mg. The dosage is adjusted according to reassessments of the clinical and psychological status of the patient.

Less than daily dosing of Suboxone Sublingual Film. After a satisfactory period of stabilisation has been achieved the frequency of dosing may be decreased to dosing every other day at twice the individually titrated daily dose. For example, a patient stabilised to receive a daily dose of 8 mg may be given 16 mg on alternate days, with no medication on the intervening days. However, the dose given on any one day should not exceed 32 mg.

In some patients, after a satisfactory period of stabilisation has been achieved, the frequency of dosing may be decreased to 3 times a week (for example on Monday, Wednesday and Friday). The dose on Monday and Wednesday should be twice the individually titrated daily dose, and the dose on Friday should be three times the individually titrated daily dose, with no medication on the intervening days. However, the dose given on any one day should not exceed 32 mg.

Reducing dosage and stopping treatment. The decision to discontinue therapy with Suboxone Sublingual Film should be made as part of a comprehensive treatment plan. A gradual dose taper over a period of 21 days is shown in Table 5.

Suboxone Sublingual Film **Table 5**

Gradual dose taper schedule

Week	20 mg maintenance dose	16 mg maintenance dose	8 mg maintenance dose
1	16 mg	12 mg	8 mg
2	8 mg	8 mg	4 mg
3	4 mg	4 mg	4 mg

Overdosage Manifestations of acute overdose include pinpoint pupils, sedation, hypotension, respiratory depression and death.

In the event of accidental overdose, general supportive measures should be instituted including close monitoring of respiratory and cardiac status of the patient. The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death. If the patient vomits, care must be taken to prevent aspiration of the vomitus.

Treatment. In the event of depression of respiratory or cardiac function, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. High doses of naloxone hydrochloride 10-35 mg/70 kg may be of limited value in the management of buprenorphine overdose.

The long duration of action of Suboxone Sublingual Film should be taken into consideration when determining the length of treatment needed to reverse the effects of an overdose.

Presentation Sublingual film (soluble orange rectangular with white printed logo), buprenorphine 2 mg, naloxone 0.5 mg; buprenorphine 8 mg, naloxone 2 mg: 28's (individual child resistant polyethylene terephthalate (PET)/ low density polyethylene (LDPE)/ aluminium/ ethylene acrylic acid (EAA) sachets in pack).

Product Image: Suboxone Sublingual Film 2 mg/0.5 mg

Product Image: Suboxone Sublingual Film 8 mg/2 mg

Storage Store below 25deg. C.

Poisons Schedule S8.

Date of TGA approval or last amendment 04/02/2011

Appendix 12

MIMS Full Prescribing Information

Suboxone

Company Reckitt Benckiser

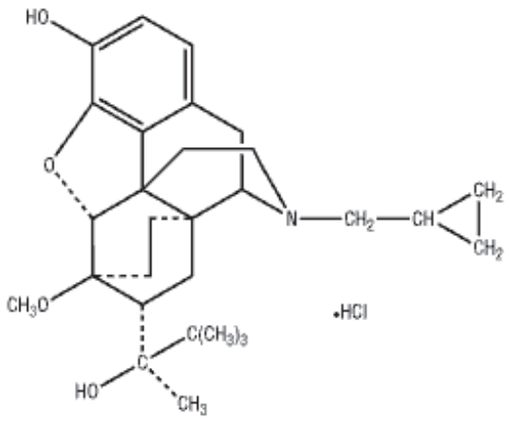
Primary Section: Poisoning, Toxicity and Drug Dependence - Agents used in drug dependence

ARTG Registered medicine

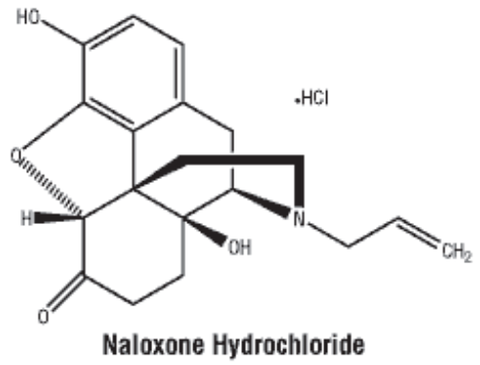
MIMS revision date: 01 Feb 2012

Composition Buprenorphine hydrochloride and naloxone hydrochloride at a ratio of 4:1 buprenorphine:naloxone.

Excipients Lactose, mannitol, maize starch, povidone, anhydrous citric acid, sodium citrate, magnesium stearate, acesulfame potassium and lemon and lime flavour.



Buprenorphine hydrochloride



Naloxone Hydrochloride

Description ***Buprenorphine hydrochloride.*** Chemical name: 21- cyclopropyl-7alpha-[(S) -1- hydroxy-1, 2, 2 - trimethylpropyl]-6, 14-endo-ethano-6, 7, 8, 14-tetrahydrooripavine hydrochloride. Molecular formula: $C_{29}H_{41}NO_4$.HCl. MW: 504.09. CAS: 53152-21-9. Buprenorphine hydrochloride is a white powder, weakly acidic with limited solubility in water (19.5 mg/mL at 37deg. C, pH 4.1).

Naloxone hydrochloride. Chemical name: (-)-17-allyl-4, 5alpha-epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride dihydrate. Molecular formula: $C_{19}H_{21}NO_4$.HCl.$2H_2O$. MW: 399.87. CAS: 51481-60-8. Naloxone hydrochloride is a white to slightly off white powder that exists as the dihydrate and is soluble in water, in dilute acids and in strong alkali.

Actions **Pharmacology.Pharmacodynamic properties.** Buprenorphine is a mu opioid receptor partial agonist, kappa opioid receptor antagonist. Its activity in opioid maintenance treatment is attributed to its slow dissociation from the mu receptors in the brain which reduces craving for opioids and opiate withdrawal symptoms. This minimises the need of the addicted patient for illicit opiate drugs.

During clinical pharmacology studies in opiate dependent subjects, buprenorphine demonstrated a ceiling effect on a number of parameters, including positive mood, 'good effect' and respiratory depression.

Naloxone is an antagonist at mu opioid receptors. Because of its almost complete first-pass metabolism, naloxone

administered orally or sublingually has no detectable pharmacological activity. However, when administered intravenously to opiate dependent persons, the presence of naloxone in Suboxone produces marked opiate antagonist effects and opiate withdrawal, thereby deterring intravenous abuse.

Pharmacokinetics.*Absorption.* When taken orally, buprenorphine undergoes first-pass metabolism with N-dealkylation and glucuroconjugation in the small intestine and the liver. The use of Suboxone by the oral route is therefore inappropriate. Suboxone tablets are for sublingual administration.

Plasma levels of buprenorphine and naloxone increased with the sublingual dose of Suboxone although the increases were not directly dose proportional (see Table 1). The levels of naloxone were too low to determine area under the curve values. There was a wide interpatient variability in the sublingual absorption of buprenorphine and naloxone from Suboxone tablets, but within subjects the variability was low. Naloxone did not appear to affect the pharmacokinetics of buprenorphine and Subutex and Suboxone are expected to deliver similar plasma concentrations of buprenorphine with sublingual dosing.

Suboxone **Table 1**

Mean Cmax and AUC of buprenorphine and naloxone following single sublingual doses of Suboxone tablets

	4 mg Suboxone (4 mg buprenorphine + 1 mg naloxone)	8 mg Suboxone (8 mg buprenorphine + 2 mg naloxone)	16 mg Suboxone (16 mg buprenorphine + 4 mg naloxone)	24 mg Suboxone (24 mg buprenorphine + 6 mg naloxone)
Buprenorphine				
Subjects	22	22	21	12
C_{max}	2.16	3.33	5.87	6.44
nanog/mL	(0.68-4.33)	(1.10-6.36)	(2.48-10.0)	(3.43-10.5)
AUC_{0-tn}	12.88	22.14	37.67	47.55
h. nanog/mL	(5.18-23.24)	(8.62-44.11)	(18.71-74.13)	(24.23-96.43)
Naloxone				
Subjects	20	21	20	12
C_{max}	0.12	0.23	0.39	0.47
nanog/mL	(0.06-0.25)	(0.09-0.42)	(0.07-1.15)	(0.08-1.02)

Naloxone did not affect the pharmacokinetics of buprenorphine and both Suboxone and Subutex deliver similar plasma concentrations of buprenorphine. Compared with intravenous administration, the mean absolute bioavailability of buprenorphine from sublingual Suboxone 8 mg tablets was 13.6% (range 5.1 to 24.9%) and that of naloxone was approximately 3%.

Distribution. The absorption of buprenorphine is followed by a rapid distribution phase (distribution half-life of two to five hours). Following intravenous administration, naloxone is rapidly distributed (distribution half-life of around four minutes).

Buprenorphine is highly lipophilic which leads to rapid penetration of the blood brain barrier. The drug is around 96% protein bound primarily to alpha and beta globulin. Naloxone is approximately 45% protein bound, primarily to alpha and beta globulin.

Metabolism and elimination. In animals and humans buprenorphine is metabolised by phase 1 (oxidative) and phase 2 (conjugation) reactions. It is oxidatively metabolised by N-dealkylation to norbuprenorphine by CYP3A4. In *in vitro* metabolic studies, addition of specific inhibitors of CYP3A4 (e.g. ketoconazole, gestodene, nifedipine, norfluoxetine, ritonavir) inhibited formation of norbuprenorphine (see also Precautions and Interactions with Other Medicines). There was no indication of the involvement of CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 or 2E1 in the N-dealkylation of buprenorphine. Buprenorphine was a weak competitive inhibitor of CYP2D6 and CYP3A4.

Norbuprenorphine is a mu agonist with weak intrinsic activity and is considered to be an inactive metabolite.

Naloxone undergoes direct glucuroconjugation to naloxone-3-glucuronide as well as N-dealkylation and reduction of the 6-oxo group.

Elimination of buprenorphine is biexponential or triexponential, with a long terminal elimination phase (mean half-life of 34.6 hours, range 20.4 to 72.9 hours), due in part to reabsorption of buprenorphine after intestinal hydrolysis of the conjugated metabolite, and in part to the highly lipophilic nature of the molecule. Naloxone has a short elimination half-life (mean 1.1 hours, range 0.63 to 1.94 hours).

Buprenorphine is essentially eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites

(70%), the rest being eliminated in the urine. Naloxone is excreted in the urine.
Elderly. No pharmacokinetic data in elderly patients are available.
Clinical trials. All trials used buprenorphine in conjunction with psychosocial counselling as part of a comprehensive addiction treatment program. There have been no clinical studies conducted to assess the efficacy of buprenorphine as the only component of treatment.
Clinical pharmacology studies demonstrate an aversive effect if Suboxone is misused by the injection route by opioid dependent patients. However, there have been no clinical trials to demonstrate a reduction in injection episodes because of the inherent difficulties and ethics in obtaining realistic outcomes of such a measure in a controlled study environment. Efficacy and safety data for Suboxone are primarily derived from a one year clinical trial, comprising a four week randomised double blind comparison of Suboxone, buprenorphine and placebo tablets followed by a 48 week safety study of Suboxone (study CR96/013 + CR96/014).
In the double blind placebo and active controlled study, 326 heroin addicted subjects were randomly assigned to either Suboxone 16 mg/day, buprenorphine 16 mg/day or placebo tablets. For subjects randomised to either active treatment, dosing began with one 8 mg tablet of buprenorphine on day 1, followed by 16 mg (two 8 mg tablets) of buprenorphine on day 2. On day 3, those randomised to receive Suboxone were switched to the combination tablet. Subjects were seen daily in the clinic (Monday through Friday) for dosing and efficacy assessments. Take home doses were provided for weekends. The primary study comparison was to assess the efficacy of buprenorphine and Suboxone individually against placebo. The percentage of thrice weekly urine samples that were negative for nonstudy opioids was statistically higher for both Suboxone versus placebo ($p < 0.0001$) and buprenorphine versus placebo ($p < 0.0001$).
Indications Treatment of opiate dependence within a framework of medical, social and psychological treatment.
Contraindications Hypersensitivity to buprenorphine or naloxone or any other component of the tablet.
Children less than 16 years of age.
Severe respiratory or hepatic insufficiency (Child-Pugh B or C).
Acute intoxication with alcohol or other central nervous system (CNS) depressant.
Pregnant women.
Breastfeeding.
Precautions **General.** Suboxone should be administered with caution in elderly or debilitated patients and those with impairment of hepatic, pulmonary or renal function; myxoedema or hypothyroidism, adrenal cortical insufficiency (e.g. Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens or kyphoscoliosis.
Buprenorphine increases intracholedochal pressure as do other opiates. Therefore, caution should be exercised when Suboxone is to be administered to patients with dysfunction of the biliary tract.
As with other opioids, caution is advised in patients using buprenorphine and having hypotension, prostatic hypertrophy and urethral stenosis.
As with other mu opiate receptor agonists, the administration of Suboxone may obscure the diagnosis or clinical course of patients with acute abdominal conditions.
Respiratory depression. Suboxone is intended for sublingual use only. Significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. A number of deaths have occurred when addicts have intravenously misused buprenorphine, usually with benzodiazepines concomitantly. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other opioids. Patients should be warned of the potential danger of the self administration of benzodiazepines or other CNS depressants at the same time as receiving Suboxone.
In the event of depression of respiratory or cardiac function, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. High doses of naloxone hydrochloride 10 to 35 mg/70 kg may be of limited value in the management of buprenorphine overdose.
Suboxone should be used with caution in patients with compromised respiratory function (e.g. chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia or pre-existing respiratory depression).
CNS depression. Patients receiving Suboxone in the presence of other narcotic analgesics, general anaesthetics, benzodiazepines, phenothiazines, other tranquillizers, sedatives/ hypnotics or other CNS depressants (including alcohol) may exhibit increased CNS depression. When such combined therapy is contemplated, reduction of the dose of one or both agents should be considered. Suboxone should be used cautiously with monoamine oxidase inhibitors (MAOIs), based on experience with morphine.
Hepatitis, hepatic events. Hepatic necrosis and hepatitis with jaundice have been reported with buprenorphine

use. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome and hepatic encephalopathy. Serious cases of acute hepatic injury have also been reported in a context of misuse, especially by the intravenous route. These hepatic injuries were dose related, and could be due to mitochondrial toxicity. Pre-existing or acquired mitochondrial impairment (genetic diseases, viral infections particularly chronic hepatitis C, alcohol abuse, anorexia, associated mitochondrial toxins, e.g. aspirin, isoniazid, valproate, amiodarone, antiviral nucleoside analogues) could promote the occurrence of such hepatic injuries. These cofactors must be taken into account before prescribing Suboxone and during treatment monitoring. Measurements of liver function tests prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function tests during treatment is also recommended. A biological and aetiological evaluation is recommended when a hepatic event is suspected. Depending upon the findings, the medicinal product may be discontinued cautiously so as to prevent withdrawal syndrome and to prevent a return to drug addiction. If the drug treatment is continued, hepatic function should be monitored closely.

Hepatic disease. Because buprenorphine is metabolised by the liver, its activity may be increased and/or extended in those individuals with impaired hepatic function. Naloxone metabolism may also be impaired in hepatic failure patients. Because hepatic elimination plays a relatively large role (~70%) in the overall clearance of Suboxone, lower initial doses and cautious titration of dosage may be required in patients with hepatic dysfunction.

CYP3A4 inhibitors. Because CYP3A4 inhibitors may increase concentrations of buprenorphine, patients already treated with CYP3A4 inhibitors should have their dose of Suboxone titrated carefully since a reduced dose may be required in these patients (see Interactions with Other Medicines).

Renal disease. Renal elimination plays a relatively small role (approximately 30%) in the overall clearance of buprenorphine. Therefore no dose modification based on renal function is required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment (ClCr < 30 mL/minute).

Use in ambulatory patients. Suboxone may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Patients should be cautioned accordingly. Like other opiates, Suboxone may produce orthostatic hypotension in ambulatory patients.

Head injury and increased intracranial pressure. Suboxone, like other potent opiates, may itself elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased. Suboxone can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

Opiate withdrawal effects. Because Suboxone contains naloxone, it is highly likely to produce marked and intense opiate withdrawal symptoms if injected.

Suboxone may produce withdrawal symptoms in opiate dependent subjects if it is administered too soon after another opiate. Discontinuation of treatment may result in a withdrawal syndrome that may be delayed. Studies in animals, as well as clinical experience, have shown that buprenorphine may produce dependence but at a lower level than morphine. Consequently, it is important to follow the recommendations in Dosage and Administration.

Neonatal abstinence syndrome. Neonatal withdrawal has been reported in the infants of women treated with buprenorphine during pregnancy. Time to onset of withdrawal symptoms ranged from day 1 to day 8 of life with most (69%) occurring on day 1. Adverse events associated with neonatal withdrawal syndrome included hypertonia, neonatal tremor, neonatal agitation and myoclonus. There have been rare reports of convulsions and in one case, apnoea and bradycardia were also reported. In many cases the withdrawal was serious and required treatment (see Use in pregnancy).

Allergic reactions. Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the postmarketing experience. The most common signs and symptoms include rash, hives and pruritus. Cases of bronchospasm, angioneurotic oedema and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine or naloxone is a contraindication to Suboxone use.

Carcinogenicity and mutagenicity.*Carcinogenicity.* In mice, no evidence for carcinogenicity due to buprenorphine was noted in life-time studies at dietary doses of up to 100 mg/kg/day, which equates to approximately 14-fold human exposure at the maximum recommended clinical dose of 32 mg based on body surface area.

In rats, statistically significant (trend test adjusted for survival) dose related increases in testicular interstitial (Leydig) cell tumours occurred at a dietary buprenorphine dose of 55 mg/kg/day (16-fold the maximal recommended human sublingual dose of 32 mg, on a mg/m^2 basis); the no effect dose was 5.4 mg/kg/day (twice the maximal human dose, on a mg/m^2 basis).

The carcinogenic potential of naloxone alone has not been investigated in long-term animal studies.

In a two year dietary study with Suboxone in rats, Leydig cell adenomas were found at doses of 6 to 115 mg/kg/day,

associated with respective exposures (plasma AUC) to buprenorphine and naloxone of 2 to 21-fold, and up to 58-fold, anticipated human exposure. A no observed effect level (NOEL) was not established in the study.

Mutagenicity. In genotoxicity studies using buprenorphine and naloxone (9:2), assays for bacterial gene mutations and chromosomal damage (human lymphocytes *in vitro* and rat micronucleus test *in vivo)* were negative.

Impairment of fertility. There were no effects on mating performance or fertility in rats following buprenorphine treatment at oral doses approximately 20 times the maximum clinical dose of 32 mg/day (based on mg/m^2). Dietary administration of Suboxone to rats at doses of 47 mg/kg/day or greater (estimated respective buprenorphine and naloxone exposures 14 and 24 times the anticipated clinical exposure, based on plasma AUC) resulted in reduced female conception rates. A dietary dose of 9.4 mg/kg/day (twice the anticipated clinical exposure for both buprenorphine (based on AUC) and naloxone (based on mg/m^2) had no adverse effect on fertility.

Use in pregnancy (Category C)

In rats, oral administration of buprenorphine at doses up to 20 times the maximum clinical dose of 32 mg/day (based on mg/m^2) prior to and during gestation and lactation resulted in reduced implantation, fewer live births and reduced pup weight gain and survival. There was no evidence of teratogenicity in rats and rabbits following parenteral administration of buprenorphine during the period of organogenesis, although there was embryofetal toxicity and reduced pup viability and developmental delays in rats. There was no evidence of teratogenicity in rats and rabbits following oral or intramuscular administration of maternally toxic doses of combinations of buprenorphine + naloxone during the period of organogenesis, although postimplantation losses were increased. In rats, oral (20 times maximum clinical dose, based on mg/m^2) or intramuscular administration of buprenorphine from late gestation to weaning was associated with increased stillbirths, reduced postnatal survival and delayed postnatal development including weight gain and some neurological functions (surface righting reflex and startle response).

There are no adequate or well controlled studies of Suboxone in pregnant women. Buprenorphine readily crosses the placental barrier, and may cause respiratory depression in neonates. During the last three months of pregnancy, chronic use of buprenorphine may be responsible for a withdrawal syndrome in neonates. Suboxone is contraindicated in pregnancy (see Contraindications). Continued use of heroin during pregnancy is associated with significant risk to the mother and the fetus and neonate.

Use in lactation Animal studies indicate buprenorphine has the potential to inhibit lactation or milk production. In rats, oral (20 times maximum clinical dose, based on mg/m^2) or intramuscular administration of buprenorphine from late gestation to weaning was associated with increased stillbirths, reduced postnatal survival and delayed postnatal development including weight gain and some neurological functions (surface righting reflex and startle response).

The no effect level for developmental effects was twice the maximum clinical dose, based on mg/m^2. Because buprenorphine is excreted into human milk, Suboxone should not be used in breastfeeding women.

Use in children Suboxone is not recommended for use in children. The safety and effectiveness of Suboxone in subjects below the age of 16 have not been established.

Interactions A number of deaths and cases of coma have occurred when addicts have intravenously misused buprenorphine and benzodiazepines concomitantly. Patients should be warned of the potential danger of the intravenous self administration of benzodiazepines or other CNS depressants at the same time as receiving Suboxone (see Precautions).

CYP3A4 inhibitors. An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased Cmax and AUC of buprenorphine (approximately 50 and 70%, respectively) and, to a lesser extent, of norbuprenorphine. Patients receiving Suboxone should be closely monitored and may require dose reduction if combined with potent CYP3A4 inhibitors, e.g. protease inhibitors like ritonavir, nelfinavir or indinavir, azole antifungals like ketoconazole or itraconazole, calcium channel antagonists and macrolide antibiotics (see Precautions).

CYP3A4 inducers. The interaction of buprenorphine with CYP3A4 inducers has not been investigated; therefore it is recommended that patients receiving Suboxone should be closely monitored if inducers (e.g. phenobarbitone, carbamazepine, phenytoin, rifampicin) are coadministered.

Effect on laboratory tests Athletes should be aware that this medicine may cause a positive reaction to antidoping tests.

Adverse Reactions Adverse events reported to occur by at least 1% of patients being treated in clinical trials of Suboxone (CR96/013 + CR96/014) are shown below.

Very common adverse events reported by at least 10% of subjects.*Body as a whole.* Headache, withdrawal syndrome.

Digestive system. Constipation, nausea.

Nervous system. Insomnia.

Skin and appendages. Sweating.

Common adverse events reported by at least 1% of subjects.*Body as a whole.* Asthenia, chills, fever, flu syndrome, infection, malaise, abdominal pain, back pain, chest pain, pain, accidental injury.
Cardiovascular system. Migraine, hypertension, vasodilatation.
Digestive system. Anorexia, diarrhoea, nausea/ vomiting, vomiting, dyspepsia, liver function abnormal, flatulence.
Metabolic/ nutritional disorders. Peripheral oedema, weight decreased.
Musculoskeletal system. Arthralgia, leg cramps, myalgia.
Nervous system. Anxiety, depression, dizziness, hypertonia, nervousness, paraesthesia, somnolence, thinking abnormal, libido decreased.
Respiratory system. Cough increased, pharyngitis, rhinitis.
Skin and appendages. Rash, pruritus, urticaria.
Special senses. Lacrimation disorder, amblyopia.
Urogenital system. Impotence, urine abnormality.
The most common adverse events reported were those related to withdrawal symptoms (e.g. abdominal pain, diarrhoea, muscle aches, anxiety, sweating). In patients with marked drug dependence, initial administration of buprenorphine can produce a withdrawal effect similar to that associated with naloxone.
As with other opiates, orthostatic hypotension can occur (see Precautions).
Postmarketing experience with buprenorphine alone and Suboxone. Postmarketing experience with buprenorphine alone for treatment of opiate dependency has been associated with the following rare side effects: respiratory depression and coma, hallucinations, neonatal withdrawal syndrome, neonatal tremor, neonatal feeding disorder, fetal disorders, convulsions, confusion, miosis, weight decrease, asphyxia, hypoventilation, pruritus, angioedema, heart rate and rhythm disorders and deaths.
Additionally, postmarketing experience with Suboxone for treatment of opiate dependency has been associated rarely with the following side effects: insomnia, reduced feeling, anorexia (see also list above), amnesia, convulsions, blood in vomit, fatigue, jaundice, swollen joints, miscarriage, shortness of breath and suicide ideation.
Cases of hepatitis with jaundice, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and asymptomatic elevations in hepatic transaminases have been reported with buprenorphine use (see Precautions).
In cases of intravenous misuse of buprenorphine, local reactions, sometimes septic and potentially serious acute hepatitis have been reported.
Cases of acute or chronic hypersensitivity have been reported with buprenorphine with symptoms including rash, hives, pruritus and reported cases of bronchospasm, angioneurotic oedema and anaphylactic shock (see Precautions and Contraindications).
Dosage and Administration Treatment with Suboxone sublingual tablets is intended for adults and children aged 16 years or over who have agreed to be treated for addiction. When initiating Suboxone treatment, the doctor should be aware that it can precipitate withdrawal in opioid dependent patients if given too soon after the administration of heroin, methadone or another opiate.
The route of administration of Suboxone is sublingual. Suboxone tablets should not be swallowed as this reduces the bioavailability of the medicine. Doctors must advise patients that the sublingual route is the only effective and safe route of administration for this drug.
Note. The following instructions refer to the buprenorphine content of each dose. Suboxone 8 mg/2 mg (buprenorphine/ naloxone) is referred to as the 8 mg dose and Suboxone 2 mg/0.5 mg (buprenorphine/ naloxone) is referred to as the 2 mg dose.
Method of administration. Suboxone tablets are to be placed under the tongue until dissolved, which usually requires two to ten minutes. The dose is made up from 2 and 8 mg sublingual tablets, which may be taken all at the same time or in two divided portions; the second portion to be taken directly after the first portion has dissolved.
Starting Suboxone. An adequate maintenance dose, titrated to clinical effectiveness, should be achieved as rapidly as possible to prevent undue opiate withdrawal symptoms due to inadequate dosage.
Prior to induction, consideration should be given to the type of opiate dependence (i.e. long or short acting opiate), the time since last opiate use and the degree or level of opiate dependence.
Induction onto Subutex (buprenorphine tablets) is recommended when there is doubt about the level of dependence or previous drug use, to avoid precipitating opiate withdrawal. Patients can be switched to Suboxone on the third day.
Patients taking street heroin (or other short acting opiates). When treatment starts the dose of Suboxone should be taken at least six hours after the patient last used opiates or when the early signs of withdrawal appear. The recommended starting dose is Suboxone 4 mg on day 1, with a possible additional 4 mg depending on the individual patient's requirement.
Patients on methadone. Before starting treatment with Suboxone, the maintenance dose of methadone should

be reduced to a maximum of 30 mg/day. The first dose of Suboxone should be taken at least 24 hours after the patient last used methadone. The initial Suboxone 4 mg induction dose should ideally be administered when early signs of withdrawal are evident.

Dosage adjustment and maintenance. The dose of Suboxone should be increased progressively according to the clinical effect in the individual patient and should not exceed a maximum daily dose of 32 mg. The dosage is adjusted according to reassessments of the clinical and psychological status of the patient.

Less than daily dosing of Suboxone. After a satisfactory period of stabilisation has been achieved the frequency of dosing may be decreased to dosing every other day at twice the individually titrated daily dose. For example, a patient stabilised to receive a daily dose of 8 mg may be given 16 mg on alternate days, with no medication on the intervening days. However, the dose given on any one day should not exceed 32 mg.

In some patients, after a satisfactory period of stabilisation has been achieved, the frequency of dosing may be decreased to three times a week (e.g. on Monday, Wednesday and Friday). The dose on Monday and Wednesday should be twice the individually titrated daily dose and the dose on Friday should be three times the individually titrated daily dose, with no medication on the intervening days. However, the dose given on any one day should not exceed 32 mg.

Reducing dosage and stopping treatment. The decision to discontinue therapy with Suboxone should be made as part of a comprehensive treatment plan. A gradual dose taper over a period of 21 days is shown in Table 2.

Suboxone **Table 2**

Gradual dose taper schedule

Week	20 mg maintenance dose	16 mg maintenance dose	8 mg maintenance dose
1	16 mg	12 mg	8 mg
2	8 mg	8 mg	4 mg
3	4 mg	4 mg	4 mg

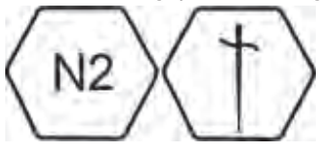
Overdosage Manifestations of acute overdose include pinpoint pupils, sedation, hypotension, respiratory depression and death.

In the event of accidental overdose, general supportive measures should be instituted including close monitoring of respiratory and cardiac status of the patient. The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death. If the patient vomits, care must be taken to prevent aspiration of the vomitus.

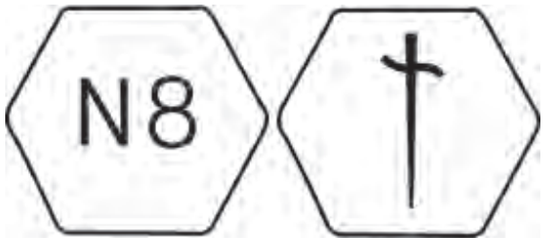
Treatment. In the event of depression of respiratory or cardiac function, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. High doses of naloxone hydrochloride 10 to 35 mg/70 kg may be of limited value in the management of buprenorphine overdose.

The long duration of action of Suboxone should be taken into consideration when determining the length of treatment needed to reverse the effects of an overdose.

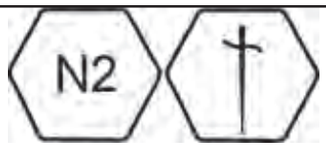
Presentation Sublingual tablets, buprenorphine 2 mg, naloxone 0.5 mg (white, hexagonal); buprenorphine 8 mg, naloxone 2 mg (white, hexagonal): 28's (blister pack).



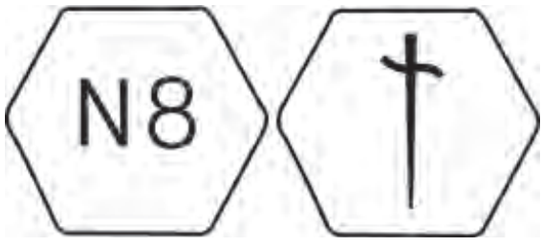
Product Image: Suboxone Sublingual Tablets 2 mg/0.5 mg



Product Image: Suboxone 8 mg/2 mg



Product Image: Suboxone Sublingual Tablets 2 mg/0.5 mg



Product Image: Suboxone 8 mg/2 mg

Storage Store below 30deg. C.

Poisons Schedule S8.

Date of TGA approval or last amendment 27/07/2005

Appendix 13

MIMS Full Prescribing Information

Subutex

Company Reckitt Benckiser

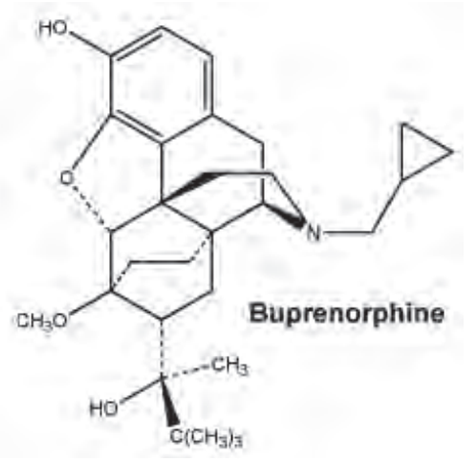
Primary Section: Poisoning, Toxicity and Drug Dependence - Agents used in drug dependence

ARTG Registered medicine

MIMS revision date: 01 Mar 2012

Composition Buprenorphine hydrochloride.

Excipients Lactose, mannitol, maize starch, povidone, anhydrous citric acid, sodium citrate and magnesium stearate.



Buprenorphine

Description Chemical name: 21-cyclopropyl-7alpha-[(S) -1-hydroxy-1,2,2- trimethylpropyl]-6,14-*endo* -ethano-6,7,8,14- tetrahydrooripavine hydrochloride. Molecular formula: $C_{29}H_{41}NO_4HCl$. MW: 504.09. CAS: 53152-21-9.

Buprenorphine hydrochloride is a white powder, weakly acidic with limited solubility in water (19.5 mg/mL at 37deg. C, pH 4.1).

Actions **Pharmacology.Pharmacodynamic properties.** Buprenorphine is a mu (mu) opioid receptor partial agonist, kappa (kappa) opioid receptor antagonist. Its activity in opioid maintenance treatment is attributed to its slow dissociation from the mu receptors in the brain which reduces craving for opioids and opiate withdrawal symptoms. This minimises the need of the addicted patient for illicit opiate drugs.

During clinical pharmacology studies in opiate dependent subjects, buprenorphine demonstrated a ceiling effect on a number of parameters, including positive mood, 'good effect' and respiratory depression.

Pharmacokinetic properties.*Absorption.* When taken orally, buprenorphine undergoes first-pass metabolism with N-dealkylation and glucuroconjugation in the small intestine and the liver. The use of Subutex by the oral route is therefore inappropriate. Subutex tablets are for sublingual administration.

Plasma levels of buprenorphine increased with the sublingual dose of Subutex although the increases were not directly dose proportional (see Table 1). There was a wide interpatient variability in the sublingual absorption of buprenorphine from Subutex tablets, but within subjects the variability was low.

Subutex **Table 1**

Mean C_{max} and AUC of buprenorphine following single sublingual doses of Subutex tablets in 23 (16M, 7F) subjects

	4 mg Subutex	8 mg Subutex	16 mg Subutex	24 mg Subutex
C_{max} nanog/mL	2.00 (0.31-3.76)	2.65 (1.09-4.82)	4.42 (1.79-8.58)	5.41 (1.67-17.3)
AUC_{0-tn} nanog.h/mL	9.37 (2.11-24.64)	19.92 (6.19-64.81)	34.94 (9.25-101.6)	48.81 (15.7-135)

Compared with intravenous administration, the bioavailability of sublingual buprenorphine 0.4 and 0.8 mg tablet doses was 30 to 35%. With sublingual buprenorphine 8 mg delivered as a solution the buprenorphine bioavailability compared to intravenous administration was 42%.

Distribution. The absorption of buprenorphine is followed by a rapid distribution phase (distribution half-life of two to five hours).
Buprenorphine is highly lipophilic which leads to rapid penetration of the blood brain barrier. The drug is around 96% protein bound primarily to alpha and beta globulin.
Metabolism and elimination. In animals and humans buprenorphine is metabolised by phase 1 (oxidative) and phase 2 (conjugation) reactions. It is oxidatively metabolised by N-dealkylation to norbuprenorphine by CYP3A4. The reported K_m for buprenorphine for CYP3A4 in human liver microsomes was 89 mM, and addition of specific inhibitors of CYP3A4 (e.g. ketoconazole, gestodene, nifedipine, norfluoxetine, ritonavir) inhibited formation of norbuprenorphine. There was no indication of the involvement of CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 in the N-dealkylation of buprenorphine. Buprenorphine was a weak competitive inhibitor of CYP2D6 and CYP3A4 (reported mean K_i in human liver microsomes was 10.3 micromolar and 40.2 micromolar respectively).

Norbuprenorphine is a mu agonist with weak intrinsic activity and is considered to be an inactive metabolite.
Elimination of buprenorphine is biexponential or triexponential, with a long terminal elimination phase (mean half-life of 34.6 hours, range 20.4 to 72.9 hours), due in part to reabsorption of buprenorphine after intestinal hydrolysis of the conjugated metabolite, and in part to the highly lipophilic nature of the molecule.
Buprenorphine is essentially eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites (70%), the rest being eliminated in the urine.
Elderly. No pharmacokinetic data in elderly patients are available.
Clinical trials. Efficacy and safety data for Subutex are primarily derived from two clinical trials of buprenorphine sublingual tablets (studies CR96/005 and CR96/013). All trials used buprenorphine in conjunction with psychosocial counselling as part of a comprehensive addiction treatment program. There have been no clinical studies conducted to assess the efficacy of buprenorphine as the only component of treatment.
Study CR96/005. In a double blind, double dummy, flexible dose ranging, parallel group, comparative, 13 week study, 405 opioid dependent subjects were randomised to receive daily Subutex sublingual tablets or methadone syrup. During weeks 1 to 6, doses were individually titrated until a stable dose was achieved (to a maximum of Subutex 32 mg or methadone 150 mg). Induction over seven days was too slow for Subutex and resulted in early drop outs. Once an adequate clinical dose of Subutex was attained it was maintained. During weeks 1 to 6, the most used daily dose of Subutex was 8 mg/day and the average prescribed dose of buprenorphine in week 6 was 10.9 mg/day. During weeks 7 to 13 Subutex was dosed on alternate days by doubling the daily dose, with placebo tablets administered on intervening days. The most used Subutex dose during this phase was 16 mg given every other day. Methadone was dosed daily throughout the study with the most used doses being 40 mg/day in weeks 1 to 6 and 50 mg/day in weeks 7 to 13. The average prescribed dose of methadone in week 6 was 53 mg/day. Take home doses were not permitted except on weekends. Daily or alternate day Subutex had similar efficacy to daily methadone. In both parts of the study there were no differences between the groups in the percentages of urine samples that were negative for opiates. The secondary efficacy parameters complemented the results of the primary parameters. Heroin use and heroin craving were reduced in both treatment groups and other measures reflecting problems associated with illicit drug use also improved with treatment and there were no treatment group differences overall and in the two phases of the study.
Study CR96/013. In a double blind, multicentre, placebo controlled study, 326 heroin addicted subjects were randomly assigned to either placebo, Subutex 16 mg/day, or combination treatment of buprenorphine 16 mg and naloxone 4 mg (combination tablet) per day. For subjects randomised to active treatment, dosing began with one Subutex 8 mg tablet on day 1, followed by Subutex 16 mg (two 8 mg tablets) on day 2. Subjects randomised to Subutex continued on 16 mg/day for four weeks. Subjects randomised to buprenorphine and naloxone were switched to the combination tablet on day 3. Subjects were seen daily in the clinic (Monday through Friday) for dosing and efficacy assessments. Take home doses were permitted for the weekend or holidays only. Subjects received one hour of individual counselling per week and a single session of HIV education. The percentage of thrice weekly urine samples that were negative for opiates was significantly higher for subjects treated with Subutex or the combination tablet than for those who received placebo.
Indications Treatment of opiate dependence, including maintenance and detoxification, within a framework of medical, social and psychological treatment.
Contraindications Hypersensitivity to buprenorphine or any other component of the tablet.
Children less than 16 years of age.
Severe respiratory or hepatic insufficiency.
Acute intoxication with alcohol or other central nervous system depressant.
Pregnant women.
Breastfeeding.

Precautions ***General.*** Subutex should be administered with caution in elderly or debilitated patients and those with severe impairment of hepatic, pulmonary or renal function; myxoedema or hypothyroidism; adrenal cortical insufficiency (e.g. Addison's disease); central nervous system (CNS) depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.
Buprenorphine increases intracholedochal pressure as do other opiates. Therefore, caution should be exercised when Subutex is to be administered to patients with dysfunction of the biliary tract.
As with other opioids, caution is advised in patients using buprenorphine and having: hypotension; prostatic hypertrophy and urethral stenosis.
As with other mu opiate receptor agonists, the administration of Subutex may obscure the diagnosis or clinical course of patients with acute abdominal conditions.
Respiratory depression. Subutex is intended for sublingual use only. Significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. A number of deaths have occurred when addicts have intravenously misused buprenorphine, usually with benzodiazepines concomitantly. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other opioids. Patients should be warned of the potential danger of the self administration of benzodiazepines or other CNS depressants at the same time as receiving Subutex.
In the event of depression of respiratory or cardiac function, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. High doses of naloxone hydrochloride 10 to 35 mg/70 kg may be of limited value in the management of buprenorphine overdose.
Subutex should be used with caution in patients with compromised respiratory function (e.g. chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia or pre-existing respiratory depression).
Patients receiving Subutex in the presence of other narcotic analgesics, general anaesthetics, benzodiazepines, phenothiazines, other tranquillizers, sedative/ hypnotics or other CNS depressants (including alcohol) may exhibit increased CNS depression. When such combined therapy is contemplated, reduction of the dose of one or both agents should be considered. Subutex should be used cautiously with monoamine oxidase inhibitors (MAOIs), based on experience with morphine.
Hepatitis, hepatic events. Hepatic necrosis and hepatitis with jaundice have been reported. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome and hepatic encephalopathy. Serious cases of acute hepatic injury have also been reported in a context of misuse, especially by the intravenous route. These hepatic injuries were dose related and could be due to mitochondrial toxicity. Pre-existing or acquired mitochondrial impairment (genetic diseases, viral infections particularly chronic hepatitis C, alcohol abuse, anorexia, associated mitochondrial toxins, e.g. aspirin, isoniazid, valproate, amiodarone, antiviral nucleoside analogues) could promote the occurrence of such hepatic injuries. These cofactors must be taken into account before prescribing Subutex and during treatment monitoring. Measurement of liver function tests prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function tests during treatment is also recommended. A biological and aetiological evaluation is recommended when a hepatic event is suspected. Depending upon the findings, the medicinal product may be discontinued cautiously so as to prevent withdrawal syndrome and to prevent a return to drug addiction. If the drug treatment is continued, hepatic function should be monitored closely.
Hepatic disease. Because buprenorphine is metabolised by the liver, its activity may be increased and/or extended in those individuals with impaired hepatic function. Naloxone metabolism may also be impaired in hepatic failure patients. Because hepatic elimination plays a relatively large role (approx. 70%) in the overall clearance of Subutex, lower initial doses and cautious titration of dosage may be required in patients with hepatic dysfunction.
CYP3A4 inhibitors. Because CYP3A4 inhibitors may increase concentrations of buprenorphine, patients already treated with CYP3A4 inhibitors should have their dose of Subutex titrated carefully since a reduced dose may be required in these patients (see Interactions with Other Medicines).
Renal disease. Renal elimination plays a relatively small role (approx. 30%) in the overall clearance of Subutex. Therefore no dose modification based on renal function is required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment (CL_{cr} < 30 mL/minute).
Use in ambulatory patients. Subutex may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Patients should be cautioned accordingly. Like other opiates, Subutex may produce orthostatic hypotension in ambulatory patients.
Head injury and increased intracranial pressure. Subutex, like other potent opiates, may itself elevate

cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased. Subutex can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

Opiate withdrawal effects. Subutex may produce withdrawal symptoms in opiate dependent subjects if it is administered too soon after another opiate. Discontinuation of treatment may result in a withdrawal syndrome that may be delayed.

Studies in animals, as well as clinical experience, have showed that buprenorphine may produce dependence but at a lower level than morphine. Consequently, it is important to follow the dosage and administration recommendations.

Neonatal abstinence syndrome. Neonatal withdrawal has been reported in the infants of women treated with Subutex during pregnancy. Time to onset of withdrawal symptoms ranged from day 1 to day 8 of life with most (69%) occurring on day 1. Adverse events associated with neonatal withdrawal syndrome included hypertonia, neonatal tremor, neonatal agitation and myoclonus. There have been rare reports of convulsions and in one case, apnoea and bradycardia were also reported. In many cases the withdrawal was serious and required treatment (see Use in pregnancy).

Allergic reactions. Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the postmarketing experience. The most common signs and symptoms include rashes, hives and pruritus. Cases of bronchospasm, angioneurotic oedema and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine is a contraindication to Subutex.

Carcinogenicity and mutagenicity.*Carcinogenicity.* Studies conducted in animals (rats and mice) show that buprenorphine is not carcinogenic at oral doses of up to 56 and 100 mg/kg/day, respectively, both of which equate to approximately 16-fold human exposure at the maximum recommended clinical dose of 32 mg based on body surface area.

Mutagenicity. The conclusion from Ames tests, chromosome aberration studies and a mouse lymphoma assay is that buprenorphine is not mutagenic in any of these test systems.

Impairment of fertility. There were no effects on mating performance or on fertility of male rats following short-term treatment with buprenorphine at systemic exposures up to 38 times the maximum anticipated human exposure (based on plasma AUC).

Use in pregnancy (Category C)

Treatment with buprenorphine during pregnancy was associated with difficult parturition and fetotoxicity, including postimplantation loss and decreased postnatal survival, in rats and rabbits at systemic exposures similar to the maximum anticipated human exposure (32 mg/day). Evidence for teratology was not evident in animal studies. Maternal oral administration at high doses (80 mg/kg/day) during gestation and lactation resulted in a delayed postnatal development of some neurological functions (surface righting reflex and startle response) in neonatal rats with a no obvious effect level (NOEL) of 8 mg/kg/day per oral (representing a systemic exposure of approx. 30% of the maximum anticipated clinical exposure).

Continued use of heroin during pregnancy is associated with significant risk to the mother and the fetus and neonate.

There are no adequate and well controlled studies of Subutex in pregnant women. Buprenorphine readily crosses the placental barrier, and may cause respiratory depression in neonates. During the last three months of pregnancy, chronic use of buprenorphine may be responsible for a withdrawal syndrome in neonates. Subutex is contraindicated in pregnant women (see Contraindications).

Use in lactation Animal studies indicate buprenorphine has the potential to inhibit lactation or milk production. Decreases in postnatal survival, growth and development were also observed in animals treated with buprenorphine during lactation. Because buprenorphine passes into the mother's milk, Subutex should not be used in breastfeeding women.

Use in children Subutex is not recommended for use in children. The safety and effectiveness of Subutex in subjects below the age of 16 have not been established.

Interactions A number of deaths and cases of coma have occurred when addicts have intravenously misused buprenorphine and benzodiazepines concomitantly. Patients should be warned of the potential danger of the intravenous self administration of benzodiazepines or other CNS depressants at the same time as receiving Subutex (see Precautions).

CYP3A4 inhibitors. An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased Cmax and AUC of buprenorphine (approximately 50 and 70%, respectively) and, to a lesser extent, of norbuprenorphine. Patients receiving Subutex should be closely monitored, and may require dose reduction if combined with potent CYP3A4 inhibitors, e.g. protease inhibitors like ritonavir, nelfinavir or indinavir, azole antifungals like ketoconazole or itraconazole, calcium channel antagonists and macrolide antibiotics (see Precautions).

CYP3A4 inducers. The interaction of buprenorphine with CYP3A4 inducers has not been investigated, therefore it is recommended that patients receiving Subutex should be closely monitored if inducers (e.g. phenobarbital (phenobarbitone), carbamazepine, phenytoin, rifampicin) are coadministered.

Effects on laboratory tests Athletes should be aware that this medicine may cause a positive reaction to 'antidoping' tests.

Adverse Reactions Adverse events reported to occur by at least 1% of patients being treated in clinical trials of Subutex (CR96/005 and CR96/013) are shown in Table 2.

Subutex **Table 2**

	Very common adverse events reported by at least 10% of subjects
Body as a whole	Headache, pain, withdrawal syndrome
Digestive system	Nausea
Nervous system	Insomnia
Skin and appendages	Sweating
	Common adverse events reported by at least 1% of subjects
Body as a whole	Asthenia, chills, fever, flu syndrome, hostility, infection, malaise, abdominal pain, back pain, chest pain, neck pain
Cardiovascular	Migraine palpitations, syncope, vasodilation
Digestive system	Anorexia, constipation, diarrhoea, dry mouth, dyspepsia, flatulence, gastrointestinal disorder, nausea/ vomiting, tooth disorder, vomiting
Haemic and lymphatic system	Lymphadenopathy
Metabolic/ nutritional disorder	Peripheral oedema
Musculoskeletal system	Arthralgia, leg cramps, myalgia, bone pain, spasm (general)
Nervous system	Agitation, anxiety, depression, dizziness, hypertonia, nervousness, paranoid reaction, paresthesia, somnolence, thinking abnormal, tremor
Respiratory system	Bronchitis, cough increased, dyspnoea, pharyngitis, rhinitis, yawning
Skin and appendages	Rash
Special senses	Lacrimation disorder, mydriasis
Urogenital system	Dysmenorrhoea

The most common adverse events reported were those related to withdrawal symptoms (e.g. abdominal pain, diarrhoea, muscle aches, anxiety, sweating). In patients with marked drug dependence, initial administration of buprenorphine can produce a withdrawal effect similar to that associated with naloxone.

As with other opiates, orthostatic hypotension can occur (see Precautions).

Postmarketing experience with Subutex for treatment of opiate dependency has been associated with the following rare side effects: respiratory depression and coma, hallucinations, neonatal withdrawal syndrome, neonatal tremor, neonatal feeding disorder, fetal disorders, convulsions, confusion, miosis, weight decrease, asphyxia, hypoventilation, pruritus, angioedema, heart rate and rhythm disorders and deaths.

Cases of hepatitis with jaundice, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and asymptomatic elevations in hepatic transaminases have been reported (see Precautions).

In cases of intravenous misuse, local reactions, sometimes septic, and potentially serious acute hepatitis have been reported.

Cases of acute or chronic hypersensitivity to buprenorphine have been reported with symptoms including rashes, hives, pruritus and reported cases of bronchospasm, angioneurotic oedema and anaphylactic shock. (See Precautions and Contraindications.)

Dosage and Administration Treatment with Subutex sublingual tablets is intended for adults and children aged 16 years or over who have agreed to be treated for addiction. When initiating Subutex treatment, the doctor should be aware that it can precipitate withdrawal in opioid dependent patients if given too soon after the administration of heroin, methadone or another opiate. The route of administration of Subutex is sublingual. Doctors

must advise patients that the sublingual route is the only effective and safe route of administration for this drug.

Method of administration. Subutex tablets should be placed under the tongue until dissolved. This usually occurs within two to ten minutes. The initial dose of Subutex may precipitate a mild abstinence syndrome in opioid dependent subjects. This may last up to 24 hours, but resolves with continued daily administration of Subutex.

Starting Subutex. An adequate maintenance dose, titrated to clinical effectiveness, should be achieved as rapidly as possible to prevent undue opiate withdrawal symptoms due to inadequate dosage.

Prior to induction, consideration should be given to the type of opiate dependence (i.e. long or short acting opiate), the time since last opiate use and the degree or level of opiate dependence.

Patients taking street heroin (or other short acting opiates). When treatment starts the dose of Subutex should be taken at least six hours after the patient last used opiates or when the early signs of withdrawal appear. The recommended starting dose is Subutex 4 mg on day 1, with a possible additional 4 mg depending on the individual patient's requirement.

Patients on methadone. Before starting treatment with Subutex, the maintenance dose of methadone should be reduced to 30 mg/day. The first dose of Subutex should be taken at least 24 hours after the patient last used methadone. The initial Subutex 4 mg induction dose should ideally be administered when the early withdrawal signs are evident.

Dosage adjustment and maintenance. The dose of Subutex should be increased progressively according to the clinical effect in the individual patient and should not exceed a maximum daily dose of 32 mg. The dosage is adjusted according to reassessments of the clinical and psychological status of the patient.

Less than daily dosing of Subutex. After a satisfactory period of stabilisation has been achieved the frequency of dosing may be decreased to dosing every other day at twice the individually titrated daily dose. For example, a patient stabilised to receive a daily dose of 8 mg may be given 16 mg on alternate days, with no medication on the intervening days. However, the dose given on any one day should not exceed 32 mg.

In some patients, after a satisfactory period of stabilisation has been achieved, the frequency of dosing may be decreased to three times a week (for example on Monday, Wednesday and Friday). The dose on Monday and Wednesday should be twice the individually titrated daily dose, and the dose on Friday should be three times the individually titrated daily dose, with no medication on the intervening days. However, the dose given on any one day should not exceed 32 mg.

Reducing dosage and stopping treatment. The decision to discontinue therapy with Subutex should be made as part of a comprehensive treatment plan. A gradual dose taper over a period of 21 days is shown in Table 3.

Subutex **Table 3**

Gradual dose taper schedule

Week	Maintenance dose		
	20 mg	16 mg	8 mg
1	16 mg	12 mg	8 mg
2	8 mg	8 mg	4 mg
3	4 mg	4 mg	4 mg

Detoxification. Examples of two ten day detoxification schedules using Subutex are shown in Tables 4 and 5. These have been used to treat subjects who wish to stop using heroin and do not want to undergo a prolonged period of maintenance treatment on Subutex.

In the first detoxification schedule heroin dependent subjects are transferred to Subutex at doses up to 8 mg/day. The dose of buprenorphine was gradually decreased in a flexible ten day schedule (Table 4).

Subutex **Table 4**

Detoxification schedule 1

Day	Subutex (mg)
1	8
2	6
3	6
4	4
5	4
6	2
7	2
8	1
9	1
10	0

A similar schedule employed Subutex treatment only on the first five days (Table 5). The Subutex dose was increased over the first three days and then decreased.

Subutex **Table 5**

Detoxification schedule 2

Day	Subutex (mg)
1	6
2	10 ± 2
3	10 ± 2
4	8 ± 2
5	4

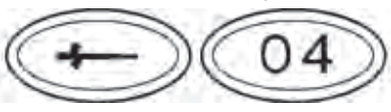
Overdosage Manifestations of acute overdose include pinpoint pupils, sedation, hypotension, respiratory depression and death.

In the event of accidental overdose, general supportive measures should be instituted including close monitoring of respiratory and cardiac status of the patient. The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death. If the patient vomits, care must be taken to prevent aspiration of the vomitus.

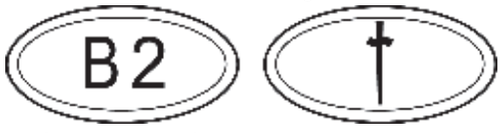
Treatment. In the event of depression of respiratory or cardiac function, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. High doses of naloxone hydrochloride 10 to 35 mg/70 kg may be of limited value in the management of buprenorphine overdose.

The long duration of action of Subutex should be taken into consideration when determining the length of treatment needed to reverse the effects of an overdose.

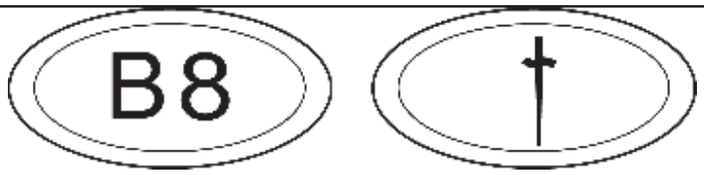
Presentation Sublingual tablets (white, oval), 0.4 mg, 2 mg, 8 mg: 7's (PVC/PVdC/aluminium blister).



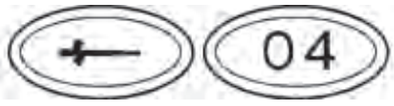
Product Image: Subutex 0.4 mg



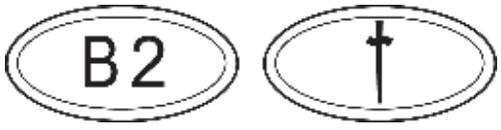
Product Image: Subutex 2 mg



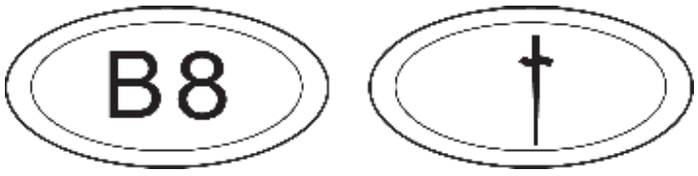
Product Image: Subutex 8 mg



Product Image: Subutex 0.4 mg



Product Image: Subutex 2 mg



Product Image: Subutex 8 mg

Storage Store below 25deg. C. Protect from prolonged exposure to light. Protect from moisture.

Poisons Schedule S8.

Date of TGA approval or last amendment 21/08/2003

Appendix 14

Possible drug interactions with buprenorphine or buprenorphine/naloxone

Drug	Status of interaction	Effect	Mechanism
Alcohol	Clinically important	Increased sedation, increased respiratory depression. Combination may also have increased hepatotoxic potential	Additive central nervous system depression
Benzodiazepines	Clinically important	Enhanced sedative effect	Additive CNS depression
Methadone and other opioids	Clinically important	Buprenorphine's antagonist effect may precipitate withdrawal in patients taking other opioids, or enhanced sedative and respiratory depression	Buprenorphine is a partial agonist of opiate receptors
Naltrexone and naloxone	Clinically important	Greatly reduced antagonist effect of naltrexone and naloxone	Buprenorphine has higher affinity for opioid receptors than naltrexone and naloxone
Drugs that inhibit CYP 3A4			
Erythromycin and other macrolide antibiotics	Clinically important	Raised buprenorphine levels	Decreased buprenorphine metabolism
HIV protease inhibitors such as indinavir, ritonavir, saquinavir	Clinically important	Raised buprenorphine levels	Decreased buprenorphine metabolism
Ketoconazole and other azole antifungal agents	Clinically important	Raised buprenorphine levels	Decreased buprenorphine metabolism
Drugs that induce CYP 3A4			
Carbamazapine	Theoretical	Reduced buprenorphine levels	Increased buprenorphine metabolism
Barbiturates e.g. phenobarbitone	Clinically important	Reduced buprenorphine levels. Increased sedation. Additive CNS depression	Increased buprenorphine metabolism
Phenytoin	Theoretical	Reduced buprenorphine levels	Increased buprenorphine metabolism
Rifampicin	Theoretical	Reduced buprenorphine levels	Increased buprenorphine metabolism

Appendix 15

Queensland Opioid Treatment Program – Consent to Treatment form

I, _____ consent to commencing methadone/

buprenorphine treatment at _____ .

In starting methadone/buprenorphine treatment, the following has been explained to me, I understand:

- Methadone (Biodone) and buprenorphine (Subutex®, Suboxone®) are drugs of dependence.
- I must provide honest and accurate information regarding my drug use.
- The use of other drugs (alcohol, benzodiazepines and other opioids) together with methadone or buprenorphine may impair my ability to drive a vehicle or operate heavy machinery during the stabilisation period.
- Take-away doses will not be replaced if lost, stolen or broken. It is my responsibility to ensure they are kept in a safe place and out of the reach of children.
- It is my responsibility to ensure I make regular payments to the pharmacy. All debts must be cleared before transfer to another pharmacy.
- Failure to pick up my medication for more than 3 days will result in my having to attend my prescriber/clinic for a review before dosing recommences.
- I need to give my prescriber/clinic 24 hours of notice when requesting changes in my take-away arrangements.
- Services are confidential unless I provide written consent. This is subject to the legal obligations of the clinic/prescriber and duty of care. I am aware that my case will be discussed at case conferences.
- I must attend my clinic/prescriber for regular reviews as requested. Failure to attend my review appointments may mean that my dosing will be ceased until I am reviewed.
- Violence, threatened violence or verbal abuse towards staff or other patients, diversion of my medication, doctor shopping and unlawful activity (e.g. drug dealing around the pharmacy or clinic) will result in my treatment being reviewed by my prescriber/clinic. This may result in termination of my treatment.

I agree to abide by the conditions of the Queensland Opioid Treatment Program as above and have been given the following information:

- methadone booklet/Subutex® booklet/Suboxone® booklet including information on side effects
- clinic information
- *Your guide to making a complaint* – Health Quality and Complaints Commission leaflet
- *Your Legal Obligations* leaflet
- copy of this Consent to Treatment form.

Signed: _____

Witness: _____

Date: _____

Appendix 16

Sample client/pharmacist agreement

I, _____ (pharmacist), agree to provide the following services:

- professional, fair and non-prejudiced treatment
- adequate and accurate information on treatment and services available
- handling of your information consistent with privacy legislation
- discreet and confidential handling of records.

I, _____ (client), agree to abide by the following treatment conditions:

- I will cooperate with pharmacy staff, or clearly and respectfully communicate the reasons behind the decision not to cooperate.
- I will attend the pharmacy for dosing at times set out by the pharmacist. I understand that if I do not attend within these times I will not be dosed and I will contact my case manager or prescriber.
- I will not contribute to crowding around the pharmacy by bringing friends or associates to the dispensary unnecessarily. In addition, I will not remain around the premises for longer than necessary.
- I will consume my dose as prescribed, under supervision of the pharmacist.
- I will not attempt to take supervised doses out of the pharmacy in any way. I understand that not taking a supervised dose in the prescribed manner (diversion) could result in my removal from the treatment program.
- Authorised take-away doses will remain my responsibility. I understand that these will not be replaced under any circumstances whether lost, stolen, vomited, leaking or broken.
- I will store take-away doses safely, out of reach of children or any other person who may be likely to misuse them. I acknowledge that any misuse or diversion of take-away doses may result in the take-aways being revoked and, potentially, my removal from the program.
- If I require any alteration in dose arrangement, I will contact my prescriber or case manager.
- I will present for review by my case manager or prescriber at their request in order to ensure my written instructions (prescriptions) remain current. I understand I will not receive a dose if the pharmacy does not have a current written instruction.
- I will contact my case manager or prescriber if I miss 1 or more doses.
- I will present for review by my prescriber if I miss 3 or more doses.
- I will tell any other doctor, dentist or health professional that I am on the opioid treatment program, and will not obtain prescriptions for any other opioid medication from anyone other than my clinic or prescriber.
- I will not present for dosing while intoxicated by any substance.
- I will assist in maintaining a safe environment for pharmacy staff and other patients by not being verbally or physically threatening or violent, not damaging property, and keeping the environment free from smoke and unrestrained animals. I understand that if I behave inappropriately, I will be removed from this pharmacy.
- I will not participate in any criminal activity in or around the pharmacy, including shoplifting and drug dealing. I understand that if I do, the police will be called immediately.
- I consent to my pharmacist, prescriber or case manager exchanging information regarding my social wellbeing, medical history and any other information that relates to my participation in the opioid treatment program.
- I agree to pay $_____ every____day(s)/week(s) ahead of time for dosing at this pharmacy. I understand that if I do not maintain these payments, the pharmacist may refuse to supply doses or take-away doses, or may insist on extra payments until the outstanding balance is repaid.

Client signature:_____ Date:_____

Client name:_____

Client address:_____

_____

Pharmacist signature:_____ Date:_____

Pharmacist name:_____

Pharmacy name and address:_____

_____

Appendix 17

Example of letter of introduction to pharmacy

26 March, 2012

Dr John Prescriber
Local GP Practice
123 Prescriber Crescent
Brisbane Qld 4000

Ph: 07 3333 3333
Fax: 07 4444 4444

Local Day & Night Chemist
111 Apothecary Way
Brisbane Qld 4000

Dear Sir/Madam

Re: CLIENT EXAMPLE - D.O.B. 01.01.1961

Thank you for accepting this client at your pharmacy for dosing on the Queensland Opioid Treatment Program. The first dose is scheduled for 1 April, 2012. The client's details are below:

Name:	Client Example
Address:	111 Client Street Brisbane Qld 4001
Date of birth:	01.01.1961
Sex:	Female
Height:	172 cm
Weight:	80 kg
Comments and distinguishing features:	Dolphin tattoo (R) shoulder. 10 cm scar on (L) calf. Star tattoo above (L) ankle.

AFFIX CLIENT PHOTO HERE

Should you have any queries or concerns, please do not hesitate to contact me on the above number.

Thank you for your assistance.

Yours faithfully,

Dr John Prescriber
Local GP Practice

Appendix 18

Outline of steps pharmacists should take in their record-keeping

It is important that dosing pharmacists ensure client records, records of administration and details of communications with the prescriber are clearly and consistently maintained and available to all persons administering doses.

It is recommended that a separate record for each patient be maintained so all necessary information is readily available to the person administering doses. Separate records also help to ensure that information relating to one patient is not available to another.

Ideally, client records should include:

- A recent client photograph (generally provided by the clinic or prescriber)
- The current written instruction, as well as an archive or previous written instructions. The QOTP written instruction suffices as a record of administration, with the total amount dispensed for that instruction being recorded in the pharmacy's controlled drug register. It is also a good idea to record the time that a patient presents for dosing. While there is not a designated space on the written instructions to do so, it could be annotated in the margins or in another section of the client's record.
- A signed client/pharmacist agreement *(refer to Appendix 16)*.
- Relevant patient details that could affect dosing. For example, a locum pharmacist may mistake a client with a speech impediment as being intoxicated.
- Details, including details of communications with the prescriber, variations in dosage and details of take-away dose authorisation. It is recommended that such details be recorded in a permanent, readily retrievable and consistent manner.
- Records of incidents such as lost/stolen/dropped doses, diversions, presentation of prescriptions from prescribers other than the QOTP prescriber that may be detrimental to treatment (e.g. other opioids and benzodiazepines).
- Records of payment (see example on next page).

The Pharmacy Guild of Australia, Queensland Branch, can advise pharmacies on record-keeping and can also provide general support to sites participating in QOTP.

Payment Summary Sheet

(adapted from the Pharmacy Guild of Australia, Queensland branch)

Client Details

Name: _____

Medication type (highlight)

Methadone
Biodone
Subutex tablet
Suboxone tablet
Suboxone film

Take-away doses authorised for: (highlight)

Mon Tue Wed Thu Fri Sat Sun

Remarks/special instructions

_____

_____

_____

_____

_____

Date paid	Amount paid	Next payment due	Staff initials	Client initials	Notes

Reference List

ACT Health, (2009). *The ACT opioid maintenance treatment guidelines*. Canberra: ACT Government.

Alford DP, Compton P, Samjet JH, (2006). 'Acute pain management for patients receiving maintenance methadone or buprenorphine therapy'. *Annals of Internal Medicine*. 144, pp.127-134.

Amato L, Minozzi S, Davoli M, Vecchi S, Ferri M, Mayet S, (2009). 'Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence'. *Cochrane Library Systematic Review*.

American Psychiatric Association, (1994). *Diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV)*. Washington: American Psychiatric Press.

Anthony JC, Warner LA, Kessler RC, (1994). 'Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the national comorbidity survey'. *Experimental and Clinical Psychopharmacology*. 2 (3), pp.244-268.

Auriacombe M, Franque P, Daulouède, J-P, Brisseau-Gimenez S, Tignol J, (2002). 'Traitements de substitution: le médicament est... celui qui le donne'. *Le Courrier des Addictions*. 4 (3), pp.104-106.

Australian Drug Reactions Advisory Committee, (2005). 'Cardiac vigilance recommended for methadone'. *Prescriber Update 2005*. 26 (2), pp.23-25.

Australian Institute of Health and Welfare, (2011). *2010 national drug strategy household survey report no. 25 cat. no. PHE 145*. Canberra: Australian Institute of Health and Welfare.

Rossi S (ed), (2011). *Australian medicines handbook 2011*. Adelaide: Australian Medicines Handbook.

Australian National Council on Drugs, (2012). *ANCD position statement: naltrexone sustained release preparations (injectible & implants)*. ACT: Australian National Council on Drugs.

Australasian Society for HIV Medicine, (2008). *HIV, viral hepatitis and STIs: a guide for primary care*. 15th ed.

Australasian Society for HIV Medicine, (2009). *Hepatitis C clinical management in opiate pharmacotherapy settings*. Revised edition.

Bell J, Kimber J, Lintzeris N, White J, Monheit B, Henry-Edwards S, Mattick R, Ali R, Ritter A, Quigley A, (2003). *Clinical guidelines and procedures for the use of naltrexone in the management of opioid dependence*. Australia: Department of Health and Ageing.

Beswick T, Best D, Rees S, Bearn J, Gossop M, Strang J, (2003). 'Major disruptions of sleep during treatment of the opiate withdrawal syndrome: differences between methadone and lofexidine detoxification treatments'. *Addiction Biology*. 8 (1), pp.49-57.

Bruce RD, Altice FL, (2007). 'Clinical care of the HIV-infected drug user'. *Infect Dis Clin North Am*. 21 (1), pp.149-179.

Brunton L, Chabner B, Knollman B, (2011). *Goodman and Gilman's the pharmacological basis of therapeutics*. 12th ed. USA: McGraw-Hill Professional.

Commonwealth of Australia, (2006). *National clinical guidelines for the management of drug use during pregnancy, birth and the early development years of the newborn*. Sydney: NSW Department of Health.

Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, Fry-Smith A, Day E, Lintzeris N, Roberts T, Burls A, Taylor RS, (2007). 'Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation'. *Health Technology Assessment*. 11 (9), pp.1-192.

Dhalla IA, (2012). 'Opium, opioids, and an increased risk of death'. *British Medical Journal*. 11 (9), pp.244:e2617.

Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L, (2009). 'Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved'. *Drug and Alcohol Dependence*. 105, pp.9-15.

Drugs of Dependence Advisory Committee, (2006). *Policy for maintenance pharmacotherapy for opioid dependence*. Victoria: State of Victoria.

Drugs of Dependence Unit, (2012). *Queensland opioid treatment program: suboxone film*. Queensland Health.

Dunlop A, Panjari M, O'Sullivan H, Henschke P, Love V, Ritter A, Lintzeris N, (2003). *Clinical guidelines for the use of buprenorphine in pregnancy*. Fitzroy: Turning Point Alcohol and Drug Centre.

Reckitt Benckiser. *Buprenorphine product information*. [ONLINE] Available at: https://www.mimsonline.com.au. [Last Accessed February 2012].

Sigma Pharmaceuticals. *Methadone syrup full product information*. [ONLINE] Available at: https://www.mimsonline.com.au. [Last Accessed February 2012].

Faggiano F, Vigna-Taglianti F, Versino E, Lemma P, (2008). 'Methadone maintenance at different dosages for opioid dependence'. *Cochrane Library Systematic Review*.

Finnegan LP, (1988). 'Drug addiction and pregnancy: the newborn'. In: Chasnoff IJ (ed), *Drugs, alcohol, pregnancy and parenting*. Dordrecht, The Netherlands: Kluwer Academic Publishers. pp.59-71.

Finnegan LP, (1991). 'Treatment issues for opioid-dependent women during the perinatal period'. *Journal of Psychoactive Drugs*. 23 (2), pp.191-201.

Gibbie TM, Hides L, Cotton SM, Lubman DI, Aitken C, Hellard M, (2011). 'The relationship between personality disorders and mental health, substance use severity and quality of life among injecting drug users'. *The Medical Journal of Australia*. 195 (3), pp.s16-s21.

Gibson A, Degenhardt L, (2005). *Mortality related to naltrexone in the treatment of opioid dependence: a comparative analysis. NDARC technical report no. 229*. Sydney: National Drug and Alcohol Research Centre.

Gibson A, Degenhardt L, Mattick RP, Ali R, White J, O'Brien S, (2008). 'Exposure to opioid maintenance treatment reduces long-term mortality'. *Addiction*. 103, pp.462-468.

Gillman PK, (2005). 'Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity'. *British Journal of Anaesthesia*. 95 (4), pp.434-441.

Glatstein MM, Garcia-Bournissen F, Finkelstein Y, Koren G, (2008). 'Methadone exposure during lactation'. *Canadian Family Physician*. 54 (12), pp.1689-1690.

Gordon AJ, Kunins HV, Rastegar DA, Tetrault JM, Walley AY, (2011). 'Update in addiction medicine for the generalist'. *J Gen Intern Med*. 26 (1), pp.77-82.

Linda G, Farrell MF, Bornemann R, Sullivan LE, Ali R, (2011). 'Oral substitution treatment of injecting opioid users for prevention of HIV infection'. *Cochrane Database of Systematic Reviews 2011*. 8.

Greenwald MK, Johanson CE, Moody DE, Woods JH, Kilbourn MR, Koeppe RA, Schuster CR, Zubieta JK, (2003). 'Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers'. *Neuropsychopharmacology*. 28, pp.2000-2009.

Haber P, Lintzeris N, Proude E, Lopatko O, (2009). *Guidelines for the treatment of alcohol problems*. Australia: Department of Health and Ageing.

Hagan H, Pouget ER, Des Jarlais DC, (2011). 'A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs'. *The Journal of Infectious Diseases*. 204, pp.74-83.

Hallinan R, Byrne A, Amin J, Dore GJ, (2005). 'Hepatitis C virus prevalence and outcomes among injecting drug users on opioid replacement therapy'. *Journal of Gastroenterology and Hepatology*. 20, pp.1082-1086.

Hallinan R, Ray J, Byrne A, Agho K, Attia J, (2006). 'Therapeutic thresholds in methadone maintenance treatment: a receiver operating characteristic analysis'. *Drug and Alcohol Dependence*. 81 (2), pp.129-136.

Handford C, (2011). *Buprenorphine/naloxone for opioid dependence: clinical practice guideline*. Canada: Centre for Addiction and Mental Health.

Henry-Edwards S, Gowing L, White J, Ali R, Bell J, Brough R, Lintzeris N, Ritter A, Quigley A, (2008). 'Clinical guidelines and procedures for the use of methadone in the maintenance treatment of opioid dependence'. In: Mattick RP, Ali R, Lintzeris N (eds), *Pharmacotherapies for the treatment of opioid dependence: efficacy, cost-effectiveness and implementation guidelines*. New York: Informa Healthcare USA.

Henry-Edwards S, Gowing L, White J, Ali R, Bell J, Brough R, Lintzeris N, Ritter A, Quigley A, (2003). *Clinical guidelines and procedures for the use of methadone in the maintenance treatment of opioid dependence*. Commonwealth of Australia: Department of Health and Ageing.

Isenberg D, Wong SC, Curtis JA, (2008). 'Serotonin syndrome triggered by a single dose of suboxone'. *The American Journal of Emergency Medicine* . 26 (7), pp.840.

Jansson LM, DiPietro JA, Velez M, Elko A, Williams E, Milio L, O'Grady K, Jones HE, (2011). 'Foetal neurobehavioral effects of exposure to methadone or buprenorphine'. *Neurotoxicology and Teratology*. 33, pp.240-243.

Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, O'Grady KE, Selby P, Martin PR, Fischer G, (2010). 'Neonatal abstinence syndrome after methadone or buprenorphine exposure'. *New England Journal of Medicine*. 363, pp.2320-2331.

Jones HE, Martin PR, Heil SH, Kaltenbach K, Selby P, Coyle MG, Stine SM, O'Grady KE, Arria AM, Fischer G, (Oct 2008). 'Treatment of opioid-dependent pregnant women: clinical and research issues'. *Journal of Substance Abuse Treatment*. 35 (3), pp.245-259.

Kadden RM, Litt MD, (2011). 'The role of self-efficacy in the treatment of substance use disorders'. *Addictive Behaviors*. 36, pp.1120-1126.

Kakko J, Heilig M, Sarman I, (2008). 'Buprenorphine and methadone treatment of opiate dependence during pregnancy: comparison of foetal growth and neonatal outcomes in two consecutive case series'. *Alcohol and Drug Dependence*. 96, pp.69-78.

Kim TW, Alford DP, Malabanan A, Holick MF, Samet JH, (2006). 'Low bone density in patients receiving methadone maintenance treatment'. *Drug and Alcohol Dependence*. 85, pp.258-262.

Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MCP, (2009). 'QTc interval screening in methadone treatment'. *Annals of Internal Medicine*. 150, pp.387-395.

Lintzeris N, Batey R, (Unpublished paper). *Transfer of patients from methadone to buprenorphine (including high dose transfer)*. Personal communication.

Lintzeris N, Clark N, Muhleisen P, Ritter A, Ali R, Bell J, Gowing L, Hawkin L, Henry-Edwards S, Mattick R, Monheit B, Newton I, Quigley A, Whicker S, White J, (2009). 'National clinical guidelines and procedures for the use of buprenorphine in the treatment of heroin dependence'. In: Mattick RP, Ali R, Lintzeris N (eds), *Pharmacotherapies for the treatment of opioid dependence: efficacy, cost-effectiveness and implementation guidelines*. New York: Informa Healthcare. pp.390-446.

Lintzeris N, Clark N, Winstock A, Dunlop A, Muhleisen P, Gowing L, Ali R, Ritter A, Bell J, Quigley A, Mattick R, Monheit B, White J, (2006). *National clinical guidelines and procedures for the use of buprenorphine in the treatment of opioid dependence*. Commonwealth of Australia: Department of Health and Ageing.

Lintzeris N, Mitchell TB, Bond A, Nestor L, Strang J, (2006). 'Interactions on mixing diazepam with methadone or buprenorphine in maintenance patients'. *Journal of Clinical Psychopharmacology*. 26 (3), pp.274-283.

Lintzeris N, Mitchell TB, Bond AJ, Nestor L, Strang J, (2007). 'Pharmacodynamics of diazepam co-administered with methadone or buprenorphine under high dose conditions in opioid dependent patients'. *Drug and Alcohol Dependence*. 91 (2-3), pp.187-194.

Lowinson JH, Ruiz P, Millman RB, Langrod JG, (2004). *Substance abuse: a comprehensive textbook*. 4th ed. Philadelphia: Lippincott Williams & Wilkins.

McCance-Katz EF, Rainey PM, Moody DE, (2010). 'Effect of cocaine use on buprenorphine pharmacokinetics in humans'. *The American Journal on Addictions*. 19 (1), pp.38-46.

McCance-Katz EF, Jatlow P, Rainey PM, (2010). 'Effect of cocaine use on methadone pharmacokinetics in humans'. *The American Journal on Addictions*. 19 (1), pp.47-52.

McKetin R, McLaren J, Kelly E, (2005). *The Sydney methamphetamine market: Patterns of supply, use, personal harms and social consequences. Monograph series no. 13*. Commonwealth of Australia: National Drug Law Enforcement Research Fund.

Malpas TJ, Darlow BA, (1999). 'Neonatal abstinence syndrome following abrupt cessation of breastfeeding'. *The New Zealand Medical Journal*. 112 (1080), pp.12-13.

Malpas TJ, Horwood J, Darlow BA, (1997). 'Breastfeeding reduces the severity of neonatal abstinence syndrome'. *Journal of Paediatrics and Child Health*. August, 33 (4), pp.A38.

Marquet P, (2002). 'Pharmacology of high-dose buprenorphine'. In: Kintz P, Marquet P (eds), *Buprenorphine therapy of opiate addiction*. New Jersey: Humana Press.

Martin PR, Arria AM, Fischer G, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Selby P, Jones HE, (2009). 'Psychopharmacologic management of opioid-dependent women during pregnancy'. *Am J Addict*. 18 (2), pp.148-156.

Mattick RP, Kimber J, Breen C, Davoli M, (2008). 'Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence'. *Cochrane Library Systematic Review*.

Mattick RP, Breen C, Kimber J, Davoli M, (2009). 'Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence'. *Cochrane Library Systematic Review*.

Mattick RP, Kimber J, Breen C, Davoli M, (2008). 'Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence'. *Cochrane Database of Systematic Reviews 2011*. CD002207.

Mattick RP, Ali R, Lintzeris N (eds), (2008). *Pharmacotherapies for the treatment of opioid dependence: efficacy, cost-effectiveness and implementation guidelines*. New York: Informa Healthcare USA.

Mayet S, Gossop M, Lintzeris , Markides V, Strang J, (2011). 'Methadone maintenance, QTc and torsade de pointes: who needs an electrocardiogram and what is the prevalence of QTc prolongation?'. *Drug and Alcohol Review*. 30, pp.388-396.

Mégarbane B, Buisine A, Jacobs F, Résière D, Chevillard L, Vicaut E, Baud FJ, (2010). 'Prospective comparative assessment of buprenorphine overdose with heroin and methadone: clinical characteristics and response to antidotal treatment'. *Journal of Substance Abuse Treatment*. 38, pp.403-407.

Mental Health and Drug and Alcohol Office, (2006). *Opioid treatment program: clinical guidelines for methadone and buprenorphine treatment*. Sydney: NSW Department of Health.

Miller W, Rollnick S, (2002). *Motivational interviewing: preparing people for change*. 2nd ed. New York: The Guilford Press.

Ministerial Council on Drug Strategy, (2011). *National drug strategy 2010–2015: a framework for action on alcohol, tobacco and other drugs*. Commonwealth of Australia: Department of Health and Ageing.

Nosyk B, Sun H, Evans E, Marsh DC, Anglin MD, Hser YI, Anis AH, (2012). 'Defining dosing pattern characteristics of successful tapers following methadone maintenance treatment: results from a population-based retrospective cohort study'. *Addiction*. 107 (9), pp.1621-1629.

O'Grady MJ, Hopewell J, White MJ, (2009). 'Management of neonatal abstinence syndrome: a national survey and review of practice'. *Archives of Disease in Childhood. Foetal and Neonatal Edition*. 94 (4), pp.F249-252.

Pani PP, Vacca R, Trogu E, Amato L, Davoli M, (2010). 'Pharmacological treatment for depression during opioid agonist treatment for opioid dependence'. *Cochrane Library Systematic Review*. Issue 9.

Petry NM, Bickel WK, Piasecki D, Marsch LA, Badger GJ, (2000). 'Elevated liver enzyme levels in opioid-dependent patients with hepatitis treated with buprenorphine'. *American Journal on Addictions*. 9 (3), pp.265-269.

Peyrière H, Tatem L, Bories C, Pageaux GP, Blayac JP, Larrey D, (2009). 'Hepatitis after intravenous injection of sublingual buprenorphine in acute hepatitis C carriers: report of two cases of disappearance of viral replication after acute hepatitis'. *The Annals of Pharmacotherapy*. 43 (5), pp.973-977.

Pharmaceutical Services Branch, (2004). *Supply of methadone and buprenorphine under the New South Wales pharmacotherapy drug treatment programs: guidelines for community pharmacists*. NSW Health Department.

Pirnay S, Borron SW, Giudicelli CP, Tourneau J, Baud FJ, Ricordel I, (2004). 'A critical review of the causes of death among post-mortem toxicological investigations: analysis of 34 buprenorphine-associated and 35 methadone-associated deaths'. *Addiction*. August, 99 (8), pp.978-988.

Queensland Government, (2011). *Health Act 1937 (reprint 6C)*. Queensland: Office of the Queensland Parliamentary Counsel.

Queensland Government, (2011). *Hospital and Health Boards Act 2011 (reprint 1B)*. Queensland: Office of the Queensland Parliamentary Counsel.

Queensland Government, (1996). *Health (Drugs and Poisons) Regulation 1996*. Brisbane: Office of the Queensland Parliamentary Counsel.

Queensland Health, (2012). *Queensland drug and alcohol withdrawal clinical practice guidelines*. Queensland: Mental Health and Drug and Alcohol Directorate, Queensland Health.

Rastogi R, Swarm RA, Patel TA, (2011). 'Case scenario: opioid association with serotonin syndrome: implications to the practitioners'. *Anesthesiology*. 115 (6), pp.1291-1298.

Razali K, Thein HH, Bell J, Cooper-Stanbury M, Dolan K, Dore G, George J, Kaldor J, Karvelas M, Li J, Maher L, McGregor S, Hellard M, Poeder F, Quaine J, Stewart K, Tyrrell H, Weltman M, Westcott O, Wodak A, Law M, (2007). 'Modelling the hepatitis C virus epidemic in Australia'. *Drug and Alcohol Dependence*. 91, pp.228-235.

Ruiz P, Strain EC, Langrod JG, (2007). *The substance abuse handbook*. USA: Lippincott Williams & Wilkins.

Schottenfeld RS, Pakes J, O'Connor P, Chawarski M, Oliveto A, Kosten TR, (2000). 'Thrice-weekly versus daily buprenorphine maintenance'. *Biological Psychiatry*. 47 (12), pp.1072-1079.

Simoens S, Ludbrook A, Matheson C, Bond C, (2006). 'Pharmaco-economics of community maintenance for opiate dependence: a review of evidence and methodology'. *Drug and Alcohol Dependence*. 84 (1), pp.28-39.

Smirnov A, Kemp R, (2012). 'Use and misuse of opioid replacement therapies: a Queensland study'. *Substance Use & Misuse*. 47 (1), pp.78-85.

Smith HS, (2009). 'Opioid metabolism'. *Mayo Clin Proc*. 84 (7), pp.613-624.

Smith WM, (2008). 'Cardiac repolarisation: the long and short of it'. *The Medical Journal of Australia*. 188 (12), pp.688-689.

Srivastava A, Kahan M, (2006). 'Methadone induction doses: are our current practices safe?'. *Journal of Addictive Diseases*. 25 (3), pp.5-13.

Strain EC, Stitzer ML, (2006). *The treatment of opioid dependence*. Baltimore: John Hopkins University Press.

Strang J, McCambridge J, Best D, Beswick T, Bearn J, Rees S, Gossop M, (2003). 'Loss of tolerance and overdose mortality after inpatient opiate detoxification: follow up study'. *British Medical Journal*. 326 (7396), pp.959-960.

Sylvestre D, (2007). 'Hepatitis C for addiction professionals'. *Addiction Science & Clinical Practice*. 4 (1), pp.34-41.

Thomson WM, Poulton R, Broadbent JM, Al-Kubaisy S, (2006). 'Xerostomia and medications among 32-year-olds'. *Acta Odontologica Scandinavica*. 64 (4), pp.249-254.

Van Dorp E, Yassen A, Sarton E, Romberg R, Olofsen E, Teppema L, Danhof M, Dahan A, (2006). 'Naloxone reversal of buprenorphine-induced respiratory depression'. *Anesthesiology*. 105 (1), pp.51-57.

Wahawisan J, Kolluru S, Nguyen T, Molina C, Speake J, (2011). 'Methadone toxicity due to smoking cessation – a case report on the drug-drug interaction involving cytochrome P450 isoenzyme 1A2'. *The Annals of Pharmacotherapy*. 45 (6), pp.e34.

White JM, Lopatko OV, (2007). 'Opioid maintenance: a comparative review of pharmacological strategies'. *Expert Opinion on Pharmacotherapy*. 8 (1), pp.1-11.

White JM, Irvine RJ, (1999). 'Mechanisms of fatal opioid overdose'. *Addiction*. 94 (7), pp.961-972.

Wilbourne P, Wallerstedt C, Dorato V, Curet L (2001). 'Clinical management of methadone dependence during pregnancy'. *Journal of Perinatal & Neonatal Nursing*. 14 (4), pp.26-45.

Winklbaur B, Jung E, Fischer G, (2008). 'Opioid dependence and pregnancy'. *Current Opinion in Psychiatry*. 21 (3), pp.255-259.

Winklbaur B, Kopf N, Ebner N, Jung E, Thau K, Fischer G, (2008). 'Treating pregnant women dependent on opioids is not the same as treating pregnancy and opioid dependence: a knowledge synthesis for better treatment for women and neonates'. *Addiction*. 103 (9), pp.1429-1440.

World Health Organization, (2009). *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*. Geneva: WHO Press.

Dykes MY, (2007). 'Management of opioid dependence in pregnancy: a review of the evidence'. *International Journal of Mental Health and Addiction*. 5 (3), pp.187-194.

[ONLINE] Available at: http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm. [Last Accessed 20 June 2012].

[ONLINE] Available at: http://www.nationaldrugstrategy.gov.au/internet/drugstrategy/publishing.nsf/Content/nds2015. [Last Accessed 20 June 2012].

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Declaration of interest

Dr Sue Ballantyne, Peter Cahill, Dora Cocker, Dr Jeremy Hayllar, Margo Hickman and Dr Catherine Wren have all previously received untied educational grants from Reckitt Benckiser to attend conferences. Dr Jeremy Hayllar has also previously received a stipend from Eli Lilly for running a workshop.

Quick reference guide for prescribers

Guide for induction to QOTP

Day 1

- Take a detailed history, over more than one appointment if required *(Section 3.1)*.
- Make a diagnosis of opioid dependence according to DSM criteria *(Section 4)*.
- Choose an appropriate evidence-based treatment *(Section 4.4)*.
  - For withdrawal management: buprenorphine (see *Queensland Alcohol and Drug Withdrawal Clinical Practice Guidelines*, 2012).
  - For maintenance: methadone or buprenorphine.
- Obtain informed consent, providing information regarding the effects and side effects of methadone *(Section 2.1)* and buprenorphine *(Section 2.2)*.
- Advise the client about the processes for their first dose of methadone *(Section 5.5)* or buprenorphine *(Section 5.10)*. Unless the client is pregnant or breastfeeding, it is recommended they commence the buprenorphine/naloxone combination product.
- Administer first dose, or inform an approved pharmacy of the initial dose *(sections 5.1 and 5.2)*.
- Methadone 5–20 mg/1–4 ml *(Table 7, p38)*
- Buprenorphine 4–8 mg *(Section 5.10)* **(Note: Clear objective signs of withdrawal should be present before commencing buprenorphine)**
- Review 2–4 hours after initial dose (optional) *(sections 5.5 and 5.10)*. For methadone clients, if objective withdrawal persists, up to 5 mg/1 ml methadone (to a total of ≤30 mg/6 ml) may be ordered. For buprenorphine clients, if objective withdrawal persists without evidence of precipitated withdrawal *(Section 5.10)* then a further 2–6 mg (to a total of 8 mg) may be ordered.

Day 2

- Review prior to second dose *(sections 5.8 and 5.12)*.

The approach for methadone stabilisation is: start low and go slow.

The approach for buprenorphine stabilisation is: start low and go quickly.

- **For methadone clients:** decrease the dose if there are no signs of withdrawal 24 hours after initial dose *(Section 2.1.4 – accumulation effects)*. Maintain the dose if the client was initially comfortable and not sedated but develops withdrawal prior to review. Increase the dose by 5 mg/1 ml if the client shows marked withdrawal and reports no suppression of withdrawal during the previous 24 hours. Maximum dose day 2 ≤ 35 mg.
- **For buprenorphine clients:** decrease the dose only if there is evidence of significant sedation in the previous 24 hours. Maintain the dose if the client is comfortable at review. Increase the dose by 4–8 mg if the client shows evidence withdrawal. Maximum dose day 2 = 16 mg *(Section 5.1.4)*.

Day 3

- Review prior to third dose *(sections 5.8 and 5.12)*.
- As above, maximum dose ≤ 40 mg methadone; ≤ 24 mg buprenorphine.

Day 4

- Review prior to fourth dose *(sections 5.8 and 5.12)*.
- As above, maximum dose ≤ 40 mg methadone; ≤ 24 mg buprenorphine.
- Daily review is essential due to dose accumulation effects as the long half-lives result in increased effects even without increase in oral dose. (The effect is not unlike that seen with warfarin dosing.)

Day 5 and ongoing

- If the above doses are not achieving control of withdrawal symptoms by day 4–5, consult with an addiction specialist or clinic.
- Review weekly for 4–6 weeks and then fortnightly for a further 6–8 weeks *(sections 5.8 and 5.13)*.

Target doses

- Target doses for effective maintenance are 60–100 mg/12–20 ml methadone and 8–24 mg buprenorphine. Maximum approved doses are 150 mg/30 ml methadone and 32 mg buprenorphine *sections 6.1.1 and 6.5.1)*.
- Buprenorphine clients should be expected to achieve 8 mg or more during initial stabilisation.
- Methadone clients **must** be commenced on lower initial doses and gradually increased.

Increases in methadone to achieve the target dose should not exceed 5–10 mg/1–2 ml at a time, with a maximum of 20 mg/4 ml per week. Physical assessment to exclude sedation should occur both before and after the increase.

Take-away doses

- Buprenorphine clients should be offered double dosing once stabilised *(sections 6.5.3 to 6.5.5)*.
- Take-away (unsupervised, take-home) medication should only be provided based on criteria *(sections 6.5.7 and 6.5.21)*.

Extra information

- Common clinical issues are addressed in Section 7.
- Pregnancy, breastfeeding, blood-borne viruses and therapeutic opioid dependence are addressed in Section 8.
- Planned and unplanned completion of treatment is discussed in Section 9.

Quick reference guide for pharmacists

Storage and preparation of doses *(refer to Section 10.10)*

- Methadone and buprenorphine are Schedule 8 drugs and must be stored in a Controlled Drugs safe. Ensure that methadone and buprenorphine products are never accessible to clients except at the time of dosing when they should remain under strict supervision of the pharmacist.
- Ideally, each methadone or buprenorphine dose should be prepared at the time the client presents at the pharmacy. After preparation of a dose, the stock package or bottle should be returned to the safe immediately.

Administration of dose *(refer to Sections 10.6, 10.7, 10.8)*

- *Identity of the client:* Refer to the client's photograph (should be attached to a letter of introduction provided by the prescriber/clinic) and ask for a new photo when required. Confirm the name and date of birth of the client. A third party may not collect any doses unless specifically authorised by the prescriber/clinic.
- *Check the current dose:* Check the dose with the current written instruction before every dose.
- *Is the client safe to dose?* In the event of missed doses or intoxication, the pharmacist should contact the prescriber to discuss the situation.
- *Dispense doses:* Regular doses of methadone or buprenorphine should be administered using disposable cups, etc. The client must be supervised to prevent diversion or inappropriate dosing technique. Dispense take-away doses if applicable.
- *Complete documentation:* Fill out the written instruction and any payment records at the time of administration. Ensure that QOTP guidelines, client records and photographs, written instructions and all communications with prescribers or case managers are documented, maintained and easily accessible by all pharmacists, especially locums. *(See Appendix 16, 17 and 18)*

Take-away doses *(refer to Section 10.9)*

- Take-away doses can only be authorised by the prescriber but it is acceptable practice for any QOTP clinician to notify the client's pharmacist of the authorised take-away doses.
- The take-away doses must be given to the client on the day before the scheduled days of absence from the usual dispensing location as stipulated in the written instruction, and should be labelled and packaged appropriately. *(Refer to Section 10.9.2)*
- Take-away doses should be stored in a locked box or secure lockable cupboard or safe. Clients are responsible for the care and proper consumption of each take-away dose once they have taken possession of it. In the event that a client reports that take-away doses have been lost, stolen or damaged, they should not be replaced without authorisation by the prescriber.

When should the pharmacist contact the prescriber or clinic?

- Missed dose *(Refer to Section 10.19.)*
- Intoxication *(Refer to Section 10.15.)*
- Suspected diversion *(Refer to Section 10.16.)*
- Administration of incorrect methadone or buprenorphine dose *(Refer to Section 10.17.)*
- Vomited doses *(Refer to Section 10.18.)*
- Inappropriate behaviour (Note: Payment of a 'dispensing fee' is between the client and the dosing pharmacy. Prescribers/clinics do not become involved in issues regarding payment of dispensing fees.) *(Refer to sections 10.21, 10.23, 10.24.)*
- Suspicion of inappropriate use of other substances including over-the-counter and prescription medicines *(Refer to Section 10.26.)*

Pharmacy/client agreements

- It may be helpful to use a written agreement that is negotiated when the client first attends the pharmacy to manage payment and behaviour issues and it is strongly recommended that accurate payment records are maintained. *(See Appendix 16 and 18.)*

Written instructions & Controlled Drug records *(refer to Section 10.11)*

- Methadone and buprenorphine for the purposes of QOTP will always be prescribed on a specific Queensland Opioid Treatment Program Written Instruction form (even if the prescriber is interstate)
- At the end of each month, the top (white) copy of the written instruction/s must be forwarded to the Drugs of Dependence Unit. The bottom (green) copy is kept at the pharmacy.
- Queensland Health uses a computer-based system (ATODS–IS vII) when creating written instructions. One printed copy of this printed written instruction with the prescriber's signature is sent to the pharmacist. At the end of the month, the original completed Queensland Health Written Instruction is to be forwarded to the Drugs of Dependency Unit and a photocopy or scan of the completed document kept for the pharmacy record.
- Written instructions issued for persons on the opioid treatment program have provision for the details of daily administration or supply and it is considered that this is an adequate record on the day-to-day use of methadone and buprenorphine.
- On completion of the written instruction, the total dispensed should be entered into the Controlled Drugs Book.
- There is no minimum time specified for keeping these records. However, it is recommended that they be retained for two years.
- Under no circumstances should a written instruction be given to a client.

Confidentiality *(refer to Section 10.14)*

- The QOTP advocates a strict policy of confidentiality for clients on the program.
- Pharmacists may have to deal with difficult scenarios, for example clients purchasing needles and syringes. In the interest of harm reduction, it is not considered necessary for pharmacists to report such behaviour.

IF IN DOUBT, PLEASE DO NOT HESITATE TO CONTACT THE CLIENT'S PRESCRIBER OR CLINIC