Methadone 1 mg/ml Oral Solution

PL 17507/0192

PL 17507/0193

PL 17507/0194

UKPAR

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METHADONE 1 MG/ML ORAL SOLUTION

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) for the medicinal product Methadone 1 mg/ml Oral Solution (product licence numbers: PL 17507/0192-4) on 26 November 2010. Methadone 1 mg/ml Oral Solution is available by prescription only.

Methadone 1 mg/ml Oral Solution belongs to group of medicines called narcotic analgesics and is used to treat opioid drug addiction.

Methadone 1 mg/ml Oral Solution raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
METHADONE 1 MG/ML ORAL SOLUTION

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal product Methadone 1 mg/ml Oral Solution to Auden Mckenzie (Pharma Division) Ltd on 26 November 2010.

These are abridged applications submitted under Article 10(c) of EC Directive 2001/83, last paragraph. The applicant claims that these products are identical to Methadone 1 mg/ml Oral Solution (PL 17507/0032) which was licensed for use in the UK on 11 August 2009 to Auden Mckenzie (Pharma Division) Ltd.

No new data were submitted, nor was it necessary for these simple applications, as the data are identical to those of the previously granted cross-reference products.

Methadone 1 mg/ml Oral Solution is indicated for use in the treatment of opioid drug addictions (as a narcotic abstinence syndrome suppressant).
PHARMACEUTICAL ASSESSMENT

METHADONE HYDROCHLORIDE
The methadone hydrochloride used in these products complies with the current EDQM Certificate of Suitability and is, therefore, satisfactory.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT
The products are clear green oral solutions containing the pharmaceutical excipients tartrazine (E102), sunset yellow (E110), green S (E142), sucrose, hydrochloric acid (E507), sodium benzoate (E211), glycerol (E422) and purified water.

The products are stored in 500ml, amber, Type III glass bottles with a child resistant, tamper evident, high density polypropylene cap with a polyethylene lining. The bottles come with a 5 ml/2.5ml double ended polypropylene spoon.

There appears to be no difference between the composition and packaging of the proposed products and those of the already licensed cross reference product.

The proposed shelf-life (2 years) and storage conditions (Use within 4 weeks of opening, Do not store above 25°C, Store in original container) are consistent with the details registered for the reference product.

ADDITIONAL DATA REQUIREMENTS
The manufacturing process, finished product specifications and active ingredient specification are in line with those for the reference product and are satisfactory.

The applicant is also the Marketing Authorisation Holder of the reference product. Letters of Access are, therefore, not required

EXPERT REPORTS
Satisfactory expert reports in the form of quality, non-clinical and clinical overall summaries are provided, with signed declarations from each expert confirming that the applicant’s product is identical to the reference products in all particulars. Expert CVs are also submitted and are acceptable.

PRODUCT LITERATURE
The proposed SPCs, PILs and labels are identical to those for the reference product and are satisfactory.

ASSESSOR’S OVERALL CONCLUSIONS
Marketing Authorisations may be granted for these products.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none is required for an application of this type.
CLINICAL ASSESSMENT

OVERVIEW
A statement has been provided confirming that the clinical particulars for Methadone 1 mg/ml Oral Solution are identical to those for the already licensed product; Methadone 1 mg/ml Oral Solution (PL 17507/0032). This is satisfactory.

BIOAVAILABILITY AND BIOEQUIVALENCE
No bioequivalence study has been performed to support these applications and none is needed.

PRODUCT LITERATURE
All product literature is medically satisfactory.

ASSESSOR’S OVERALL CONCLUSIONS
It is recommended that Marketing Authorisations can be granted.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
Methadone 1 mg/ml Oral Solution (PL 17507/0192-4) is identical to the already licensed reference product. These products are, therefore, pharmaceutically satisfactory.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
The efficacy of methadone is well established. The SPCs, PILs and labelling are satisfactory and consistent with those for the cross-reference products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with methadone. The risk benefit ratio is, therefore, considered to be acceptable.
**METHADONE 1 MG/ML ORAL SOLUTION**

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**STEPS TAKEN FOR ASSESSMENT**

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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
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.
- Sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. The product contains 1.67g of sucrose per 5ml and should be taken into account in patients with diabetes mellitus. It may be harmful to teeth.

4.5 Interaction with other medicinal products and other forms of interaction
CNS depressants:
Alcohol, anaesthetics, hypnotics and sedatives, barbiturates, phenothiazines, some other major tranquillisers and tricyclic antidepressants may increase the general depressant effects of methadone when used concomitantly. (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 H₂ Antagonists:**
Histamine H₂ 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 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
Bradyarrhythmia 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 reported.

### 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 pA₂ 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
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
Auden Mckenzie (Pharma Division) Ltd
McKenzie House
Bury Street
Ruislip
Middx
HA4 7TL

8 MARKETING AUTHORITY NUMBER(S)
PL 17507/0192
PL 17507/0193
PL 17507/0194

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY
26/11/2010

10 DATE OF REVISION OF THE TEXT
26/11/2010
PATIENT INFORMATION LEAFLET

The following text is the approved Product Information Leaflet (PIL) text. No PIL mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the PIL mock-ups has been obtained.

PATIENT INFORMATION LEAFLET

Methadone 1 mg/ml Oral Solution

Read all of this leaflet carefully before you start taking Methadone 1mg/ml Oral Solution. It contains important information on how to take it.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What is Methadone Oral Solution and what it is used for
2. Before taking Methadone Oral Solution
3. How to take Methadone Oral Solution
4. Possible side effects
5. How to store Methadone Oral Solution
6. Further information

1. What is Methadone Oral Solution and what it is used for

The name of your medicine is Methadone 1mg/1ml Oral Solution (now called Methadone Oral Solution throughout the leaflet). It contains methadone hydrochloride as an active ingredient. This belongs to a group of medicines called Narcotic Analgesics.

Methadone is used:

- to treat opioid drug addiction
2. **Before taking Methadone Oral Solution**

Do not take Methadone Oral Solution if:

- you are allergic (hypersensitive) to methadone or any other ingredients in this liquid (see section 6 below). An allergic reaction can include a rash, itching or shortness of breath
- you have severe breathing problems or a history of asthma. You must not use this medicine during an asthma attack. If you give this medicine to yourself (self-administration), wait until the asthma attack has passed and you are fully recovered
- you are taking Monoamine Oxidase Inhibitors (MAOIs) used to treat depression or if you have taken a MAOI medicine in the past two weeks (see ‘Taking Other Medicines’)
- you are dependent on any other drugs
- you are in labour
- children must **not** be given this medicine.
- You have liver or kidney problems
- You have a bowel problem called ulcerative colitis
- You are addicted to alcohol
- You have recently had a head injury

Do not take this medicine if any of the above points apply to you. If you are not sure, talk to your doctor before taking methadone.

**Take special care with Methadone Oral Solution**

Before you take this medicine, tell your doctor if:

- you have epilepsy
- you have low thyroid function (hypothyroid)
- you have problems with your adrenal glands. These are linked to your kidneys
- you have an enlarged prostate gland
- you have low blood pressure
• you are in shock
• you have a muscle weakness disease called myasthenia gravis
• you have bowel problems
• you have a history of irregular heart beat
• you have a history of heart disease
• you have a family history of people dying suddenly without cause
• you have low potassium, sodium or magnesium levels
• you are pregnant or breast-feeding
• you are extremely ill or an older person. You may be more sensitive to the medicine.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking methadone.

**Taking other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines bought without a prescription, including herbal medicines. This is because methadone can affect the way some other medicines work. Also some medicines can affect the way methadone works.

You must **not** take Methadone Oral Solution

• at the same time or within 2 weeks of taking Monoamine Oxidase Inhibitors (MAOIs).

Some medicines can increase the risk of heart problems when used with methadone. Talk to your doctor before taking methadone if you are taking:

• medicines for heart problems such as verapamil and enalapril
• medicines which affect electrolyte balance such as diuretics (water tablets) or lithium.

Tell your doctor if you are taking any of the following medicines:

• medicines that dull your senses such as medicine for depression (for example, fluvoxamine, fluoxetine), medicines to help you sleep (including anaesthetics) and medicines to calm you down called tranquillisers
- cimetidine, used to treat stomach ulcers
- rifampicin, used to treat tuberculosis (TB)
- medicines used to treat epilepsy such as phenytoin, carbamazepine, phenobarbital and primidone
- medicines that make your urine acidic such as ascorbic acid (vitamin C)
- narcotic painkillers such as codeine and pentazocine
- naloxone used to reverse the effects of opioid drugs
- medicines used to stop opioid drugs working such as naltrexone and buprenorphine
- medicines used to treat HIV such as nevirapine, efavirenz and nelfinavir. The doctor may have to change the amount of methadone you take whilst on these medicines
- antibiotics such as ciprofloxacin or macrolide antibiotics for example erythromycin
- medicines used to treat fungal infections such as ketoconazole or fluconazole
- St. John’s Wort - a herbal preparation for depression.

If any of the above applies to you, talk to your doctor before taking Methadone Solution.

**Taking Methadone Oral Solution with food and drink**

Do not drink alcohol whilst taking Methadone Oral Solution. This is because Methadone Oral Solution can make you feel sleepy and drinking alcohol will make you even more sleepy.

**Pregnancy and Breast-feeding**

- talk to your doctor before taking Methadone Oral Solution if you are pregnant or likely to become pregnant
- take care if you are taking a pregnancy test as the methadone may interfere with the results
- you should not take this medicine whilst you are in labour
- do not breast-feed if you are taking Methadone Oral Solution.
Driving and using machines
Methadone Oral Solution will severely affect your ability to drive or use machines, whilst taking it and afterwards. You should only start doing these activities again with the permission of your doctor.

Important information about what is in Methadone Oral Solution:

- This product contains sucrose (1.67 g per 5 ml). You should take this into account if you have diabetes. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this product. It may also be harmful to teeth.

- This product also contains Tartrazine (E102) and Sunset Yellow (E110), which may cause allergic reactions.

How to take Methadone Oral Solution
Take this medicine as your doctor or pharmacist has told you. Look on the label and ask your doctor or pharmacist if you are not sure.

Taking this medicine
- this medicine contains 1mg of methadone in each 1ml
- take this medicine by mouth.

Adults
For addiction
- the starting dose is 10mg to 20mg (10ml to 20ml) each day
- the doctor can increase this to 40mg to 60mg (40ml to 60ml) each day.

Older people and very ill people
- if you have to have repeated doses of this medicine, the doctor may want to monitor you more closely.

Children
Children must not take this medicine.
If you take more Methadone Oral Solution than you should
If you accidentally take an overdose of your medicine, either call your doctor straight away, or go to your nearest hospital casualty department. Do not drive yourself there you may begin to feel sleepy. Always take any remaining medicine, the container and the label with you, so that the medicine can be identified.

You may experience the following symptoms if you take too much of this medicine:
- Difficulty in breathing
- Extreme drowsiness, being unaware (stupor) or loss of consciousness (coma)
- Very small pupils
- Cold and clammy skin
- A very slow pulse rate
- Muscle weakness.

In extreme cases, heart and blood pressure can be affected, leading to heart attack and death.

If you forget to take Methadone Oral Solution
- if you forget a dose do not take it. Wait until the next dose is due and take only that amount
- do not take a double dose (two doses at the same time) to make up for a forgotten dose.

If you stop taking Methadone Oral Solution
- do not stop taking this medicine unless your doctor tells you to as you may suffer withdrawal effects
- your doctor will tell you how to lower the dose gradually.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.
4. Possible side effects

Like all medicines, Methadone can cause side effects although not everybody gets them.

Stop taking this medicine and see a doctor straight away if you have an allergic reaction to Methadone Oral Solution.

An allergic reaction may include:

- swelling of your face, lips, tongue or throat or difficulty breathing or swallowing
- severe itching of your skin with raised lumps.

Stop taking this medicine and see a doctor straight away if you have any of the following:

- heart problems. The signs of this may include changes in the way your heart beats, such as it beating faster or missed heart beats, breathing difficulties and dizziness
- if your breathing become slow and shallow.

Keep taking the medicine but tell your doctor straight away if you get any of the following side effects:

- if you have asthma and it gets worse
- worsening of the pressure inside your head if you already have this condition following an injury to your brain or brain disease.

Tell your doctor if you get any of these side effects:

- feeling sick (nausea) or being sick (vomiting)
- constipation
- sweating a lot more than usual
- feeling dizzy, particularly when standing up. This may be a sign that you have low blood pressure
- small pupils
- breast growth and production of breast milk
- difficulty in passing water (urine), pain in the lower back and abdomen caused by muscle spasms
- dry mouth, eyes or nose, facial flushing
- feeling drowsy, confused or restless
6. **Further information**

Methadone 1 mg/ml Oral Solution is a clear green solution.

Each 1 ml of oral solution contains 1 mg of methadone hydrochloride.
It also contains:
Tartrazine (E102), Sunset yellow (E110), Green S (E142), sucrose, hydrochloric acid, sodium benzoate (E211), glycerol and purified water.

Each bottle contains 500ml of oral solution. A double ended 5ml and 2.5ml polypropylene spoon is also included to help measure the dose.

**Marketing Authorisation holder:**
Auden Mckenzie (Pharma Division) Ltd
McKenzie House
Bury Street
Ruislip
Middx
HA4 7TL

**Manufacturer**
Percuro Medica Ltd
Unit 5 Powergate Business Park
Volt Avenue
Park Royal
London
NW10 6PW

Date of approval of this leaflet:

For information in large print, tape, CD or Braille, telephone 01895 627 420
LABELLING

The following text is the approved label text. No label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained.
Approved label text (PL 17507/0192):

Carton text

1. NAME OF THE MEDICINAL PRODUCT

   Methadone 1mg/ml Oral Solution
   Methadone hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

   Each 1 ml contains 1mg of Methadone hydrochloride.

3. LIST OF EXCIPIENTS

   It also contains: Sucrose, tartrazine (E102), sunset yellow (E110) and sodium benzoate. See enclosed leaflet for full list of ingredients.

4. PHARMACEUTICAL FORM AND CONTENTS

   Oral Solution

   500ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

   For Oral use
   Read the package leaflet before use.

   Dosage: Use as directed by your doctor
   Administration: Use the enclosed spoon to measure the dose.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

   Keep out of the reach and sight of children.
7. OTHER SPECIAL WARNING(S), IF NECESSARY
   Not applicable

8. EXPIRY DATE

   Do not use 4 weeks after first opening.

   Date opened: __/__/____

   Expiry date to be overprinted with the batch number as EXP: mm/yyyy

9. SPECIAL STORAGE CONDITIONS

   Do not store above 25°C. Store in the original container.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL
    PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH
    MEDICINAL PRODUCTS, IF APPROPRIATE

    Not applicable

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

    Auden Mckenzie (Pharma Division) Ltd
    McKenzie House
    Bury Street
    Ruislip
    Middx
    HA4 7TL

12. MARKETING AUTHORISATION NUMBER(S)

    PL 17507/0192
13. BATCH NUMBER
   To be over printed

14. GENERAL CLASSIFICATION FOR SUPPLY

   POM
   CD

15. INSTRUCTION ON USE

   To be completed nationally

16. INFORMATION IN BRAILLE

   Methadone 1mg/ml Oral Solution
BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Methadone 1mg/ml Oral Solution
Methadone hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml contains 1mg of Methadone hydrochloride.

3. LIST OF EXCIPIENTS

It also contains: Sucrose, tartrazine (E102), sunset yellow (E110) and sodium benzoate. See enclosed leaflet for full list of ingredients.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral Solution

500ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For Oral use
Read the package leaflet before use.

Dosage: Use as directed by your doctor
Administration: Use the enclosed spoon to measure the dose.
6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
   Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
   Not applicable

8. EXPIRY DATE

   Do not use 4 weeks after first opening.

   Date opened: __/__/____

   Expiry date to be overprinted with the batch number as EXP: mm/yyyy

9. SPECIAL STORAGE CONDITIONS

   Do not store above 25°C. Store in the original container.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

   Not applicable
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14. GENERAL CLASSIFICATION FOR SUPPLY

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15. INSTRUCTION ON USE

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16. INFORMATION IN BRAILLE

Not applicable
Approved label text (PL 17507/0193):

1. **NAME OF THE MEDICINAL PRODUCT**

   Methadone 1mg/ml Oral Solution
   Methadone hydrochloride

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   Each 1 ml contains 1mg of Methadone hydrochloride.

3. **LIST OF EXCIPIENTS**

   It also contains: Sucrose, tartrazine (E102) and sunset yellow (E110) and sodium benzoate. See enclosed leaflet for full list of ingredients.

4. **PHARMACEUTICAL FORM AND CONTENTS**

   Oral Solution

   500ml

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   For Oral use
   Read the package leaflet before use.

   Dosage: Use as directed by your doctor
   Administration: Use the enclosed spoon to measure the dose.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

   Keep out of the reach and sight of children.
7. OTHER SPECIAL WARNING(S), IF NECESSARY
   Not applicable

8. EXPIRY DATE

   Do not use 4 weeks after first opening.

   Date opened: __/__/____

   Expiry date to be overprinted with the batch number as EXP: mm/yyyy

9. SPECIAL STORAGE CONDITIONS

   Do not store above 25°C. Store in the original container.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

   Not applicable

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14. GENERAL CLASSIFICATION FOR SUPPLY

   POM
   \[\text{CD}\]

15. INSTRUCTION ON USE

   \textit{To be completed nationally}

16. INFORMATION IN BRAILLE

   Methadone #1mg/ml Oral Solution
BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT
Methadone 1mg/ml Oral Solution
Methadone hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each 1 ml contains 1mg of Methadone hydrochloride.

3. LIST OF EXCIPIENTS
It also contains: Sucrose, tartrazine (E102) and sunset yellow (E110) and sodium benzoate. See enclosed leaflet for full list of ingredients.

4. PHARMACEUTICAL FORM AND CONTENTS
Oral Solution
500ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION
For Oral use
Read the package leaflet before use.

Dosage: Use as directed by your doctor
Administration: Use the enclosed spoon to measure the dose.
6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

Not applicable

8. **EXPIRY DATE**

Do not use 4 weeks after first opening.

Date opened: __/__/____

Expiry date to be overprinted with the batch number as EXP: mm/yyyy

9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25°C. Store in the original container.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

*Not applicable*

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13. BATCH NUMBER

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14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTION ON USE

To be completed nationally

16. INFORMATION IN BRAILLE

Not applicable
Approved label text (PL 17507/0194):

**Carton text**

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Methadone 1mg/ml Oral Solution
   Methadone hydrochloride

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**
   
   Each 1 ml contains 1mg of Methadone hydrochloride.

3. **LIST OF EXCIPIENTS**
   
   It also contains: Sucrose, tartrazine (E102) and sunset yellow (E110) and sodium benzoate. See enclosed leaflet for full list of ingredients.

4. **PHARMACEUTICAL FORM AND CONTENTS**
   
   Oral Solution
   
   500ml

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   
   For Oral use
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   Dosage: Use as directed by your doctor
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   \[ \Delta \]
   CD

15. INSTRUCTION ON USE
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16. INFORMATION IN BRAILLE
   Methadone #1mg/ml Oral Solution
1. NAME OF THE MEDICINAL PRODUCT

Methadone 1mg/ml Oral Solution
Methadone hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml contains 1mg of Methadone hydrochloride.

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Oral Solution

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16. INFORMATION IN BRAILLE
Not applicable