SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Methadone 1mg/ml Oral Solution BP-Sugar Free

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Methadone Hydrochloride 1mg/ml.

Excipient(s) with known effect
Benzoic Acid Solution (contains benzoic acid and propylene glycol)
Sorbitol
Sunset Yellow (E110)

For excipients, see 6.1

3. PHARMACEUTICAL FORM

An oral solution, which is a green coloured free flowing mobile liquid.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For the treatment of dependence on opioid drugs.

4.2 Posology and method of administration

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with methadone in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4). The decision to maintain a patient on a long-term opioid prescription should be an active decision agreed between the clinician and patient with review at regular intervals (usually at least three-monthly, depending on clinical progress). In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Posology
Adults:

10 – 20mg (10 – 20ml) should be taken as an initial daily dose by oral administration. The dose should be increased cautiously by 10 – 20mg daily until no signs of withdrawal or intoxication occur. The usual dose for maintenance is 40 – 60mg daily. The dose can then be gradually decreased, when appropriate, until total withdrawal is achieved.

Elderly:
Methadone 1mg/ml Oral Solution B.P. - Sugar Free, should be used cautiously in elderly patients.

Paediatric population:
Not suitable for use in children (see section 4.3).

Method of administration
For oral administration only

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Respiratory depression, obstructive airways disease and during an acute asthma attack,
- Patients dependent on non-opioid drugs,
- Concurrent administration with monoamine oxidase inhibitors (including moclobemide) or within 2 weeks of discontinuation of them.
- Head injury and raised intracranial pressure (further rise in intracranial pressure – papillary response affected; see section 4.8).
- Where there is a risk of paralytic ileus.
- Acute alcoholism (see section 4.5).
- Use during labour (prolonged duration of action increases the risk of neonatal depression).
- Methadone is not suitable for children (serious risk of toxicity).

4.4 Special warnings and precautions for use

In the case of elderly or ill patients, repeated doses should only be given with extreme caution. Methadone is a drug of addiction and is controlled under the Misuse of Drugs Act 1971 (Schedule 2).

Tolerance and dependence of the morphine type may occur. Methadone should be given with caution to patients with a history of asthma (see section 4.3), convulsive disorders, depressed respiratory reserve, hypotension, shock, prostatic hyperplasia, adrenocortical insufficiency, inflammatory or obstructive bowel disorders, myasthenia gravis or hypothyroidism. In cases of hepatic or renal impairment the use of methadone should be avoided or given in reduced doses.

Methadone 1mg/ml Oral Solution B.P. - Sugar Free, contains benzoic acid and dyes. Benzoic acid is a mild irritant to the skin, eyes and mucous membrane. It may increase the risk of jaundice in newborn babies.

E110 can cause allergic-type reactions including asthma. Allergy is more common in those people who are allergic to aspirin.

When taken according to the dosage recommendations each 5ml dose supplies up to 1.4g of sorbitol. Unsuitable in hereditary fructose intolerance. Can cause stomach upset and diarrhoea.

This product contains 0.19% v/v of ethanol. Harmful for those suffering from liver disease, alcoholism, epilepsy, brain injury or disease as well as for pregnant women and children. May modify the effect of other medicines.

Cases of QT interval prolongation and torsade de pointes have been reported during treatment with methadone, particularly at high doses (>100mg/d). Methadone should be administered with caution to patients at risk of 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 treatments with drugs that have a potential for QT-prolongation,
- concomitant treatment with drugs which may cause electrolyte abnormalities,
- concomitant treatment with cytochrome P450 CYP 3A4 inhibitors (see section 4.5).

In patients with recognised risk factors of 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.

<u>Opioid Use Disorder (abuse and dependence)</u>
Methadone is an opioid analgesic and is highly addictive in its own right. It has a long half-life and can therefore accumulate. A single dose which will relieve symptoms may, if repeated on a daily basis, lead to accumulation and possible death.

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

Abuse or intentional misuse of Methadone 1mg/ml Oral Solution B.P. - Sugar Free may result in overdose and/or death.

The risk of developing Opioid Use Disorder is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g., major depression, anxiety and personality disorders).

Patients will require monitoring for signs of drug-seeking behaviour (e.g., too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

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

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:

Concomitant use of methadone and sedative drugs such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe methadone concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

Drug dependence, tolerance and potential for abuse

Prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression). Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else. Patients should be closely monitored for signs of misuse, abuse, or addiction. The clinical need for continuing opioid substitution therapy should be reviewed regularly.

Drug withdrawal syndrome
Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with methadone. The decision to maintain a patient on a long-term opioid prescription should be an active decision agreed between the clinician and

patient with review at regular intervals (usually at least three-monthly, depending on clinical progress).

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations.

Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy, there is a risk that their new-born infants will experience neonatal withdrawal syndrome.

Hepatobiliary disorders
Methadone may cause dysfunction and spasm of the sphincter of Oddi, increasing the risk of biliary tract symptoms and pancreatitis. Therefore, methadone has to be administered with caution in patients with pancreatitis and disease of the biliary tract.

Hyperalgesia
As with other opioids, in case of insufficient pain control in response to an increased dose of methadone, the possibility of opioid-induced hyperalgesia should be considered. A dose reduction or treatment review may indicated.

Adrenal insufficiency
Opioid analgesics may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of adrenal insufficiency may include nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.

Decreased Sex Hormones and increased prolactin

Long-term use of opioid analgesics may be associated with decreased sex hormone levels and increased prolactin. Symptoms include decreased libido, impotence or amenorrhea.

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

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

There are reports of neonates exposed to methadone during pregnancy developing visual disorders, including reduced visual acuity, strabismus and nystagmus. The causal relationship to methadone in isolation has not been established as factors such as other drugs taken during pregnancy e.g. benzodiazepines, intake of alcohol, and drugs used to treat neonatal abstinence syndrome e.g. phenobarbital, could play a role in the adverse reactions seen. However, there is sufficient evidence to suggest that an association is possible and therefore consideration of this risk should be taken during prescribing decisions.

Ingredient information

This medicine contains the following ingredients which have a known pharmacological effect:

- Benzoic Acid (~0.10% w/v). Benzoic acid may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).
- Propylene Glycol (<1mg/kg/day)
- Sorbitol (2.8g/10ml dose) which is a source of fructose and may cause gastrointestinal discomfort and a mild laxative effect. The additive effect of concomitantly administered products containing sorbitol (or fructose) should be taken into account. The content of sorbitol in this medicine may affect the bioavailability of other medicinal products for oral use administered concomitantly. Patients with hereditary fructose intolerance (HFI) should not take / be given this medicinal product
- Sunset Yellow (E110) which may cause allergic reactions

This medicine contains less than 1mmol (23mg) sodium per 10ml dose therefore can be considered to be essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

Interactions potentiating the effects of methadone;

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, ciprofloxacin and azole antifungal agents (since the metabolism of methadone is mediated by the CYP3A4 isoenzyme).

Cimetidine and phenytoin – may lead to potentiation of opioid activity due to displacement of methadone from protein binding sites. However, as phenytoin is also a hepatic enzyme inducer, it may lower plasma methadone levels (see below).

Fluvoxamine may increase plasma concentrations of methadone.

The depressant effects of methadone are likely to be enhanced by depressants of the CNS, such as other opioid analgesics, alcohol (see below), anaesthetics, antipsychotics, anxiolytics, hypnotics and sedatives, major and minor tranquilisers and phenothiazines. As well as CNS depression, there may be respiratory depression and/or hypotension. Tricyclic antidepressants may exert a similar effect.
Alcohol may enhance the sedative and hypotensive effects of methadone and increase respiratory depression. As a result, caution is advised and acute alcoholism is contraindicated during treatment (see section 4.3).

Sedative medicines such as benzodiazepines or related drugs: The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of CNS depressant effects. The dose and duration of concomitant use should be limited (see section 4.4).

Interactions reducing the effects of methadone;

The opioid antagonists, naloxone and naltrexone, will precipitate an acute withdrawal syndrome in methadone-dependent individuals. Naloxone will also antagonise the analgesic, CNS and respiratory depressant effects of methadone.

Buprenorphine and pentazocine may also rapidly precipitate withdrawal symptoms in patients addicted to methadone.
The hepatic enzyme-inducing drugs, nevirapine, rifampicin (and other rifamycins), phenytoin, phenobarbital and carbamazepine may lower plasma methadone levels and produce symptoms of withdrawal in methadone dependent patients. Similar effects have been reported with efavirenz nelfinavir, ritonavir and possibly abacavir.

Urinary acidifiers: Acidification of the urine will increase the rate of elimination of methadone by the kidney thereby reducing plasma concentrations.

Co-administration of methadone with metamizole, which is an inducer of metabolising enzymes including CYP2B6 and CYP3A4 may cause a reduction in plasma concentrations of methadone with potential decrease in clinical efficacy. Therefore, caution is advised when metamizole and methadone are administered concurrently; clinical response and/or drug levels should be monitored as appropriate.

Effects of methadone on other drugs;

Methadone may increase plasma desipramine levels and increase desipramine side-effects when given concurrently.
Zidovudine – methadone may increase the plasma concentrations of zidovudine.
Mexiletine – methadone may delay mexiletine absorption.

Metoclopramide and domperidone – the gastrointestinal effects may be antagonised by methadone.
Methadone treatment has been found to decrease the rate of absorption and decrease the bioavailability of the nucleoside reverse transcriptase inhibitors didanosine and to a lesser extent stavudine.
Other serotonergic drugs: Methadone is a weak serotonin uptake inhibitor. There is an increased risk of serotonin syndrome when methadone is co-administered with other serotonergic drugs (e.g. SSRIs, SNRIs, TCAs, MAOIs, serotonergic anti-emetics, serotonergic anti-migraine drugs, St. John's Wort). This is not an exhaustive list.

Other important interactions;

In patients taking drugs affecting cardiac conduction, which may affect electrolyte balance or may affect QT prolongation (e.g. centrally acting alpha-adrenergic blockers such as lofexidine and clonidine), there is an increased risk of hypotension, cognitive effects and cardiac events (including ECG changes) when methadone is taken concurrently – see section 4.4.

As serious and sometimes fatal reactions have occurred following administration of pethidine to patients receiving MAOIs, other drugs related to pethidine are contraindicated in patients taking MAOI's (including moclobemide) or within 14 days of stopping such treatment, (see section 4.3) as there is a risk of CNS excitation or depression.

Cross tolerance and cross dependence can be expected between other opioids acting at the same receptors.

Serotonergic drugs:
Serotonergic syndrome may occur with concomitant administration of methadone with pethidine, monoamine oxidase (MAO) inhibitors and serotonin agents such as Selective Serotonin Re-uptake Inhibitor (SSRI), Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) and tricyclic antidepressants (TCAs). The symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

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

Hypoglycaemia
Hypoglycaemia has been observed in the context of methadone overdose or dose escalation. Regular monitoring of blood sugar is recommended during dose escalation (see section 4.8 and section 4.9).

Fluconazole may raise methadone levels due to decreased methadone metabolism.

4.6 Fertility, pregnancy and lactation

Pregnancy:
Some observational studies have reported congenital malformations and neurodevelopmental impairment in children born to women treated with methadone for opioid use disorder during pregnancy. However, due to study limitations and confounding by maternal, familial and socioenvironmental factors associated with opioid use disorders no conclusions can be drawn regarding the contribution of methadone.

Methadone should only be used in pregnancy if the physician considers that the potential benefits outweigh the risks. It should be used cautiously under the close supervision of a physician if the physician considers it essential to continue or initiate (in the case of an i.v. opioid user) methadone maintenance. It may be necessary to increase the dose of methadone if withdrawal symptoms develop as increased clearance and reduced plasma levels have been reported during pregnancy.

Infants of methadone-maintained mothers may experience symptoms of withdrawal *in utero* and following birth.

Reports of visual disorders have been reported in neonates and children following exposure to methadone during pregnancy. Although other factors have also been present, there is sufficient evidence to suggest that an association is possible (see section 4.4).

Methadone should not be used during labour as the prolonged duration of action increases the risk of neonatal depression.

Breast-feeding:
Methadone is excreted in breast milk at low levels. The decision to recommend breast-feeding should take into account clinical specialist advice and consideration should be given to whether the woman is on a stable maintenance dose of methadone and any continued use of illicit substances. If breastfeeding is considered, the dose of methadone should be as low as possible. Prescribers should advise breastfeeding women to monitor the infant for sedation and breathing difficulties and to seek immediate medical care if this occurs. Although the amount of methadone excreted in breast milk is not sufficient to fully suppress withdrawal symptoms in breast-fed infants, it may attenuate the severity of neonatal abstinence syndrome. If it is necessary to discontinue breastfeeding it should be done gradually, as abrupt weaning could increase withdrawal symptoms in the infant.

4.7 Effects on ability to drive and use machines

Methadone may produce drowsiness and patients should be advised not to drive or operate machinery if affected. Once affected, the time after which such activities may be resumed is extremely variable between patients and should be decided by the physician.
This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in

regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called "statutory defence") if:
  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
  - It was not affecting your ability to drive safely

4.8 Undesirable effects

Tabulated list of adverse reactions

Adverse reactions frequency are defined using the following convention:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

System organ class (MedDRA)	**Frequency**	**Adverse event**
Blood and lymphatic system disorders	Not known	Lymphocytosis
Endocrine disorders	Not known	Adrenal insufficiency, increased prolactin concentrations, decreased testosterone concentrations, hypogonadism, hypoglycaemia
Metabolism and nutrition disorders	Not known	Hypoglycaemia
Psychiatric disorders	Not known	Drug dependence (see section 4.4), hallucinations, confusion, mood changes including dysphoria, decreased libido
Nervous system disorders	Not known	Methadone may increase intra-cranial pressure, particularly when it is already raised. Dizziness, headache, drowsiness
Eye disorders	Not known	Miosis, nystagmus[1], strabismus[1], visual acuity reduced[1]

Ear and labyrinth disorders	Not known	Vertigo
Cardiac disorders	Not known	Cases of QT prolongation and torsade de pointes have been rarely reported. Bradycardia, palpitations, tachycardia
Vascular disorders	Not known	Hypotension, facial flushing
Respiratory, thoracic and mediastinal disorders	Not known	Respiratory depression, Exacerbation of existing asthma, central sleep apnoea syndrome
Gastrointestinal disorders	Not known	Nausea, vomiting, constipation, dry mouth, acute pancreatitis
Hepatobiliary disorders	Not known	Biliary spasm, sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorders	Not known	Rashes, pruritus, urticaria, excessive sweating
Renal and urinary disorders	Not known	Difficulty in micturation, ureteric spasm, antidiuretic effect
Reproductive system and breast disorders	Not known	Erectile dysfunction, reductions in the ejaculate volume and seminal vesicular and prostatic secretions
General disorders and administration site conditions	Unknown	Drug withdrawal syndrome. In prolonged use it should not be administered more than twice daily to avoid the risk of accumulation and overdosage.
	Not known	Hypothermia.
Investigations	Not known	Globulins increased, blood albumin increased

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at:

www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' in the Google Play or Apple App Store.

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Symptoms
Overdose of methadone is characterised by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), pulmonary oedema, extreme somnolence, progressing to stupor or coma, maximally constricted pupils, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. Hypoglycaemia has been reported. The presence and signs of drug abuse supports the diagnosis.

In children, methadone overdose produces drowsiness, floppiness, constricted pupils and apnoea.

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

Toxic leukoencephalopathy has been observed with methadone overdose.

Emergency procedures
If ingestion is recent, gastric aspiration and lavage can be employed after acute poisoning.

Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Narcotic antagonists can be used to counteract the potentially lethal respiratory depression in a non-tolerant individual, especially a child. Methadone is, however, a long-acting depressant (36-48 hours) whereas the antagonists act for much shorter periods (1-3 hours). The patient must, therefore, be monitored continuously for recurrence of respiratory depression and treated repeatedly with the narcotic antagonist as needed. If the respiratory depression is only due to overdosage with methadone, the use of other respiratory stimulants is not indicated.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Intravenously administered narcotic antagonists (naloxone, nalorphine or levallorphan) can be used to reverse signs of intoxication and should be given repeatedly until the patient's status remains satisfactory.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

In an individual physically dependent on narcotics, the administration of the usual dose of a narcotic antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of the antagonist administered. The use of a narcotic antagonist in such a person should be avoided if possible. If it must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.

Patients should be monitored for signs of relapse for at least 48 hours.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in opioid dependence
ATC code: N07BC02

Methadone is an 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 κ and σ 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 automotor nerve, and perhaps on opioid receptors in the pupillary muscles causes pupillary constriction. All these effects are reversible by naloxone with a 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

Its long duration of action enables it to be used daily on a supervised basis in opioid dependent individuals.

5.2 Pharmacokinetic properties

Absorption
Methadone is well absorbed from the gastrointestinal tract with peak plasma levels occurring 1-5 hours after a single dose. Wide variations in plasma levels occur during maintenance therapy. Plasma levels may decrease on long term maintenance suggesting tolerance to develop possibly as a result of auto-induction of hepatic microsomal enzymes.

Distribution

Methadone is widely distributed in the tissues. It diffuses across the placenta and is excreted in breast milk. Plasma protein binding is 60-90%. After repeated administration, there is a gradual accumulation in the tissues and on discontinuation low concentrations in the plasma are maintained by slow release from extravascular binding sites accounting for the relatively mild but protracted withdrawal syndrome.

Biotransformation / Elimination

N-demethylation to the inactive major metabolite 2-ethylidine-1, 5-dimethyl-3, 3-diphenylpyrrolidine and other pyrrolidines and pyrroline occurs in the liver. These metabolites are excreted in the faeces and urine together with unchanged methadone. Urinary excretion is increased with an acidic urine. The elimination half-life is long and varies considerably with a range of 15-60 hours having been reported. Decreased excretion of methadone and its metabolites occur in liver dysfunction and urinary elimination is reduced in renal failure.

In methadone-maintained pregnant women, trough plasma levels have been found to be significantly lower and total or unbound methadone clearance greater during pregnancy than after delivery.

5.3. Preclinical Safety Data

No data of relevance, which is additional to that already, included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzoic Acid Solution (contains benzoic acid and propylene glycol)
Green S Dye (E142)
Sorbitol Solution (70% non-crystallising)
Saccharin Sodium
Quinoline Yellow (E104)
Yellow Dye Sunset (E110)
Purified Water

6.2. Incompatibilities

None reported.

6.3 Shelf life

3 years unopened.
Use within 56 days of first opening.

6.4. Special Precautions for Storage

Do not store above 25^{o}C.

Keep this medicine out of the sight and reach of children. Store this medicine in a safe and secure storage space, where other people cannot access it. It can cause serious harm and even be fatal to people when it has not been prescribed for them.

6.5 Nature and contents of container

500ml: Round high density polythene bottle with 28mm tamper evident cap with polyethylene laminate wad.
1Lt, 2Lt and 5Lt HDPE bottle with 38mm polypropylene, tamper evident cap with polyethylene laminate wad.

6.6. Instruction for Use/Handling

None.

7. MARKETING AUTHORISATION HOLDER

Thornton & Ross Ltd
Linthwaite
Huddersfield
HD7 5QH
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00240/0044

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/03/2009

10 DATE OF REVISION OF THE TEXT

18/05/2026