Professional Information for LOMETASAN 1 mg/mL

SCHEDULING STATUS

S6

1. NAME OF THE MEDICINE

LOMETASAN 1 mg/mL oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL contains 1 mg methadone hydrochloride.

Excipients with known effect:

Contains sweetener (0,4 mL maltitol liquid per 1 mL).

Sodium benzoate 0,1 % *m/v* as preservative.

Sunset Yellow (E110) 0,008 mg/mL.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

A green coloured solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Substitution treatment in opiate dependence in conjunction with medical, psychological and social therapy.

4.2 Posology and method of administration

Posology

Treatment with LOMETASAN assumes that the patient is taking part in a programme including medicine-assisted rehabilitation for narcotics abuse, approved by a relevant authority.
For oral administration only. The dose must be tailored for each individual patient.

Adults: The standard initial dose is 20 mg once daily.

The dose is increased in steps of 10 mg at a time over a period of three weeks, usually to 70 or 80 mg. After a recommended stabilisation period of four weeks, the dose is adjusted until the patient feels well, does not feel a need for intoxication and is without clinical signs of psychomotor function effects or abstinence symptoms. The normal dose is 60 to 120 mg of methadone per 24 hours, but some individuals may require higher doses.

The dosage must be determined based on a clinical evaluation, supported by serum level monitoring. The recommended serum level is 600 to 1 200 nmol/L (200 to 400 ng/mL). Great importance is attached to the clinical assessment.

LOMETASAN is usually administered once daily. More frequent administration carries a risk of accumulation and overdose.

Certain patients develop auto-induction, which leads to the medicine being metabolised more rapidly in the body. In such cases, the dose must be adjusted upwards once or more to maintain the optimum effect.

Treatment withdrawal

Treatment must be stopped if it is insufficiently effective or if the patient cannot tolerate it. The effect

must be evaluated in accordance with national guidelines.

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

Special populations

Elderly:

Caution must be exercised when LOMETASAN is administered to elderly or ill patients.

Patients with renal or hepatic impairment:

Dose adjustment may be necessary in cases of impaired hepatic function (see section 4.4).

Patients with hypothyroidism or prostatic hypertrophy:

Dose adjustment may be necessary in cases of impaired hepatic function (see section 4.4). Patients with hypothyroidism or prostatic hypertrophy must receive a lower initial dose.

Paediatric population

LOMETASAN must not be administered to children.

Method of administration

For oral administration only.

LOMETASAN may only be used under medical supervision.

4.3 Contraindications

- Hypersensitivity to methadone hydrochloride or to any of the excipients (see section 6.1).
- Respiratory depression.
- Obstructive airways disease.

- Acute asthma attack.
- Acute alcoholism (see section 4.5).
- Head injury and raised intracranial pressure (further rise in intracranial pressure [see section 4.8] papillary response affected).
- Where there is a risk of paralytic ileus (including medicine induced gastrointestinal hypotonia).
- Concomitant administration of monoamine oxidase (MAO) inhibitors or administration within two weeks after finished MAO inhibitor treatment (see section 4.5).
- Use during labour (prolonged duration of action increases the risk of neonatal depression).
- Children (serious risk of toxicity).
- Patients dependent on non-opioid medicines.
- Phaeochromocytoma.

4.4 Special warnings and precautions for use

Drug dependence, tolerance and potential for abuse

Prolonged use of LOMETASAN may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g. major depression). Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse. A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

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 LOMETASAN 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.

Tolerance and dependence of the morphine type may occur, though it is said that methadone, as in LOMETASAN, has a greater respiratory depressive effect and a lesser sedative effect than an equianalgesic dose of morphine. Toxic doses are highly variable, regular usage giving tolerance. Pulmonary oedema is a frequent corollary of overdosage whilst the dose-related histamine-releasing property of LOMETASAN may account for at least some of the urticaria and pruritus associated with methadone administration. LOMETASAN may lead to an increase in intracranial pressure.

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. 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. Tapering from a high dose may take weeks to months.

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 LOMETASAN during pregnancy, there is a risk that their new-born infants will experience neonatal withdrawal syndrome.

The withdrawal period is longer for LOMETASAN than for heroin because methadone has a longer half-life.

Respiratory depression

LOMETASAN should be used with caution in patients with asthma, obstructive pulmonary disease, depressed respiratory reserve or hypotension, hypothyroidism or cor pulmonale and in patients with lessened respiratory reserve, hypoxia or hypercapnia.

Due to the slow accumulation of methadone in the tissues, respiratory depression may not be fully apparent for a week or two. Asthma may be exacerbated due to histamine release. Concomitant treatment with other medicines with central nervous system (CNS) depressant activity is not advised due to the potential for CNS and respiratory depression (see also section 4.5).

Risk from concomitant use of sedative medicines, such as benzodiazepines or related medicines:
Concomitant use of LOMETASAN and sedative medicines such as benzodiazepines or related medicines 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 LOMETASAN 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 to be aware of these symptoms (see section 4.5).

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).

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.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

Other warnings

LOMETASAN should be given with caution to patients with convulsive disorders, hypotension, hypothyroidism, prostatic hypertrophy, possible head injury, conditions involving increased intracranial pressure and inflammatory or obstructive bowel disorders. In cases of hepatic or renal impairment the use of methadone should be avoided or given in reduced doses. Caution is advised in elderly patients and patients suffering from cardiovascular diseases. They are at increased risk of hypotension and syncope.

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

QT prolongation and torsades de pointes have been reported during treatment with methadone, as

in LOMETASAN, particularly at high doses (> 100 mg/day). LOMETASAN should be administered with caution to patients at risk for the development of prolonged QT interval, e.g. in case of:

- history of cardiac conduction abnormalities,
- advanced heart disease or ischaemic heart disease, known history of QT prolongation,
- hepatic disease,
- family history of sudden death,
- electrolyte abnormalities, i.e. hypokalaemia, hypomagnesaemia,
- concomitant treatment with medicines that have a potential for QT-prolongation,
- concomitant treatment with medicines which may cause electrolyte abnormalities,
- concomitant treatment with cytochrome P450 CYP3A4 inhibitors (see section 4.5).

In patients with recognised risk factors for QT-prolongation, or in case of concomitant treatment with medicines that have a potential for QT-prolongation, electrocardiogram (ECG) monitoring is recommended prior to LOMETASAN 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/day and at seven days after titration.

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

The precautions to be taken in the use of LOMETASAN are the same as those applying to opiates in general.

LOMETASAN contains sweetener

LOMETASAN contains maltitol liquid. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

LOMETASAN contains preservative

LOMETASAN contains sodium benzoate (E211). This medicine contains 1 mg sodium benzoate in each mL.

LOMETASAN contains colourant

LOMETASAN contains Sunset Yellow FCF (E110) which may cause allergic reactions.

Paediatric population

Children are more sensitive than adults and intoxication may follow a low dose intake of methadone. To avoid such intoxication following dose administration by mistake, LOMETASAN should be kept in a safe place out of reach by children when located at home.

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase (MAO) inhibitors

The concurrent use of MAO inhibitors is contraindicated as they may prolong and enhance the respiratory depressant effects of LOMETASAN, as well as serious hypotonia. LOMETASAN should not be combined with MAO inhibitors and for two weeks after treatment (see section 4.3).

CNS depressants

Anaesthetics, hypnotics (including benzodiazepines, chloral hydrate and chlormethiazole), anxiolytics, sedatives, barbiturates, phenothiazines, some other major tranquillizers and tricyclic antidepressants may increase the general depressant effects of methadone when used concomitantly (see section 4.4). This may result in increased respiratory depression, hypotension,

strong sedation or coma, therefore it may be necessary to reduce the dose of one or both of the medicines. With LOMETASAN treatment, the slowly eliminated substance methadone, give rise to a slow tolerance development and every dose increase may after 1 – 2 weeks give rise to symptoms of respiratory depression. The dose adjustments must therefore be made with caution and the dose increased gradually with careful observation. Antipsychotics may enhance the sedative effects and hypotensive effects of LOMETASAN.

LOMETASAN may increase desipramine levels by up to a factor of two. There are reports that antidepressant medicines (e.g. fluvoxamine and fluoxetine) may increase serum levels of methadone. Alcohol may enhance the sedative and hypotensive effects of methadone and increase respiratory depression.

Histamine H_2 antagonists

Histamine H_2 antagonists such as cimetidine, can reduce the protein binding of methadone resulting in increased opiate action.

Antibacterial medicines

Rifampicin: Reduced plasma levels and increased urinary excretion of methadone can occur with concurrent administration of rifampicin. Adjustment of the dose of LOMETASAN may be necessary.
Ciprofloxacin: Plasma levels of methadone may increase with concurrent administration of ciprofloxacin due to inhibition of CYP1A2 and CYP3A4. Reduced serum concentrations of ciprofloxacin may occur. Concomitant use may lead to sedation, confusion and respiratory depression.
Erythromycin: Theoretically this may increase methadone levels due to decreased methadone metabolism.
Antifungals: Fluconazole, voriconazole and ketoconazole: May raise methadone levels, due to decreased methadone metabolism.

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 LOMETASAN should be considered.

pH of urine

Medicines that acidify or alkalinise the urine may influence the clearance of methadone as it is increased at acidic pH and decreased at alkaline pH. Patients that are treated with LOMETASAN are recommended to avoid products containing ammonium chloride.

Opioid agonist analgesics

Additive CNS depression, respiratory depression and hypotension may occur.

Opioid antagonists

Naloxone and naltrexone antagonise the analgesic, CNS and respiratory depressant effects of methadone and can rapidly precipitate withdrawal symptoms (see section 4.9). Similarly, buprenorphine and pentazocine may precipitate withdrawal symptoms.

Antiretroviral medicines such as nevirapine, efavirenz, nelfinavir, ritonavir, abacavir, amprenavir

Based on the known metabolism of methadone, these medicines may decrease plasma concentrations of methadone by increasing its hepatic metabolism.

Zidovudine: Methadone may increase the plasma concentration of zidovudine. This is more noticeable after oral than after intravenous use of zidovudine. These observations are likely caused by inhibition of zidovudine glucuronidation, and therefore decreased clearance of zidovudine. During treatment with LOMETASAN, patients must be carefully monitored for signs of toxicity caused by zidovudine, why it may be necessary to reduce the dose of zidovudine. Because of mutual

interactions between zidovudine and LOMETASAN (zidovudine is a CYP3A4 inducer), typical opioid abstinence symptoms may develop during concomitant use (headache, myalgia, fatigue and irritability).

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

Narcotic withdrawal syndrome has been reported in patients treated with some retroviral medicines and LOMETASAN concomitantly. Methadone maintained patients beginning antiretroviral therapy should be monitored for evidence of withdrawal and the dose of LOMETASAN should be adjusted accordingly.

Cyclizine and other sedating antihistamines

May have additive psychoactive effects; antimuscarinic effects at high doses.

Other medicines

LOMETASAN may influence other medicines as a consequence of reduced gastrointestinal motility.

Pregnancy tests

LOMETASAN may interfere with the urine testing for pregnancy.

Cytochrome P450 3A4 inhibitors

Methadone is a substrate of CYP3A4 (see section 5.2). Methadone clearance is decreased when co-administered with medicines which inhibit CYP3A4 activity, such as cannabinoids, some human immunodeficiency virus (HIV) medicines (e.g. delavirdine), macrolide antibiotics (e.g. clarithromycin, erythromycin), cimetidine, nefazodone, fluoxetine, fluvoxamine, telithromycin and azole antifungal

medicines (e.g. fluconazole, ketoconazole, itraconazole), since the metabolism of methadone is mediated by the CYP3A4 isoenzyme. A 40 – 100 % increase of the quote between the serum levels and the methadone dose has been shown with concomitant fluvoxamine treatment. If these medicines are prescribed to patients on LOMETASAN maintenance treatment, one should be aware of the risk of overdose.

Cytochrome P450 3A4 inducers

Methadone is a substrate of CYP3A4 (see section 5.2). By induction of CYP3A4, clearance of methadone will increase and the plasma levels of LOMETASAN decrease. Inducers of this enzyme (barbiturates, carbamazepine, phenytoin, nevirapine, rifampicin, efavirenz, amprenavir, spironolactone, dexamethasone, *Hypericum perforatum* (St John's wort), may induce hepatic metabolism.

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

Grapefruit juice

There are several reports of raised methadone levels due to decreased methadone metabolism.

Medicines affecting gastric emptying

Domperidone and metoclopramide may increase the speed of onset but not the extent of methadone absorption by reversing the delayed gastric emptying associated with opioids. Conversely, methadone may antagonise the effect of domperidone/metoclopramide on gastrointestinal activity.

Concomitant use of LOMETASAN and peristalsis inhibiting medicines (loperamide and diphenoxylate) may result in severe obstipation and increase the CNS depressant effects. Opioid

analgesics, in combination with antimuscarinics, may result in severe obstipation or paralytic ileus, especially in long-term use.

Antidysrhythmics

Methadone delays the absorption of mexiletine.

Methadone and QT interval prolongation

In patients taking medicines affecting cardiac conduction, or medicines which may affect electrolyte balance there is a risk of cardiac events when LOMETASAN is taken concurrently (see section 4.4).

Sedative medicines such as benzodiazepines or related medicines

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

Co-administration of LOMETASAN 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 LOMETASAN are administered concurrently; clinical response and/or medicine levels should be monitored as appropriate.

Serotonergic medicines

Serotonergic syndrome may occur with concomitant administration of LOMETASAN with pethidine, MAO inhibitors and serotonin medicines 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.

P-glycoprotein inhibitors

Methadone is a substrate of P-glycoprotein; all medicines that inhibit P-glycoprotein (e.g. quinidine, verapamil, ciclosporin), may therefore raise the serum concentration of methadone. The pharmacodynamic effect of LOMETASAN may also increase because of increased blood brain barrier passage.

Diagnostic/lab interactions

Gastric emptying studies

Opioid analgesics delay gastric emptying, thereby invalidating test results.

Hepatobiliary imaging using technetium Tc 99m disofenin

Delivery of technetium Tc 99m disofenin to the small bowel may be prevented because opioid analgesics may cause constriction of the sphincter of Oddi and increased biliary tract pressure; these actions result in delayed visualisation and thus resemble obstruction of the common bile duct.

Cerebrospinal fluid pressure

Cerebrospinal fluid pressure (CSF) may be increased; effect is secondary to respiratory depression – induced carbon dioxide retention.

Plasma amylase or lipase levels

Plasma amylase or lipase levels may be increased because LOMETASAN can cause contractions of the sphincter of Oddi and increased biliary tract pressure; the diagnostic utility of determination of these enzymes may be compromised for up to 24 hours after the medication has been given.

4.6 Fertility, pregnancy and lactation

Pregnancy

Neonatal abstinence syndrome, respiratory depression and low birth weight have been reported in neonates after methadone treatment during pregnancy, increasing the rate of stillbirths. Increased clearance and reduced plasma levels have been reported during pregnancy.

During labour there is a risk of gastric stasis and inhalation pneumonia in the mother and foetal distress. LOMETASAN should not be administered during pregnancy.

Breastfeeding

LOMETASAN is distributed into breast milk and should not be used during lactation.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

LOMETASAN may affect the psychomotor functions until the patient has been stabilised at a suitable level, so he/she should not drive or use machines until stabilisation has been achieved and there have been no symptoms of abuse for six months.

When driving and use of machines can be resumed is largely dependent on the individual patient and must be determined by a doctor.

4.8 Undesirable effects

The side effects of LOMETASAN treatment are generally the same as those in treatment with other opioids, most frequently nausea and vomiting.

The most serious side effect is respiratory depression, which may emerge during the stabilisation phase.

Blood and lymphatic system disorders

Frequency unknown: Reversible thrombocytopenia has been reported in opioid patients with chronic hepatitis.

Endocrine disorders

Less frequent: Hypothyroidism.

Frequency unknown: Hyperprolactinaemia.

Metabolism and nutrition disorders

Frequent: Fluid retention.

Less frequent: Anorexia.

Frequency unknown: Hypokalaemia, hypomagnesaemia.

Psychiatric disorders

Frequent: Euphoria, hallucinations.

Less frequent: Dysphoria, dependence, agitation, insomnia, disorientation.

Frequency unknown: Drug dependence (see section 4.4).

Nervous system disorders

Frequent: Sedation, headache, dizziness, confusional state, sleep disturbances.

Less frequent: Syncope.

Eye disorders

Frequent: Blurred vision, miosis, dry eyes.

Less frequent: Visual disturbances.

Frequency unknown: Nystagmus.

Ear and labyrinth disorders

Frequent: Vertigo.

Cardiac disorders

Less frequent: Bradycardia, palpitations, cases of prolonged QT-intervals and torsades de pointes have been reported (especially at high doses of methadone).

Vascular disorders

Less frequent: Facial flush, hypotension.

Respiratory, thoracic and mediastinal disorders

Less frequent: Pulmonary oedema, exacerbation of asthma, dry nose, respiratory depression (at high doses).

Frequency unknown: Central sleep apnoea syndrome.

Gastrointestinal disorders

Frequent: Nausea, vomiting, constipation.

Less frequent: Dry mouth, glossitis.

Hepatobiliary disorders

Less frequent: Bile duct dyskinesia.

Skin and subcutaneous tissue disorders

Frequent: Transient rash, sweating.

Less frequent: Pruritus, urticaria, other rash and less frequently bleeding urticaria.

Renal and urinary disorders

Less frequent: Urinary retention, antidiuretic effect.

Reproductive system and breast disorders

Frequent: Libido decreased.

Less frequent: Reduced potency, galactorrhoea, dysmenorrhoea and amenorrhoea.

General disorders and administration site conditions

Frequent: Fatigue, drowsiness.

Less frequent: Oedema of the lower extremities, asthenia, oedema, hypothermia, drug withdrawal syndrome.

Investigations

Frequent: Weight increase.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of LOMETASAN is important. It allows continued monitoring of the benefit/risk balance of LOMETASAN. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the
Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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

Serious overdose 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 overdose, particularly by the intravenous route, apnoea, circulatory collapse, cardiac arrest and death may occur. Hypoglycaemia has been reported.

Toxic leukoencephalopathy has been observed with methadone overdose.

Treatment

A patent airway and assisted or controlled ventilation must be assured. Narcotic antagonists may be required but it should be remembered that LOMETASAN 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. Observation and supportive measures must be continued for 36 – 48 hours.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 2.9 Other analgesics

Pharmacotherapeutic group: Nervous system, other nervous system drugs, drugs used in addictive disorders, methadone.

ATC code: N07BC02

5.1 Pharmacodynamic properties

Methadone is a narcotic analgesic that belongs to the same group as morphine. Methadone has an agonist effect on the opiate receptors in the brain, bone marrow and nervous system; high affinity with the μ-receptors and some affinity with the σ- and κ-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. Methadone operates in a similar way to morphine but has a less sedative effect. The use of methadone can reduce or eliminate the effect of other opiates.

5.2 Pharmacokinetic properties

Absorption

Methadone is one of the more lipid soluble opioids, is rapidly absorbed following oral administration and has high oral bioavailability. Methadone undergoes considerable first-pass metabolism.

Distribution

Methadone is widely distributed in the tissue with higher concentrations in the liver, lungs and kidneys than in the blood. It diffuses across the placenta and is distributed into breast milk. It is extensively protein bound (60 to 90 %), but with great individual differences. Methadone binds to albumin and other plasma and tissue proteins. 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.

Biotransformation

Methadone is metabolised in the liver, mainly by *N*-demethylation and cyclisation. Metabolism is primarily catalysed by CYP3A4, although other cytochrome P450 isoenzymes are also involved. Methadone is metabolised to the major metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and the minor metabolite 2-ethyl-5-methyl 3,3-diphenyl-1 pyrrolidine (EMDP), both inactive. Hydroxylation to methadol succeeded by *N*-demethylisation to normethadol also occurs to some degree.

Other metabolic reactions also occur and at least eight other metabolites are known.

Elimination

The elimination half-life varies considerably after single (10 to 25 hours) and repeated doses (13 to 55 hours). Plasma clearance is around 2 mL/min/kg. About 20 to 60 % of the dose is eliminated in urine over 24 hours (about 33 % in unmodified form; about 43 % as EDDP and about 5 to 10 % as EMDP).

The ratio between EDDP and unmodified methadone is usually much higher in urine in patients receiving methadone treatment than in normal overdoses. Elimination of unmodified methadone in urine is pH dependent and increases (by a factor of at least three) with greater urinary acidity. About 30 % of the dose is eliminated in faeces, but this percentage will normally be reduced at higher doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

D&C Yellow (E104)

Green S (E142)

Hydrochloric acid (pH adjuster)

Maltitol liquid

Purified water

Sodium benzoate (preservative)

Sunset Yellow FCF (E110).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from light.

6.5 Nature and contents of container

100 mL white rectangular HDPE bottle with a transparent window and a white PP screw cap with an induction wad.

500 mL white rectangular HDPE bottle with a transparent window and a white PP screw cap with an induction wad.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

LeBasi Pharmaceuticals (Pty) Ltd

San Domenico Building, Unit 6, Ground Floor

10 Church Street

Durbanville

7551

Tel. no.: 087 551 3245

8. REGISTRATION NUMBER

57/2.9/0847

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 June 2025

10. DATE OF REVISION OF THE TEXT

Not applicable