Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Methadone 1 mg/ml Oral Solution Sugar Free

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of solution contains 1mg of methadone hydrochloride
Also contains:
Tartrazine 0.07mg per ml
Sunset yellow. 0.008mg 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

For oral administration only.

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.

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.

Addiction/Tolerance/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 possibly death.

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.

Withdrawal

Abrupt cessation of treatment can lead to withdrawal symptoms which, although similar to those with morphine, are less intense but more prolonged. Withdrawal of treatment should therefore be gradual.

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.

Neonates/children

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).

Further warnings

Babies born to mothers receiving methadone may suffer withdrawal symptoms.

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, adrenocortical insufficiency, 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.

Excipient warnings:

This product contains

- E102 and E110, which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

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 concomintantly. (See 4.4 Special warnings and precautions for use).
There are reports that antidepressant drugs (e.g. fluvoxamine and fluoxetine) may increase serum levels of methadone.

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.

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.

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.

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

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. Apart from the risk of prolonged respiratory depression in the neonate, the immediate problems are withdrawal syndrome *in utero* and following birth and low birth weight; increased stillbirth rates have also been reported.

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.

It should not be used during labour, see “contra-indications”

Methadone is excreted in breast milk, though it is unclear whether this contributes to adverse effects on the nursing 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.

4.8 Undesirable effects

Cardiac Disorders
Bradycardia and palpitations can occur. Cases of QT prolongation and torsades de pointes have been rarely 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

Ear and labyrinth disorders
Vertigo.

Respiratory, thoracic and mediastinal disorders
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.

Renal and urinary disorders
Less commonly micturition difficulties are observed.

Skin and subcutaneous tissue disorders
Rashes. Long-term administration may produce excessive sweating

Endocrine Disorders
Raised prolactin levels with long-term administration.

Vascular disorders
Orthostatic hypotension, facial flushing.

General disorders
Hypothermia

Reproductive system and breast disorders
Galactorrhoea, dysmenorrhoea, amenorrhoea

Psychiatric disorders
Dependence, confusion particularly at the start of the treatment can occur
Changes of mood, including euphoria, and hallucinations are occasionally
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 HPRA Pharmacovigilance, Earlsfort Terace, IRL – Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, E-mail: medsafety@hpra.ie

4.9 Overdose

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. In severe overdosage, particularly by the intravenous route, apnoea, circulatory collapse, cardiac arrest and death may occur.

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)
Sodium Saccharin
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

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

7 MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1986/060/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th January 2010

Date of last renewal: 31st December 2012

10 DATE OF REVISION OF THE TEXT

August 2018