

New Zealand Data Sheet

1 PRODUCT NAME

METHADONE MOLTENI 1 mg/mL, 5 mg/mL, 10 mg/mL Oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Methadone hydrochloride 1 mg/mL, 5 mg/mL, 10 mg/mL

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Methadone Molteni is an oral solution containing methadone hydrochloride. Each strength is presented in a 100 mL amber plastic bottle with child resistant cap in an outer carton for storage purposes. A measuring device is included, and a Consumer Medicine Information leaflet is enclosed in the carton.

The 1 mg/mL strength is coloured green, the 5 mg/mL strength is light amber and the 10 mg/mL strength is blue.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral methadone is used in detoxification and maintenance treatment as a substitute for heroin or other morphine-like drugs to suppress the opiate-agonist abstinence syndrome in patients who are dependent on these drugs.

4.2 Dose and method of administration

Methadone is to be administered by the oral route only. Initial doses should be based on the individual's history of quantity, frequency and route of administration of opiates and should also take into account the person's hepatic and renal functioning. There may be some withdrawal symptoms not covered by the first dose. Initial doses will generally be in the range of 15 - 35 mg per day and should never be higher than 40 mg.

Subsequent dosage should be adjusted according to the requirements and response of the patient. Stabilisation of maintenance dosage usually occurs at 60-120 mg daily although a higher dosage is sometimes required. A single dose of methadone daily usually adequately maintains the patient and there generally is no apparent advantage to divided doses. However, rapid metabolisers of methadone may not maintain adequate plasma methadone concentrations with usual dosing regimens. Maintenance dosage requirements should be reviewed regularly and reduced as indicated.

The dose of methadone required is to be measured accurately, using a calibrated dropper or other appropriate method.

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Special populations**Elderly**

Methadone has a long plasma half-life, which may lead to accumulation, particularly if renal function is impaired. In common with other opioids, methadone may cause confusion in this age group, therefore careful monitoring is advised.

Renal impairment

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

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 section 4.3 **Contraindications**).

Paediatric population

The fatal dose of methadone in children is 10 – 20 mg. Symptoms of opioid overdose in children are similar to those in adults, with pupillary miosis; however, the pupils may be normoreactive or, rarely, fixed and dilated. Infants may have drowsiness, coma and apnoea.

Children are usually, but not always, symptomatic. Known or suspected methadone-intoxicated children should be hospitalised, since respiratory depression may be observed as long as 48 hours after ingestion. Successful resuscitation with a narcotic antagonist may be followed by relapse. Treatment must include establishment of an airway, maintenance of adequate respiratory ventilation, precise supportive care to maintain fluid and electrolyte balance, naloxone, emptying of upper and lower gastrointestinal tracts, and prevention of aspiration of gastric contents.

Method of administration

Methadone should be used in accordance with "*Opioid Substitution Treatment, New Zealand Practice Guidelines*" published by the Ministry of Health, February 2003. Substantial portions of this data sheet have been prepared from this publication, which may be downloaded from the publications page of www.moh.govt.nz.

4.3 Contraindications

Methadone is contraindicated in the following situations:

- individuals who are hypersensitive to methadone or to the colouring agents present in Methadone Molteni
- in patients with respiratory depression, especially in the presence of cyanosis and excessive bronchial secretions
- during an attack of bronchial asthma
- in the presence of acute alcoholism, head injury and raised intracranial pressure
- in individuals receiving monoamine oxidase (MAO) inhibitors or within 14 days of stopping such treatment
- in patients with ulcerative colitis, since it may precipitate toxic dilation or spasm of the colon
- in patients with severe hepatic impairment as it may precipitate hepatic encephalopathy
- in biliary and renal tract spasm

4.4 **Special warnings and precautions for use**

Methadone can cause a morphine-like drug dependence. Following repeated administrations, psychic dependence, physical dependence and tolerance can occur, therefore it must be prescribed and administered with the same caution utilised for morphine.

Extreme caution must be taken in the following cases (see also section 4.3 ***Contraindications***):

Cranial lesions and high intracranial pressure

The respiratory depressant effects of methadone and its capacity to increase the cerebrospinal fluid pressure can be considerably increased in the presence of an increase of the intracranial pressure; furthermore narcotics produce undesirable effects, that can hide neurological symptoms in patients with cranial lesions.

Asthma and other respiratory conditions

In patients with acute asthma attacks, in those with chronic obstructive pulmonary disease or cor pulmonale and in individuals with a substantially decreased respiratory reserve in pre-existing respiratory depression, hypoxia or hypercapnia, even the usual therapeutic dosages of narcotics may reduce the respiratory drive and increase the airway resistance to the point of apnoea.

Acute abdominal conditions

Methadone may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Plasma amylase and lipase determinations should not be performed within 24 hours after a methadone dose, which may increase the activity of these markers.

Hypotensive effect

The administration of methadone can cause serious hypotension in hypovolemic subjects or with concomitant intake of medicinal products like phenothiazine or certain anaesthetics. Patients with reduced blood volume may be more sensitive to the hypotensive effects of methadone than other patients.

Outpatient use

In outpatients methadone may cause orthostatic hypotension.

Use of narcotic antagonists

In an individual with narcotic physical addiction, the administration of the usual dose of a narcotic antagonist can trigger an acute withdrawal syndrome. The severity of the syndrome will depend on the degree of physical dependence and on the dose of antagonist administered. The use of a narcotic antagonist in this subject should possibly be avoided. When this must be used for treatment of a severe respiratory depression in a patient physically addicted, the antagonist must be administered with extreme caution and gradually with dosages below the usual ones.

Special risk patients

Methadone must be administered with caution and the initial dose must be reduced in elderly and debilitated patients and patients with hypothyroidism, Addison's disease, prostatic hypertrophy, urethral stricture.

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Hepatic impairment

Caution should be exercised in patients with hepatic dysfunction or renal dysfunction. Methadone may have a prolonged duration and cumulative effect in these patients.

As with other opioids methadone may cause troublesome constipation, which is particularly dangerous in patients with severe hepatic impairment, and measures to avoid constipation should be initiated early.

Severe risk patients

Suicide attempts with opiates, especially combined with tricyclic antidepressants, alcohol and other substances affecting the central nervous system, are part of the clinical features of dependency.

Use with CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Methadone Molteni with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, medicines with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of medicine-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see Section 4.5 Interactions with other medicines and other forms of interaction].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Methadone Molteni is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [see Section 4.5 Interactions with other medicines and other forms of interaction].

Methadone may interfere with evaluation of CNS function, thereby masking the patient's clinical course.

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The use of methadone in patients with chronic ulcerative colitis may stimulate motility in the colon; in patients with acute ulcerative colitis, toxic dilation may occur.

Methadone induced increase in intraluminal pressure may endanger surgical anastomosis.

Patients with prostatic hypertrophy or urethral stricture may be more prone to urinary retention and oliguria than other patients. Methadone may increase the risk of water intoxication in postoperative patients because of the stimulation of the release of vasopressin. Suppression of gonadotrophic function may cause impotence and a decline in libido.

Cardiac conduction effects – QT prolongation

Laboratory studies, both *in vitro* and *in vivo*, 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 treatment 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 diseases 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, medicines which might cause electrolyte abnormalities, and medicines 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.

Paediatric population

Methadone is not recommended for use in children less than 18 years of age.

4.5 Interaction with other medicines and other forms of interaction

Benzodiazepines and other Central Nervous System (CNS) Depressants	
Clinical Impact	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see Section 4.4 Special warnings and precautions for use].
Examples	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, drugs with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol.

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	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.	Stimulates 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 psychoactive effects; anti-muscarinic effects 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.

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Drug	Status of effect	Interaction	Mechanism
Erythromycin	In theory should interact but combination has not been studied.	Increase in methadone levels.	Decreased methadone metabolism.
Fluconazole	In theory the same as ketoconazole.		
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 several anecdotal reports.	Raised methadone levels.	Decreased methadone metabolism.
Indinavir	Clinically important.	Raised methadone levels.	Decreased methadone metabolism.
Ketoconazole	Clinically important.	Raised methadone levels.	Decreased methadone metabolism.
MAOI (including selegiline and moclobemide).	Severe with pethidine 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 <i>in vitro</i> only.	Increased nifedipine levels; no effect on methadone levels.	Methadone decreases the metabolism of nifedipine.
Omeprazole	To date, demonstrated only in animals.	Increased methadone levels.	Possibly affects methadone absorption from the gut.
Phenobarbitone	Clinically important.	Reduced methadone levels; increased 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.	Decreased methadone levels.	Increased methadone metabolism.
Ritonavir	Clinically important.	Ritonavir may increase plasma 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.

Drug	Status of effect	Interaction	Mechanism
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.

4.6 **Fertility, pregnancy and lactation**

Pregnancy

Use in pregnancy (Category C)

There is no, or inadequate evidence of safety in human pregnancy.

Methadone maintenance therapy during pregnancy can improve the health of the mother and the chances of a full-term healthy baby. The main risk to the health of the foetus is for the pregnant woman to start and stop opiate use, particularly where this precipitates the opioid withdrawal syndrome. Women receiving methadone during their pregnancy should be under the care of a specialist midwifery drug and alcohol service or a General Practitioner approved or authorised to prescribe Controlled Drugs for the treatment of dependence under the Misuse of Drugs Act 1975. The clinician should ensure that pregnant women have information regarding the effect of methadone maintenance therapy and illicit opioid use with nicotine, alcohol and other drug use on the foetus.

A careful risk-benefit assessment should be made before administration to pregnant women. Possible adverse effects on the foetus and neonate include respiratory depression, low birth weight, neonatal withdrawal syndrome and increased rate of stillbirths. During labour there is a risk of gastric stasis and inhalation pneumonia in the mother.

Breastfeeding

Methadone is excreted in breast milk and may cause respiratory depression in the newborn. Breast feeding is usually not recommended but a careful risk-benefit assessment case by case is suggested. Methadone could prevent the possibility of an overdose syndrome in the newborn, and the benefits of breastfeeding may outweigh the risks (except in the case of maternal HIV positive status).

Breastfeeding mothers should be advised to wean slowly off breastfeeding when they decide to stop to reduce the possibility of mild withdrawal symptoms being experienced by the baby. Breastfeeding mothers should be under the care of a specialist midwifery drug and alcohol service or a General Practitioner approved or authorised to prescribe Controlled Drugs for the treatment of dependence under the Misuse of Drugs Act 1975.

Fertility

No information held by the sponsor.

4.7 Effects on ability to drive and use machines

Methadone may cause drowsiness and reduce the ability to drive. Patients who are well stabilised may continue to drive and operate machinery as part of their normal activities. If methadone dosage has not been stabilised or is changed for any reason caution must be exercised due to the potential for increased drowsiness and other side effects.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequently observed adverse reactions include lightheadedness, 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.

b. Tabulated summary of adverse reactions

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

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: pulmonary oedema, respiratory depression

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Skin and subcutaneous tissue: pruritus, 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.

c. Description of selected adverse reactions

No information held by the sponsor.

d. Paediatric population

Methadone is not recommended for use in children less than 18 years of age.

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

For non-tolerant adults, doses of 50 mg or less have been known to be fatal, including doses taken orally. Potentially lethal overdoses of methadone can occur within 30 minutes to six hours after ingestion by non-tolerant or partially tolerant individuals.

Signs of methadone intoxication in an adult include pinpoint pupils, hypothermia, respiratory depression, bradycardia, pulmonary oedema (not always), hypotension, coma and seizures. Rhabdomyolysis, myoglobinuria, muscle necrosis and renal failure may occur secondary to methadone intoxication and may result from muscle damage related to prolonged coma and immobilisation or from a direct toxic effect of methadone.

To treat overdose, ensure that the airway is clear and perform emergency cardiopulmonary resuscitation as necessary. Take the person to hospital as soon as possible where treatment with an infusion of naloxone can be commenced. Overdose patients should remain in hospital for 24 – 72 hours due to methadone's long half-life.

Paediatric population

The fatal dose of methadone in children is 10 – 20 mg. Symptoms of opioid overdose in children are similar to those in adults, with pupillary miosis; however, the pupils may be normoreactive or, rarely, fixed and dilated. Infants may have drowsiness, coma and apnoea.

Children are usually, but not always, symptomatic. Known or suspected methadone-intoxicated children should be hospitalised, since respiratory depression may be observed as long as 48 hours after ingestion. Successful resuscitation with a narcotic antagonist may be followed by relapse. Treatment must include establishment of an airway, maintenance of adequate respiratory ventilation, precise supportive care to maintain fluid and electrolyte balance, naloxone, emptying of upper and lower gastrointestinal tracts, and prevention of aspiration of gastric contents.

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 category: Drugs used in opioid dependence.

ATC code: N07BC02.

Mechanism of action

Methadone hydrochloride is an opiate agonist and exerts its principal pharmacological effect on the CNS and on the intestines. It interacts at specific receptor binding sites in the CNS and other tissues. Several subtypes of opiate receptors have been described including the μ type. Methadone interacts with the μ receptor to suppress opiate withdrawal. Methadone acts at several sites within the CNS involving several systems of neurotransmitter to produce analgesia but the precise mechanism of action has not been fully elucidated. Methadone alters the perception of pain at the spinal cord and higher levels in the CNS and the patient's emotional response to pain.

In addition to analgesia, the effects of methadone on the CNS cause suppression of the cough reflex, respiratory depression, drowsiness, sedation, change in mood, euphoria, dysphoria, mental clouding, nausea and vomiting, and EEG changes. Methadone causes miosis which is antagonised by atropine.

Methadone increases smooth muscle tone in the urinary tract and induces spasms. In the urinary bladder, tone of the detrusor muscle is increased, possibly resulting in urinary urgency. Methadone also increases the tone of the vesical sphincter, which may make urination difficult. These effects, in conjunction with the central effects of the drug on the release of vasopressin, may produce oliguria. Methadone has little cardiovascular effect when given in therapeutic doses to supine patients. When the patient assumes a "head-up" position, orthostatic hypotension and fainting may occur as a result of peripheral vasodilation. This peripheral vasodilation may be caused by opiate agonist-induced release of histamine or by depression of the vasomotor centre in the medulla. Methadone exerts endocrinologic effects, some of which may be related to CNS effects. Methadone generally simulates the release of vasopressin and inhibits the release of corticotropin, gonadotropins and thyrotropin.

Paediatric population

Methadone is not recommended for use in children less than 18 years of age.

5.2 Pharmacokinetic properties

Absorption

Methadone hydrochloride is readily absorbed after administration by mouth and has high oral bioavailability. Peak plasma concentrations occur at 4 hours but this varies widely among individuals.

Distribution

Methadone undergoes considerable tissue distribution and protein binding is reported to be 60 to 90% with α_1 -acid glycoprotein being the main binding protein in the plasma. The volume of distribution is 5 L/kg.

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Biotransformation

Metabolism to the major metabolite 2-ethylidine-1,5-dimethyl, 3,3-diphenylpyrrolidine and the minor metabolite 2-ethyl-3,3-diphenyl-5-methylpyrrolidine, both of them inactive, occurs in the liver. These metabolites are excreted in the faeces and urine together with unchanged methadone. Other metabolites, including methadol and normethadol (reported to be pharmacologically active), have also been described but account for a small proportion of the dose. The liver may also serve as a major storage site of unchanged methadone, which is taken up, bound non-specifically by the liver and released again mainly unchanged.

Elimination

Marked inter-individual variations in kinetics have been observed with methadone. Elimination half-lives vary considerably (a range of 15 to 60 hours has been reported) and careful adjustment of dosage is necessary with repeated administration, after which there is a gradual accumulation in the tissues.

Plasma concentrations have been found to vary widely during methadone maintenance therapy, with large differences between patients and wide fluctuations in individual patients. Declining concentrations have been reported during methadone maintenance suggesting that tolerance occurs, possibly as a result of auto-induction of hepatic microsomal enzymes.

5.3 Preclinical safety data

No information held by the sponsor.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Name of the excipients

- Xylitol
- Glycerol
- Sodium benzoate
- Citric acid monohydrate
- Cherry flavour
- Hydroxyethylcellulose
- Purified water

- Colouring agents
 - 1 mg/mL: Brilliant blue FCF (E133), Tartrazine (E102)
 - 5 mg/mL: Caramel - Ammonia (E150C)
 - 10 mg/mL: Brilliant blue FCF (E133)

6.2 Incompatibilities

Methadone Molteni is incompatible with alkaline solutions, which cause precipitation.

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6.3 Shelf life

The shelf life of Methadone Molteni is 36 months from date of manufacture. Once opened, use within 12 months.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate. Store in outer carton to protect from light.

Pharmacists should emphasise the importance of storing takeaway doses in a safe and secure cool place, out of sight and reach of children. Takeaway doses should be locked away if possible.

6.5 Nature and contents of container

100 mL bottle

6.6 Special precautions for disposal and other handling

Methadone hydrochloride is a Controlled Drug (B3) and must be stored in a Controlled Drug safe. All usage must be recorded in a Controlled Drug register.

Takeaway doses are to be dispensed as individual daily doses with each day's dose packed in appropriately labelled bottles with child-resistant closures. The requirement for a child-resistant closure (CRC) may be omitted if the prescriber has endorsed (or the pharmacist annotates) the prescription not to be dispensed in a container with a safety cap because of patient infirmity. Pharmacists should ensure that those receiving methadone can open and close the CRC correctly and are aware of the need for them.

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
Browns Bay
Auckland 0753

Phone 0800 565 633

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
09 October 2013

10 DATE OF REVISION OF TEXT

27 July 2017

Summary table of changes

Section changed	Summary of new information
All sections	Text reformatted into new Medsafe data sheet format
4.4 Special warnings and precautions for use	Information included on warnings for use with Central Nervous System (CNS) Depressants
4.5 Interaction with other medicines and other forms of interaction	Information included on interactions between Benzodiazepines and other Central Nervous System (CNS) Depressants