SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Physeptone 50mg/ml Solution for injection
Methadone 50mg/ml Solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 50mg of Methadone Hydrochloride

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear colourless solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of opioid drug addiction as a narcotic abstinence syndrome suppressant.

The use of injectable methadone for this indication must be initiated by physicians with adequate expertise and experience in addiction therapy.

The use of methadone in opiate addiction must be part of a broader treatment programme, including regular treatment reviews, supervised by specialist services.

4.2 Posology and method of administration

Method of administration

Treatment goals and discontinuation

Before initiating treatment with Methadone/Physeptone 10mg/ml Solution for injection, 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 hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Posology

Adults
Initially 10-20mg per day, increasing by 10-20mg per day, until there are no signs of withdrawal or intoxication.

Treatment must be managed by physicians with suitable experience.

The initial dose, safe dosage increments and the establishment of a dose that prevents withdrawal symptoms needs to be individualised. The degree of tolerance or neuroadaptation, any additional consumption of oral methadone or other opiates, the cumulative potential of methadone treatment (as opposed to shorter acting opiates) and the general health of the patient must be taken into account. Typical doses for heavily addicted users can be fatal to those without such neuroadaptation.

The usual dose of injectable methadone, when the addict is stabilised, may need to exceed 100mg daily to prevent symptoms of opiate withdrawal.

The aims of treatment should include reducing criminality and to improve patient's health and social productivity.

Elderly and debilitated patients:
If repeated doses are required, use with caution due to the long plasma half-life.
There may be a greater risk of respiratory depression, with or without any associated renal or hepatic impairment, in this age group.

Paediatric population:
As methadone has not been studied in children it should not be used in children under the age of 16 years.

Hepatic impairment:
In patients with severe liver damage the dose of methadone should be carefully controlled as there is a risk that methadone might precipitate porto-systemic encephalopathy.

Renal Impairment:
The dose may need to be reduced in moderate or severe renal impairment.

Method of administration:

intramuscular, subcutaneous or intravenous injection.

Volumes greater than 2ml given intramuscularly may need to be administered in divided doses at different sites.

4.3 Contraindications

In the treatment of opioid addiction, the following are contraindicated:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Patients not already receiving methadone (on account of the high methadone concentration).
- Patients with respiratory depression and obstructive airways disease.
- Use during an acute asthma attack.
- Concurrent administration with monoamine oxidase inhibitors, or within 2 weeks of discontinuation of treatment with them.
- Phaeochromocytoma. Opiates may induce the release of endogenous histamine and stimulate catecholamine release.
- Risk of paralytic ileus.
- Comatose patients.

4.4 Special warnings and precautions for use

*Opioid Use Disorder (abuse and dependence)*Methadone is a drug of addiction and is controlled under the Misuse of Drugs Act 1971 (Schedule 2). Methadone 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.

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.

As with other opioids, tolerance, physical, and/or psychological dependence may develop upon repeated administration of methadone.

When used for the treatment of pain, repeated use of [product name] 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 [product name] 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 [product name] 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.

Tolerance and dependence may occur as with morphine.
Methadone can produce drowsiness and reduce consciousness although tolerance to these effects can occur after repeated use.

Drug withdrawal syndrome
Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with methadone. The decision to maintain a patient on a longterm opioid prescription should be an active decision agreed between the clinician and patient with review at regular intervals (usually at least three-monthly, depending on clinical progress).

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations.

Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy, there is a risk that their new-born infants will experience neonatal withdrawal syndrome.
Sleep-related breathing disorders

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 total opioid dosage.

Respiratory depression
Due to the slow accumulation of methadone in the tissues, respiratory depression may not be fully apparent for a week or two. Asthma may be exacerbated due to histamine release. Concomitant treatment with other agents with CNS depressant activity is not advised due to the potential for CNS and respiratory depression (see also section 4.5 Interactions).

Adrenal insufficiency
Opioid analgesics may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of adrenal insufficiency may include nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure

Decreased Sex Hormones and increased prolactin
Long-term use of opioid analgesics may be associated with decreased sex hormone levels and increased prolactin. Symptoms include decreased libido, impotence or amenorrhea.

Hypoglycaemia
Hypoglycaemia has been observed in the context of methadone overdose or dose escalation. Regular monitoring of blood sugar is recommended during dose escalation (see section 4.8 and section 4.9)

Hyperalgesia
As with other opioids, in case of insufficient pain control in response to an increased dose of methadone, the possibility of opioid-induced hyperalgesia should be considered. A dose reduction or treatment review may be indicated.

Hepatobiliary disorders
Methadone may cause dysfunction and spasm of the sphincter of Oddi, increasing the risk of biliary tract symptoms and pancreatitis. Therefore, methadone has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

Pregnancy and risks to the neonate (see also section 4.6 Pregnancy and Lactation):

Female addicts who are pregnant will require specialised care from obstetric and paediatric staff with experience in such management. Methadone should not be withdrawn abruptly and infants will require careful monitoring for signs of respiratory depressions and / or opioid withdrawal.

There are reports of neonates and children exposed to methadone during pregnancy developing visual disorders, including reduced visual acuity, strabismus and nystagmus. The causal relationship to methadone in isolation has not been established as factors such as other drugs taken during pregnancy e.g. benzodiazepines, intake of alcohol, and drugs used to treat neonatal abstinence syndrome e.g. phenobarbital, could play a role in the adverse reactions seen. However, there is sufficient evidence to suggest that an

association is possible and therefore consideration of this risk should be taken during prescribing decisions.

Hepatic impairment
Special care should be taken with patients with severe liver damage, as there is a risk that methadone might precipitate porto-systemic encephalopathy or precipitate coma.

Renal impairment
Reduce doses to avoid increased and prolonged effect, increased cerebral sensitivity.

Cardiac effects
Cases of QT interval prolongation and torsade de pointes have been reported during treatment with methadone, particularly at high doses (>100 mg/d).
Methadone should be administered with caution to patients at risk for development of prolonged QT interval, e.g. in case of:
- history of cardiac conduction abnormalities,
- advanced heart disease or ischaemic heart disease,
- liver disease,
- family history of sudden death,
- low serum magnesium,
- hypokalaemia,
- concomitant treatment with drugs that have a potential for QT-prolongation,
- concomitant treatment with drugs which might cause electrolyte abnormalities,
- concomitant treatment with cytochrome P450 CYP 3A4 inhibitors (see section 4.5).

In patients with recognised risk factors for QT prolongation, or in case of concomitant treatment with drugs that have a potential for QT-prolongation, ECG monitoring is recommended prior to methadone treatment, with a further ECG test at dose stabilisation.
ECG monitoring is recommended, in patients without recognised risk factors for QT prolongation, before dose titration above 100 mg/d and at seven days after titration.

Other warnings
Methadone should be used with great caution in patients with acute alcoholism, convulsive disorders and head injuries.

Methadone, as with other opiates, has the potential to increase intracranial pressure especially where it is already raised.

Children (under 16 years): Even at low doses methadone is a special hazard to children if ingested accidentally. Children under 6 months, particularly neonates may be more sensitive to respiratory depression than adults

Methadone should be used with caution in elderly or debilitated patients due to its long half-life.

Use with caution in patients with hypothyroidism, adrenocortical insufficiency, prostatic hyperplasia, hypotension, shock, biliary tract disorders, inflammatory or obstructive bowel disorders or myasthenia gravis.

Local injection site reactions can occur therefore injection sites should be inspected regularly. Injections may be painful.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs

Concomitant use of Physeptone 50mg/ml Solution for injection Methadone 50mg/ml Solution for injection and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Physeptone 50mg/ml Solution for injection

Methadone 50mg/ml Solution for injection concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

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

Methadone is metabolised by the liver cytochrome P450 isoenzymes including CYP 3A4. CYP 1A and CYP 2D6. Interactions are likely with enzyme inhibitors or inducers.

Cytochrome P450 3A4 inhibitors:
Methadone clearance is decreased when co-administered with drugs which inhibit CYP3A4 activity, such as some anti-HIV agents, macrolide antibiotics, cimetidine and azole antifungal agents (since the metabolism of methadone is mediated by the CYP3A4 isoenzyme). Please see further details of specific interactions with antiviral-HIV agents, erythromycin, cimetidine and fluconazole/ketoconazole/voriconazole given later in this section.

Monoamine Oxidase Inhibitors:
The concurrent use of MAOIs is contra-indicated (see also section 4.3 Contra-indications) as they may prolong and enhance the respiratory depressant effects of methadone. Severe CNS excitation, delirium, hyperpyrexia,

convulsions or respiratory depression is possible with concurrent use of opiates and MAOIs. With moclobemide, either CNS excitation or depression (hypertension or hypotension) is possible.

Opioid agonists:
Concomitant use of pethidine and other opioid agonist analgesics is not advised because of the potential for additive effects on CNS depression, respiratory depression and hypotension.

Opioid antagonists:
Naloxone and naltrexone antagonise the analgesic, CNS and respiratory depressant effects of methadone and can rapidly precipitate withdrawal symptoms (see section 4.9 Overdose). Similarly, buprenorphine and pentazocine may precipitate withdrawal symptoms.

CNS drugs:
Concomitant use of other CNS depressants is not advised. Hypnotics (including benzodiazepines, chloral hydrate and chlormethiazole) and anxiolytics may increase the general depressant effects of methadone. Antipsychotics may enhance the sedative and hypotensive effects of methadone. The plasma concentration of methadone may be increased by fluvoxamine and to a lesser extent, fluoxetine and theoretically other SSRIs due to decreased methadone metabolism. There may be increased sedation with tricyclic antidepressants.
There is an increased risk of ventricular arrhythmias when methadone is given with the CNS stimulant, atomoxetine.

Alcohol:
Alcohol may enhance the sedative and hypotensive effects of methadone and increase respiratory depression.

Antiviral Drugs used in HIV:
Plasma concentrations of methadone may be reduced by the nucleoside reverse transcriptase inhibitor abacavir, and the protease inhibitors nelfinavir and ritonavir (which are metabolised by cytochrome P450 enzyme systems) and the non-nucleoside reverse transcriptase inhibitors efavirenz and nevirapine, which may interact with a number of drugs metabolised in the liver. Methadone may increase the plasma concentration of the nucleoside reverse transcriptase inhibitor zidovudine.

Antibacterials:
Reduced plasma levels and increased urinary excretion of methadone can occur with concurrent administration of rifampicin. Adjustment of the dose of methadone may be necessary. Plasma levels of methadone may increase with concurrent administration of ciprofloxacin due to the inhibition of CYP1A2 and CYP3A4. Reduced serum concentrations of ciprofloxacin may occur. Erythromycin theoretically may increase methadone levels due to decreased methadone metabolism. Rifabutin may decrease methadone levels due to increased metabolism.

Anticonvulsants:
Phenytoin and carbamazepine increase the metabolism of methadone. Adjustment of the dose of methadone should be considered.

Barbiturates:
May stimulate hepatic enzymes that increase methadone metabolism, reducing methadone levels. There may be increased sedation and additive CNS depression.

Cyclizine and other sedating antihistamines:
May have additive psychoactive effects; antimuscarinic effects at high doses.

Antifungals: e.g. Fluconazole, ketoconazole and voriconazole:
May raise methadone levels, due to decreased methadone metabolism. Reducing the dose of methadone should be considered.

Grapefruit Juice:
There are several anecdotal reports of raised methadone levels due to decreased methadone metabolism.

Cimetidine:
Retards oxidative hepatic drug metabolism by binding to microsomal cytochrome P450. The metabolism of methadone may be inhibited leading to increased plasma concentration and opiate action.

Antimuscarinics:
Concomitant antimuscarinics (e.g. atropine and synthetic anticholinergics) may increase the risk of severe constipation and/or urinary retention.

Drugs affecting gastric emptying:
Domperidone and metoclopramide may increase the speed of onset but not the extent of methadone absorption by reversing the delayed gastric emptying associated with opioids. Conversely, methadone may antagonise the effect of domperidone / metoclopramide on gastro-intestinal activity.

pH of urine:
Drugs that acidify (e.g. ascorbic acid) or alkalinise (e.g. sodium bicarbonate) the urine may have an effect on clearance of methadone as it is increased at acidic pH, and decreased at alkaline pH.

Effects of methadone on other drugs:
Methadone may have an effect on other drugs as a consequence of reduced gastro-intestinal motility.
Methadone may delay the absorption of the antiarrhythmic mexiletine.
Methadone may increase desipramine levels by up to a factor of two.

In patients taking drugs affecting cardiac conduction, or drugs which may affect electrolyte balance there is a risk of cardiac events when methadone is taken concurrently.
The hypnotic effect of sodium oxybate may be enhanced by opioid analgesics;

concomitant use should be avoided.

Sedative medicines such as benzodiazepines or related drugs:

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Co-administration of Methadone with metamizole, which is an inducer of metabolising enzymes including CYP2B6 and CYP3A4 may cause a reduction in plasma concentrations of Methadone with potential decrease in clinical efficacy. Therefore, caution is advised when metamizole and Methadone are administered concurrently; clinical response and/or drug levels should be monitored as appropriate.

Serotonergic drugs:

Serotonergic syndrome may occur with concomitant administration of methadone with pethidine, monoamine oxidase (MAO) inhibitors and serotonin agents such as Selective Serotonin Re-uptake Inhibitor (SSRI), Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) and tricyclic antidepressants (TCAs). The symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

Cannabidiol

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

Fluconazole:

Fluconazole may raise methadone levels due to decreased methadone metabolism.

4.6 Fertility, pregnancy and lactation

Pregnancy:
There is inadequate evidence of safety in human pregnancy.

Female addicts who are pregnant will require specialised care from obstetric and paediatric staff with experience in such management.

A careful risk/benefit assessment should be made before administration to pregnant women because of possible adverse effects on the foetus and neonate include respiratory depression, low birth weight, neonatal withdrawal syndrome and increased rate of stillbirths.

In labour there is a greater risk of gastric stasis and inhalation pneumonia in the mother.

Some observational studies have reported congenital malformations and neurodevelopmental impairment in children born to women treated with methadone for opioid use disorder during pregnancy. However, due to study limitations and confounding by maternal, familial and socioenvironmental factors associated with opioid use disorders no conclusions can be drawn regarding the contribution of methadone.

Reports of visual disorders have been reported in neonates and children following exposure to methadone during pregnancy. Although other factors have also been present, there is sufficient evidence to suggest that an association is possible (see section 4.4).

Breast-feeding:
Methadone is excreted in breastmilk at low levels. The decision to recommend breast-feeding should take into account clinical specialist advice and consideration should be given to whether the woman is on a stable maintenance dose of methadone and any continued use of illicit substances. If breastfeeding is considered, the dose of methadone should be as low as possible. Prescribers should advise breastfeeding women to monitor the infant for sedation and breathing difficulties and to seek immediate medical care if this occurs. Although the amount of methadone excreted in breast milk is not sufficient to fully suppress withdrawal symptoms in breast-fed infants, it may attenuate the severity of neonatal abstinence syndrome. If it is necessary to discontinue breastfeeding it should be done gradually, as abrupt weaning could increase withdrawal symptoms in the infant.
Specialised care from obstetric and paediatric staff with experience in such management is required.

4.7 Effects on ability to drive and use machines

Patients should not drive or use machines whilst taking methadone.
Methadone may cause drowsiness and reduce alertness and the ability to drive. after the administration of methadone.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and

It was not affecting your ability to drive safely

4.8 Undesirable effects

Methadone is associated with undesirable effects similar to other opioid analgesics. 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.

Psychiatric Disorders
Confusion, mood change including euphoria and dysphoria, hallucinations, restlessness, sleep disturbances. Drug dependence (see section 4.4).

Nervous System Disorders
Drowsiness, dizziness, vertigo.

Eye Disorders
Dry eyes, visual disturbances such as miosis. Nystagmus[1], strabismus[1], visual acuity reduced[1]. ([1]Visual effects have been reported in infants and children exposed to methadone during pregnancy- frequency not known).

Cardiac Disorders
Bradycardia, tachycardia, palpitations, QT prolongation, torsades de pointes.

Vascular Disorders
Orthostatic hypotension.

Respiratory, Thoracic & Mediastinal Disorders
Respiratory depression (see also section 4.9 overdose), dry nose. Central sleep apnoea syndrome.

Hepatobiliary disorders
Sphincter of Oddi dysfunction (frequency not known).

Gastrointestinal Disorders
Nausea, vomiting (particularly at the start of treatment), constipation, biliary spasm, dry mouth. Acute pancreatitis (frequency not known).

Skin & Subcutaneous Tissue Disorders
Sweating, facial flushing, rashes (urticaria, pruritus), oedema.

Musculoskeletal, Connective Tissue & Bone Disorders
Muscle rigidity.

Renal & Urinary Disorders
Micturition difficulties, urinary retention, ureteric spasm

Reproductive System & Breast Disorders

Decreased libido, dysmenorrhoea, amenorrhoea, sexual dysfunction

Metabolism and nutrition disorders SOC
Hypoglycaemia (frequency not known).

General & Administration Site Disorders:
Hypothermia, drug withdrawal syndrome.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Signs:
Similar to those for morphine.
Respiratory depression, extreme somnolence progressing to stupor or coma, cyanosis, maximally constricted pupils, skeletal muscle flaccidity, cold and clammy skin, bradycardia and hypotension have been observed.
Hypoglycaemia has been reported.

In severe overdose apnoea, circulatory collapse, pulmonary oedema, cardiac arrest and death may occur.

Management
Treatment is supportive. Patients should be kept conscious wherever possible.

A patent airway must be established with assisted or controlled ventilation. Narcotic antagonists may be required if there is evidence of significant respiratory or cardiovascular depression. However, treatment with these antagonists must be repeated as necessary because of the longer duration of depressant activity of methadone (36 to 48 hours) compared to the antagonists (1 to 3 hours). Nalorphine or Levallorphine should be given intravenously as soon as possible and repeated every 15 minutes if necessary. In a person addicted to narcotics, administration of the usual dose of a narcotic antagonist will precipitate an acute withdrawal syndrome. In such cases, use of an antagonist should be avoided unless there is serious respiratory depression when they should be administered with great care.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Toxic leukoencephalopathy has been observed with methadone overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N07BC02
Pharmacotherapeutic group: (Nervous system, other nervous system drugs, drugs used in addictive disorders, methadone).

Methadone is a drug of addiction and repeated administration can result in dependence and tolerance. Cross tolerance with other opioids can occur.

It is a synthetic opioid analgesic similar to morphine although less sedative. It acts on the CNS system and smooth muscles via the peripheral nervous system.

The analgesic effect of methadone occurs about 10 to 20 minutes following parenteral administration. Miosis and respiratory depression can occur for more than 24 hours after a single dose. Methadone also reduces heart rate, systolic blood pressure and body temperature. Sedation is seen in some patients receiving repeated doses and sudden cessation of treatment can result in withdrawal symptoms.

Like morphine, it also has effects on bowel motility, biliary tone and secretion of pituitary hormones as well as on cough suppression. Methadone also causes the release of histamine from mast cells resulting in a number of allergic type reactions.

5.2 Pharmacokinetic properties

Absorption

Methadone is rapidly absorbed following injection; however there are wide inter-individual variations.

Distribution

Methadone is widely distributed in the tissues, diffuses across the placenta and is excreted in breast milk. It is extensively protein bound.

Biotransformation

It is metabolised in the liver (forming inactive metabolites) and excreted via the bile and urine. Urinary excretion is pHdependent, the lower the pH the greater the clearance.

Elimination

Methadone has a prolonged half-life (15 to 40 hours) and can accumulate on repeated administration

5.3 Preclinical safety data

No additional data of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methadone Injection contains Water for Injection.

6.2 Incompatibilities

No major incompatibilities, but do not mix with other medicinal products.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C.
Keep container in the outer carton.

6.5 Nature and contents of container

Clear, colourless Type I glass ampoules.
Pack size: 10 x 1ml ampoules in a cardboard carton.

6.6 Special precautions for disposal

Methadone is controlled under the Misuse of Drugs Act 1971 (Schedule 2).

7 MARKETING AUTHORISATION HOLDER

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T/A Martindale Pharma
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Harold Hill
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8 MARKETING AUTHORISATION NUMBER(S)

PL 01883/0064

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th November 2004

10 DATE OF REVISION OF THE TEXT

19/05/2026