New Zealand Data Sheet

1 PRODUCT NAME

BUPRENORPHINE NALOXONE BNM 2mg/0.5mg and 8mg/2mg sublingual tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BUPRENORPHINE NALOXONE BNM 2mg/0.5mg

Each sublingual tablet contains buprenorphine hydrochloride 2.16mg (equivalent to 2mg buprenorphine) naloxone hydrochloride dihydrate 0.61mg (equivalent to 0.5mg naloxone).

Excipient 42mg of lactose monohydrate per tablet

BUPRENORPHINE NALOXONE BNM 8mg/2mg

Each sublingual tablet contains buprenorphine hydrochloride 8.64mg (equivalent to 8mg buprenorphine) naloxone hydrochloride dihydrate 2.44mg (equivalent to 2mg naloxone).

Excipient 168mg of lactose monohydrate per tablet

For the full list of excipients, see section **6.1 List of excipients**.

3 PHARMACEUTICAL FORM

BUPRENORPHINE NALOXONE BNM 2mg/0.5mg - White to off-white, round and biconvex tablets, with embossing “L” on one side and a diameter of about 6.5mm.

BUPRENORPHINE NALOXONE BNM 8mg/2mg - White to off-white, round and biconvex tablets, with embossing “H” on one side and a diameter of about 11.5mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of opioid dependence, within a framework of medical, social and psychological treatment. Naloxone is included in BUPRENORPHINE NALOXONE BNM to deter intravenous misuse of the product.

4.2 Dose and method of administration

Treatment with BUPRENORPHINE NALOXONE BNM sublingual tablets is intended for adults and children aged 16 years or over who have agreed to be treated for opioid dependence. When initiating BUPRENORPHINE NALOXONE BNM treatment, the physician should be aware of the partial agonist profile of the molecule to the μ opioid receptors, which can precipitate withdrawal in opioid-dependent patients if given too soon after the administration of heroin, methadone or another opioid. To avoid precipitating withdrawal, induction with buprenorphine should be undertaken when objective and clear signs of withdrawal are evident.

The route of administration of BUPRENORPHINE NALOXONE BNM is sublingual. The sublingual formulation is not designed to be split or broken. BUPRENORPHINE NALOXONE BNM tablets should not be swallowed 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. BUPRENORPHINE NALOXONE BNM 8mg/2mg (buprenorphine/naloxone) is referred to as the 8mg dose and BUPRENORPHINE NALOXONE BNM 2mg/0.5mg (buprenorphine/naloxone) is referred to as the 2mg dose.

Method of Administration

BUPRENORPHINE NALOXONE BNM tablets are to be placed under the tongue until dissolved, which usually requires 2 to 10 minutes. Patients should not swallow or consume food or drink until the tablet is completely dissolved. The dose is made up from 2mg and 8mg 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 BUPRENORPHINE NALOXONE BNM

An adequate maintenance dose, titrated to clinical effectiveness, should be achieved as rapidly as possible to prevent undue opioid withdrawal symptoms due to inadequate dosage.

Prior to induction, consideration should be given to the type of opioid dependence (i.e., long- or short-acting opioid), the time since last opioid use and the degree or level of opioid dependence.

Patients taking Street Heroin (or Other Short-acting Opioids): When treatment starts, the dose should be taken at least 6 hours after the patient last used opioids or when objective signs of withdrawal appear. A score of 12 on the validated Clinical Opioid Withdrawal Scale (COWS) may be a useful reference assessment. The recommended starting dose is 4-8 mg BUPRENORPHINE NALOXONE BNM on Day One, with a possible additional 4mg depending on the individual patient's requirement. The suggested target total dose for Day One is in the range of 8-12 mg BUPRENORPHINE NALOXONE BNM.

Patients on Methadone: Before starting treatment with BUPRENORPHINE NALOXONE BNM, the maintenance dose of methadone should be reduced to the minimum methadone daily dose that the patient can tolerate. The first dose of BUPRENORPHINE NALOXONE BNM should be taken at least 24 hours after the patient last used methadone. The initial 4-8 mg induction dose should ideally be administered when objective signs of withdrawal are evident (e.g. COWS score > 12). The suggested target total dose for Day One is in the range of 8-12 mg BUPRENORPHINE NALOXONE BNM.

During the initiation of treatment, closer dosing supervision is recommended to ensure proper sublingual placement of the dose and to observe patient response to treatment as a guide to effective dose titration according to clinical effect.

Dosage Adjustment and Maintenance
The dose of BUPRENORPHINE NALOXONE BNM should be increased progressively according to the clinical effect in the individual patient. The dosage is adjusted in increments or decrements of 2 – 8 mg buprenorphine to a level that maintains the patient in treatment and suppresses opioid withdrawal effects according to reassessments of the clinical and psychological status of the patient.

In clinical studies many patients were stabilised on a daily maintenance dose of 12 mg/3 mg to 16 mg/4 mg of buprenorphine/naloxone, although some patients may require higher doses. A maximum daily dose of 32 mg should not be exceeded. During maintenance therapy, it may be necessary to periodically restabilise patients to new maintenance doses in response to changing patient needs.

Dose adjustment in hepatic impairment
Use of BUPRENORPHINE NALOXONE BNM is contraindicated in patients were severe hepatic impairment. Buprenorphine and Naloxone sublingual tablets may not be appropriate for patients with moderate hepatic impairment. It may be used with caution for maintenance treatment in patients with moderate hepatic impairment, who have initiated treatment on a buprenorphine-only product. Patients with moderate hepatic impairment prescribed BUPRENORPHINE NALOXONE BNM should be monitored for signs and symptoms of precipitated opioid withdrawal. In addition, lower initial doses and cautious titration of dosage may be required in patients with moderate hepatic impairment. No dosage adjustment is needed in patients with mild hepatic impairment.

Less than Daily Dosing of BUPRENORPHINE NALOXONE BNM
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 8mg may be given 16mg on alternate days, with no medication on the intervening days. However, the dose given on any one day should not exceed 32mg.

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 32mg.

The patient should be observed following the first multi-dose administration to initiate the less-than daily dosing regimen and whenever treated with high doses. Patients who sporadically use concomitant CNS-active medications or substances should be monitored closely.

Reducing Dosage and Stopping Treatment
The decision to discontinue therapy with BUPRENORPHINE NALOXONE BNM should be made as part of a comprehensive treatment plan. A gradual dose taper over a period of 21 days is shown in Table 1.

Table 1	**Gradual dose taper schedule**		
Week	**20mg Maintenance dose**	**16mg Maintenance dose**	**8mg Maintenance dose**
1	16mg	12mg	8mg
2	8mg	8mg	4mg
3	4mg	4mg	4mg

4.3 Contraindications

Hypersensitivity to buprenorphine or naloxone or to any of the excipients listed in section **6.1 List of excipients**.
Children less than 16 years of age.
Severe respiratory or hepatic insufficiency. (Child-Pugh C)
Acute intoxication with alcohol or other CNS depressant.

4.4 Special warnings and precautions for use

General: BUPRENORPHINE NALOXONE BNM should be administered with caution in debilitated patients and those with impairment of hepatic, pulmonary, or renal function; myxoedema or hypothyroidism, adrenal cortical insufficiency (eg Addison's disease); CNS depression or coma; toxic psychoses; acute alcoholism; or delirium tremens.

Buprenorphine increases intracholedochal pressure as do other opioids. Therefore, caution should be exercised when BUPRENORPHINE NALOXONE BNM 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 or urethral stenosis.

As with other mu-opioid receptor agonists, the administration of Buprenorphine and Naloxone sublingual tablets may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Opioids may produce orthostatic hypotension in ambulatory patients.

Elderly: The safety and efficacy of buprenorphine in elderly patients over 65 years of age has not been established.

Misuse, abuse and diversion
BUPRENORPHINE NALOXONE BNM contains the opioid Buprenorphine and Naloxone and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed BUPRENORPHINE NALOXONE BNM at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed BUPRENORPHINE NALOXONE BNM.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see section 6.4 Special precautions for storage and section 6.6 Special precautions for disposal). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Patients should be advised not to share BUPRENORPHINE NALOXONE BNM with anyone else.

BUPRENORPHINE NALOXONE BNM can be misused or abused in a manner similar to other opioids, legal or illicit. Some risks of misuse and abuse include overdose, spread of blood borne viral infections, respiratory depression and hepatic injury. BUPRENORPHINE NALOXONE BNM misuse by someone other than the intended patient poses the additional risk of new opioid dependent individuals using buprenorphine as the primary opioid of abuse, and may occur if the medicine is distributed for illicit use directly by the intended patient or if the medicine is not safeguarded against theft. Sub-optimal treatment with BUPRENORPHINE NALOXONE BNM may prompt medication misuse by the patient, leading to overdose or treatment dropout. A patient who is under-dosed with Buprenorphine and Naloxone sublingual tablets may continue responding to uncontrolled withdrawal symptoms by self-medicating with opioids, alcohol or other sedative-hypnotics such as benzodiazepines. To minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and dispensing BUPRENORPHINE NALOXONE BNM, such as to avoid prescribing multiple refills early in treatment, and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's level of stability.

Patients dependent upon concomitant CNS-active substances, including alcohol, should not be treated with the increased doses required by the less-than-daily dosing regimen intended for use in a supervised dose setting. Patients with sporadic use of concomitant non-opioid medications should be monitored closely, and all patients dosed on a less-than-daily basis should be observed following the first multi-dose administration initiating less-than-daily- dosing or whenever treated with high doses.

Respiratory Depression
Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of BUPRENORPHINE NALOXONE BNM but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients and in patients with existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease; asthma). Opioids should be used with caution and with close monitoring in these patients (see section 4.2 Dose and method of administration). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see section 4.3 Contraindications).

The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and modified release formulations, and in opioid naïve patients. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations, (see section 4.2 Dose and method of administration).

BUPRENORPHINE NALOXONE BNM 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 buprenorphine was used in combination with benzodiazepines in opioid naïve individuals, or when buprenorphine was otherwise not used according to prescribing information. 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 BUPRENORPHINE NALOXONE BNM.

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

In the event of depression of respiratory or cardiac function, see section **4.9 Overdose**.

BUPRENORPHINE NALOXONE BNM should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression, or kyphoscoliosis).

BUPRENORPHINE NALOXONE BNM may cause severe, possibly fatal, respiratory depression in children who accidentally ingest it. Protect children against exposure.

CNS Depression
Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of BUPRENORPHINE NALOXONE BNM with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants, should be reserved for patients for whom other treatment options are not possible. If a decision is made to prescribe BUPRENORPHINE NALOXONE BNM concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking BUPRENORPHINE NALOXONE BNM.

BUPRENORPHINE NALOXONE BNM may cause drowsiness, particularly when used together with alcohol or other central nervous system depressants (such as benzodiazepines, tranquillisers, sedatives or hypnotics (see section **4.5 Interaction with other medicines and other forms of interaction)**. When such combined therapy is contemplated, reduction of the dose of one or both agents should be considered. BUPRENORPHINE NALOXONE BNM should be used cautiously with MAOIs, based on experience with morphine.

Hepatitis, Hepatic Events
Cases of acute hepatic injury have been reported in opioid-dependent patients, both in clinical trials and post marketing adverse reaction reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of cytolytic hepatitis, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. 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, liver enzyme abnormalities, alcohol abuse, anorexia, associated mitochondrial toxins, e.g. aspirin, isoniazid, valproate, amiodarone, antiviral nucleoside analogues, or drug misuse by injection) could promote the occurrence of such hepatic injuries. These co-factors must be taken into account before prescribing Buprenorphine and Naloxone sublingual tablets and during treatment monitoring. Baseline liver function tests and documentation of viral hepatitis status are recommended prior to commencing therapy. Patients who are positive for viral hepatitis, on concomitant medicines (see section **4.5 Interaction with other medicines and other forms of interaction**) and/or have existing liver dysfunction are at greater risk of liver injury. Regular monitoring of liver function is recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending upon the findings, the medicine may be discontinued cautiously so as to prevent withdrawal syndrome and to prevent a return to opioid dependence. If treatment is continued, hepatic function should be monitored closely.

Hepatic Impairment
Buprenorphine and naloxone are extensively metabolised by the liver. The effects of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study, in which a Buprenorphine and Naloxone sublingual 2/0.5mg tablet was administered to healthy subjects and subjects with varying degrees of

hepatic impairment. Plasma levels were found to be elevated for buprenorphine and naloxone in patients with moderate to severe hepatic impairment (Table 2).
Patients with severe hepatic impairment experienced substantially greater increases in exposure to naloxone relative to buprenorphine, and patients with moderate hepatic impairment experienced greater increases in exposure to naloxone relative to buprenorphine. The clinical impact in terms of efficacy/safety is unknown, but it is likely to be greater for those with severe hepatic impairment than those with moderate hepatic impairment.

The doses of buprenorphine and naloxone in BUPRENORPHINE NALOXONE BNM cannot be individually titrated. As such BUPRENORPHINE NALOXONE BNM should be avoided in patients with severe hepatic impairment. Use of Buprenorphine and Naloxone sublingual tablets may not be appropriate in those with moderate hepatic impairment. It may be used with caution for maintenance treatment in patients with moderate hepatic impairment who have initiated treatment on a buprenorphine-only product. Patients with moderate hepatic impairment should be monitored for signs and symptoms of precipitated opioid withdrawal. In addition, lower doses and cautious titration of dosage may be required in patients with moderate hepatic impairment. As with all patients treated with Buprenorphine and Naloxone sublingual tablets, liver function tests should be monitored prior to and during treatment. See also section **4.2 Dose and method of administration.**

Table 2: Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine and naloxone following buprenorphine/naloxone administration (change relative to healthy subjects)

PK parameter	Mild Hepatic Impairment (Child-Pugh Class A) (n=9)	Moderate Hepatic Impairment (Child-Pugh Class B) (n=8)	Severe Hepatic Impairment (Child-Pugh Class C) (n=8)
BUPRENORPHINE			
C_{max}	1.2 fold increase	1.1 fold increase	1.7 fold increase
AUC_{last}	Similar to control	1.6 fold increase	2.8 fold increase
NALOXONE			
C_{max}	Similar to control	2.7 fold increase	11.3 fold increase
AUC_{last}	0.2 fold increase	3.2 fold increase	14 fold increase

In the same study, changes in C_{max} and AUC_{last} of buprenorphine and naloxone in subjects with HCV infection without hepatic impairment were not clinically significant in comparison to the healthy subjects.

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 generally required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment (CLcr <30 ml/min), which may require dose adjustment.

Head Injury and Increased Intracranial Pressure
BUPRENORPHINE NALOXONE BNM**,** like other potent opioids may itself elevate cerebrospinal fluid pressure, which may cause seizures and should be used with caution in patients with head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased, or history of seizure. Buprenorphine and Naloxone sublingual tablets can produce miosis and changes in the level of consciousness, or changes in the perception of pain as a symptom of disease and may interfere with patient evaluation or obscure the diagnosis or clinical course of concomitant disease.

Tolerance, dependence and Opioid Withdrawal Effects
Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.
Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced.
Because BUPRENORPHINE NALOXONE BNM contains naloxone, it is highly likely to produce marked and intense opioid withdrawal symptoms if injected. BUPRENORPHINE NALOXONE BNM may produce withdrawal symptoms in opioid dependent subjects if it is administered too soon after another opioid. Buprenorphine is a partial agonist at the μ (mu)-opiate receptor and chronic administration produces dependence of the opioid type, but at a lower level than a full agonist (e.g. morphine). The withdrawal syndrome is typically milder than seen with full agonists, and may be delayed in onset. Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate. Abrupt discontinuation of treatment is not recommended as it may result in a withdrawal syndrome that may be delayed in onset. When discontinuing BUPRENORPHINE NALOXONE BNM in a person who may be physically-dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see Ceasing opioids and section 4.2 Dose and Method of Administration). Consequently, it is important to follow the **Dose and method of administration** recommendations.

Withdrawal symptoms may also be associated with sub-optimal dosing.

Neonatal Abstinence Syndrome
Chronic use of buprenorphine by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, convulsions, apnoea or bradycardia) in the neonate. In many reported cases, the withdrawal was serious and required treatment. The syndrome is generally delayed for several hours to several days after birth (see section **4.6 Fertility, pregnancy and lactation**). Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

Allergic Reactions
Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the post-marketing 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 BUPRENORPHINE NALOXONE BNM use.

Use in children:
BUPRENORPHINE NALOXONE BNM is not recommended for use in children. The safety and effectiveness of Buprenorphine and Naloxone sublingual tablets in subjects below the age of 16 has not been established. Due to the limited amount of available data, patients below the age of 18 years should be closely monitored during treatment.

Effects on Laboratory Tests
Athletes should be aware that this medicine may cause a positive reaction to "anti-doping" tests.

Use in Opioid Naïve Patients
There have been reported deaths of opioid naïve individuals who received doses as low as 2mg of buprenorphine sublingual tablet for analgesia. BUPRENORPHINE NALOXONE BNM is not appropriate as an analgesic.

Use of opioids in chronic (long-term) non-cancer pain (CNCP)
Opioid analgesics have an established role in the treatment of acute pain, cancer pain and palliative and end-of-life care. Current evidence does not generally support opioid analgesics in improving pain and function for most patients with chronic non-cancer pain. The development of tolerance and physical dependence and risks of adverse effects, including hazardous and harmful use, increase with the length of time a patient takes an opioid. The use of opioids for long-term treatment of CNCP is not recommended.

The use of an opioid to treat CNCP should only be considered after maximised non-pharmacological and non-opioid treatments have been tried and found ineffective, not tolerated or otherwise inadequate to provide sufficient management of pain. Opioids should only be prescribed as a component of comprehensive multidisciplinary and multimodal pain management.

Opioid therapy for CNCP should be initiated as a trial in accordance with clinical guidelines and after a comprehensive biopsychosocial assessment has established a cause for the pain and the appropriateness of opioid therapy for the patient (see Hazardous and harmful use, above). The expected outcome of therapy (pain reduction rather than complete abolition of pain, improved function and quality of life) should be discussed with the patient before commencing opioid treatment, with agreement to discontinue treatment if these objectives are not met.

Owing to the varied response to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose and titrated to achieve an adequate level of analgesia and functional improvement with minimum adverse reactions. Immediate-release products should not be used to treat chronic pain, but may be used for a short period in opioid-naïve patients to develop a level of tolerance before switching to a modified-release formulation. Careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment. Discontinue opioid therapy if there is no improvement of pain and/or function during the trial period or if there is any evidence of misuse or abuse. Treatment should only continue if the trial has demonstrated that the pain is opioid responsive and there has been functional improvement.

The patient's condition should be reviewed regularly and the dose tapered off slowly if opioid treatment is no longer appropriate (see Ceasing Opioids).

Accidental ingestion/exposure
Accidental ingestion or exposure of BUPRENORPHINE NALOXONE BNM, especially by children, can result in a fatal overdose of Buprenorphine and Naloxone. Patients and their caregivers should be given information on safe storage and disposal of unused BUPRENORPHINE NALOXONE BNM (see section 6.4 Special precautions for storage and section 6.6 Special precautions for disposal).

Hyperalgesia
Hyperalgesia may occur with the use of opioids, particularly at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain. Hyperalgesia should not be confused with tolerance (see Tolerance, dependence and withdrawal). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

Ceasing opioids
Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see Tolerance, dependence and withdrawal). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks (see section 4.2 Dose and Method of Administration). If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

4.5 Interaction with other medicines and other forms of interaction

Alcohol
Alcohol increases the sedative effect of buprenorphine/naloxone. BUPRENORPHINE NALOXONE BNM should not be used together with alcoholic drinks, and must be used cautiously with medicines containing alcohol (see section **4.4 Special warnings and precautions for use**).

Benzodiazepines
This combination may result in death due to respiratory depression of central origin; therefore, patients must be closely monitored when prescribed this combination, and this combination should be avoided where there is a risk of misuse. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking this product, and should also be cautioned to use benzodiazepines concurrently with this product only as prescribed (see section **4.4 Special warnings and precautions for use**).

Other central nervous system depressants
Combining central nervous system depressants with buprenorphine increases central nervous system depressant effects. The reduced level of alertness can make driving and using machinery hazardous. Examples include opioids (eg methadone, analgesics, antitussives), certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics, neuroleptics, clonidine.

Opioid analgesics
The analgesic properties of other opioids such as methadone and level III analgesics may be reduced in patients receiving treatment with buprenorphine/naloxone for opioid dependence. Adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving BUPRENORPHINE NALOXONE BNM. Conversely, the potential for overdose should be considered with higher than usual doses of full agonist opioids, such as methadone or level III analgesics, especially when attempting to overcome buprenorphine partial agonist effects, or when buprenorphine plasma levels are declining. Patients with a need for analgesia and opioid dependence treatment may be best managed by multidisciplinary teams that include both pain and opioid dependence treatment specialists (see section **4.4 Special warnings and precautions for use**).

Naltrexone and other opioid antagonists
Since buprenorphine is a partial mu-opioid agonist, concomitantly administered opioid antagonists such as naltrexone can reduce or completely block the effects of BUPRENORPHINE NALOXONE BNM. Patients maintained on BUPRENORPHINE NALOXONE BNM may experience a sudden onset of prolonged and intense opioid withdrawal symptoms if dosed with opioid antagonists that achieve pharmacologically relevant systemic concentrations.

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 BUPRENORPHINE NALOXONE BNM 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.

CYP3A4 inducers
Concomitant use of CYP3A4 inducers with buprenorphine may decrease buprenorphine plasma concentrations, potentially resulting in under-treatment of opioid dependence with buprenorphine therefore, it is recommended that patients receiving BUPRENORPHINE

NALOXONE BNM should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered.

Paediatric population
No information held by the sponsor.

4.6 Fertility, pregnancy and lactation

Pregnancy *(Category C)*

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 (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions). The syndrome is generally delayed for several hours to several days after birth. Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

BUPRENORPHINE NALOXONE BNM should be used during pregnancy only if the potential benefits justifies the potential risk to the foetus. Continued use of heroin during pregnancy is associated with significant risk to the mother and the foetus and neonate.

Breastfeeding

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, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BUPRENORPHINE NALOXONE BNM and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

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 32mg/day (based on mg/m^2). Dietary administration to rats at doses of 47mg/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 9.4mg/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.

4.7 Effects on ability to drive and use machines

BUPRENORPHINE NALOXONE BNM may influence the ability to drive and use machinery when administered to opioid dependent patients. This product may cause drowsiness, dizziness, or impaired thinking, especially during treatment induction or dose adjustment. If used together with alcohol or central nervous system depressants, the effect is likely to be more pronounced (see also section **4.4 Special warnings and precautions for use** and **4.5 Interaction with other medicines and other forms of interaction)**. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that BUPRENORPHINE NALOXONE BNM therapy does not adversely affect their ability to engage in such activities.

4.8 Undesirable effects

a. Summary of the safety profile

Table 3 summarises adverse reactions reported from pivotal clinical studies in which, 342 of 472 patients (72.5%) reported adverse reactions. The frequency of possible side effects listed below is defined using the following convention:
Very common (≥ 1/10), Common (≥ 1/100 to <1/10), Uncommon (≥ 1/1,000 to <1/100), Rare (≥ 1/10,000 to <1/1,000), Very rare (<1/10,000).

b. Tabulated summary of adverse reactions

Table 3: Treatment- related adverse reactions reported in clinical studies		
Very common (≥ 1/10)	**Common (≥ 1/100 to <1/10)**	**Uncommon (≥ 1/1,000 to <1/100**
Infections and infestations		
	Influenza Infection Pharyngitis Rhinitis	Urinary tract infection Vaginal infection
Blood and lymphatic system disorders		
		Anaemia Thrombocytopenia Leukopenia Lymphadenopathy Leukocytosis
Immune system disorders		
		Hypersensitivity
Metabolism and nutrition disorders		
	Decreased appetite	Hyperglycaemia Hyperlipidaemia Hypoglycaemia

Table 3: Treatment- related adverse reactions reported in clinical studies		
Very common (≥ 1/10)	**Common (≥ 1/100 to <1/10)**	**Uncommon (≥ 1/1,000 to <1/100**
Psychiatric disorders		
Insomnia	Anxiety Nervousness Depression Libido decreased Thinking abnormal	Agitation Drug dependence Hostility Depersonalisation Abnormal dreams Apathy Euphoric mood
Nervous system disorders		
Headache	Somnolence Dizziness Paraesthesia Hypertonia Migraine	Convulsion Tremor Hyperkinesia Speech disorder Amnesia
Eye disorders		
	Lacrimal disorder Amblyopia	Miosis Conjunctivitis
Cardiac disorders		
		Myocardial infarction Angina pectoris Palpitations Tachycardia Bradycardia
Vascular disorders		
	Vasodilatation Hypertension	Hypotension
Respiratory, thoracic and mediastinal disorders		
	Cough	Dyspnoea Asthma Yawning
Gastrointestinal disorders		
Constipation Nausea	Abdominal Pain Vomiting Dyspepsia Diarrhoea Flatulence	Mouth ulceration Tongue discolouration

Table 3: Treatment- related adverse reactions reported in clinical studies		
Very common (≥ 1/10)	**Common (≥ 1/100 to <1/10)**	**Uncommon (≥ 1/1,000 to <1/100**
Skin and subcutaneous tissue disorders		
Hyperhidrosis	Rash Pruritus Urticaria	Dermatitis exfoliative Acne Skin mass Alopecia Dry skin
Musculoskeletal and connective tissue disorders		
	Arthralgia Back Pain Myalgia Muscle spasms Leg cramps	Arthritis
Renal and urinary disorders		
	Urine Abnormality	Haematuria Nephrolithiasis Dysuria Urinary retention Albuminuria
Reproductive system and breast disorders		
	Erectile Dysfunction	Amenorrhoea Ejaculation disorder Menorrhagia Metrorrhagia
General disorders and administration site conditions		
Drug withdrawal syndrome	Asthenia Pyrexia Malaise Chills Chest Pain Pain Oedema peripheral Injury	Hypothermia Heat stroke
Investigations		
	Liver function test abnormal Weight decreased	Blood creatinine increased

The most common adverse events reported were those related to withdrawal symptoms (e.g. abdominal pain, diarrhoea, muscle aches, anxiety, sweating, insomnia, headache, constipation, nausea). In patients with marked opioid dependence, initial administration of buprenorphine can produce a withdrawal effect similar to that associated with naloxone.

Some reports of seizure, vomiting, diarrhoea and elevated liver function tests were considered serious.

Post-marketing experience with buprenorphine alone and buprenorphine- naloxone combination
Post-marketing experience with buprenorphine alone has been associated with the following side effects: respiratory depression (see section **4.4 Special warnings and precautions for use**) and coma, hallucinations, neonatal withdrawal syndrome, neonatal tremor, neonatal feeding disorder, foetal disorders, convulsions, confusion, miosis, weight decrease, asphyxia, hypoventilation, urinary retention, vertigo, drug dependence, headache, nausea, vomiting, drug withdrawal syndrome, peripheral oedema, orthostatic hypotension, syncope, heart rate and rhythm disorders, and deaths.

Cases of hepatitis, acute hepatitis, cytolytic hepatitis, jaundice, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy, and elevations in hepatic transaminases have been reported with buprenorphine use (see section **4.4 Special warnings and precautions for use**).

In cases of intravenous misuse of buprenorphine, local reactions such as cellulitis or abscess that are sometimes septic, potentially serious acute hepatitis, pneumonia, endocarditis and other serious infections 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 section **4.3 Contraindications** and **4.4 Special warnings and precautions for use**).

The most commonly reported adverse event for buprenorphine- naloxone combination reported during post-marketing surveillance, are mentioned in Table 4 below. Events occurring in at least 1% of reports be healthcare professionals and considered to be at least possibly related to treatment are included. Adverse drug reactions are presented by MedDRA System Organ Class in internationally agreed order by preferred term and frequency of reporting.

Table 4: Spontaneous adverse drug reactions collected through post-marketing surveillance reported by body system, buprenorphine- naloxone combination

System Organ Class	**Preferred Term**
Psychiatric disorders	Anxiety
Nervous system disorders	Headache
Gastrointestinal disorders	Nausea Vomiting
Skin and subcutaneous disorders	Rash Urticaria Hyperhidrosis
General disorders and administration site conditions	Drug withdrawal syndrome Oedema periphera; Oedema

Additionally, post-marketing experience with buprenorphine- naloxone combination for treatment of opioid dependence has been associated rarely with the following side effects: insomnia, reduced feeling, anorexia, amnesia, convulsions, blood in vomit, fatigue, jaundice, swollen joints, miscarriage, shortness of breath, and suicide ideation. Treatment with buprenorphine-naloxone combination has been associated with orthostatic hypotension.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms

Manifestations of acute overdose include miosis, sedation, hypotension, respiratory depression and death. Nausea and vomiting may be observed.

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 following standard intensive care measures. The patient should be transferred to an environment within which full resuscitation facilities are available. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. High doses of naloxone hydrochloride 10-35mg/70kg may be of limited value in the management of buprenorphine overdose.

The long duration of action of BUPRENORPHINE NALOXONE BNM should be taken into consideration when determining the length of treatment needed to reverse the effects of an overdose. Naloxone can be cleared more rapidly than buprenorphine, allowing for a return of previously controlled buprenorphine overdose symptoms, so a continuing infusion may be necessary. Ongoing IV infusion rates should be titrated to patient response. If infusion is not possible, repeated dosing with naloxone may be required.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

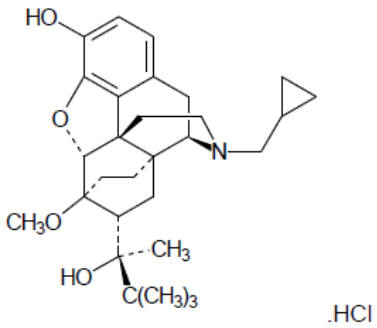
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Buprenorphine is μ (mu) Opioid receptor partial agonist, ϰ (kappa) opioid receptor antagonist and Naloxone is μ (mu), δ (delta) and ϰ (kappa) opioid receptors.

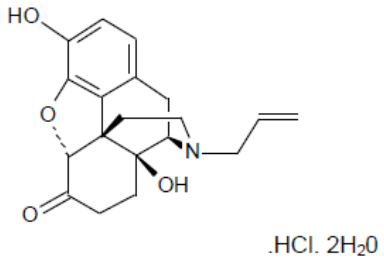
ATC code: N07BC51

Chemistry information

The chemical structures of buprenorphine hydrochloride and naloxone hydrochloride dihydrate are:



buprenorphine hydrochloride



naloxone hydrochloride dihydrate

Buprenorphine hydrochloride is a white powder, weakly acidic with limited solubility in water (19.5mg/mL at 37ºC, pH 4.1). Chemically, it is 21-Cyclopropyl-7α-[(S) -1-hydroxy-1,2,2–trimethylpropyl]-6,14-*endo*–ethano-6,7,8,14-tetrahydrooripavine hydrochloride.
Molecular formula: $C_{29}H_{41}NO_4HCl$
Molecular weight: 504.09
CAS number: 53152-21-9

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. Chemically, it is (-)-17-Allyl-4,5α-epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride dihydrate.
Molecular formula: $C_{19}H_{21}NO_4HCl.2H_2O$
Molecular weight: 399.87
CAS number: 51481-60-8

Mechanism of action

Buprenorphine is a μ (mu) opioid receptor partial agonist, κ (kappa) opioid receptor antagonist. Its activity in opioid maintenance treatment is attributed to its slow dissociation from the μ receptors in the brain which reduces craving for opioids and opioid withdrawal symptoms. This minimises the need of the opioid dependent patient for illicit opioid medicines.

During clinical pharmacology studies in opioid 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 μ (mu), ō (delta) and κ (kappa) 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 opioid dependent persons, the presence of naloxone in buprenorphine-naloxone combination produces marked opioid antagonist effects and opioid withdrawal, thereby deterring intravenous abuse.

5.2 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 BUPRENORPHINE NALOXONE BNM by the oral route is therefore inappropriate. BUPRENORPHINE NALOXONE BNM tablets are for sublingual administration.

Plasma levels of buprenorphine and naloxone increased with the sublingual dose of Buprenorphine - Naloxone sublingual tablets although the increases were not directly dose-proportional (Table 5). The levels of naloxone were too low to determine area under the curve values. There was a wide inter-patient variability in the sublingual absorption of buprenorphine and naloxone from Buprenorphine - Naloxone sublingual tablets, but within subjects the variability was low.

Table 5. Mean Cmax and AUC of buprenorphine and naloxone following single sublingual doses of Buprenorphine - Naloxone tablets.

	4mg buprenorphine + 1mg naloxone)	8mg buprenorphine + 2mg naloxone)	16mg buprenorphine + 4mg naloxone)	24mg buprenorphine + 6mg naloxone)
Buprenorphine				
Subjects	22	22	21	12
C_{max} ng/mL	2.16 (0.68-4.33)	3.33 (1.10-6.36)	5.87 (2.48-10.0)	6.44 (3.43-10.5)
$AUC_{0\text{-}tn}$ h. ng/mL	12.88 (5.18-23.24)	22.14 (8.62-44.11)	37.67 (18.71-74.13)	47.55 (24.23-96.43)
Naloxone				
Subjects	20	21	20	12
C_{max} ng/mL	0.12 (0.06-0.25)	0.23 (0.09-0.42)	0.39 (0.07-1.15)	0.47 (0.08-1.02)

Naloxone did not affect the pharmacokinetics of buprenorphine and both Buprenorphine - Naloxone sublingual tablets and buprenorphine deliver similar plasma concentrations of buprenorphine. Compared with intravenous administration, the mean absolute bioavailability of buprenorphine from sublingual 8mg tablets was 13.6% (range 5.1-24.9%) and that of naloxone was approximately 3%.

Distribution

The absorption of buprenorphine is followed by a rapid distribution phase (distribution half-life of 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 medicine is around 96% protein bound primarily to alpha and beta globulin. Naloxone is approximately 45% protein bound, primarily to alpha and beta globulin.

Biotransformation

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 **4.4 Special warnings and precautions for use** and **4.5 Interaction with other medicines and other forms of interaction**). 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 μ (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

Elimination of buprenorphine is bi- or tri-exponential, 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.

CLINICAL TRIALS

All trials used buprenorphine in conjunction with psychosocial counselling as part of a comprehensive opioid dependence 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 buprenorphine and naloxone sublingual tablet 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 buprenorphine and naloxone sublingual tablet are primarily derived from a one-year clinical trial, comprising a 4 week randomised double blind comparison of naloxone

sublingual tablet, buprenorphine and placebo tablets followed by a 48-week safety study (Study CR96/013 + CR96/014).

In the double-blind placebo- and active controlled study, 326 heroin-dependent subjects were randomly assigned to either buprenorphine - naloxone tablets 16mg per day, 16mg buprenorphine per day or placebo tablets. For subjects randomised to either active treatment, dosing began with one 8mg tablet of buprenorphine on Day 1, followed by 16mg (two 8mg tablets) of buprenorphine on Day 2. On Day 3, those randomised to receive buprenorphine - naloxone tablets 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 buprenorphine - naloxone tablets individually against placebo. The percentage of thrice weekly urine samples that were negative for non-study opioids was statistically higher for both buprenorphine - naloxone tablets versus placebo ($p < 0.0001$) and buprenorphine versus placebo ($p < 0.0001$).

5.3 Preclinical safety data

Carcinogenicity:

In mice, no evidence for carcinogenicity due to buprenorphine was noted in life-time studies at dietary doses of up to 100mg/kg/day, which equates to ca 14-fold human exposure at the maximum recommended clinical dose of 32mg 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 55mg/Kg/day (16 fold the maximal recommended human sublingual dose of 32mg, on a $mg/^{m2}$ basis); the no-effect dose was 5.4mg/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 in rats, Leydig cell adenomas were found at doses of 6-115mg/kg/day, associated with respective exposures (plasma AUC) to buprenorphine and naloxone of 2-21fold, and up to 58fold, anticipated human exposure. A NOEL was not established in the study.

Mutagenicity:

In genotoxic 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Mannitol

Maize starch
Povidone
Citric acid monohydrate
Sodium citrate
Magnesium stearate
Acesulfame potassium
Lemon flavour
Lime flavour.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30ºC.

6.5 Nature and contents of container

The tablets are packaged in Alu-Alu blister pack of 28 sublingual tablets.

6.6 Special precautions for disposal

No special requirements.

7 MEDICINE SCHEDULE

Controlled Drug C4

8 SPONSOR

BNM Group
39 Anzac Road
Browns Bay
Auckland 0753

Phone 0800 565 633

9 DATE OF FIRST APPROVAL

16 May 2019

10 DATE OF REVISION OF TEXT

19 August 2022

Summary table of changes

Section changed	Summary of new information
4.5	Deletion of section Serotonergic Drugs as per Medsafe & MARC recommendations dated 12 July 2022.