Public Assessment Report

Decentralised Procedure

METHADONE 1MG/ML ORAL SOLUTION

UK/H/1201/001/DC
UK Licence No: PL 17507/0032

AUDEN MCKENZIE LIMITED
LAY SUMMARY

On 11th August 2009, the UK granted Auden McKenzie Limited a Marketing Authorisation (licence) for the medicine Methadone 1mg/ml Oral Solution.

Methadone 1mg/ml Oral Solution contains the active ingredient methadone hydrochloride, which belongs to a group of medicines called Narcotic Analgesics.

Methadone 1mg/ml Oral Solution is used to treat opioid drug addiction.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Methadone 1mg/ml Oral Solution outweigh the risks; hence a Marketing Authorisation has been granted.
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# Module 1

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<td><strong>Type of Application</strong></td>
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<td><strong>Strength</strong></td>
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| **MA Holder** | Auden McKenzie (Pharma Division) Ltd  
Unit 30 Stadium Business Centre, North End Road, Wembley, Middlesex, HA9 0AT |
| **Reference Member State (RMS)** | UK |
| **CMS** | Ireland |
| **Procedure Number** | UK/H/1201/001/DC |
| **End of Procedure** | Day 150 – 6th August 2009 |
Module 2

Summary of Product Characteristics

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 tranquilizers 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 andazole 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
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.

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 L-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 (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
Unit 30 Stadium Business Centre
North End Road
Wembley
Middlesex
HA9 0AT
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 17507/0032

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
11/08/2009

10 DATE OF REVISION OF THE TEXT
11/08/2009
Module 3

Product Information Leaflet

The Patient Information Leaflet (PIL) below is the leaflet agreed at the end of the decentralised procedure. The marketing authorisation holder has stated that it is not intending to market either product and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PIL and labelling for review to the regulatory authority before marketing either product.

Methadone 1 mg/ml Oral Solution

Read all of this leaflet carefully before you start taking Methadone 1mg/ml Oral Solution (now called Methadone Oral Solution throughout the leaflet). 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.

**3. 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 as 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
- changes in your mood, feeling "high" or over excited
- seeing or hearing things that are not there (hallucinations)
- headache, rashes
- low body heat (hypothermia)
- lower sexual urge or desire
- painful periods or lack of periods.

You may notice that some of the side effects become less severe with time as you get used to the methadone.

When taken for a long period of time, it is possible that you may become dependent on methadone solution.

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.

**5. How to store Methadone Oral Solution**
• Keep out of the reach and sight of children
• Do not store above 25°C. Store in the original container. Discard after 4 weeks of first opening.
• Do not use Methadone Oral Solution after the expiry date which is stated on the bottle after Exp:. The expiry date refers to the last day of that month.
• Medicines should not be disposed via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

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.

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Date of approval of this leaflet:

For information in large print, tape, CD or Braille, telephone 020 8900 2122
Module 4
Labelling

The labelling below is the label agreed at the end of the decentralised procedure. The marketing authorisation holder has stated that it is not intending to market either product and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PIL and labelling for review to the regulatory authority before marketing either product.

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). 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

Anden Mckenzie (Pharma Division) Ltd
30 Stadium Business Centre
North End Road
Middlesex
HA9 0AT
UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 17507/0032
PA 1352/3/1

13. BATCH NUMBER

To be over printed

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTION ON USE

To be completed nationally

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)

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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
30 Stadium Business Centre
North End Road
Middlesex
HA9 0AT UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 17507/0032
PA 1352/3/1

13. BATCH NUMBER

To be over printed

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTION ON USE

To be completed nationally

16. INFORMATION IN BRAILLE

Not applicable
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Ireland and the UK considered that the application for Methadone 1mg/ml Oral Solution could be approved. This prescription only medicine (POM) is indicated for the treatment of opioid drug addictions (as a narcotic abstinence syndrome suppressant).

This application for Methadone 1mg/ml Oral Solution is submitted as an abridged standard application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product to Methadone Oral Solution DTF 1mg/ml, first authorised in the UK to Rosemont Pharmaceuticals Limited in December 1994.

The product contains the active substance methadone hydrochloride, which is a diphenylheptane derivative.

Methadone hydrochloride, an opioid analgesic, is primarily a μ opioid agonist. Single doses of methadone have a less marked sedative action than single doses of morphine. Methadone is a racemic mixture and levomethadone is the active isomer.

Methadone hydrochloride is readily absorbed from the gastrointestinal tract and from subcutaneous or intramuscular injections. It is widely distributed in the tissues, diffuses across the placenta, and is distributed into breast milk. It is extensively protein bound. Methadone is metabolised in the liver, mainly by N-demethylation and cyclisation, and the metabolites are excreted in the bile and urine.

No new preclinical studies were conducted, which is acceptable given that the product contains a widely-used, well-known active substance. No clinical studies have been performed and none are required for this application as the pharmacology of methadone hydrochloride is well-established. No clinical pharmacology data is required for this generic oral solution.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Methadone 1mg/ml Oral Solution</th>
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</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Methadone hydrochloride</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Nervous system, other nervous system drugs, drugs used in addictive disorders, methadone (N07BC02)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>1mg/ml Solution</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/1201/001/DC</td>
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<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Ireland</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 17507/0032</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Auden McKenzie (Pharma Division) Ltd Unit 30 Stadium Business Centre, North End Road, Wembley, Middlesex, HA9 0AT</td>
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</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

Name: Methadone hydrochloride
INN/Ph.Eur name: Methadone hydrochloride
Chemical name: (RS)-6-(Dimethylamino)-4,4-diphenylheptan-3-one

Structural formula:

Molecular formula: C\textsubscript{21}H\textsubscript{27}NO

Appearance: A white powder.
Solubility: It is soluble in water.
Molecular weight: 309.4

Methadone hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture of the active substance methadone hydrochloride from its starting materials are controlled by a Certificate of Suitability.

An appropriate retest period has been proposed based on stability data submitted for the active substance methadone hydrochloride.

An appropriate specification is provided for the active substance, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specification.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients tartrazine (E102), sunset yellow (E110), green S (E142), sucrose, hydrochloric acid (E507), sodium benzoate (E211), glycerol (E422) and purified water.
All excipients comply with their European Pharmacopoeia monograph, with the exception of sunset yellow (E110), green S (E142) and tartrazine, which comply with in-house specifications.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical Development**
The objective of the development programme was to produce a product that could be considered a generic medicinal product of Methadone Oral Solution DTF 1mg/ml (Rosemont Pharmaceuticals Limited, December 1994).

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished product versus the reference product Methadone Oral Solution DTF 1mg/ml (Rosemont Pharmaceuticals Limited).

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with three pilot-scale batches and has shown satisfactory results. The applicant has committed to perform process validation with the first three commercial-scale batches of the drug product.

**Finished Product Specification**
The finished product specification proposed for the product is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working reference standards used.

**Container-Closure System**
The product is packaged in bottles composed of type III amber glass and sealed with a 28mm high density polypropylene child-resistant and tamper-evident cap with a polyethylene lining. The product comes with a 5ml and 2.5ml double ended polypropylene spoon.

The product is packaged in 500ml bottles.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the European Pharmacopoeia Type I and relevant regulations regarding use of materials in contact with food.

**Stability of the product**
Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of two years for an unopened product with storage conditions “Do not store above 25°C” and “Store in original container”.

Once the product has been opened, the product should be used within 4 weeks.
Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labelling are pharmaceutically acceptable.

User testing results have been submitted for a typical PIL for this product. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA form
The MAA form is pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of a marketing authorisation is recommended.

III.2 PRE-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of methadone hydrochloride are well-known. As methadone hydrochloride is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required.

The pre-clinical expert report is based on literature sources and has been written by an appropriately qualified person.
III.3 CLINICAL ASPECTS

1. Introduction
This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

2. Clinical study reports
No bioequivalence studies have been performed and none are required for this application, as per the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, if the test product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived, if the excipients contained in it do not affect gastrointestinal transit, absorption, solubility or in-vivo stability of the active substance.

3. Post marketing experience
Methadone hydrochloride has a well-recognised efficacy and an acceptable level of safety in the indications approved for Methadone Oral Solution DTF 1mg/ml, and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the marketing authorisation is supported.

4. Benefit-Risk assessment
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s product and the innovator product are interchangeable. Extensive clinical experience with methadone hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

5. Conclusions
The grant of a marketing authorisation for Methadone 1mg/ml Oral Solution is recommended from a clinical viewpoint.
IV  OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Methadone 1mg/ml Oral Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

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

CLINICAL
No bioequivalence studies have been performed and none are required for this application, given the composition of the product and its intended route of administration.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with methadone hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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