NEW ZEALAND DATA SHEET

1. METHADONE INJECTION BP 10 mg/mL solution for injection

Methadone Injection BP 10 mg/mL solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 10 mg of methadone hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution with a pH of 4.0–7.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Methadone Injection is used as an analgesic for the relief of moderate to severe pain. Single doses of methadone have a less marked sedative action than morphine.

4.2 Dose and method of administration

Dose

Methadone Injection should be administered in the smallest effective dose in order to minimize development of tolerance and physical dependence.

The usual adult dosage is 2.5-10 mg every 3-4 hours as necessary. The analgesic effect begins about 15 minutes after subcutaneous injection. In patients with severe, chronic pain dosage should be adjusted according to the severity of the pain and the response and tolerance of the patient. In patients with exceptionally severe, chronic pain or in those that have become tolerant to the analgesic effects of opiate agonists, it may be necessary to exceed the usual dosage.

Special populations

Hepatic impairment

Hepatic dysfunction does not unduly affect methadone metabolism, and dosage of methadone need not be changed in stable chronic liver disease. However, abrupt changes in hepatic status might result in substantial alterations in methadone disposition requiring dosage adjustments.

Renal impairment
Urinary excretion of methadone is reduced in renal failure, but plasma concentration remain within the usual range and faecal elimination accounts for the majority of the dose. Very little methadone is removed by dialysis.

Elderly
Dosage should be reduced in elderly or debilitated patients.

Paediatric population
Use in children is not recommended as there has been insufficient clinical experience to establish a dosage regimen. A paediatric analgesic dosage of 0.7 mg/kg daily given in divided doses every 4-6 hours has been suggested, but dosage should be carefully individualised.

Method of administration
Subcutaneous or intramuscular injection. If repeated injections are required, the intramuscular route is preferred to the subcutaneous.

Methadone is considerably more lipid soluble than morphine – more rapid and greater relief of pain may be achieved if it is injected into the deltoid rather than the gluteal muscle.

4.3 Contraindications

Methadone is contraindicated in respiratory depression and obstructive airways disease. It is also contraindicated, or should be used with great caution, in acute alcoholism, convulsive disorders, head injuries and conditions in which intracranial pressure is raised.

Methadone should not be given to comatose patients.

Methadone Injection should not be used for obstetric analgesia, as the drug's long duration of effect may increase the risk of neonatal respiratory depression.

4.4 Special warnings and precautions for use

This medicine should not be used for the treatment of chronic pain of non-malignant origin unless all other conservative methods of analgesia have been tried and have failed and there is no psychological contraindication, drug seeking behaviour or history of drug misuse.

Therapy should only be initiated by a specialist with experience in chronic pain management and in accordance with guidelines approved by the New Zealand Medical Association.

Methadone should be given with caution or in reduced doses to patients with hypothyroidism, adrenocortical insufficiency, asthma, impaired kidney or liver function, prostatic hyperplasia, hypotension, shock, inflammatory or obstructive bowel disorders or myasthenia gravis.

Discontinuation of therapy with methadone should be carried out gradually in patients who may have developed physical dependence to the drug in order to avoid precipitating withdrawal symptoms.

Methadone should be given with great care to infants, especially neonates.

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 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 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.

Concomitant use with benzodiazepines or other CNS depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Methadone Injection 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).

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 Injection 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).

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 as listed below:

<u>Monoamine Oxidase Inhibitors (MAOIs)</u>
Methadone should be avoided or given with extreme caution to patients on MAOIs and selegiline.

<u>Anticonvulsants (phenytoin, phenobarbital, carbamazepine and primidone)</u>
Induces the metabolism of methadone and there may be a risk of precipitating withdrawal syndrome. Adjustment of the dose of methadone should be considered.

<u>Antibacterial</u>
Methadone is metabolized in the liver to inactive metabolites by the mixed function oxidase system and thus interactions are likely with enzyme inducers such as rifampicin, ciprofloxacin, erythromycin, fluconazole and ketoconazole.

<u>Antiretroviral (nevirapine, efavirenz, nelfinavir, ritonavir, abacavir)</u>
Based on the known metabolism of methadone, these agents may decrease plasma concentrations of

methadone by increasing its hepatic metabolism. Methadone may increase the plasma concentration of zidovudine. Narcotic withdrawal syndrome has been reported in patients treated with some retroviral agents and methadone concomitantly. Methadone maintained patients beginning antiretroviral therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

Opioid analgesics

Naloxone and naltrexone antagonises the analgesic, CNS and respiratory depressant effects of methadone and can rapidly precipitate withdrawal symptoms. Similarly buprenorphine and pentazocine may precipitate withdrawal symptoms.

Histamine H2 antagonists

Cimetidine has been reported to enhance the effects of some opioid analgesics, and this may apply to methadone.

Benzodiazepines and CNS depressants

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants such as alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.

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).

Examples include benzodiazepines and other sedatives/hypnotics (including chloral hydrate and chlormethiazole), anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, drugs with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol, and tricyclic antidepressants.

Cyclizine and other sedating antihistamines

May have additive psychoactive effects; antimuscarinic effects at high doses.

Selective Serotonin Re-uptake Inhibitors (SSRIs)

May decrease the metabolism of methadone, particularly fluvoxamine. Therefore, this may increase the likelihood of methadone toxicity.

pH of urine

Drugs that acidify or alkalinise the urine may have an effect on clearance of methadone as it is increased at acidic pH and decreased at alkaline pH.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category C.

It is not known whether methadone can cause foetal harm. Therefore, methadone should be used during pregnancy only when the potential benefits justify the possible risks.

Use of methadone for obstetric analgesia is NOT recommended (see section 4.3).

Breastfeeding

Methadone should generally not be taken by nursing women. However, concentrations in the breast milk are considered unlikely to have any clinical effect, and methadone may be used if, in the opinion of the physician, the benefits outweigh the likely effects on the infant.

Fertility

No data.

4.7 Effects on ability to drive and use machines

Methadone is likely to severely affect patient's ability to drive and use machines, and patients should be warned not to do so while under the effect of methadone.

4.8 Undesirable effects

Summary of the safety profile

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.

Tabulated list of adverse reactions

There are no modern clinical studies available that can be used to determine the frequency of undesirable effects. Therefore, all the undesirable effects listed are classed as “frequency unknown”.

Endocrine disorders:	Hyperprolactinaemia, hypogonadism.
Metabolism and nutrition disorders:	Hypokalaemia, hypomagnesaemia, weight gain.
Psychiatric disorders:	Dependence, agitation, confusion, mood change including euphoria and dysphoria, hallucinations, restlessness, sleep disturbances, disorientation.
Nervous system disorders:	Drowsiness, dizziness, vertigo, raised intracranial

	pressure, sedation.
Eye disorders:	Dry eyes, visual disturbances such as miosis.
Cardiac disorders:	Arrhythimias, bigeminal rhythms, bradycardia, cardiomyopathy, ECG abnormalities, extrasystoles, heart failure, hypotension, phlebitis, syncope, T-wave inversion, tachycardia, palpitations, QT prolongation, torsades de pointes, ventricular fibrillation, ventricular tachycardia.
Vascular disorders:	Orthostatic hypotension.
Respiratory, thoracic & mediastinal disorders:	Respiratory depression (see also section 4.9), dry nose, pulmonary oedema.
Gastrointestinal disorders:	Abdominal pain, anorexia, nausea, vomiting (particularly at the start of treatement), constipation, biliary spasm, dry mouth, glossitis.
Skin & subcutaneous tissue disorders:	Sweating, facial flushing, rashes (urticaria, pruritus), oedema.
Musculoskeletal & connective tissue disorders:	Muscle rigidity, decreased muscle mass and strength, osteoporosis and fractures.
Renal and urinary disorders:	Micturition difficulties, urinary retention, ureteric spasm.
Reproductive system & breast disorders:	Decreased libido, dysmenorrhoea, amenorrhoea, sexual dysfunction, reduced ejaculate volume, reduced seminal vesicle and prostate secretions, decreased sperm motility, abnormalities in sperm morphology.
General & administration site disorders:	Hypothermia, local tissue reactions (pain, erythema, swelling), particularly with continuous subcutaneous infusion.

Description of selected adverse reactions

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

Methadone overdosage can induce pulmonary oedema. After gross overdosage symptoms are similar to those of morphine poisoning - rhabdomyolysis progressing to renal failure and respiratory failure.

Intensive supportive therapy may be required to correct respiratory failure and shock. In addition, the specific antagonist naloxone is used to counteract very rapidly the severe respiratory depression and coma produced by excessive doses. Since naloxone has a short duration of action, patients who have already responded should be kept under close observation for signs of relapse and repeated injections given according to the respiratory rate and depth of coma. In situations where a longer acting opioid such as methadone is know or suspected to be the cause of symptoms a continuous intravenous infusion of naloxone adjusted according to response, may be used.

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: Diphenylpropylamine derivatives, ATC code: N07BC02.

Methadone hydrochloride is a synthetic diphenylheptane-derivative opiate agonist. It is an analgesic with the general properties of morphine.

Methadone is a racemic mixture and levomethadone is the active isomer.

Methadone is readily absorbed and is widely distributed in the tissues. It has a prolonged half-life and is subject to accumulation. Following IM or subcutaneous administration of a single dose of methadone, onset and duration of action are similar to those of morphine; duration is approximately 4-6 hours. Duration of action increases with repeated administration.

5.2 Pharmacokinetic properties

Methadone is highly bound to tissue protein, which may explain its cumulative effects and slow elimination. It is widely distributed in the tissues, diffuses across the placenta and is excreted in breast milk.

Methadone is metabolised chiefly in the liver; the drug undergoes N-demethylation and cyclisation and does not appear to be conjugated.

Methadone is excreted by glomerular filtration and undergoes renal reabsorption. Reabsorption of methadone decreases as urinary pH decreases. Urinary excretion of methadone and its metabolic end products is dose dependent and comprises the major route of excretion only in dosages exceeding 55 mg daily. Methadone metabolites are also excreted in the faeces via the bile.

5.3 Preclinical safety data

No additional data of relevance to the prescriber.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections.

6.2 Incompatibilities

Methadone Injection is physically or chemically incompatible with solutions containing aminophylline, ammonium chloride, amobarbital, chlorothiazide sodium, phenytoin sodium, heparin sodium, methicillin sodium, nitrofurantoin sodium, pentobarbital sodium, phenobarbital sodium, sodium bicarbonate, sodium iodide, sulphadiazine sodium, sulphaferazole dienthanolamine or thiopental sodium.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25 °C. Protect from light.

6.5 Nature and contents of container

Methadone Injection is supplied in 1 mL glass vials, in packs of 10.

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Class B3 Controlled Drug.

8. SPONSOR

AFT Pharmaceuticals Ltd
PO Box 33-203
Takapuna
Auckland 0740
New Zealand
Phone: 0800 423 823
Email: customer.service@aftpharm.com

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10. DATE OF REVISION OF THE TEXT

4 July 2017

Summary table of changes:

Section changed	**Summary of new information**
4.4	Warning added regarding concomitant use with benzodiazepines.
4.5	Interaction information added regarding concomitant use with benzodiazepines.
4.8	Undesirable effects information updated.
All	Format updated.