New Zealand Data Sheet

WARNINGS

Limitations of use
Because of the risks associated with the use of opioids, Methadone BNM should only be used in patients for whom other treatment options, including non-opioid analgesics, are ineffective, not tolerated or otherwise inadequate to provide appropriate management of pain (see section 4.4 Special Warnings and Precautions for Use).

Hazardous and harmful use
Methadone BNM poses risks of hazardous and harmful use which can lead to overdose and death. Assess the patient's risk of hazardous and harmful use before prescribing and monitor the patient regularly during treatment (see section 4.4. Special Warnings and Precautions for Use).

Life threatening respiratory depression
Serious, life-threatening or fatal respiratory depression may occur with the use of Methadone BNM. Be aware of situations which increase the risk of respiratory depression, modify dosing in patients at risk and monitor patients closely, especially on initiation or following a dose increase (see section 4.4 Special Warnings and Precautions for Use).

Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol
Concomitant use of opioids with benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required; and monitor patients for signs and symptoms of respiratory depression and sedation. Caution patients not to drink alcohol while taking Methadone BNM.

1 METHADONE BNM

METHADONE BNM 5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of methadone hydrochloride.

Excipient(s) with known effect: lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White, or almost white, round, flat uncoated tablets of 7 mm, imprinted with "M5" on one side and concave with a score line on other side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Methadone BNM is indicated for:

The treatment of severe pain
Methadone is indicated for relief of severe pain. Methadone is sometimes used as an antitussive when severe pain is present and coughing cannot be relieved by other means. Methadone is not recommended for obstetric analgesia because its long duration of action increases the risk of neonatal respiratory depression.

The treatment of dependence on opioid drugs
Methadone is indicated as a suppressant to permit detoxification. Oral Methadone is also indicated as maintenance therapy to discourage addicts from returning to illicit use of other opioid drugs.

4.2 Dose and method of administration

Dose

Treatment of severe pain
Starting oral doses of Methadone may range from 5 to 10mg (1 to 2 tablets) given every 6 to 8 hours or longer and thereafter adjusted as necessary.

Treatment of dependence on opioid drugs
A dose of 10 to 20 mg (2 to 4 tablets) by mouth may be given initially and increased as necessary by 5 to 10 mg daily. The dose must not be increased by more than 5 to 10 mg daily, and by no more than 30 mg in any 7-day period. After stabilisation, which can often be achieved with a dose of 30 to 50 mg daily (up to a maximum of 80 mg daily), the dose of Methadone is gradually decreased until total withdrawal is achieved. Some treatment schedules for opioid dependence involved prolonged maintenance therapy with Methadone where the daily dose is adjusted carefully for the individual.

Treatment goals and discontinuation
Before initiating treatment with Methadone BNM, a treatment strategy including treatment duration and treatment goals should be agreed together with the patient in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider

discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with methadone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal (see section 4.4). In absence of adequate pain control, the possibility of tolerance and progression of underlying disease should be considered (see section 4.4).

4.3 Contraindications

Methadone is contraindicated in individuals who are hypersensitive to Methadone or other components in Methadone Tablets:

Like other opioids, Methadone is contraindicated in patients with respiratory depression, especially in the presence of cyanosis and excessive bronchial secretions.

Methadone should not be given during an attack of bronchial asthma. Methadone is contraindicated in the presence of acute alcoholism, head injury and raised intracranial pressure.

Methadone is contraindicated in individuals receiving monoamine oxidase inhibitors or within 14 days of stopping such treatment (see Interactions Section 4.5).

As with other opioids, Methadone is contraindicated in patients with ulcerative colitis, since it may precipitate toxic dilation or spasm of the colon. As with all narcotics, Methadone should not be administered to patients with severe hepatic impairment as it may precipitate hepatic encephalopathy (see Section 4.4 Special warnings and precautions for use).

Methadone is contraindicated in biliary and renal tract spasm.

4.4 Special warnings and precautions for use

Hazardous and harmful use
Methadone BNM contains the opioid methadone hydrochloride and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed Methadone BNM at recommended doses.

Strategies to reduce the risks of misuse and abuse 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 Methadone BNM with anyone else.

Opioid Use Disorder and withdrawal
Methadone is an opioid analgesic and is highly addictive in its own right. It has a long half-life and can therefore accumulate. A single dose which will relieve symptoms may, if repeated on a daily basis, lead to accumulation and possible death.

When used for the treatment of pain, repeated use of Methadone BNM can lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD.

Before initiating treatment with Methadone BNM and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Abuse or intentional misuse of Methadone BNM may result in overdose and/or death.
The risk of developing Opioid Use Disorder is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g., major depression, anxiety and personality disorders).

Patients will require monitoring for signs of drug-seeking behaviour (e.g., too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

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.

Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). 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.

When discontinuing Methadone 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).

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 Methadone 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).

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.

Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol

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 Methadone 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 Methadone 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 Methadone BNM.

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 Methadone BNM, especially by children, can result in a fatal overdose of Methadone. Patients and their caregivers should be given information on safe storage and disposal of unused Methadone 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 Opioid Use Disorder 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 Opioid Use Disorder 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.

Cardiac Conduction Effects

Laboratory studies, both in vivo and in vitro, have demonstrated that Methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with Methadone. These cases appear to be more commonly associated with, but not limited to, higher dose treatment (> 100 mg/day). Most cases involve patients being treated for pain with large, multiple daily doses of Methadone although cases have been reported in patients receiving doses commonly used for maintenance of opioid addiction.

Methadone should be administered with particular caution to patients already at risk for development of prolonged QT interval. These risks include cardiac hypertrophy, history of cardiac conduction abnormalities, advanced heart disease or ischaemic heart disease, liver disease, family history of sudden death, hypokalaemia, hypomagnesaemia, concomitant treatments with medicines that have a potential for QT prolongation, concomitant treatment with medicines which may cause electrolyte abnormalities (e.g. diuretics) and concomitant treatment with CYP3A4 inhibitors.

QT prolongation has also been reported in patients with no prior cardiac history who have received high doses of Methadone. Patients developing QT prolongation while on Methadone treatment should be evaluated for the presence of modifiable risk factors, such as concomitant medications with cardiac effects, drugs which might cause electrolyte abnormalities, and drugs which might act as inhibitors of Methadone metabolism.

In patients with recognised risk factors of QT prolongation, or in case of concomitant treatment with medicines that have a potential for QT prolongation, ECG monitoring is recommended prior to methadone treatment, at dose stabilisation, after dose increases, or after starting any potentially interacting medicine. In patients without recognised risk factors for QT prolongation, ECG monitoring is recommended before dose titration above 100 mg/day, and at seven days after titration.

For use of Methadone to treat pain, the risk of QT prolongation and development of dysrhythmias should be weighed against the benefit of adequate pain management and the availability of alternative therapies.

Serotonin syndrome

The development of serotonin syndrome, which is potentially life-threatening, has been reported with opioid use, including with methadone. This is mainly applicable to the use of methadone at higher doses such as in opioid substitution therapy. Serotonin syndrome has generally occurred when methadone was used concomitantly with other serotonergic drugs (see section 4.5 Interactions with other medicines and other forms of interactions).

Serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma, confusion), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia, diaphoresis), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity, tremor, myoclonus), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

If serotonin syndrome is suspected, a dose reduction or discontinuation of at least one of the serotonergic medicines being taken should be considered depending on the severity of symptoms.

Mutagenicity
Methadone did not exhibit demonstrable mutagenic activity in a wide range of standard in vitro and in vivo mutagenicity assays. However, in a Dominant Lethal assay in mice, treatment with Methadone at doses of 1 to 6 mg/kg was associated with increased pre-implantation deaths and chromosomal aberrations of sperm cells, when compared with controls.

Carcinogenicity
Long term carcinogenicity tests in rodents did not reveal any evidence of Methadone-related neoplasia.

Teratogenicity
No teratogenic effects have been observed in standard teratogenicity studies in rats and rabbits given Methadone at doses from 10 to 50 times the average daily human maintenance dose. Developmental abnormalities of the central nervous system have been reported in hamsters and mice given high doses in early pregnancy.

Paediatric population
Methadone is not recommended for use in children less than 18 years of age since documented clinical experience has been insufficient to establish a suitable dosage regimen; furthermore, children are particularly sensitive to the respiratory and central nervous system effects of Methadone.

Use in the Elderly
Methadone has a long plasma half-life which may lead to accumulation, particularly if renal function is impaired (see Renal Impairment Section 4.5).
In common with other opioids, Methadone may cause confusion in this age group, therefore careful monitoring is advised.

Hepatic Impairment
Particular care should be taken when Methadone is to be used in patients with hepatic impairment as these patients metabolise Methadone more slowly than normal patients. Where not contraindicated, Methadone should be given at less than the normal recommended dose and the patient's response used as a guide to further dosage requirements (see Contraindications Section 4.3).

Renal Impairment
Methadone should be used with caution in patients with renal dysfunction.

4.5 Interaction with other medicines and other forms of interaction

The medicines listed below are known to affect methadone metabolism and should therefore be used with caution by those being treated with methadone.

NOTE: Patients with hepatitis C may have impaired liver function. This needs to be taken into account when the use of medicines metabolised by the liver is considered. The dose

of paracetamol, for example, needs to be well within the standard 4 g per day.

Drug	Status of effect	Interaction	Mechanism
Alcohol	Clinically important	Increased sedation, increased respiratory depression, combination may also have increased hepatotoxic potential	Additive central nervous system depression
Benzodiazepines and hypnotics	Clinically important	Enhanced sedative effect	Additive CNS depression
Buprenorphine	Clinically important	Antagonistic effect or enhanced sedative and respiratory depression	Partial agonist of opiate receptors
Carbamazepine	Clinically important	Reduced methadone levels	Stimulated hepatic enzymes involved in methadone metabolism
Chlormethiazole	Clinically important	Enhanced sedative effect	Additive CNS depression
Cimetidine	Two cases have been shown in patients taking methadone as analgesia	Possible increase in methadone plasma levels	Inhibits hepatic enzymes involved in methadone metabolism
Cisapride, domperidone, metoclopramide	Theoretical	Theoretically might increase the speed of onset of methadone absorption but not the extent	Possibly by reversing the delayed gastric emptying associated with opioids
Cyclizine and other sedating antihistamines	Clinically important	Anecdotal reports of injection of cyclizine with opioids causing hallucinations	Additive sedative and psychoactive effects, anti-muscarinic effect at high doses
Desipramine	Clinically important	Raised desipramine levels by up to a factor of two	Unknown interaction not seen with other tricyclic antidepressants
Other tricyclic antidepressants	Theoretical	Enhanced sedative effect which is dependent	Additive CNS dose depression

Efavirenz		Induction of methadone metabolism	Reduced methadone levels
Erythromycin	In theory should interact by combination has not been studied	Increase in methadone levels.	Decreased methadone metabolism
Fluconazole	In theory the same as ketoconazole	Inhibition of methadone metabolism	Increased methadone levels
Fluoxetine	Clinically important	Raised methadone levels but not as significant as for fluvoxamine	Decreased methadone metabolism
Fluvoxamine, other SSRI	Clinically important, theoretical	Raised plasma methadone levels	Decreased methadone metabolism
Grapefruit juice	Should interact in theory and there have been anecdotal reports	Raised methadone levels	Decreased methadone metabolism
Indinavir	Clinically important	Raised methadone levels	Decreased methadone metabolism
Ketoconazole	Clinically important	Raised methadone levels	Decreased methadone metabolism
MAOI (including selegiline and moclobemide)	Sever with pethidine though unlikely with methadone and has never been described	CNS excitation delirium, hyperpyrexia, convulsions, hypotension or respiratory depression	Unclear: avoid the combination if possible
Naltrexone	Clinically important	Blocks effect of methadone (long acting)	Opioid agonist – competes for opiate receptors
Naloxone	Clinically important	Blocks effect of methadone (long acting), but may be needed if overdose suspected	Opioid agonist – competes for opiate receptors
Nevirapine	Clinically important	Decreased methadone levels	Increased methadone metabolism
Nifedipine	Has been demonstrated *in vitro* only	Increased nifedipine levels; no effect on methadone levels	Methadone decreased the metabolism of nifedipine

Omeprazole	To date, demonstrated only in animals	Increased methadone levels	Possibly affects methadone absorption from gut
Phenobarbitone	Clinically important	Reduced methadone levels; increase sedation, additive CNS depression.	Barbiturates stimulate hepatic enzymes involved in methadone metabolism
Phenytoin	Clinically important	Reduced methadone levels	Phenytoin stimulates hepatic enzymes involved in methadone metabolism
Rifampicin	Very important: most patients are likely to be affected	Reduced methadone levels	Rifampicin stimulates hepatic enzymes involved in methadone metabolism
Rifabutin	Occasionally clinically important	Ritonavir may increase methadone levels	Inhibits methadone metabolism
Ritonavir	Clinically important	Ritonavir may increase plasmas methadone levels	Inhibits methadone metabolism
Other protease inhibitors	Theoretical	May raise or lower plasma methadone levels	Inhibits methadone metabolism
Urine acidifiers (e.g. ascorbic acid / vitamin C)	Clinically important	Reduced plasma methadone levels	Raised urinary excretion of methadone
Urine alkalinisers (e.g. sodium bicarbonate)	Clinically important	Increased plasma methadone levels	Reduced urinary excretion of methadone
Zidovudine	Clinically important	Raised plasma levels of zidovudine; no effect on methadone levels	Unknown
Zopiclone	Clinically important	Enhanced sedative effects	Additive CNS depression
Other opioids	May be clinically important	Enhanced sedative effect	Additive CNS depression; enhanced respiratory depression
Other CNS depressant medicines (e.g. neuroleptics, hyoscine)	Clinically important	Enhanced sedative effects, which are dose dependent	Additive CNS depression

Gabapentinoids

The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression, and death.

Cannabidiol

Concomitant administration of cannabidiol may result in increased plasma concentrations of methadone.

Serotonergic drugs

Co-administration of methadone with serotonergic drugs may increase the risk of serotonin syndrome, a potentially life-threatening condition (see section 4.4).

Drugs that affect the serotonergic neurotransmitter system include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs).

4.6 Fertility, pregnancy and lactation

Pregnancy

There is inadequate evidence of the safety of Methadone in human pregnancy although it has been in selected use for many years without apparent ill consequence. Autopsies on five infants who died in utero did not reveal any abnormality attributable to Methadone use by their dependent mothers. Nevertheless, the use of methadone in pregnancy should be avoided unless there is no safer alternative.

Narcotics may cause respiratory depression in the newborn infant. During the last 2 to 3 hours before expected delivery, narcotics should therefore only be used after weighing the needs of the mother against the risk to the foetus.

Breastfeeding

Assays of breast milk from Methadone-maintained mothers showed Methadone concentrations of 0.17 to 5.6 mcg/ml.

Methadone is transferred into breast milk at very low levels. Caution should be exercised when methadone is administered to a breastfeeding mother due to the risks of sedation and respiratory depression in the infant.

Breastfeeding mothers receiving methadone for opioid substitution treatment should be under specialist care from obstetric and paediatric staff with experience in monitoring for neonatal abstinence syndrome. The baby should be monitored for sedation and poor feeding particularly during the first three weeks of life. Breastfeeding mothers should receive specific information on how to identify respiratory depression and sedation in their babies and when it may be necessary to seek immediate medical care.

Breastfeeding mothers should be advised to wean slowly off breastfeeding when they decide to stop to reduce the possibility of withdrawal symptoms in the baby.

The evaluation of the risks and benefits of breastfeeding while on methadone for opioid substitution treatment should be done jointly by the prescriber and patient.

Fertility

Methadone does not appear to impair human female fertility. Studies in men on Methadone maintenance programmes have shown that Methadone reduces serum testosterone and markedly depresses the ejaculate volume and sperm motility. The sperm counts of Methadone subjects were twice that of controls, reflecting the lack of dilution through reduced seminal secretions.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses are advisable.

The major hazards of methadone are respiratory depression and, to a lesser degree, systemic hypotension. Respiratory arrest, shock, cardiac arrest, and death have occurred.

Other adverse reactions include the following:

Body as a whole: weakness, oedema, headache

Cardiovascular: arrhythmias, bigeminal rhythms, bradycardia, cardiomyopathy, ECG abnormalities, extrasystoles, flushing, heart failure, hypotension, palpitations, phlebitis, QT interval prolongation, syncope, T-wave inversion, tachycardia, torsade de pointes, ventricular fibrillation, ventricular tachycardia

Endocrine: hypogonadism

Gastrointestinal: abdominal pain, anorexia, biliary tract spasm, constipation, dry mouth, glossitis

Hematologic: reversible thrombocytopenia has described in opioid addicts with chronic hepatitis

Metabolic: hypokalaemia, hypomagnesaemia, weight gain and hypoglycaemia

Musculoskeletal: decreased muscle mass and strength, osteoporosis and fractures Nervous

system disorders: raised intracranial pressure, sedation

Psychiatric: agitation, changes of mood, dependence, disorientation, dysphoria, euphoria, hallucinations, insomnia

Renal: antidiuretic effect, urinary retention or hesitancy

Reproductive: amenorrhoea, reduced libido and/or potency, reduced ejaculate volume, reduced seminal vesicle and prostate secretions, decreased sperm motility, abnormalities in sperm morphology

Respiratory: Central sleep apnoea syndrome, pulmonary oedema, respiratory depression

Skin and subcutaneous tissue: pruritus, urticaria, other skin rashes, and rarely, haemorrhagic urticaria

Maintenance on a stabilised dose: during prolonged administration of methadone, as in a methadone maintenance programme, constipation and sweating often persist and hypogonadism, decreased serum testosterone and reproductive effects are thought to be related to chronic opioid use.

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

Signs and Symptoms
The symptoms and signs of overdosage with Methadone parallel those for other opioids, namely profound respiratory depression, pin-point pupils, hypotension, circulatory failure and pulmonary oedema and coma. Rare events of leukoencephalopathy may occur in serious cases of overdosage. Hypoglycaemia has been reported.

Mydriasis may replace miosis as asphyxia intervenes. Drowsiness, floppiness, pin-point pupils and apnoea have been reported in children.

Treatment:
General supportive measures should be employed as required. The specific opioid antagonist naloxone is the treatment of choice for the reversal of coma and the restoration of spontaneous respiration. A dose of 0.4 to 2mg is given by intravenous injection repeated at intervals of 2 to 3 minutes if necessary, up to 10mg. Naloxone may also be given by subcutaneous or intramuscular injection or intravenous infusion.
Patients should be monitored closely for at least 48 hours after apparent recovery in case of relapse, since the duration of action of the antagonist may be substantially shorter than that of Methadone.

The use of other respiratory or central stimulants is not recommended. Acidification of the urine will enhance urinary excretion of Methadone. Methadone is not dialysable by either peritoneal dialysis or haemodialysis.

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: Drugs used in opioid dependence
ATC code: N07BC02

Mechanism of action

Methadone hydrochloride is a synthetic opioid analgesic. Methadone is a racemic mixture and levo-methadone is the active isomer.

The pharmacological actions of Methadone are qualitatively similar to those of morphine. Significant quantitative differences are its effective analgesic activity after administration by the oral route and its tendency to show persistent effects with repeated administration.

5.2 Pharmacokinetic properties

Methadone hydrochloride is readily absorbed after administration by mouth and has high oral bioavailability. Peak plasma concentrations have been reported 1 to 5 hours after oral administration of a single dose in tablet form. It undergoes considerable tissue distribution, and protein binding is reported to be 60 to 90% with oc-acid glycoprotein being the main binding protein in plasma. Metabolism to the major metabolite 2-ethylidine-1,5- dimethyl-3,3-diphenyl-5–methypyrrolidine, both of them inactive, occurs in the liver. The metabolites are excreted in the faeces and urine together with unchanged Methadone. Other metabolites, including methanol and nor-methadol (reported to be pharmacologically active), have also been described, but account for a small proportion of the dose. The liver may also serve as a major storage site of unchanged Methadone which is taken up, bound non-specifically by the liver and released again mainly unchanged.

Marked inter individual variation in kinetics have been observed with Methadone. Elimination half-lives vary considerably (a range of 15-to 60 hours has been reported) and careful adjustment of dosage is necessary with repeated administration.

Plasma concentrations have been found to vary widely during Methadone maintenance therapy with large differences between patients and wide fluctuations in individual patients.

Declining concentrations have been reported during Methadone maintenance suggesting that tolerance occurs, possibly as a result of auto-induction of hepatic microsomal enzymes.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those included in other sections (see Special warnings and precautions for use Section 4.4).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Povidone
Purified water
Colloidal anhydrous silica
Talc
Magnesium stearate

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Methadone BNM tablets 5 mg are presented in PVC/PVdC/Aluminium blisters packed in a carton. Pack size 10 tablets.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Controlled Drug B3.

8 SPONSOR

BNM Group
39 Anzac Road

METHADONE BNM
Methadone Hydrochloride Tablets 5 mg

Browns Bay
Auckland 0753

Phone 0800 565 633

9 DATE OF FIRST APPROVAL

4 April 2019

10 DATE OF REVISION OF TEXT

28 July 2023

Summary table of changes

Section changed	Summary of new information
4.2 Dose and method of administration	Addition of information regarding treatment goals and discontinuation as per PRAC recommendation.
4.4 Special warnings and precautions for use	Amendments has been made with respect to Opioid use disorder as per PRAC recommendation.
4.5 Interaction with other medicines and other forms of interaction	Addition of information regarding concomitant use of Gabapentinoids and Cannabidiol with opioids as per PRAC recommendation.
4.8 Undesirable effects	Addition of Central sleep apnoea syndrome as per PRAC recommendation
4.9 Overdose	Addition of information regarding Hypoglycaemia as per MEDSAFE recommendation.