

1 NAME OF THE MEDICINAL PRODUCT

Methadone 5mg/ml Oral Solution Sugar-Free

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of solution contains 5mg of Methadone hydrochloride.

Also contains sunset yellow (E110) 0.008mg/ml

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.

Clear, pale orange solution with odour of oranges.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Maintenance therapy in patients dependent on opioids concomitant with medical and psychological treatment and social rehabilitation.

4.2 Posology and method of administration

A criterion for treatment with methadone is that the patient is taking part in a “methadone programme” with drug-assisted rehabilitation for drug abusers, approved by a relevant authority.

For oral administration only. The medicinal product must not be injected.

The dose must be adjusted for each individual patient.

The usual initial dose is 10-30 mg. For patients with high opioid tolerance, the initial dose is 25-40 mg. The dose is increased in steps of 10 mg at a time over a period of three weeks, usually to 70 or 80 mg. After a recommended stabilisation period of four weeks, the dose is adjusted, until the patient, does not have a need for intoxication and is without clinical signs

of psychomotor function effects or abstinence symptoms. The usual dose is 60-120 mg of methadone per day, but some individuals may require higher doses. The dosage should be determined based upon clinical assessment supported by serum level monitoring. The recommended steady state 24 h serum level is 600-1200 nmol/l (200-400 ng/ml). Great importance is attached to the clinical assessment. Methadone is normally administered once daily. If administered more frequently, there will be a risk of accumulation and overdose. The highest recommended dose, that rarely should be used, is 150 mg/day (unless national guidelines recommend otherwise). The reason for this dose limitation is an increased frequency of QT-prolongation, Torsade's de Pointes and cases of cardiac arrest within higher dose ranges (see section 4.4). High doses may also elicit low-grade (but unwanted) euphoria during a couple of hours after the daily dose.

Patients should be observed in relation to dose increases to discover unwanted reactions. The patient obtains an increased serum level for up to two hours, and it is important that signs of overdose or other serious/unpleasant reactions are discovered.

Some patients develop auto-induction, which leads to that the medication is being more rapidly metabolised in the body. In such cases, the dose must be increased once or more to maintain the optimal effect.

If the patient has been treated with a combined agonist/antagonist (e.g. buprenorphine), the dose should be reduced gradually when the methadone treatment is initiated. If the methadone treatment is interrupted and a switch to sublingual buprenorphine treatment is planned (especially in combination with naloxone), the methadone dose should be reduced to 30 mg/day initially to avoid withdrawal symptoms caused by buprenorphine/naloxone.

Caution must be exercised after administration to elderly or ill patients. Methadone must not be administered to children (see section 4.3). Patients with hypothyroidism, myxoedema, urethral stricture, asthma or decreased lung volume or prostatic hypertrophy must receive a lower initial dose.

Hepatic impairment

Chronic viral hepatitis is common in drug addicts. Caution is advised if Methadone must be used in patients with hepatic impairment. In patients with liver cirrhosis the metabolism is delayed and the first pass effect is decreased. This may result in higher plasma levels of methadone. Methadone should be administered in a lower than the recommended dose and the clinical response of the patient should be used as guidance in the following dosage.

Renal impairment

Caution is advised if methadone is used in patients with renal impairment. The dosage interval should be prolonged to a minimum of 32 hours if GFR is 10-50 ml/min, and to a minimum of 36 hours if GFR is lower than 10 ml/min.

Treatment should be discontinued if the efficacy is not sufficient or if the patient cannot tolerate it. The effect must be evaluated in accordance with national guidelines.

If treatment has to be discontinued, this should be done by gradual dose reduction. The dose may be reduced relatively rapidly in the beginning, but reduction must be slow in the final phase (from 20 mg daily and downwards).

4.3 Contraindications

Respiratory depression.

Hypersensitivity to the active substance or to any of the excipients.

Acute obstructive airway disease

Concomitant administration of MAO-inhibitors or administration within two weeks after finished MAO inhibitor treatment.

Contraindicated in children.

4.4 Special warnings and precautions for use

Cases of QT interval prolongation and torsade de pointes have been reported during treatment with methadone, particularly at high doses (>100 mg/day). Methadone should be administered with caution to patients at risk for development of prolonged QT interval, e.g. in case of:

- known history of QT prolongation
- advanced heart disease,
- concomitant treatment with drugs that have a potential for QT-prolongation,
- concomitant treatment with CYP3A4 inhibitors

ECG-monitoring should be considered in patients with risk factors for QT-prolongation particularly in women.

Children are more sensitive than adults that is why poisoning may occur at very low doses. To avoid unintentional intake of methadone by children, methadone should in cases when it is taken home, be kept in a safe place where children cannot reach it.

The precautions to be taken when using methadone are the same as those applying to opiates in general.

Opioid Use Disorder (abuse and dependence)

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.

Abuse or intentional misuse of Methadone 5mg/ml oral solution 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.

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.

Acute asthma attacks, severe obstructive pulmonary disease, cor pulmonale, lessened respiratory reserve, hypoxia, hypercapnia are relative contraindications. Each case must be assessed individually.

Concurrent administration of other opiates, alcohol, barbiturates, benzodiazepines and other strong sedative psychoactive drugs may potentiate the effects and side effects of methadone and should be avoided.

Concurrent treatment with narcotic antagonists or mixed agonist/antagonists should be avoided (with the exception of treatment of overdose) as it may precipitate withdrawal symptoms in physically dependant patients.

At the beginning of the dose increase period the patient must be observed after administration to record any abnormal/adverse reactions. The patient will have increased serum levels for up to two hours, and it is important that any overdose reactions or other dangerous/severe reactions can be recorded.

In cases of impaired hepatic and renal function, methadone must be used with caution. The metabolism of methadone may be reduced in cases of impaired hepatic function, and dose adjustment may be necessary (see 4.2). A lower initial dose must be administered to patients with hypothyroidism, myxedema, (it can increase the risk of respiratory depression and prolonged CNS depression), renal (increased risk of convulsions) and hepatic impairment (opioids metabolised in liver), asthma or decreased lung volume (it may decrease respiratory drive and increase airway resistance) urethral stricture or prostatic hypertrophy (it may cause urinary retention) (see 4.2).

Great caution must be exercised in cases of possible head injury or conditions involving increased intracranial pressure. Methadone should not be used in patients with intestinal pseudo-obstruction, acute abdomen and inflammatory bowel disease.

In patients with kidney calculi and in patients with gallstones it may be necessary to administer atropine or other spasmolytic prophylactically.

Elderly patients and patients suffering from cardiovascular diseases are at increased risk of hypotension and syncope.

This medicinal product contains sunset yellow (E110), which may cause allergic reactions and orange flavour (including propylene glycol) which may cause alcohol-like symptoms.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

P-glycoprotein inhibitors: Methadone is a substrate of p-glycoprotein; all medicinal

products that inhibit P-glycoprotein (e.g. quinidine, verapamil, ciclosporin), may therefore raise the serum concentration of methadone. The pharmacodynamic effect of methadone may also increase because of increased blood brain barrier passage.

CYP3A4-enzyme inducers: Methadone is a substrate of CYP3A4 (see section 5.2). By induction of CYP3A4, clearance of methadone will increase and the plasma levels decrease.

Inducers of this enzyme (barbiturates, carbamazepine, phenytoin, nevirapine, rifampicine, efavirenz, amprenavir, spironolactone, dexamethasone, *Hypericum perforatum* (St John's Wort), may induce hepatic metabolism. For instance, after three weeks treatment with 600 mg efavirenz daily, the mean maximal plasma concentration and AUC decreased by 48 % and 57

% respectively, in patients treated with methadone (35-100 mg daily).

The consequences of enzyme induction are more marked if the inducer is administered after treatment with methadone has begun. Abstinence symptoms have been reported following such interactions and hence, it may be necessary to increase the methadone dose. If treatment with a CYP3A4 inducer is interrupted, the methadone dose should be reduced.

CYP3A4-enzyme inhibitors: Methadone is a substrate of CYP3A4 (see section 5.2). By inhibition of CYP3A4 clearance of methadone is lowered. Concomitant administration of CYP3A4 inhibitors (e.g. cannabinoids, clarithromycin, delavirdine, erythromycin, fluconazole, grapefruit juice, itraconazole, ketoconazole, fluoxetine, fluvoxamine, nefazodone and telithromycin) may result in increased plasma concentrations of methadone. A 40-100 % increase of the ratio between the serum levels and the methadone dose has been shown with concomitant fluvoxamine treatment. If these medicinal products are prescribed to patients on methadone maintenance treatment, one should be aware of the risk of overdose.

Products that affect the acidity of the urine: Methadone is a weak base. Acidifiers of the urine (such as ammonium chloride and ascorbic acid) may increase the renal clearance of methadone. Patients that are treated with methadone are recommended to avoid products containing ammonium chloride.

Concomitant HIV infection treatment: Some protease inhibitors (amprenavir, nelfinavir, lopinavir/ritonavir and ritonavir/saquinavir) seem to decrease the serum levels of methadone. When ritonavir is administered alone, a two-fold AUC of methadone has been observed. The plasma levels of zidovudine (a nucleoside analogue) increase with methadone use after both oral and intravenous administration of zidovudine. This is more noticeable after oral than after intravenous use of zidovudine. These observations are likely caused by inhibition of zidovudine glucuronidation, and therefore decreased clearance of zidovudine. During treatment with methadone, patients must be carefully monitored for signs of toxicity caused by zidovudine, why it may be necessary to reduce the dose of zidovudine. Because of mutual interactions between zidovudine and methadone (zidovudine is a CYP3A4 inducer), typical opioid abstinence symptoms may develop during concomitant use (headache, myalgia, fatigue and irritability).

Didanosine and stavudine: Methadone delays the absorption and increases the first pass metabolism of stavudine and didanosine which results in a decreased bioavailability of stavudine and didanosine.

Methadone may double the serum levels of desipramine.

Pharmacodynamic interactions

Opioid antagonists:

Naloxone and Naltrexone counteracts the effects of methadone and induces abstinence.

CNS depressants: Medicinal products with a sedative effect on the central nervous system may result in increased respiratory depression, hypotension, strong sedation or coma, therefore it may be necessary to reduce the dose of one or both of the medicinal products. With methadone treatment, the slowly eliminated substance methadone, give rise to a slow tolerance development and every dose increase may after 1-2 weeks give rise to symptoms of respiratory depression. The dose adjustments must therefore be made with caution and the dose increased gradually with careful observation.

Peristalsis inhibition: Concomitant use of methadone and peristalsis inhibiting medicinal products (loperamide and diphenoxylate) may result in severe obstipation and increase the CNS depressant effects. Opioid analgesics, in combination with antimuscarinics, may result in severe obstipation or paralytic ileus, especially in long-term use.

QT-prolongation: Methadone should not be combined with medicinal products that may prolong the QT interval such as antiarrhythmics (sotalol, amiodarone, flecainid), antipsychotics (thioridazine, haloperidol, sertindol, phenothiazines), antidepressants (paroxetine, sertraline) or antibiotics (erythromycin, clarithromycin).

MAO-inhibitors: Concomitant administration of MAO-inhibitors may result in reinforced CNS-inhibition, serious hypotonia and or apnoea. Methadone should not be combined with MAO-inhibitors and two weeks after such treatment (see section 4.3).

Opioid analgesics delay gastric emptying, thereby invalidating test results. Delivery of Technetium Tc 99m disofenin to the small bowel may be prevented and plasma amylase and plasma lipase activity may be increase because opioid analgesics may cause constriction of the sphincter of Oddi and increased biliary tract pressure; these actions result in delayed visualization and thus resemble obstruction of the common bile duct. The diagnostic utility of determinations of these enzymes may be compromised for up to 24 hours after the medication has been given. Cerebrospinal Fluid Pressure (CSF) may be increased; effect is secondary to respiratory depression – induced carbon dioxide retention.

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).

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.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Limited data on the use of methadone in pregnancy in humans show no elevated risk of congenital abnormalities. Withdrawal symptoms / respiratory depression may occur in neonates of mothers that were treated with methadone chronically during pregnancy. A QT prolonging effect following maternal methadone exposure cannot be excluded, and a 12-lead electrocardiogram should be performed if the neonate has bradycardia, tachycardia or an irregular heart rate.

Data from animal studies have shown reproduction toxicity (see section 5.3). It is generally advisable not to detoxify the patient, especially after the 20th week of pregnancy, but to administer maintenance treatment with methadone. The use of Methadone oral solution just before and during birth is advised against because of the risk of neonatal respiratory depression.

Lactation:

Methadone is excreted in breast milk and the average milk/plasma ratio is 0.8. Breast feeding may be given at doses of up to 20mg per day. At higher doses the benefits of breast feeding must be weighed against the possible adverse effects on the infant.

4.7 Effects on ability to drive and use machines

Methadone will affect the psychomotor functions until the patient has been stabilised at a suitable level. The patient should therefore not drive or use machines until stabilisation has been achieved and there have been no symptoms of abuse for the last six months. When driving and use of machines can be resumed is largely dependent on the individual patient and must be determined by the physician. For further information see the national guidelines for methadone treatment.

This medicine can affect your ability to drive.

Do not drive whilst taking this medicine until you know how this medicine affects you.

4.8 Undesirable effects

The undesirable effects of methadone treatment are in general the same as when treated with other opioids. The most common side effects are nausea and vomiting that is observed in approximately 20 % of the patients that go through methadone outpatient treatment, where the medicinal control is often unsatisfactory.

The most serious side effect of methadone is respiratory depression, which may emerge during the stabilisation phase. Apnoea, shock and cardiac arrest have occurred.

Adverse reactions listed below are classified according to frequency and system organ class. These side effects are more frequently observed in non-opioid tolerant individuals. Frequency groupings are defined according to the following convention:

Very common ($\geq 1/10$),

common ($\geq 1/100$ to $< 1/10$),

uncommon ($\geq 1/1,000$ to $< 1/100$),

rare ($\geq 1/10,000$ to $< 1/1,000$),

very rare ($< 1/10,000$),

not known (cannot be estimated from the available data).

System organ class MedDRA	Frequency	Adverse event
Investigations	Common	Weight increase
Metabolism and nutrition disorders.	not known	hypokalemia, hypomagnesemia
	common	Fluid retention
	uncommon	anorexia
Blood and lymphatic system disorders	not known	reversible thrombocytopenia has been reported in opiod patients with chronic hepatitis
Respiratory, thoracic and mediastinal disorders	Uncommon	pulmonary oedema, respiratory depression
	Not known	central sleep apnoea syndrome
Gastrointestinal disorders	very	nausea, vomiting
	common	obstipation
	common	xerostomia, glossitis
Psychiatric disorders	Common	euphoria, hallucinations
	uncommon	dysphoria, agitation, insomnia, disorientation, reduced libido
	Not known	dependence
Ear and labyrinth disorders	Common	Vertigo
Eye disorders	Common	Blurred vision, miosis
Nervous system disorders	Common	sedation headache,
	Uncommo	syncope
Skin and subcutaneous tissue disorders	Common	transient rash, sweating,
	uncommon	pruritus, urticaria, other rash and in very uncommon cases bleeding urticaria

General disorders and administration site conditions	Common	fatigue
	uncommon	oedema of the lower extremities, asthenia, oedema
Hepatobiliary disorders	uncommon	bile duct dyskinesia
Vascular disorders	uncommon	facial flush, hypotension
Cardiac disorders	Rare	bradycardia, palpitations, cases of prolonged QT intervals and “torsade de pointes” have been reported in treatment with methadone, especially with high doses.
Renal and urinary disorders	uncommon	Urinary retention and antidiuretic effect
Reproductive system and breast disorders	uncommon	Reduced potency and amenorrhea

In long term use of methadone, as for maintenance treatment, the undesirable effects diminish successively and progressively during a period of several weeks. However, obstipation and perspiration often remain.

Long-term use of methadone may lead to morphine-like dependence. The abstinence syndromes are similar to the ones observed with morphine and heroine, however less intense, but more long-lasting.

4.9 Overdose

Symptoms:

Severe overdose is characterised by respiratory failure, extreme drowsiness that develops into stupor or coma, maximum pupillary constriction, skeletal-muscle flaccidity, cold and clammy skin and occasionally bradycardia and hypotension. Apnoea, cardiovascular failure, cardiac arrest and death may occur in serious cases of overdose, especially in intravenous administration.

Toxic leukoencephalopathy has been observed with methadone overdose.

Treatment:

Ensure the airways by assisted or controlled ventilation.

It may be necessary to use opioid antagonists, but since the duration of action of methadone is long (36-48 hours) and that of most widely used antagonist, naloxone is only 1-3 hours,

antagonist treatment must be repeated as necessary. Antagonists must not be used if there are no signs of respiratory failure or loss of consciousness. If the patient is physically dependent on narcotics, administration of an antagonist may lead to acute abstinence symptoms. If possible, the use of antagonists should be avoided in such patients, but if it nevertheless proves necessary to administer antagonists because of severe respiratory depression, great caution must be exercised and the antagonist dose should be low if methadone-poisoning is suspected.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: drugs in opioid dependency.

ATC code: N07BC02.

Methadone is a narcotic analgesic that belongs to the same group as morphine. The substance has an agonist effect on the opiate receptors in the brain, bone marrow and nervous system, with high affinity for the μ receptors, and also some affinity for the σ and κ receptors.

Methadone acts in a similar way as morphine, but has a less sedative effect. The use of methadone can reduce or eliminate the effect of other opiates. Methadone, at a carefully titrated dose can be given orally, with no euphoria but simply a state of "straight" for 24-32 hours, followed by gradually increasing withdrawal symptoms, unless a new dose is applied.

5.2 Pharmacokinetic properties

Absorption: methadone is rapidly absorbed following oral administration, but undergoes considerable first-pass metabolism. The bioavailability is above 80 %. Steady state concentrations are reached within 5-7 days.

Distribution: distribution volume: 5 L/kg. Protein binding: up to 90 %, but with great individual differences. Methadone binds mainly to α_1 -glycoprotein acid, but also to albumin and other plasma and tissue proteins. Plasma: the full blood ratio is around 1:3. It is distributed to tissue with higher concentrations in the liver, lungs and kidneys than in the blood.

Metabolism: catalysed primarily by CYP3A4, but CYP2D6 and CYP2B6 are also involved, but to a smaller extent. Metabolism is mainly N-demethylation, which produces the most important metabolites: 2-ethylidine, 1,5-dimethyl-3,3 - diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenyl-1-pyrrolidine (EMDP), which are both inactive. Hydroxylation to methanol succeeded by N-demethylation to normethadol also occurs to some extent. Other metabolic reactions also occur, and at least eight other metabolites are known.

Elimination: elimination half-life: single dose: 10-25 hours. Repeated doses: 13-55 hours. Plasma clearance is around 2 ml/min/kg. About 20-60 % of the dose is eliminated in urine over 96 hours (about 33 % in unmodified form, about 43 % as EDDP and about 5-10 % as EMDP). The ratio between EDDP and unmodified methadone is usually much higher in urine in patients receiving methadone treatment compared to normal overdoses. Elimination of unmodified methadone in urine is pH-dependent and increases with increasing acidity of the urine. About 30 % of the dose is eliminated in faeces, but this percentage will normally be reduced at higher doses. About 75 % of overall elimination is unconjugated.

Special populations

There are no significant differences in the pharmacokinetics between men and women. The clearance of methadone is decreased only to some extent in elderly (>65 years).

Because of increased exposure, caution is advised in the treatment of patients with renal and hepatic impairment (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Methadone at high doses caused birth abnormalities in marmots, hamsters and mice, in which most reports were of exencephaly and defects in the central nervous system. Rachischis in the cervical region was found occasionally in mice. Non-closure of the neural tube was found in chicken embryos. Methadone was not teratogenic in rats and rabbits. Also a reduced number of young was found in rats and increased mortality, growth retardation, neurological behavioural effects and reduced brain weight were found in the pups. Reduced ossification of the digits, sternum and skull was found in mice and a smaller number of foetuses per litter.

No carcinogenicity studies have been carried out.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium benzoate (E211)

Sodium cyclamate

Saccharin sodium

Sunset Yellow FCF (E110)

Blood orange flavour (including propylene glycol)

Hydrochloric acid

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 3 years.

Use within 1 month of opening.

6.4 Special precautions for storage

Store below 30°C and protect from light.

6.5 Nature and contents of container

The product is supplied in 1L and 2.5L HDPE plastic bottles with tamper evident caps or Type III amber glass bottles containing 1L.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

1L and 2.5L pack size are dispensing packs and are only to be used by healthcare professionals.

7 MARKETING AUTHORISATIONHOLDER

Martindale Pharmaceuticals Ltd.
Bampton Road, Harold Hill
Romford, RM3 8UG
United Kingdom.

8 MARKETING AUTHORISATIONNUMBER(S)

H2020/CTD7586/14768

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

24/01/2020

10 DATE OF REVISION OF THE TEXT

16/04/2024