# NEW ZEALAND DATA SHEET

**WARNINGS**

**Limitations of use**
Because of the risks associated with the use of opioids, Methadone Injection BP 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 Injection BP 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 Injection BP. 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 Injection BP.

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

Methadone hydrochloride 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 List of excipients**.

## 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 BP 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 BP 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 Injection BP 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 BP 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 in the presence of the following:

- hypothyroidism
- adrenocortical insufficiency
- asthma
- impaired kidney or liver function
- prostatic hyperplasia
- hypotension
- shock
- inflammatory or obstructive bowel disorders
- myasthenia gravis.

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

***Hazardous and harmful use***

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

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

addiction prior to being prescribed Methadone Injection BP.

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

Patients should be advised not to share Methadone Injection BP with anyone else.

***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 Injection BP 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 Injection BP 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 Injection BP 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 Injection BP.

***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**).

***Tolerance, dependence and withdrawal***

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 Injection BP 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**).

***Accidental ingestion/exposure***

Accidental ingestion or exposure of Methadone Injection BP, especially by children, can result in a fatal overdose of methadone hydrochloride. Patients and their caregivers should be given information on safe storage and disposal of unused Methadone Injection BP (see **Section 6.4 Special precautions for storage** and **Section 6.6 Special precautions for disposal**).

***Hyperalgesia***

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

***Ceasing opioids***

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

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

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

***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.

***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.

## 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:

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

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

***Antibacterial***
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.

***Antiretroviral (nevirapine, efavirenz, nelfinavir, ritonavir, abacavir)***
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 $H_2$-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 Special warnings and precautions for use**).

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.

***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***
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 Contraindications**).

***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 Injection BP 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:* | Hypoglycaemia (frequency not known), 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:* | Arrhythmias, 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 Overdose**), 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. Hypoglycaemia has been reported.

Rare events of leukoencephalopathy may occur in serious cases of overdosage.

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 known 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 intramuscular 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 BP 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 BP 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
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Takapuna
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Free phone: 0800 423 823
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## 9. DATE OF FIRST APPROVAL

27 November 1986

## 10. DATE OF REVISION OF THE TEXT

November 2022

**Summary table of changes:**

| Section changed | Summary of new information |
|---|---|
| 4.8 and 4.9 | Information regarding hypoglycaemia added |