Professional Information for RuTrex

SCHEDULING STATUS

S6

1. NAME OF THE MEDICINE

RuTrex 10 mg/mL concentrate for oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL contains 10 mg methadone hydrochloride.

Excipients with known effect

Contains sugar (400 mg sucrose per 1 mL).

Propylene glycol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for oral solution.

A clear, red coloured liquid.

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

RuTrex 10 mg/ml concentrate for oral solution should be diluted by a health care provider before use. Please refer to section 6.6 for further instructions.

RuTrex should always be taken orally with or without food.

RuTrex must not be injected.

Dosage should be titrated to individual needs of patients.

Substitution treatment with methadone should be prescribed by a doctor with experience of treating opiate/opioid-dependent patients, preferably at centres that are specialised in the treatment of opiate/opioid dependency.

The dose is based on the occurrence of withdrawal symptoms and must be adjusted for each patient according to his or her individual situation and the way he or she feels. In general, after adjustment of the dose, the aim is to administer the lowest possible maintenance dose.

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

The dose is increased at 10 mg increments 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 the clinical evaluation, supported by serum level monitoring. The recommended serum level is 600 to 1200 nmol/L (200 to 400 ng/mL). Great importance is attached to the clinical assessment.

RuTrex 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.

The highest recommended dose, that rarely should be used, is 150 mg/day. The reason for this limitation is an increased frequency of QT-prolongation, Torsades de pointes and cases of cardiac arrest within higher dose ranges (see section 4.4).

If the patient has been treated with a combined agonist/antagonist (e.g. buprenorphine), the dose should be reduced gradually when the methadone treatment is initiated. If the methadone treatment is interrupted and a switch to sublingual buprenorphine treatment is planned (especially in combination with naloxone), the methadone dose should be reduced to 30 mg/day initially to avoid withdrawal symptoms caused by buprenorphine/naloxone.

Treatment discontinuation:

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.

Treatment discontinuation must always be done gradually by dose reduction in weekly steps of 5 – 10 mg over several weeks to months. 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).

During this period of gradual dose reduction, it is necessary to pay attention to any recurrence of withdrawal symptoms which would require a return to the previous dosage, and to any resumption of addictive behaviours.

Special populations

Elderly:

Caution must be exercised when treating elderly patients, as they may require a reduced dose (see section 4.4).

Patients with renal or hepatic impairment:

In patients with renal disorders or mild to moderate hepatic disorders it is advisable to reduce the dose (for more information see section 4.4 and also section 4.3).

Patients with hypothyroidism or prostatic hypertrophy:

Patients with hypothyroidism or prostatic hypertrophy must receive a lower initial dose (see section 4.4).

Paediatric population:

There are no data available on the use in patients under 18 years. Therefore, the use of RuTrex is not recommended for children and adolescents (see section 4.4).

Method of administration

For oral administration only.

RuTrex 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.
- Use during an acute asthma attack.
- Acute alcoholism.
- Concurrent administration with monoamine oxidase (MAO) inhibitors or within 2 weeks of discontinuation of treatment with them.
- Decreased level of consciousness or head injury.
- Individuals with QT prolongation, including congenital long QT syndrome.
- RuTrex should not be administered to patients with severe hepatic impairment, as it may precipitate portosystemic encephalopathy in patients with severe liver damage.

4.4 Special warnings and precautions for use

Drug dependence, tolerance and potential for abuse

Prolonged use of RuTrex 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). 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 RuTrex 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.

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

Tolerance and dependence may occur as with morphine. The risks of dependence are increased in individuals of current or past history of substance misuse disorders e.g., alcohol use disorder, opioid use disorder, drug use disorder.

RuTrex can produce drowsiness and reduce consciousness although tolerance to these effects can occur after repeated use.

Drug withdrawal syndrome

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 dose may be reduced relatively rapidly to start with, but reduction must be slow in the final phase (from 20 mg daily and downwards).

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

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

Respiratory depression

RuTrex should be used with caution in patients with asthma, chronic obstructive pulmonary disease or cor pulmonale and in patients with very limited respiratory reserve, a pre-existing impairment of respiratory function, hypoxia or hypercapnia. Even at the usual therapeutic doses for narcotics, these patients can experience a reduction in respiratory activity with a concomitant increase in airway resistance culminating in apnoea. In patients predisposed to such atopic phenomena, pre-existing asthma, skin eruptions and blood count changes (eosinophilia) can be exacerbated.

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 CNS depressant activity is not advised due to the potential for CNS and respiratory depression (see section 4.5).

The symptoms and signs of overdosage and toxicity of methadone are essentially those for morphine, though it is said that methadone 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 methadone may account for at least some of the urticaria and pruritus associated with methadone administration.

Head injury and increased intracranial pressure

The respiratory depressant effects of methadone and its capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increased intracranial pressure. Furthermore, opiates/opioids produce side effects that may obscure the clinical course of patients with head injuries. In such patients, RuTrex must be used with caution and only if it is deemed essential.

Methadone has the potential to increase intracranial pressure especially where it is already raised.

Hepatic disorders

Caution as RuTrex may precipitate portosystemic encephalopathy in patients with severe liver damage. RuTrex may cause troublesome constipation, which is particularly dangerous in patients with severe hepatic impairment, and measures to avoid constipation should be initiated early.

Renal impairment

Caution should be exercised in the use of RuTrex in patients with renal impairment. The dose interval should be lengthened to a minimum of 32 hours if the glomerular filtration rate (GFR) is 10 – 50 mL/min and to a minimum of 36 hours if the GFR is lower than 10 mL/min.

Gastrointestinal motility

Methadone may cause troublesome constipation, which is particularly dangerous in patients with severe hepatic impairment, and measures to avoid constipation should be initiated early.

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.

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).

Other warnings

Babies born to mothers receiving RuTrex may suffer withdrawal symptoms.

Methadone should be used with caution in patients with history of convulsive disorders, hypothyroidism, adrenocortical insufficiency, prostatic hyperplasia, hypotension, shock, inflammatory or obstructive bowel disorders or myasthenia gravis.

RuTrex should be used with caution and in reduced dosage in patients who are concomitantly using other narcotic analgesics, general anaesthetics, phenothiazines, other tranquillisers, sedative hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol) (see section 4.5).

QT prolongation and torsade de pointes have been reported with methadone use, particularly at doses above 100 mg daily.

RuTrex should be given with caution to patients at risk of developing prolongation of the QT interval including those with:

- known history of QT prolongation or family history of sudden death

- advanced heart disease or ischemic heart disease
- hepatic disease
- hypokalaemia or other electrolyte imbalances, i.e. hypomagnesaemia
- concomitant treatment with medicines that have a potential for QT-prolongation
- concomitant treatment with substances which may cause electrolyte abnormalities
- concomitant treatment with cytochrome P450 CYP3A4 inhibitors (see section 4.5).

It should also be used with caution in patients who are taking other potentially arrhythmogenic medicines, medicines likely to cause electrolyte imbalance, or medicines that inhibit the cytochrome P450 isoenzyme CYP3A4 (see section 4.5).

ECG monitoring is recommended before starting treatment in patients with risk factors for QT-prolongation, with a further test at dose stabilisation. ECG monitoring is also recommended before and at 7 days after dose titration above 100 mg daily in patients without recognised risk factors.

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 RuTrex are the same as those applying to opiates in general.

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

Concomitant use of RuTrex 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 RuTrex

concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers must be informed and made aware of these symptoms (see section 4.5).

Excipient warnings

RuTrex contains:

- Sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take RuTrex.
- Propylene glycol. RuTrex contains 200 mg propylene glycol per 1 mL.

While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case-by-case basis.

Monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

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, RuTrex is not recommended in those under 18 (see section 4.2).

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 medicines taken during pregnancy e.g. benzodiazepines, intake of alcohol, and medicines used to treat neonatal abstinence syndrome e.g. phenobarbitone, could play a role in the adverse reactions seen.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic interactions

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 methadone may also increase because of increased blood brain barrier passage.

CYP3A4-enzyme inducers:

Methadone is a substrate of CYP3A4 (see section 5.2). By induction of CYP3A4, clearance of methadone will increase, and the plasma levels decrease. Inducers of this enzyme (barbiturates, carbamazepine, phenytoin, nevirapine, rifampicin, efavirenz, amprenavir, spironolactone, dexamethasone, *Hypericum perforatum* (St John's wort)), may induce hepatic metabolism. For instance, after three weeks' treatment with 600 mg efavirenz daily, the mean maximal plasma concentration and AUC decreased by 48 % and 57 % respectively, in patients treated with methadone (35 – 100 mg daily).

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

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

CYP3A4-enzyme inhibitors:

Methadone is a substrate of CYP3A4 (see section 5.2). By inhibition of CYP3A4 clearance of methadone is lowered. Concomitant administration of CYP3A4 inhibitors (e.g. cannabinoids, clarithromycin, delavirdine, erythromycin, ciprofloxacin, fluconazole, grapefruit juice, cimetidine, itraconazole, ketoconazole, fluoxetine, fluvoxamine, nefazodone and telithromycin) may result in increased plasma concentrations of methadone. 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 RuTrex maintenance treatment, one should be aware of the risk of overdose. Dose adjustment may be necessary.

Products that affect the acidity of the urine:

Methadone is a weak base. Acidifiers of the urine (such as ammonium chloride and ascorbic acid) may increase the renal clearance of methadone. Patients that are treated with RuTrex are recommended to avoid products containing ammonium chloride.

Concomitant HIV infection treatment:

Some protease inhibitors (amprenavir, nelfinavir, abacavir, lopinavir/ritonavir and ritonavir/saquinavir) seem to decrease the serum levels of methadone. When ritonavir is administered alone, a two-fold AUC of methadone has been observed. The plasma levels of zidovudine (a nucleoside analogue) increase with methadone use after both oral and intravenous administration 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 RuTrex, patients must be carefully monitored for signs of toxicity caused by zidovudine, which may require a reduction in the zidovudine dose. Because of mutual interactions between zidovudine and methadone (zidovudine

is a CYP3A4 inducer), typical opiate/opioid abstinence symptoms may develop during concomitant use (headache, myalgia, fatigue and irritability).

Didanosine and stavudine:

Methadone delays the absorption and increases the first pass metabolism of stavudine and didanosine, which results in a decreased bioavailability of stavudine and didanosine.

Desipramine:

RuTrex may double the serum levels of desipramine.

Pharmacodynamic interactions

Opiate/opioid antagonists:

Naloxone and naltrexone counteract the effects of methadone and induces abstinence. Similarly, buprenorphine and pentazocine may precipitate withdrawal symptoms.

CNS depressants:

Medicines with a sedative effect on the central nervous system 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 RuTrex treatment, the slowly eliminated substance methadone, gives 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 and with careful observation.

Anaesthetics, sedative-hypnotics (including barbiturates, chloral hydrate and chlormethiazole), anxiolytics phenothiazines, antipsychotics and tricyclic antidepressants may increase the general depressant effects of RuTrex when used concomitantly (see section 4.4). Antipsychotics may enhance the sedative effects and hypotensive effects of RuTrex.

Sedative medicines such as benzodiazepines or related medicines:

The concomitant use of opiates/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)

Peristalsis inhibition:

Concomitant use of RuTrex and peristalsis inhibiting medicines (loperamide and diphenoxylate) may result in severe obstipation and increase the CNS depressant effects. Opiate/opioid analgesics, in combination with antimuscarinics, may result in severe obstipation or paralytic ileus, especially in long-term use.

QT-prolongation:

RuTrex should not be combined with medicines that may prolong the QT interval such as antidysrhythmics (sotalol, amiodarone, and flecainide), antipsychotics (thioridazine, haloperidol, sertindole, and phenothiazines), antidepressants (paroxetine, sertraline) or antibiotics (erythromycin, clarithromycin).

Serotonergic medicines:

Serotonergic syndrome may occur with concomitant administration of RuTrex with pethidine, monoamine oxidase (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.

MAO-inhibitors:

Concomitant administration of MAO-inhibitors may result in reinforced CNS-inhibition, serious hypotonia and or apnoea. RuTrex should not be combined with MAO-inhibitors and two weeks after such treatment (see section 4.3).

Analgesics

Maintenance patients on a stable dose of RuTrex who experience physical trauma, postoperative pain or other causes of acute pain cannot be expected to derive analgesia from their stable dose of methadone regimens. Such patients should be given analgesics, including opiates/opioids that would be indicated in other patients experiencing similar nociceptive stimulation. Due to the opiate/opioid tolerance induced by RuTrex, when opiates/opioids are required for management of acute pain in methadone patients, somewhat higher and/or more frequent doses will often be required than would be the case for other, non-tolerant patients.

Diagnostic/lab interactions

Gastric emptying studies:

RuTrex may 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 RuTrex 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 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 RuTrex 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.

Urine tests:

RuTrex may modify urine tests and give a positive result in doping control.

Pregnancy tests:

RuTrex may interfere with urine testing for pregnancy.

4.6 Fertility, pregnancy and lactation

Pregnancy

RuTrex administered to pregnant women for the management of opiate/opioid addiction has the potential for several adverse effects on the foetus and the neonate. Withdrawal symptoms/respiratory depression may occur in neonates of mothers who were treated with RuTrex chronically during pregnancy.

RuTrex should not be administered to pregnant women, because of possible adverse effects on the foetus and neonate including respiratory depression, low birth weight, neonatal withdrawal syndrome and increased rate of stillbirths. However, if maternal RuTrex substitution therapy is strongly indicated, careful monitoring is required.

It may be necessary to increase the dose of RuTrex if withdrawal symptoms develop. Increased clearance and reduced plasma levels have been reported during pregnancy. Considering the well-being of the foetus, it may be advisable to split up the daily dose in order to prevent high peak plasma concentrations and to compensate the accelerated degradation of methadone, thus preventing withdrawal symptoms. Dose reduction or withdrawal during pregnancy must always be carried out under careful monitoring of the mother and only after a stringent risk/benefit assessment. Medicine withdrawal of the neonate must be carried out at an adequate intensive care unit for children, as treatment with RuTrex may lead to habituation and addiction of the foetus as well as to withdrawal symptoms in the neonate, which require treatment. Approximately 60 – 80 % of the neonates require hospitalised treatment due to the neonatal abstinence syndrome. Dose adjustment (especially dose reduction) may be necessary within 1 – 2 weeks postnatal. The use of RuTrex just before and during birth is advised against, because of the risk of neonatal respiratory depression.

Breastfeeding

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

Fertility

Methadone does not appear to impair human female fertility. Studies in men on methadone maintenance programmes have shown that methadone reduces serum testosterone and markedly depresses the ejaculate volume and sperm motility. The sperm counts of methadone subjects were twice that of controls, but this reflected the lack of dilution from seminal secretions.

4.7 Effects on ability to drive and use machines

RuTrex 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

Blood and lymphatic system disorders

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

Metabolism and nutrition disorders

Frequent: Fluid retention.

Frequency unknown: Anorexia, hypokalaemia, hypomagnesaemia, hypoglycaemia.

Psychiatric disorders

Frequent: Euphoria, hallucinations.

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

Frequency unknown: Drug dependence (see section 4.4).

Nervous system disorders

Frequent: Dizziness, euphoria, sedation, confusion, headache, sleep disturbances, sweating.

Less frequent: Syncope.

Eye disorders

Frequent: Blurred vision, dry eyes.

Frequency unknown: Nystagmus, strabismus, reduced visual acuity.

Less frequent: Visual disturbances, miosis.

Ear and labyrinth disorders

Frequent: Vertigo.

Cardiac disorders

Less frequent: Bradycardia, palpitations, drop in blood pressure (at high doses), QT prolongation and torsade de pointes.

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).

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: Pruritis, urticaria, bleeding urticaria, tendency to oedema.

Endocrine disorders

Less frequent: Hypothyroidism.

Frequency unknown: Raised prolactin levels with long-term administration, hypoadrenalism, hypogonadism.

Renal and urinary disorders

Less frequent: Urinary retention, anti-diuretic effect.

Reproductive system and breast disorders

Frequent: Reduced libido.

Less frequent: Galactorrhoea, dysmenorrhoea and amenorrhoea.

The undesirable effects are usually moderate in patients receiving long-term treatment.

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 RuTrex is important. It allows continued monitoring of the benefit/risk balance of RuTrex. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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: Severe overdose is characterised by respiratory failure, extreme drowsiness that develops into stupor or coma, maximum miosis, slack musculature, cold and clammy skin and occasionally bradycardia and hypotension. Apnoea, cardiovascular failure, cardiac arrest and death may occur in cases of severe overdose.

Treatment: Secure the airways by assisted or controlled ventilation. It may prove necessary to use

opioid antagonists, but since the effect of RuTrex is long lasting (36 to 48 hours) and that of antagonists is only 1 to 3 hours, antagonist treatment must be repeated, as necessary. Antagonists must not be used if there is any sign of respiratory failure or loss of consciousness. If the patient is physically dependent on narcotics, administration of an antagonist may lead to acute withdrawal symptoms. If possible, the use of antagonists should be avoided in such patients, but if it nevertheless proves necessary to administer antagonists because of severe respiratory depression, great caution must be exercised.

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. 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 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.

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-demethylation 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 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

Anhydrous citric acid

Cherry flavour

D & C Red 33 (CI 17200)

FD & C Red 40 (E 129)

Methyl hydroxybenzoate (0,035 % *m/v*)

Propyl hydroxybenzoate

Propylene glycol (0,035 % *m/v*)

Purified water

Sucrose

Sodium hydroxide (pH adjuster).

6.2 Incompatibilities

None.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the container tightly closed.

6.5 Nature and contents of container

1 litre amber HDPE container with a white HDPE screw cap with an induction wad.

6.6 Special precautions for disposal and other handling

This medicine does not require any special storage conditions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

LeBasi Pharmaceuticals (Pty) Ltd

San Domenico Building, Unit 6, Ground Floor

10 Church Street

Durbanville

7551

8. REGISTRATION NUMBER

55/2.9/0235

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 March 2023

10. DATE OF REVISION OF THE TEXT