SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Methadone 10mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Methadone hydrochloride 10mg in 1ml

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection

A clear and colourless solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of opioid drug addiction as a narcotic abstinence syndrome suppressant (substitution or maintenance therapy).

This should be part of a broader treatment programme including regular treatment reviews and must be supervised by specialist services

Treatment of moderate to severe pain as an alternative to morphine

4.2 Posology and method of administration

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with methadone hydrochloride in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4.).

Posology

Adults:

In the treatment of opioid drug addiction.

Initially 10-20mg per day, increasing by 10-20mg per day until there are no signs of withdrawal or intoxication. The usual dose is 40 -60mg per day. .

The dose is adjusted according to the degree of dependence, with the aim of gradual reduction. Providing a dosage schedule is difficult as it is largely subjective based on the addict's reported drug use and a clinical assessment of their dependence. A cautious approach is usually adopted starting at a low dose and following with incremental increases as judged appropriate bearing in mind the general health of the patient. (See Sections 4.4 and 4.5 below).

Treatment of moderate to severe pain

Usually 5-10 mg at six to eight hours although doses should be adjusted according to response. In prolonged use it should not be administered more than twice a day.

Elderly and debilitated patients :

In the case of the elderly or ill patients, repeated doses should be given with extreme 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 until further data become available.

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.

Method of Administration

Sterile solution for subcutaneous or intramuscular injection.
If repeated doses are required the intramuscular route should be used.

The intramuscular route is preferred when repeated administration is required. Volumes greater than 2mI (20mg) may need to be given in divided doses at different sites

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

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

In the case of elderly or ill patients, repeated doses should only be given with extreme caution.

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 can produce drowsiness and reduce consciousness although tolerance to these effects can occur after repeated use.

Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These

could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse or addiction.

The clinical need to analgesic treatment should be reviewed regularly.

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 hydrochloride.

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. Tapering from a high dose may take weeks to months.

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 newborn infants will experience neonatal respiratory rate or heart rate.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia may resolve with a reduction of opioid dose.

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).

Cardiac effects

Cases of QT interval prolongation and torsade de points 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,

-electrolyte abnormalities, i.e. hypokalaemia, hypomagnesaemia

-concomitant treatment with drugs that have a potential for QT-prolongation,

- concomitant treatment with drugs which may cause electrolyte abnormalities,

- concomitant treatment with cytochrome P450 GYP 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, EGG monitoring is recommended prior to methadone treatment, with a further EGG test at dose stabilisation.

EGG 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.

Pregnancy and risks to the neonate (see also section 4.6 Pregnancy and Lactation):
Female addicts who discover they are pregnant will require specialised care from obstetric and paediatric staff with experience in such management. Methadone should not be withdrawn abruptly and infants require careful monitoring for signs of respiratory depression and/or opioid withdrawal.

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.

Further 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): 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.

The drug should be used with caution in elderly or debilitated patients due to its long half-life. It should also be used with caution in patients with hypothyroidism, adrenocortical insufficiency, prostatic hyperplasia, hypotension, shock, biliary tract disorders, inflammatory or obstructive bowel disorders or myasthenia gravis.

Local reactions at the site of injection can occur and therefore these sites should be inspected regularly. Injections may be painful.

4.5 Interaction with other medicinal products and other forms of interaction

Methadone is metabolised by the liver cytochrome P450 isoenzymes including CYP 3A4. CYP 1A and CYP 206. 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 antivirai-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 section 4.3) 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). 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 effects and hypotensive effects of methadone. The plasma concentrations of methadone may
be increased by fluvoxamine and, to a Jesser extent, fluoxetine and theoretically other SSRis due to decreased methadone metabolism. There may be increased sedation with tricylic 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 nucleo de reverse transcriptase inhibitor, abacavir, the protease inhibitors, nelfinavir, ritonavir and fosamprenavir which are metabolised by cytochrome P450 enzyme systems, and the non-nucleoside reverse transcriptase inhibitors, efavir nz 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.

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 *I* metoclopromide 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.

4.6 Fertility, pregnancy and lactation

Pregnancy:
Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptom in the neonate.

If opioid use is required for a prolonged period in a pregnancy woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

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 including 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.

Breast feeding
Administration to nursing women is not recommended as methadone hydrochloride be secreted in breast milk and may cause respiratory depression in the infant.

Specialist care from obstetric and paediatric staff with experience in such management is required. If breast feeding is considered, the dose of methadone should be as low as possible and the infant monitored to avoid sedation. Breast-fed infants may develop physical dependence and exhibit withdrawal symptoms.

4.7 Effects on ability to drive and use machines

Patients should not drive or use machines while 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:
Dependence, confusion, mood change including euphoria and dysphoria, hallucinations, restlessness, sleep disturbances
Frequency unknown: Drug dependence (see section 4.4)
General disorders and administration site conditions:
Uncommon: drug withdrawal syndrome

Nervous System Disorders:
Drowsiness, dizziness, vertigo.

Eye Disorders:-
Dry eyes, visual disturbances such as miosis.

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

Vascular Disorders:
Orthostatic hypotension.

Respiratory, Thoracic and Mediastinal Disorders
Respiratory depression see also section 4.9), dry nose.

Gastrointestinal Disorders
Nausea and vomiting (particularly at the start of treatment), constipation, biliary spasm and dry mouth

Skin and Subcutaneous tissue Disorders
Sweating, facial flushing, rashes (urticaria, pruritus), oedema

Musculoskeletal, Connective Tissue and Bone Disorders
Muscle rigidity

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

Reproductive System & Breast Disorders
Decreased libido, dysmenorrhoea, amenorrhoea, sexual dysfunction

General and Administration Site Disorders
Hypothermia

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 (Website: www.mhra.gov.uk/yellowcard).

4.9 Overdose

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

Symptoms

These are similar to those of morphine.
Serious overdosage is characterised by respiratory depression extreme somnolence progressing to coma or stupor, cyanosis, maximally constricted pupils, skeletal muscle flaccidity, cold clammy skin and occasionally bradycardia and hypotension.

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

Treatment

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 Levallorphan should be given intravenously as soon as possible and repeated, if necessary, every 15 minutes.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics- Diphenylpropylamine derivatives.
ATC Code: N07BC02

Methadone is a drug of addiction and repeated administration can result in dependence and tolerance. Crosstolerance 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 intramuscular or subcutaneous 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.

Elimination
Urinary excretion is pH-dependent, the lower the pH the greater the clearance.

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

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the prescriber which are additional to those already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric Acid 0.1M

Sodium Hydroxide Solution 0.01M

Water for Injections

6.2 Incompatibilities

Physical incompatibility as judged by loss of clarity was reported when an intravenous solution of methadone hydrochloride was mixed with those of aminophylline, ammonium chloride, amylobarbitone sodium, chlorothiazide sodium, heparin sodium, methicillin sodium, nitrofurantoin sodium, novobiocin sodium, pentobarbitone sodium, phenobarbitone sodium, phenytoin sodium, quinalbarbitone sodium, sodium bicarbonate, sodium iodide, sulphadiazine sodium, sulphafurazole diethanolamine or thiopentone sodium.

6.3 Shelf life

36 months (unopened).

6.4 Special precautions for storage

Protect from light.

Do not store above 25°C.

6.5 Nature and contents of container

Pack of 10 neutral glass ampoules. Each ampoule contains 1, 2, 3.5, 5, 7.5 or 10ml of solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Kensington Pharma Ltd.,
Unit A Newlands House,
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Whitestake Preston,
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PR4 4LG

8 MARKETING AUTHORISATION NUMBER(S)

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10 DATE OF REVISION OF THE TEXT

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