

NEW ZEALAND

# NATIONAL DRUG INTELLIGENCE BUREAU

JOINT OPERATION OF POLICE, CUSTOMS & HEALTH DEPARTMENTS

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## Buprenorphine in New Zealand

### 2007 Strategic Assessment

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## GLOSSARY

**Analgesic:** a drug or medicine given to reduce pain without resulting in loss of consciousness, is any member of the diverse group of drugs used to relieve pain

**Antagonist** (partial and full): a drug interacts with the receptor site and blocks or depresses the normal response for that receptor; it may also prevent any other agonist or the normal neurotransmitter from interacting with the receptor site

**Buprenorphine:** for the purposes of this document Suboxone®, the combination product containing naloxone, is identified as the main source of buprenorphine available within New Zealand.

**Endogenous:** endogenous substances are those that originate from within an organism

**IDU:** intravenous drug use or intravenous drug user. An IDU in New Zealand is likely to be a poly-drug user, in that they will use more than one drug substance during a session or over a period of time. People may combine drugs for an effect or sometimes out of habit

**Naloxone:** is an opioid antagonist drug substance

**Sublingual:** literally 'under the tongue', from Latin, refers to a pharmacological route of administration in which certain drugs are entered directly into the bloodstream via absorption under the tongue

**Perentral:** includes administration of a drug substance other than by the mouth/oral route, likely administered intra-muscularly, subcutaneously, or intravenously

**Presumption for supply/trafficable quantity:** A person in possession of more than a prescribed quantity (also known as a deeming quantity) of a drug is assumed to have it to sell or supply unless the person can prove it is for personal use only. This assumes that anyone possessing more than a 'deeming quantity' is going to distribute it and not consume it all. In Australia (NSW), if a person is found in possession of a trafficable quantity of a drug of dependence then this is prima facie (on first examination) evidence of trafficking. In this case the person is not likely to be charged with possession, but with the more serious offence of trafficking.

**Thebaine:** (paramorphine) is a phenantherene opium alkaloid. A minor constituent of opium (0.2%), thebaine is chemically similar to both morphine and codeine. Thebaine is not used therapeutically, but can be converted industrially into a variety of compounds including oxycodone, oxymorphone, nalbuphine, naloxone, naltrexone, buprenorphine and etorphine.

## 1.0 INTRODUCTION

Buprenorphine is a strong synthetic opioid analgesic. It has properties similar to opium and therefore morphine salts. In isolation buprenorphine appears to be a safer drug than related strong opioids due to its mild opioid antagonistic properties.

The drug products, Temgesic®, Subutex® and Suboxone®, are marketed internationally by Reckitt Benckiser Ltd. These are an injection and a sublingual tablet, with or without naloxone (a full opiate antagonist), respectively. Subutex® and Suboxone® are used in opioid substitution programmes and Suboxone®, the combination product (with naloxone), is most widely available in New Zealand. Additionally, a transdermal patch is registered in New Zealand for use as an analgesic.

Domestic and international data suggests that the buprenorphine tablet (Subutex®) has a high abuse potential, mainly within the intravenous drug user (IDU) population. This evidence prompted the classification of buprenorphine as a Class C controlled drug (under the Misuse of Drugs Act 1975) and the production of the combination tablet to reduce the illicit use of the drug. The buprenorphine only tablet is no longer legitimately available in New Zealand. The combination tablet appears to have reduced the illicit use of this drug substance, however it has not ceased it; continued illicit use of the combination product occurs mainly as a result of the nature of intravenous drug use.

There are some significant moves internationally toward the use of buprenorphine (with or without naloxone) for opioid substitution programmes and maintenance treatment, similar to the use of methadone. This treatment option has not been employed widely in New Zealand, which is likely to be a result of the combination drug not being funded by PHARMAC. Since the late 1990's France and other European countries, and more recently Australia, have widely used buprenorphine in opioid substitution.

Subutex® or buprenorphine availability in New Zealand is limited but is more widely available internationally. The illicit administration of buprenorphine is either oral or intravenous and the preference for the use of buprenorphine appears to be related to the availability and quality of heroin. The level of diversion of buprenorphine and its street price differs depending on dispensing and administration practices, including if it is from pharmacies or from specialist centres and if take-home-dosing is available. The availability of buprenorphine is dependant upon each jurisdictions preference and regulations regarding substitution and treatment, with or as an alternative to methadone.

In New Zealand, it has been suggested that buprenorphine be reclassified from a Class C to Class B controlled drug. It is thought that a Class B status would provide greater control over its use and provide for monitoring capabilities over its distribution and use. This would assist in establishing the effectiveness of proposed regimens and treatment settings, and reduce the potential for diversion whether as buprenorphine alone or as the safer combination product.

## 2.0 SUBSTANCE IDENTIFICATION

### 2.1 The Chemical Name/Trade Names for Buprenorphine

There are three registered buprenorphine products in New Zealand. These include: **Temgesic®**, **Suboxone®** (buprenorphine/naloxone) and **Norspan®**. **Subutex®**, a buprenorphine sublingual tablet, is also available internationally.

**Temgesic®** is a *buprenorphine hydrochloride* injection with a concentration of 300 µg/ml in a 5% glucose solution. Temgesic® is a Medsafe registered product, used as a strong analgesic for the relief of moderate to severe pain, including post-operative and terminal pain. Temgesic does not have an approved role in opioid dependence rehabilitation programs.

[www.medsafe.govt.nz/profs/Datasheet/t/Temgesicinj.htm](http://www.medsafe.govt.nz/profs/Datasheet/t/Temgesicinj.htm)

**Suboxone®** is a *buprenorphine hydrochloride/naloxone hydrochloride* sublingual tablets at 2 mg: 0.5 mg and 8 mg: 2 mg. Suboxone®, is a Medsafe registered product, used for the treatment of opiate dependence, within a framework of medical, social and psychological treatment. Naloxone is included in Suboxone® to deter intravenous misuse of the product.

[www.medsafe.govt.nz/profs/Datasheet/s/Suboxonetab.htm](http://www.medsafe.govt.nz/profs/Datasheet/s/Suboxonetab.htm)

**Norspan®** is a *buprenorphine hydrochloride* transdermal patch at 5 mg, 10 mg and 20 mg. Norspan®, is a Medsafe registered product. No datasheet is published for this product.

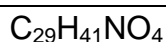
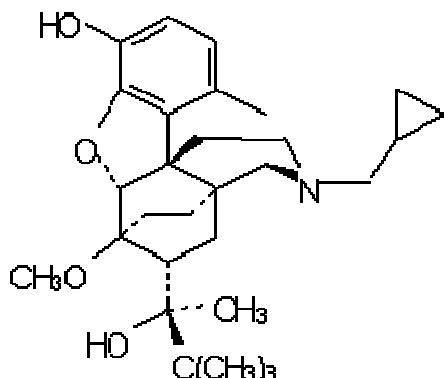
### 2.2 The Origin and History of Buprenorphine

The British firm Reckitt & Colman (now Reckitt Benckiser) first marketed buprenorphine in the 1980's under the trade names **Temgesic®** (sublingual/parenteral preparations) and **Buprenex®** (parenteral). Two more recent formulations from Reckitt Benckiser have been approved for opioid addiction treatment internationally, these are **Subutex®** (sublingual; in 2 mg and 8 mg dosages) and **Suboxone®** (flavored sublingual tablet, buprenorphine/naloxone in 2 mg and 8 mg dosages).

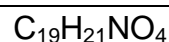
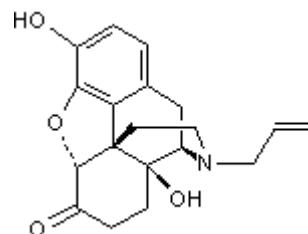
Internationally the buprenorphine-finished products are available from numerous drug manufacturers, including Schering-Plough, Grunenthal, Reckitt Benckiser, etc.

## 2.3 The Chemical Makeup of the Active Components: Buprenorphine and Naloxone

### BUPRENORPHINE



### NALOXONE (Suboxone® only)



Buprenorphine is a white or almost white crystalline powder. It is very slightly soluble in water; freely soluble in acetone; slightly soluble in cyclohexane; and soluble in methyl alcohol. It dissolves in dilute solutions of acids (Martindale; 2007).

## 2.4 Buprenorphine's Similarity to Other Known Substances

Buprenorphine is a synthetic opioid analgesic and *thebaine* derivative (*thebaine* is an opium extract and a phenanthrenes alkaloid). Buprenorphine has properties similar to opium and morphine salts and acts principally on the  $\mu$ -opioid receptor (the most prevalent of the family of endogenous opioid receptors). It is a partial opioid agonist-antagonist.

## 2.5 Consumption and Administration of Buprenorphine (Licit and Illicit Use)

In the therapeutic setting buprenorphine is administered for the relief of moderate to severe pain, including post-operative and terminal pain. Buprenorphine is administered in New Zealand as an injection, for this purpose. It is available internationally in several dose forms including a sublingual tablet, an injection or slow release transdermal patch. According to New Zealand pain clinics buprenorphine is not a first-line option for analgesia, in comparison to methadone, morphine or fentanyl.

Buprenorphine may also be used for the treatment of opioid dependence (also in combination with naloxone) and is prescribed for those already physically addicted and for substitution therapy for moderate opioid dependence. It is administered as a sublingual tablet for this purpose. Buprenorphine may precipitate withdrawal in high dose opioid dependence due to its antagonist properties. As such the daily opioid dose is reduced gradually before buprenorphine therapy initiated.

Of the two Subutex® and Suboxone®, Suboxone® the buprenorphine/naloxone combination tablet is the preferred choice for opioid maintenance therapy in New Zealand. Administration is conducted under supervision in the pharmacy setting or treatment facility. It is available as a take home dose, 3 day dosing cycles (16 mg/ 16 mg/ 24 mg) have also been employed and these appear more efficacious in terms of compliance.

In the illicit setting buprenorphine is commonly consumed/administered intravenously, but can be taken orally. The Suboxone® presentation was introduced to reduce the buprenorphine's abuse potential. Naloxone's antagonistic properties block or depress the normal opioid response of the opioid receptor, which reduces the response of buprenorphine on that receptor.

## 2.6 Known Legitimate Therapeutic Uses for Buprenorphine

Buprenorphine is used for the treatment of pain, but also for substitution, maintenance and withdrawal in high opioid use and dependence. It has been used in New Zealand for substitution of the following opioid drugs:

- intravenous morphine or home-bake (diverted, codeine based)
- oral use of morphine or poppy-seed tea
- oral or intravenous methadone.

(Ministry of Health (Mental Health) 2006)

## 2.7 Legitimate Distribution of Buprenorphine in New Zealand

Buprenorphine is available in New Zealand from Reckitt Benckiser (New Zealand) Ltd in two dose forms. The first is a buprenorphine injection with a concentration of 300 µg/ml in packs containing 5 x 1 mL clear glass snap-ampoules. The second is a sublingual tablet containing 2 mg buprenorphine (+ 0.5 mg naloxone) or 8 mg buprenorphine (+ 2 mg naloxone) in packs containing blister strips of 28 tablets. A buprenorphine transdermal patch is available from Mundipharma (NZ) Ltd and contains either 5 mg, 10 mg or 20 mg as two 2 dose units.

According to the Australian office of Reckitt Benckiser, Temgesic® (solution for injection) is mainly used by veterinarians but it is not widely available and/or used in New Zealand. Veterinaries are the likely source of most the Temgesic® within New Zealand.

**Temgesic®**, the buprenorphine injection (300 µg/mL) dose form, is a PHARMAC Scheduled drug product. Temgesic® is partially funded in the Pharmaceutical Schedule without any special authority or prescription endorsement requirements, which means it would be subsidised for any prescribed use. It would, however, incur a part charge of approximately \$0.70c per injection (cost to the patient). It is available mainly through hospital pharmacies, and requires a controlled drug prescription. Diversion of this substance is likely to be limited due to the access points and controlled drug status.

**Suboxone®**, the buprenorphine naloxone sublingual tablet, has no PHARMAC funding and is available for maintenance/substitution treatment in addiction treatment centres. This product is the most likely source of diverted product containing buprenorphine in New Zealand. However, it is not a preferred drug for recreational use due to its opioid antagonising effects.

**Norspan®**, the buprenorphine transdermal patch, is not considered to be of significant potential for diversion or misuse for illicit purposes. The transdermal patch has no PHARMAC funding.

It is worth noting that Norspan® is manufactured by Tasmanian Alkaloids Pty Ltd (Tasmania, Australia), which is affiliated with the legitimate Oceanic opium growers (please refer to [www.tasalk.com.au](http://www.tasalk.com.au)). These opium crops appear to produce only thebaine and not the other phenanthrenes alkaloids (codeine and morphine) commonly sourced from opium extracted from *papaver somniferum*.

### 3.0 REGULATION/CLASSIFICATION

#### 3.1 The Current Regulation/Classification of Buprenorphine in New Zealand

Currently buprenorphine is classified in New Zealand as a Class C(4) controlled drug substance under the Misuse of Drugs Act 1975.

#### 3.2 The Experiences and Regulation/Classification of Buprenorphine Internationally

According to the WHO (2004) buprenorphine, with or without naloxone, maintenance treatment is available in 29 countries, including: Australia, Austria, Belgium, China (Hong Kong), Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, India, Indonesia, Israel, Italy, Lithuania, Luxembourg, Malaysia, Netherlands, Norway, Portugal, Singapore, Slovak Republic, Slovenia, South Africa, Sweden, Switzerland, Ukraine, United Kingdom, and the United States of America.

##### Australia

Buprenorphine (and the combination product) is listed as one of three preferred therapies for opioid dependence in the most recent *Australian National Drug Strategy: Pharmacotherapy Policy for People Dependant on Opioids*. The buprenorphine and the combination were registered in Australia for the treatment of opioid dependence in 2000 and 2005, respectively. There were 8, 641 patients registered as receiving buprenorphine maintenance treatment at June 2003.

Buprenorphine is a Schedule 8 drug substance according to the Australian Standard for the Uniform Scheduling of drugs and poisons: No 20 (effective date: 1 June 2005). This drug is required to be labelled with a "sedation warning"

The New South Wales Drug Misuse and Trafficking Act 1985 classifies buprenorphine in Schedule I, with a corresponding trafficable quantity of 0.06 g. This is equivalent to 30 x 2 mg doses and 7.5 x 8 mg doses.

Australia has had reports of buprenorphine misuse, including diversion and intravenous injection. This was likely to have been more significant before the advent of the combination product. The odds of the intravenous use of buprenorphine are significantly associated with substitution treatment with buprenorphine. Jenkinson *et al* (2002) also suggest that buprenorphine has an abuse potential similar to morphine.

The Australian office of Reckitt Benckiser state that Suboxone® and Subutex® use is about 50:50 in Australia.

## **USA**

Buprenorphine is available in America as sublingual tablets of buprenorphine and in combination with naloxone. Under the Drug Addiction Treatment Act 2000, prescription use of buprenorphine in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements. Physicians are also required to notify the Secretary of Health and Human Services of their intent to prescribe this product for the treatment of opioid dependence.

The Australian office of Reckitt Benckiser state that the US have available an 8:1 ratio of Subutex® to Suboxone®, it is likely therefore that buprenorphine is abused to some extent.

## **Europe**

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) state in its 2005 Annual Report, that the total number of clients in substitution treatment in Europe is around half a million. Following a seven-fold increase over the last decade at least 530,000 clients now receive substitution treatment across 28 countries, whether through specialist treatment centres or general practitioners.

It is estimated that somewhere between one-quarter and a half of those with opiate problems in Europe may now be receiving treatment. The availability of substitution treatment still differs markedly across Europe, particularly between the former EU-15 countries and the new and prospective Member States.

The pharmacological action and effects of buprenorphine may make it a relatively unattractive drug to divert onto the black market (EMCDDA, 2005). Nevertheless, buprenorphine still has the potential to be misused and some countries report evidence of non-therapeutic use. It is unclear if this includes the combination product containing naloxone.

Misuse and diversion are often reported where therapeutic use is high (e.g. France & Finland) or where there is easy access to the drug through doctors' prescriptions and pharmacies. The report reinforces the need for 'measures to diminish diversion and misuse of buprenorphine.

The report further states that when buprenorphine is combined with other substances, such as alcohol, benzodiazepines, barbiturates and tranquillisers, serious interactions can occur, including overdose. Deaths resulting from the use of the buprenorphine are rare, possibly due to the fact that it is tolerated in relatively high doses and its antagonist properties protect against respiratory depression.

A clear relationship exists between the legal availability of the drug, the nature of national regulations, and diversion to the illegal market. The ease of access to buprenorphine through doctors' prescriptions or pharmacies has contributed to an increased availability on the legitimate and as a result the illegal market. A decrease in the availability of heroin is reported to be a crucial factor in the increase in buprenorphine availability in the illegal market (EMCDDA, 2005).

In Finland an 8 mg tablet of buprenorphine costs EUR 30–35, whereas the price of heroin is around EUR 60–350 per gram. In France the price of an 8 mg buprenorphine tablet varies from EUR 1 to 4. Indications of a current decrease in the price of buprenorphine on the illegal market are also reported (EMCDDA, 2005).

The Australian office of Reckitt Benckiser state that Suboxone® has just been launched in Europe and therefore Subutex® (buprenorphine only tablet) is the only widely available product.

The data outlined above is limited in that it has been taken from the single source; information compiled for the EMCDDA annual report 2005. There was no clear statement confirming if the buprenorphine product available contained naloxone, it is likely that both products are available. The EMCDDA is, however, a creditable and dependable source of European drug information.

This report can be read in its entirety at the following address:

<http://www.emcdda.europa.eu/index.cfm?fuseaction=public.content&nodeid=16222&sLanguageiso=EN>. Please refer to <http://www.emcdda.europa.eu/index.cfm> for country specific reporting of buprenorphine use in Europe; this is also described in the synopsis below:

## **France**

France has employed the use of buprenorphine since 1996. By 1998 55,000 patients were in buprenorphine treatment. Methadone is used in substitution treatment but buprenorphine is by far the most widely used substitution treatment prescribed in France. Buprenorphine treatment can be initiated by any doctor. The objective of this was to diversify location and situation of substitution treatment as well as to increase its accessibility. France state that 83,000 patients were on buprenorphine treatment in 2003.

There have been reports of the diversion and misuse of buprenorphine in France.

## **UK**

The UK did not report the number of patients on medically assisted treatment using buprenorphine. The majority of substitution treatment takes place through general practitioners although some provision takes place through specialised units. Oral methadone is used for substitution treatment but increasingly buprenorphine is also used. Furthermore, injectable methadone and heroin are to be made more available in England.

## **Denmark/Norway/Finland/Sweden**

In 1998, trials using LAAM (levo-alpha acetyl methadol) and buprenorphine were launched. Buprenorphine is now only used. In 2003 there were 484 individuals receiving buprenorphine treatment in Denmark. Methadone treatment was employed in 4971 patients in this same year.

Similar numbers are treated with buprenorphine in both Norway and Finland; Finland has given the use of buprenorphine priority over methadone.

Sweden has higher levels of buprenorphine use for opioid treatment compared to methadone.

### **3.3 The UN Classification of Buprenorphine**

International Narcotics Control Board (INCB) lists buprenorphine in Schedule III of the Green List (the UN Convention on Psychotropic Substances of 1971).

New Zealand has an INCB allocation of 9,000 grams or 9 kg for buprenorphine. This is equivalent to 1.125 million, 8 mg (combination) tablets. On a high dose (3-day cycle treatment) a typical patient would consume approximately 2912 mg per annum. Therefore the INCB quota for New Zealand would provide for up to 3090 patients.

The World Health Organisation (2004) has written a position paper suggesting that buprenorphine is included in the essential drug list. This would effectively increase buprenorphine availability worldwide.

[www.who.int/substance\\_abuse/activities/buprenorphine\\_essential\\_medicines.pdf](http://www.who.int/substance_abuse/activities/buprenorphine_essential_medicines.pdf),

## 4.0 RISK OF HARM IN NEW ZEALAND

The illicit availability, use and risk of harm associated with buprenorphine are dependent upon the therapeutic use or preference to the use of either (a) buprenorphine or (b) the buprenorphine combination product containing naloxone.

### 4.1 What are the Pharmacological, Psychoactive and Toxicological Effects of Buprenorphine?

#### Opioid Drugs

Opioid receptors are found throughout the brain and spinal cord, in the gastrointestinal system, parts of the autonomic nervous system, and on white cells. This means opioid drugs have a wide range of actions on many organ systems. The most prominent effects are exerted on the central nervous system and the gastrointestinal tract.

Clinically the three most important subtypes of opioid receptor are: mu ( $\mu$ ), kappa ( $\kappa$ ) and delta ( $\delta$ ).

Mu and delta receptors are involved in systems that influence mood, reinforcing behaviours, respiration, pain, blood pressure and endocrine and gastrointestinal function. Kappa receptors, when activated, can produce endocrine changes and analgesia, but appear to produce dysphoria rather than euphoria. Mu and delta receptors are involved in systems that influence mood, reinforcing behaviours, respiration, pain, blood pressure and endocrine and gastrointestinal function. kappa receptors, when activated, can produce endocrine changes and analgesia but appear to produce dysphoria rather than euphoria (Jaffe 1992 from the Ministry of Health, 2006).

#### Pharmacology

##### Buprenorphine:

Buprenorphine's duration of action varies depending on the dose prescribed. Clinical effects peak one to four hours after taking a sublingual dose. At low doses (e.g. 2mg) effects will usually continue to be experienced for up to 12 hours, whilst at higher doses (e.g. 16 to 32mg) effects may last as long as 48 to 72 hours. (Lintzeris *et al*, 2006 from the Ministry of Health, 2006).

##### Indication(s):

For the treatment of moderate to severe pain, peri-operative analgesia, and opioid dependence.

### Pharmacodynamics:

Buprenorphine is a synthetic opioid analgesic and thebaine derivative, with a longer duration of action than morphine. Buprenorphine interacts predominately with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissues. In clinical settings, buprenorphine exerts its principal pharmacological effects on the central nervous system (CNS). Its primary actions of therapeutic value are analgesia and sedation. Buprenorphine may increase the patient's tolerance for pain and decrease the perception of suffering, although the presence of the pain itself may still be recognised. Alterations in mood, euphoria and dysphoria, and drowsiness also commonly occur. Buprenorphine depresses the respiratory centres, depresses the cough reflex, and constricts the pupils.

Buprenorphine's analgesic effect is due to partial agonist activity at mu-opioid receptors. Buprenorphine is also a kappa-opioid receptor antagonist. Opioid receptor antagonists only partially reverse the effects of buprenorphine. The binding to the mu and kappa receptors results in hyperpolarisation and reduced neuronal excitability.

### Toxicity:

Acute overdose can induce symptoms of pinpoint pupils, sedation, hypertension, respiratory depression and death. Buprenorphine has a mean half-life of 37 hours. Buprenorphine appears to have a ceiling for cardio-respiratory and subjective effects and a high safety margin even when taken by the intravenous route (Umbricht *et al*, 2004)

### Bio-transformation/metabolism:

Buprenorphine is metabolised by the liver (hepatic metabolism). Buprenorphine undergoes both N-de-alkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated by cytochrome P-450 3A4 isozyme. Norbuprenorphine, an active metabolite, can further undergo glucuronidation.

Taken from Drug Bank:

<http://redpoll.pharmacy.ualberta.ca/drugbank/cgi-bin/getCard.cgi?CARD=APRD00670.txt>

Also refer to Temgesic® or Suboxone® datasheets for pharmacology detail:

[www.medsafe.govt.nz/profs/Datasheet/t/Temgesicinj.htm](http://www.medsafe.govt.nz/profs/Datasheet/t/Temgesicinj.htm)

[www.medsafe.govt.nz/profs/Datasheet/s/Suboxonetab.htm](http://www.medsafe.govt.nz/profs/Datasheet/s/Suboxonetab.htm)

## **4.2 Buprenorphine's Abuse Appeal in Vulnerable Populations of New Zealand**

Buprenorphine is a controlled drug (CD) available through CD prescription only. Buprenorphine's controlled drug status would make an illicit dose of this substance available from only specialised sources, including street sales from

diversion. It is unlikely therefore that buprenorphine would be available to young and inexperienced drug users or drug users that regularly use *soft drugs*.

Vulnerable populations, regarding buprenorphine, are likely to be those people that regularly use *hard drug* substances, including other opioids and or those on opioid maintenance programmes that inject their drugs.

### **4.3 Buprenorphine's Potential to Create Physical or Psychological Dependence**

Chronic narcotic use is associated with physical dependence and a withdrawal or abstinence syndrome when drug use is discontinued. In general, shorter acting narcotics tend to produce shorter, more intense withdrawal symptoms, while longer acting narcotics produce a withdrawal syndrome that is protracted but less severe. Although unpleasant, withdrawal from narcotics is rarely life threatening.

Of greater concern is that associated with withdrawal from severe alcohol abuse, such symptoms can be life threatening. Poly-drug use within the IDU population is therefore a factor to consider, especially in light of New Zealand's heavy drinking culture.

Repeated administration of buprenorphine produces or maintains opioid dependence. However, the physical dependence liability is reported to be milder than that caused by methadone or heroin use (Raisch *et al*, 2002). Even after the prolonged use of buprenorphine, spontaneous withdrawal symptoms and naloxone-precipitated withdrawal symptoms tend to be relatively moderate compared with those of other opioids such as methadone (Tzschentke, 2002 from the Ministry of Health, 2006).

Buprenorphine has a ceiling dose effect whereby increased doses after a certain point produce no further opioid effects, but extend the duration of action (e.g. buprenorphine has a long duration of action and slow onset of withdrawal symptoms). Buprenorphine alone or in combination with naloxone is effective in less-than-daily dispensing regimens (Johnson *et al*, 2003; Petry *et al*, 2001 from the Ministry of Health (Mental Health), 2006 and Dr Tom Flewett, 2007).

There are a number of issues relating to dependence. These include tolerance to narcotic drug substances, increasing doses and dose escalation, the dependence potential of the drug of choice, poly-drug use, and issues with withdrawal and progression to other drug substances of abuse specifically when the supply of that that drug of choice becomes unavailable.

The withdrawal symptoms associated with heroin/morphine addiction are usually experienced shortly before the time of the next scheduled dose. Early symptoms include watery eyes, runny nose, yawning, and sweating. Restlessness, irritability, loss of appetite, nausea, tremors, and drug craving appear as the syndrome progresses. Severe depression and vomiting are common. The heart rate and blood pressure are elevated. Chills, alternating with flushing and excessive sweating, are also characteristic symptoms. Pains in the bones and muscles of the back and extremities occur, as do muscle spasms. At any point

during this process, a suitable narcotic can be administered to dramatically reverse the withdrawal symptoms. Without intervention, the syndrome will run its course, and most of the overt physical symptoms will disappear within seven to ten days.

#### **4.4 Buprenorphine's Potential to Cause Death**

Like methadone, buprenorphine is an opioid medication, so has opioid side effects. Compared with methadone, buprenorphine causes less sweating, constipation and sedation but severe headaches are occasionally reported (Chadderton 2000). Moderate headaches with buprenorphine are common during the first few days of induction and it can induce precipitated withdrawal at induction (Ministry of Health (Mental Health) 2006 & WHO 2004).

Because buprenorphine produces partial opioid agonist activity it has a considerably lower risk of overdose than other opiates used illicitly, including morphine and methadone. Respiratory depression during buprenorphine use is shown to be less than comparable levels of morphine. The buprenorphine combination product is vastly safer than methadone, and is less abused when in this form.

Severe morbidity is more common with the illicit use of this substance, due to its preference for use within the injecting population. The injection of any drug increases the chance for transmission of blood borne disease and other behavioural risks associated to intravenous administration.

Risk of death increases when buprenorphine (with or without naloxone) is combined with other drugs, especially CNS depressants such as alcohol, benzodiazepines, barbiturates, tricyclic antidepressants and major tranquillisers. It seems that the protection from overdose caused by the ceiling effect no longer occurs when concomitant CNS depressants are abused. Overdose from poly-drug use is more likely to be associated with the use of other drugs such as benzodiazepines.

It is interesting to note that from 1994 to 1998 there were an estimated 1.4 times more buprenorphine-related deaths than methadone-related deaths in France. However, 14 times more patients received buprenorphine than methadone. The yearly estimated death rate related to methadone use was at least 3 times greater than the death rate related to buprenorphine use. If all patients in France who received either of these drugs had been treated only with methadone, the expected number of deaths would have been 288 instead of 46 (Auriacombe M *et al*, 2001). However, deaths resulting from the use of buprenorphine still remain very rare, possibly due to the fact that it is tolerated in relatively high doses.

Several such deaths have been reported especially when buprenorphine and benzodiazepines have been injected together, so extra care should be taken when prescribing buprenorphine to benzodiazepine users. Benzodiazepines have been found in over 50 percent of cases of opioid overdose. It is thought to be linked to benzodiazepines exerting significant respiratory depression at high doses when combined with opioids (Reynaud *et al*, 1998).

#### **4.5 Buprenorphine's Potential for Diversion from Legitimate Sources**

Diversion, of buprenorphine for substitution, is defined as a client removing or attempting to remove a supervised methadone or buprenorphine dose from the dosing site before the dose has been fully absorbed by the client (Winstock and Lea., 2007)

New Zealand has a history of misuse of buprenorphine, mainly of buprenorphine without naloxone, and strong evidence from around the world exists of buprenorphine tablets being diverted and misused.

The risk of diversion and misuse are increased because buprenorphine (with or without naloxone) is in a solid form. Tablets take a longer time to administer than liquid methadone and can be more easily spat out and secreted for later diversion to the black market or misuse (sublingually or intravenously). Buprenorphine takes up to 10 minutes for a dose to be consumed sublingually (Ministry of Health (Mental Health) 2006).

It has been suggested that one source of diversion of this drug is from supervised administration and take-home dosing. This is perhaps the area of most concern, as these drugs are being employed in these situations to prevent drug use/abuse.

According to Winstock and Lea (2007) the diversion of supervised opioid pharmacotherapies suggests that engagement and compliance with treatment is less than optimal. It should be noted that from their study sample only a minority of clients reported that they intended selling or injecting their doses, this aligns with that reported by pain management clinics in New Zealand. Of those that believed to have diverted their dose, an over representation were on court mandated programmes.

The extent of diversion is proportional to the level of observation that a client is subjected to when they are taking their tablets. Therefore, all doses administered should be under direct observation. All clinicians involved in a client's care are responsible for minimising the risk of diversion because diversion does not promote the rehabilitation of a person who is in treatment and causes risks to others.

If diversion or misuse is suspected, the person administering the buprenorphine should crumble the tablets into granules (but not into a powder) to reduce the possibility of the client diverting the tablets. This also reduces the tablets' resale value, which also discourages diversion (Muhleisen *et al*, 2003).

The risk of diversion and misuse of the buprenorphine combination tablet is marginal and the availability of buprenorphine alone is limited within New Zealand (Dr Tom Flewett, 2007).

As a side note, methadone has been identified as the primary drug of abuse/choice in 55% of IDU patients presenting to specialist treatment facilities. It

is thought that inappropriate GP prescribing and pain clinics (takeaways) are the primary source of diverted and misused methadone (Dr Tom Flewett, 2007).

#### **4.6 Buprenorphine Seizures by Police, Customs and Medsafe**

As buprenorphine is a controlled drug Medsafe (Compliance IMC Auckland Office) does not detain or examine any drug products containing buprenorphine.

Police have no recorded cases of buprenorphine seizures.

Customs have records of least 107 seizures characterising buprenorphine in some form up to and including 2004. The majority of these were related to Temgesic®, the injectable dose form of buprenorphine. There have been no seizures by Customs identified as buprenorphine since 2004.

#### **4.7 Known Prevalence of Buprenorphine Abuse (including Misuse from Licit Prescription and from Diversion)**

Jenkinson *et al* (2002) report in their injecting drug users study (Melbourne) that over one-third (37%) of the study sample (of 156 IDU) reported injecting buprenorphine in their life-time and 33% reported injecting the drug in the last six months. Recent buprenorphine injection was associated with the injection of other drug types (i.e. poly-drug injectors), opioid substitution treatment, injection-related health problems and involvement in crime. Almost half (47%) of those who reported recent buprenorphine injection reported obtaining the drug illicitly at least once during that time. This is of major significance when considering a buprenorphine tablet, but is limited when considering the combination product.

According to Robinson *et al* (1993) buprenorphine use was high within the IDU population during the study period of the early 1990's when buprenorphine tablets were widely available. In the study sample 81% of those presenting to treatment facilities were positive for illicit buprenorphine use. The introduction of the combination tablet (with naloxone) reduced demand, as it has less misuse potential than buprenorphine alone; however it remains a preparation that is intravenously misused.

The availability of the buprenorphine injection is limited. The needle exchange and specialist AOD clinics do not report the injection of the combination product as being common. This is likely due to as a result of induced or precipitated withdrawal inherent to buprenorphine. These effects are even more prominent in IDU that are taking diverted oxycodone, methadone or other strong opioid drugs.

#### **4.8 Patterns of Abuse of Buprenorphine by Age, Gender, Ethnicity, Geography or other Categorisation**

Robinson *et al* (1993) suggest that the use of buprenorphine correlated to an average of 10-11 years of intravenous drug use. It could be surmised that, in line with all IDU, buprenorphine misuse is mainly within males that live alone and are unemployed and are poly-drug users. These characteristics, while stereotypical of

the IDU, are likely to be those characteristics that are seen with an intravenous drug user that injects diverted pharmaceuticals/adulterated medicines.

#### **4.9 Is Buprenorphine Use Identified as a Causal Factor for Presentations at Treatment Facilities (including Hospitals, Rehabilitation and Addiction Centres)?**

Injecting diverted sublingual buprenorphine can result in fungal endophthalmitis (Aboltins *et al*, 2005) and complications related to injecting tablet formulations such as vein damage, abscesses, infections, and blood borne virus transmission; especially when proper filtration techniques are not employed (Jenkinson *et al*, 2005).

Buprenorphine use is not necessarily a casual factor for representation at treatment facilities as the effect of poly-drug use is evident in overall poor health. There is also a poor uptake of public health services within this population due to the stigma associated with IDU.

Buprenorphine (with or without naloxone) does have the advantage of being less likely to cause a fatal overdose if taken without any other central nervous system depressants.

#### **4.10 How many Hospital Admissions are Known to have been Caused by Buprenorphine in the Last 2 years**

This information is unknown due to limitations in the hospital admissions dataset.

#### **4.11 Are any Particular Sectors of the Population more Susceptible to Risk of Harm Posed by the Abuse of Buprenorphine?**

The most at risk populations are the established opioid using IDU. The IDU that are more at risk include: IDU that are new to injecting drugs or have not had a history of IDU or poly-drug use; those IDU that have had the supply of alternative drugs or their drug of choice discontinued or ceased; and those drug users that are experimenting with injecting or other type of drug use.

The injection of buprenorphine alone poses little or no risk during pregnancy or postpartum for the infant (from the Ministry of Health (Mental Health), 2006).

Illicit intravenous drug use however remains an incredibly high-risk activity.

#### **4.12 Public Health Risks Posed by the Abuse of Buprenorphine**

As with all drugs of abuse that are injected, there are significant issues relating to overall health (psychological and physical) of the individual and the effect this activity has on their community. The risk of contacting or transmitting a blood-borne viral disease (e.g. HIV, HCV) is significantly increased with the intravenous use of a drug substance.

#### **4.13 Other Risks of Harm to Society Posed by Abuse of Buprenorphine**

The overarching cost to society from pharmaceutical diversion of products used (albeit not as a funded or fully-funded product) as a legitimate treatment for drug abuse, substitution and maintenance.

Diversion for illicit use essentially reduces the overall efficacy of the treatments.

### **5.0 ANTICIPATED FUTURE TRENDS**

There appears to be a surplus of other alternative opioid drugs that have filled the void since buprenorphine tablets were taken off the market, more recently oxycodone.

Due to the absence of buprenorphine without naloxone (other than the injection) in New Zealand, and in the absence of any change to classification/regulation, it is not anticipated that there will be any significant trends from the current situation during the next five years. The risk remains that this product could be sourced from outside New Zealand and illegally imported for distribution and misuse.

### **6.0 OTHER RELEVANT INFORMATION**

It would be prudent for research to be conducted to establish:

- the price of buprenorphine and the combination product on the black market;
- its availability;
- its preference of choice over other opioid and other intravenous drugs; and
- the extent to which the availability of these other drugs influence the choice to use buprenorphine and the combination product.

## 7.0 CONCLUSION

Buprenorphine has similar abuse potential to other Class B opioids, including intravenous use. However, the risk of fatal overdose is much less.

The misuse of buprenorphine does not appear to be currently significant in New Zealand; it was an issue prior to the subsidised product being withdrawn (Temgesic-NX®). This is primarily due to the limited availability of buprenorphine without naloxone in combination, as the combination product is not entirely suitable for injection/abuse. Additionally, other drugs exist, such as methadone and oxycodone, which are more preferred options for misuse and are more widely available. Confirmation of these conclusions could be achieved by seeking further information as outlined in Section 6.0.

The risk remains that this product could be sourced from outside New Zealand and illegally imported for distribution and misuse.

The Mental Health Group, Ministry of Health has constructed guidelines for the use of buprenorphine in the treatment of opioid dependence. The methadone group under David Chaplow have been researching this since the use of Suboxone® in clinics was permitted.

The current classification of Suboxone® means that it is not necessary to write Suboxone® on an H572 controlled drug script (i.e. it is not a Class B drug), therefore Medicines Control cannot monitor the use in clinics, or its misuse. Additionally, because it is not funded there is very little opportunity to collect information or monitor its use.

The classification from Class C to Class B would allow for greater controls to be placed on this drug including monitored distribution. Class B controlled drugs require more stringent storage, meaning a lower risk of diversion. Accountability for the use of buprenorphine would be greater with a Class B classification and this should reduce the risk of diversion. The counter to this argument is the increased compliance costs associated with a Class B classification.

## 8.0 REFERENCE MATERIAL

### 8.1 What Information Gaps Exist in Relation to Buprenorphine?

There are no recorded cases of Police seizures of buprenorphine. It is possible that this is due to under reporting.

Due to limitations in the hospital admissions dataset there is no data available on hospital admissions caused by buprenorphine.

Unknown: the price of buprenorphine and the combination product on the black market; its availability; its preference of choice over other opioid and other intravenous drugs; and the extent to which the availability of these other drugs influence the choice to use buprenorphine and the combination product.

### 8.2 What Reference Material and Studies are Relevant to Buprenorphine in New Zealand?

#### Expert Opinion

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Ministry of Health Medicines Control Team

Telea Slavin, Consumer Affairs, Reckitt Benckiser (Australia) Pty Ltd (West Ryde, NSW, Australia).

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