SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Methadone 1 mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of solution contains 1ml of methadone hydrochloride.

Also contains:
Sucrose 333mg per ml,
Tartrazine 0.07mg per ml
Sunset yellow 0.008mg per ml
Sodium benzoate (E211) 1mg per ml
For further information see section 4.4.

For full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Oral solution.

Clear Green solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For use in the treatment of opioid drug addictions (as a narcotic abstinence syndrome suppressant).

4.2 Posology and method of administration

Posology

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

Addiction:

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

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

Children: Not recommended for children.

Dosage in pregnancy: Drug withdrawal needs to be achieved 4-6 weeks before delivery if neonatal abstinence syndrome is to be certain to be avoided, but abrupt withdrawal can cause intrauterine death. Detoxification to abstinence is least stressful to mother and foetus if undertaken during the mid trimester.

Abstinence syndrome may not occur in the neonate for some days after birth. In the event that withdrawal is not possible prior to delivery, methadone administered to the mother may result in prolonged respiratory depression in the neonate and the administration of opioid antagonists may be required.

Method of administration

For oral administration only.

4.3 Contraindications

- Respiratory depression, obstructive airways disease,
- Concurrent administration with MAO inhibitors or within 2 weeks of discontinuation of treatment with them.
- Use during labour is not recommended; the prolonged duration of action increases the risk of neonatal depression.
- Methadone is not suitable for children.
- Hypersensitivity to methadone or any of the excipients.
- Patients dependent on non-opioid drugs
- Patients with acute alcoholism, head injury and raised intra-cranial pressure.
- Patients with ulcerative colitis, since methadone may precipitate toxic dilation or spasm of the colon.
- Patients with severe hepatic impairment as it may precipitate hepatic encephalopathy.
- Patients with biliary and renal tract spasm.

4.4 Special warnings and precautions for use

Caution should be exercised in patients with hepatic dysfunction or renal dysfunction.

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

Opioid Use Disorder (abuse and dependence)

Methadone is an opioid analgesic and is highly addictive in its own right. It is controlled under the Misuse of Drugs Act 1971 (Schedule 2). 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 possibly death.

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

Abuse or intentional misuse of methadone may result in overdose and/or death.
The risk of developing Opioid Use Disorder (OUD) 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.

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.

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 long-term 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 newborn 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 and may exacerbate asthma due to histamine release.

Hepatic disorders
Caution as methadone may precipitate porto-systemic encephalopathy in patients with severe liver damage.

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

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).

Paediatric population
As there is a risk of greater respiratory depression in neonates and because there are currently insufficient published data on the use in children, methadone is not recommended in those under 16 (See sections 4.2, 5.2).

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.

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.

Methadone should be used with caution in patients with hypothyroidism, prostatic hyperplasia, hypotension, shock, inflammatory or obstructive bowel disorders or myasthenia gravis.

Cases of QT interval prolongation and torsades 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,
- 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 CYP3A4 inhibitors (see section 4.5).

In patients with recognized 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 100mg/d and at seven days after titration.

Caution should be exercised in patients who are concurrently taking CNS depressants.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of Methadone 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 Methadone 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).

Excipient warnings:
This product contains

- Tartrazine (E102) and sunset yellow (E110), which may cause allergic reactions.
- Sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. This product contains 1.67g of sucrose per 5ml and should be taken into account in patients with diabetes mellitus. It may be harmful to the teeth.

- Sodium benzoate. This medicine contains 1mg of sodium benzoate in each ml. Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).
- This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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.

MAOI's:

The concurrent use of MAOI's is contraindicated (see 4.3 Contraindications) as they may prolong and enhance the respiratory depressant effects of methadone.

There are reports that antidepressant drugs (e.g. fluvoxamine and fluoxetine) may increase serum levels of methadone.

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).

CNS depressants:

Alcohol, anaesthetics, hypnotics and sedatives, barbiturates, phenothiazines, some other major tranquillizers and tricyclic antidepressants may increase the general depressant effects of methadone when used concomitantly. (See 4.4 Special warnings and precautions for use).

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).

Histamine H_2- Antagonists:
Histamine H_2 antagonists such as cimetidine, can reduce the protein binding of methadone resulting in increased opiate action.

Rifampicin:
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.

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.

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

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

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.

Opioid Agonist Analgesics:
Additive CNS depression, respiratory depression and hypotension.

Opioid antagonists:
Naloxone and naltrexone antagonises 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.

Antiretroviral Agents such as Nevirapine, Efavirenz, Nelfinavir, Ritonavir:
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.

Ciprofloxacin:
Concomitant use may lead to sedation, confusion and respiratory depression.

Other Drugs:
Methadone may have an effect on other drugs as a consequence of reduced gastro-intestinal motility.

Co-administration of methadone hydrochloride with metamizole, which is an inducer of metabolising enzymes including CYP2B6 and CYP3A4 may cause

a reduction in plasma concentrations of methadone hydrochloride with potential decrease in clinical efficacy. Therefore, caution is advised when metamizole and methadone hydrochloride are administered concurrently; clinical response and/or drug levels should be monitored as appropriate.

Fluconazole may raise methadone levels due to decreased methadone metabolism.

Pregnancy Tests:
Methadone may interfere with the urine testing for pregnancy.

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).

St. John's Wort:
May lower plasma concentrations of methadone.
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.

4.6 Fertility, pregnancy and lactation

Pregnancy
Methadone administered to pregnant women for the management of opioid addiction has the potential for several adverse effects on the foetus and neonate. A careful benefit/risk assessment must be made.

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

Following birth and low birth weight; increased stillbirth rates have also been reported.

If opioid use is required for a prolonged period in a pregnant 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.
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).

The effects of methadone itself on pregnancy and infants born to methadone-treated mothers are difficult to assess in view of the complicating factors such as poor prenatal care, poor maternal nutrition, smoking, poor environmental and social

conditions. Most studies have associated methadone with a low birth weight but methadone has not convincingly been associated with congenital malformations.

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.

4.7 Effects on ability to drive and use machines

This may be severely affected during and after treatment with Methadone. The time after which such activities may be safely resumed is extremely patient dependant and must be decided by the Physician.

"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

System organ class	**Frequency**	
	Uncommon (≥1/1,000 to <1/100)	**Not known** (cannot be estimated from the available data)
Endocrine Disorders		Raised prolactin levels with long-term administration.
Metabolism and nutrition disorders		Hypoglycaemia
Psychiatric disorders		Drug dependence (see section 4.4), confusion particularly at the start of the treatment can occur,

		changes of mood, including euphoria, and hallucinations are occasionally reported.
Nervous System Disorders		Drowsiness and headache. Methadone has the potential to increase intracranial pressure, particularly in circumstances where it is already raised.
Eye Disorders		Miosis, dry eyes, nystagmus[1], strabismus[1], visual acuity reduced[1].
Ear and labyrinth disorders		Vertigo.
Cardiac Disorders		Bradycardia and palpitations can occur. Cases of QT prolongation and torsades de pointes have been rarely reported.
Vascular disorders		Orthostatic hypotension, facial flushing.
Respiratory, thoracic and mediastinal disorders		Central sleep apnoea syndrome, exacerbation of existing asthma, dry nose, respiratory depression particularly with larger doses.
Gastrointestinal disorders		Nausea and vomiting particularly at the start of treatment can occur. Constipation, dry mouth.
Skin and subcutaneous tissue disorders		Rashes. Long-term administration may produce excessive sweating
Renal and urinary disorders		Micturition difficulties are observed.
Reproductive system and breast disorders		Galactorrhoea, dysmenorrhoea, amenorrhoea
General disorders and administration site conditions	Drug withdrawal syndrome. Hypothermia	

[1]Visual effects have been reported in infants and children exposed to methadone during pregnancy.

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 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.

Symptoms: Serious overdosage is characterised by respiratory depression, extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal muscle flaccidity, cold and clammy skin and sometimes bradycardia and hypotension. Toxic leukoencephalopathy has been observed

with methadone overdose. In severe overdosage, particularly by the intravenous route, apnoea, circulatory collapse, cardiac arrest and death may occur. Hypoglycaemia has been reported.

Treatment: A patent airway and assisted or controlled ventilation must be assured. Narcotic antagonists may be required, but it should be remembered that Methadone is a long-acting depressant (36-48 hours) whereas antagonists act for 1-3 hours, so that treatment with the latter must be repeated as needed. An antagonist should not be administered, however, in the absence of clinically significant respiratory or cardiovascular depression. Nalorphine (0.1 mg per kg) or Levallorphan (0.02 mg per kg) should be given intravenously as soon as possible and repeated, if necessary, every 15 minutes.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. In a person physically dependent on narcotics, administration of the usual dose of a narcotic antagonist will precipitate an acute withdrawal syndrome; use of the antagonist in such a person should be avoided, if possible, but if it must be used to treat serious respiratory depression it should be administered with great care.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Methadone is a strong opioid agonist with actions predominantly at the μ receptor. The analgesic activity of the racemate is almost entirely due to the 1-isomer, which is at least 10 times more potent as an analgesic than the d-isomer. The d-isomer lacks significant respiratory depressant activity but does have anti-tussive effects. Methadone also has some agonist actions at the K and δ opiate receptors. These actions result in analgesia, depression of respiration, suppression of cough, nausea and vomiting (via an effect on the chemoreceptor trigger zone) and constipation. An effect on the nucleus of the oculomotor nerve, and perhaps on opioid receptors in the pupillary muscles causes pupillary constriction. All these effects are reversible by naloxone with pA_2 value similar to its antagonism of morphine. Like many basic drugs, Methadone enters mast cells and releases histamine by a non-immunological mechanism. It causes a dependence syndrome of the morphine type.

5.2 Pharmacokinetic properties

Methadone is one of the more lipid soluble opioids, and is well absorbed from the gastro-intestinal tract, but undergoes fairly extensive first pass metabolism. It is bound to albumin and other plasma proteins and to tissue proteins (probably lipoproteins), the concentrations in lung, liver and kidneys being much higher than in blood. The pharmacokinetics of Methadone are unusual, in that there is extensive

binding to tissue proteins and fairly slow transfer between some parts of this tissue reservoir and the plasma. With an intramuscular dose of 10 mg, a peak plasma concentration of 75 µg per litre is reached in one hour. With regular oral doses of 100-120 mg daily, plasma concentrations rise from trough levels of approximately 500 µg/L to a peak of about 900 µg/L in 4 hours. Marked variations in plasma levels occur in dependent persons on a stable dose of oral Methadone, without any relation to symptoms. Methadone is secreted into sweat and found in saliva and in high concentration in gastric juice. The concentration in cord blood is about half the maternal level.

The half life after a single oral dose is 12-18 (mean 15) hours, partly reflecting distribution into tissue stores, as well as metabolic and renal clearance. With regular doses, the tissue reservoir is already partly filled, and so the half life is extended to 13-47 (mean 25) hours reflecting only clearance. In the first 96 hours after administration, 15-60% can be recovered from the urine, and as the dose is increased so a higher proportion of unchanged Methadone is found there. Acidification of the urine can increase the renal clearance by a factor of at least three and thus appreciably reduce the half time of elimination.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tartrazine (E102)

Sunset yellow (E110)

Green S (E142)

Sucrose

Hydrochloric acid (E507)

Sodium benzoate (E211)

Glycerol (E422)

Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Use within 4 weeks of opening.

6.4 Special precautions for storage

Do not store above 25°C

Store in original container.

6.5 Nature and contents of container

Amber Type III Glass or Amber PET bottle

Child Resistant Tamper Evident Cap- High density polypropylene cap with a polyethylene lining.

5 ml/2.5ml double ended polypropylene Spoon

Pack sizes available: 500ml

6.6 Special precautions for disposal

Methadone is a drug of addiction and is controlled under the Misuse of Drugs Act 1971 (Schedule 2).

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0608

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/01/2025

10 DATE OF REVISION OF THE TEXT

14/05/2025