Professional Information for RUSLOPAM 1 mg/mL

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

RUSLOPAM 1 mg/mL concentrate for solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 1 mg clonazepam in 1 mL solution.

Excipients with known effect:

Each 1 mL contains 30 mg benzyl alcohol (as preservative), 159 mg ethanol and 802 mg propylene glycol.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for injection/infusion.

A clear, colourless or slightly greenish yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Epileptic disease

Status epilepticus in all its forms in infants, children or adults.

Panic disorder

RUSLOPAM is indicated for the treatment of panic disorder, with or without agoraphobia.

4.2 Posology and method of administration

Posology

Standard dosage in epilepsy

Dosage of RUSLOPAM is essentially individual and depends above all on the age of the patient. It will be determined in each patient according to clinical response and tolerance.

Intravenous administration

The IV administration is mainly used for treatment of status epilepticus. *Infants and children:* Half an ampoule (0,5 mg = 1 mL reconstituted solution) by slow intravenous injection or by intravenous infusion.

Adults: One ampoule (1 mg = 2 mL reconstituted solution) by slow intravenous injection. This dose can be repeated as required, possibly by intravenous infusion (1 - 4 mg are usually required to reverse the status). In adults, the rate of injection must not exceed 0,25 - 0,5 mg (0,5 - 1,0 mL of the prepared solution) per minute and a total dose of 10 mg should not be exceeded.

RUSLOPAM can be administered concurrently with one or several other antiepileptic medicines, in which case the dosage of each medicine must be adjusted to achieve the optimum effect.

Treatment with RUSLOPAM must not be stopped abruptly but be reduced in a stepwise fashion (see sections 4.4 and 4.8).

Dosage in panic disorder

Adults: The initial dose for adults with panic disorder is 0,25 mg twice daily (0,5 mg/day). An increase to the target dose for most patients of 1 mg/day may be made after 3 days. The recommended dose of 1 mg/day is based on the results from a fixed dose study in which the optimal effect was seen at 1 mg/day. Higher doses of 2, 3 and 4 mg/day in that study were less effective than the 1 mg/day dose and were associated with more adverse effects. Nevertheless, it

is possible that some individual patients may benefit from doses of up to a maximum dose of 4 mg/day, and in those instances the dose may be increased in increments of 0,125 to 0,25 mg twice a day, every 3 days until panic disorder is controlled or until side effects make further increases undesired. To reduce the inconvenience of somnolence, administration of one dose at bedtime may be desirable.

Treatment should be discontinued gradually, with a decrease of 0,125 mg twice a day every 3 days, until the medicine is completely withdrawn.

There is no body of evidence available to answer the question of how long the patient treated with clonazepam should remain on it. Therefore, the medical practitioner who elects to use RUSLOPAM for extended periods should periodically re-evaluate the long-term usefulness of the product for the individual patient.

Special populations

Elderly population

There is no clinical trial experience with RUSLOPAM in panic disorder patients 65 years of age and older. In general, elderly patients should be started on low doses of RUSLOPAM and observed closely (see section 4.4).

Particular care should be taken during up-titration in elderly patients.

Renal impairment

The safety and efficacy of clonazepam in patients with renal impairment has not been studied, however based on pharmacokinetic considerations no dose adjustment is required in these patients (see section 5.2).

Hepatic impairment

The safety and efficacy of clonazepam in patients with hepatic impairment has not been studied. No data are available on the influence of hepatic disease on clonazepam pharmacokinetics.

Paediatric population

The safety and efficacy of clonazepam for the treatment of panic disorder in children has not been studied.

Method of administration

For intravenous or intramuscular use.

Slow intravenous injection

The 1 mL ampoule solution containing 1 mg active ingredient may only be employed after addition of 1 mL diluent in order to avoid local irritation to the veins. A vein of sufficient calibre must be chosen. Intravenous injection should be administered slowly with continuous monitoring of ECG, respiration, and blood pressure. If the injection is rapid or the calibre of the vein is insufficient, there is a risk of thrombophlebitis, which may in turn lead to thrombosis.

Intravenous infusion

For instructions on dilution, refer to section 6.6.

Intramuscular administration

The intramuscular administration route should only be used by way of exception or if IV administration is not feasible.

4.3 Contraindications

- Patients with known hypersensitivity to benzodiazepines or any excipients listed in section 6.1.
- Severe respiratory insufficiency.
- Acute narrow angle glaucoma.
- Myasthenia gravis.
- Sleep apnoea.

RUSLOPAM ampoules contain benzyl alcohol. Since there have been associated reports of

permanent neuropsychiatric deficits and multiple system organ failure associated with benzyl alcohol, administration to neonates, and especially premature infants, must be avoided.

4.4 Special warnings and precautions for use

RUSLOPAM may give rise to salivary or bronchial hypersecretion in infants and small children; supervision is thus required to ensure that the airways remain free of secretions.

Drug abuse and dependence

Dependence

There is a potential for abuse. Treatment with RUSLOPAM can lead to physical and psychological dependence on the product. The risk is greater with higher doses; and is particularly pronounced in predisposed patients with a history of alcoholism or drug addiction.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. During long-term treatment, withdrawal symptoms may develop after a lengthy period of use, especially with high doses or if the daily dose is reduced rapidly or abruptly discontinued. The symptoms include tremor, sweating, agitation, sleep disturbances and anxiety, headaches, muscle pain, extreme anxiety, tension, restlessness, confusion, irritability and epileptic seizures which may be associated with the underlying disease. The following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations, or epileptic seizures.

Rebound effects

A transient syndrome, which may occur in withdrawal of treatment, whereby the symptoms that led to treatment with RUSLOPAM recur in an enhanced form. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

Due to the risk of withdrawal symptoms or rebound phenomena, the medicine should - even if only of short duration - be terminated by gradually reducing the daily dose.

General

RUSLOPAM must be used with care in spinal or cerebellar ataxia, in the event of acute intoxication with alcohol, other anti-epileptic medicines, hypnotics, analgesics, neuroleptic medicines, antidepressants or lithium. Particular caution should be exercised in elderly patients and patients with pre-existing disease of the respiratory system (e.g. chronic obstructive lung disease), liver or kidneys, or who are receiving treatment with other centrally acting medicines, barbiturates or anti-convulsant (antiepileptic) medicines. These patients require very careful dosage adjustment according to individual requirements (see section 4.5).

Anticonvulsant medicines, including RUSLOPAM, should not be discontinued abruptly in epileptic patients as this may precipitate status epilepticus. When, in the judgement of the medical practitioner, the need for dosage reduction or discontinuation arises, this should be done gradually.

RUSLOPAM must be used with extreme caution in patients with a history of alcohol or drug abuse. Since alcohol can provoke epileptic seizures, it is imperative that patients abstain from drinking alcohol while under treatment with RUSLOPAM. In combination with RUSLOPAM, alcohol may modify the effects of the medicine, compromise the success of therapy, or give rise to unpredictable side effects.

Patients with a history of depression and/or suicide attempts should be kept under close supervision. RUSLOPAM may, depending on the dosage, administration and individual susceptibility, modify the patient’s reactions (e.g. driving ability, behaviour in traffic) (see section 4.7).

During IV administration, a vein of sufficient calibre must be chosen and the injection administered very slowly, with continuous monitoring of respiration and blood pressure. If the injection is too rapid or the calibre of the vein is insufficient, there is a risk of thrombophlebitis, which may in turn lead to thrombosis. In adults, the rate of injection must not exceed 0,25 - 0,5 mg (0,5 - 1 mL of the prepared solution) per minute (see section 4.2).

Propylene glycol

RUSLOPAM contains 802 mg propylene glycol in each 1 mL, which is equivalent to 80 % *m/v*.

Benzyl alcohol

RUSLOPAM contains 30 mg benzyl alcohol in each ampoule.

Benzyl alcohol may cause allergic reactions.

Ethanol

RUSLOPAM contains 159 mg of alcohol (ethanol) in each ampoule. The small amount of alcohol in RUSLOPAM will not have any noticeable effects.

4.5 Interactions with other medicines and other forms of interaction

RUSLOPAM can be administered concurrently with one or more antiepileptic medicines. Adding an extra medicine to the patient's regimen should however involve a careful evaluation of the response to the treatment, because unwanted effects, such as sedation and apathy are more likely to occur. In such cases, the dosage of each medicine must be adjusted to achieve the optimum desired effect. There is an additive risk of central nervous system depression when central nervous system depressants and RUSLOPAM are taken together.

Pharmacokinetic interactions

The antiepileptic medicines phenytoin, phenobarbital (phenobarbitone), carbamazepine and sodium valproate may induce the metabolism of clonazepam, causing higher clearance and lower plasma concentrations of the latter during combined treatment. The selective serotonin reuptake inhibitors sertraline and fluoxetine do not affect the pharmacokinetics of clonazepam when administered concomitantly.

Pharmacodynamic interactions

The combination of clonazepam with valproic acid may occasionally cause petit mal status epilepticus. Concurrent use of RUSLOPAM and other centrally acting medicines, e.g. other anti-convulsant medicines, anaesthetics, hypnotics, psychoactive medicines and some analgesics can

produce mutual potentiation of medicine effects. This is especially true in the presence of alcohol. In combination with centrally acting medicines, the dosage of each medicine must be adjusted to achieve the optimum effect. Epileptic patients must not under any circumstances consume alcohol while being treated with RUSLOPAM, since alcohol may alter the effect of the medicine, reduce the efficacy of treatment or produce unexpected side effects.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established. Administration of RUSLOPAM in the last trimester of pregnancy or during labour can cause irregularities in the heartbeat of the unborn child and hypothermia, hypotonia, mild respiratory depression and poor feeding in the neonate. During labour it crosses the placenta and may cause the “floppy-infant” syndrome characterised by central respiratory depression, hypothermia and poor sucking.

Breastfeeding

RUSLOPAM must not be used during breastfeeding, since it passes into the breast milk. If there is a compelling indication for RUSLOPAM, breastfeeding should be discontinued.

Fertility

No data are available.

4.7 Effects on ability to drive and use machines

RUSLOPAM can slow reactions to such an extent that the ability to drive a vehicle or operate machinery is seriously impaired. This effect is increased if the patient has also taken alcohol. Driving, operating machinery or performing other hazardous activities should therefore be avoided. The decision should be made in each case on the basis of the patient's response to treatment and the dosage involved (see section 4.8).

4.8 Undesirable effects

Epilepsy

With certain forms of epilepsy, an increase in the frequency of seizures during long-term treatment is possible.

Panic disorder

Data from placebo-controlled clinical trials including patients on active treatment are presented in the table below. Adverse events occurring in ≥ 5 % of patients treated with 1 mg to > 3 mg/day.

System organ class	Adverse event	Frequency
Infections and infestations	Influenza	Frequent
	Sinusitis	Frequent
Psychiatric disorders	Depression	Frequent
	Impaired concentration	Frequent
	Insomnia	Frequent
	Irritability	Frequent
Nervous system disorders	Abnormal coordination	Frequent
	Ataxia	Frequent
	Balance loss	Frequent
	Dizziness	Frequent
	Headache	Frequent
	Light-headed feeling	Frequent
	Somnolence	Frequent
Respiratory, thoracic and mediastinal disorders	Upper respiratory infection	Frequent
Gastrointestinal disorders	Nausea	Frequent
General disorders and administration site	Fatigue	Frequent

conditions		

Post-marketing

Epilepsy and panic disorder

Blood and lymphatic system disorders:

Thrombocytopenia (reduction in blood platelets).

Immune system disorders:

Allergic reactions and cases of anaphylaxis have been reported to occur with RUSLOPAM.

Endocrine disorders:

Isolated cases of reversible development of premature secondary sex characteristics in children (incomplete precocious puberty) have been reported.

Psychiatric disorders:

Restlessness, confusion, disorientation have been observed. The following paradoxical reactions have been observed: excitability, irritability, aggressive behaviour, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares and vivid dreams. In rare cases decrease in sexual drive (loss of libido) may occur.

Nervous system disorders:

Confusion, slowed reaction, muscular hypotonia, dizziness (light headedness). These effects can be partially prevented by increasing the dose slowly at the start of treatment. Particularly in long-term or high-dose treatment, reversible disorders such as a slowing or slurring of speech (dysarthria), reduced coordination of movements and gait (ataxia) and disorders of vision (double vision, nystagmus) may occur. Anterograde amnesia may occur using RUSLOPAM at therapeutic dosages, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour. With certain forms of epilepsy, an increase in the frequency of seizures

during long-term treatment has been observed.

Eye disorders:

Particularly in long-term or high-dose treatment, reversible disorders of vision (double vision) have occurred.

Vascular disorders:

If the injection is rapid or the calibre of the vein insufficient, there is a risk of thrombophlebitis, which may in turn lead to thrombosis.

Respiratory, thoracic and mediastinal disorders:

Respiratory depression has occurred, particularly on IV administration of clonazepam. This effect was aggravated by pre-existing airways obstruction or brain damage or if other medicines which depress respiration were given. As a rule, this effect should be avoided by careful adjustment of the dose to individual requirements. In infants and young children, RUSLOPAM has caused increased production of saliva and bronchial secretion. Particular attention should therefore be paid to maintaining patency of the airways.

Gastrointestinal disorders:

Nausea and epigastric symptoms.

Skin and subcutaneous tissue disorders:

Urticaria, pruritus, rash, transient hair loss, pigmentation changes.

Musculoskeletal and connective tissue disorders:

Muscle weakness, this undesirable effect is usually transient and generally disappears spontaneously in the course of the treatment or on reduction of the dosage. It may be partially prevented by increasing the dose slowly at the start of treatment.

Renal and urinary disorders:

Urinary incontinence.

Reproductive system and breast disorders:

Erectile dysfunction (impotence).

General disorders and administration site conditions:

Fatigue (tiredness lassitude), this undesirable effect is usually transient and generally disappears spontaneously during the treatment or on reduction of the dosage. It could be partially prevented by increasing the dose slowly at the start of treatment. Paradoxical reactions including irritability have been observed (see also psychiatric disorders).

Injury, poisoning and procedural complications:

An increased risk for falls and fractures has been recorded in elderly patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of RUSLOPAM is important. It allows continued monitoring of the benefit/risk balance of RUSLOPAM. 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

Symptoms

Benzodiazepines such as RUSLOPAM, commonly cause drowsiness, confusion, ataxia, dysarthria and nystagmus. Coma, hypotension, cardiovascular and respiratory depression occasionally occur but are seldom serious if these medicines are taken alone. Coma, if it occurs, usually lasts only a few hours but it may be more protracted and cyclical, particularly in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory

disease. Benzodiazepines increase the effects of other central nervous system depressants, including alcohol.

Treatment

Monitor the patient's vital signs and institute supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.

If CNS depression is severe, a benzodiazepine antagonist such as flumazenil may be considered (see professional information leaflet of flumazenil). This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is contraindicated in the presence of medicines that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the professional information for flumazenil, for further information on the correct use of RUSLOPAM.

Warning

The benzodiazepine antagonist, flumazenil, is not indicated in patients with epilepsy who have been given benzodiazepines. Antagonism of the benzodiazepine effect in such patients may provoke seizures. In small children it is important to watch the airways due to possible hypersalivation and disturbance of swallowing. Excitation and hyperactivity may appear during recovery phase.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.5 – Anticonvulsants, including anti-epileptics

Pharmacotherapeutic group: Benzodiazepine derivative

ATC code: N03AE01

Clonazepam, a benzodiazepine derivative, exhibits pharmacological properties which include

anticonvulsive, sedative, muscle relaxing and anxiolytic effects. These effects are thought to be mediated mainly by postsynaptic GABA mediated inhibition. Electroencephalographic investigations have shown that clonazepam suppresses the spike and wave discharges in absence seizures (petit mal), slow spike wave, generalised spike waves, spikes with temporal or other locations as well as irregular spikes and waves.

5.2 Pharmacokinetic properties

Absorption

Clonazepam is rapidly and almost completely absorbed after oral administration of clonazepam tablets. Peak plasma concentrations of clonazepam are reached in 1 - 4 hours. The absorption half-life is around 25 minutes. The absolute bioavailability is 90 %. Clonazepam tablets are bioequivalent to an oral solution.

Plasma concentrations of clonazepam at steady state for a once-daily dosage regimen are 3-fold higher than those after a single oral dose; the predicted accumulation ratios for two times and three times daily regimen is 5 and 7, respectively. Following multiple oral doses of 2 mg three times daily steady-state pre-dose plasma concentrations of clonazepam averaged 55 ng/mL. The plasma concentration-dose relationship of clonazepam is linear. The target anticonvulsant plasma concentrations of clonazepam range from 20 to 70 ng/mL. The threshold plasma concentrations of clonazepam in patients with panic disorders is about 17 ng/mL. After IM administration, maximum plasma concentrations of clonazepam are reached in about 3 hours and the absolute bioavailability is 93 %. Irregularities in the absorption profiles of clonazepam after IM administration are occasionally observed.

Distribution

Clonazepam distributes very rapidly to various organs and body tissues with preferential uptake by brain structures. The distribution half-life is approximately 0,5 - 1 hour. The volume of distribution is 3 L/kg. The plasma protein binding is 82 – 86 %.

Biotransformation

Clonazepam is extensively metabolised by reduction to 7-amino-clonazepam and by *N*-acetylation to 7- acetamino-clonazepam. Hydroxylation at the C-3 position also occurs. Hepatic cytochrome P-450 3A4 is implicated in the nitro-reduction of clonazepam to pharmacologically inactive metabolites. 50 - 70 % of the dose is excreted in the urine and 10 - 30 % in faeces as metabolites. The urinary excretion of unchanged clonazepam is usually less than 2 % of the administered dose. The metabolites are present in urine both as free and conjugated (glucuronide and sulphate) compounds.

Elimination

The mean elimination half-life is 30 - 40 hours. The clearance is 55 mL/min. The elimination kinetics in children are similar to those observed in adults.

Special populations

Renal failure

Renal disease does not affect the pharmacokinetics of clonazepam. Based on pharmacokinetic criteria, no dose adjustment is required in patients with renal disease.

Hepatic failure

The influence of hepatic disease on clonazepam pharmacokinetics has not been investigated.

Elderly

The pharmacokinetics of clonazepam in the old age has not been established.

Neonates

The elimination half-life and clearance values in neonates are of the same order of magnitude of those reported in adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol

Ethanol (99 %)

Glacial acetic acid (pH adjuster)

Propylene glycol.

6.2 Incompatibilities

Do not prepare RUSLOPAM infusions using sodium bicarbonate solution, as precipitation of the solution may occur.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the ampoules in the outer carton to protect from light.

6.5 Nature and contents of container

1 mL amber NEG (USP type 1) glass ampoule with white OPC dot,

or

1 mL amber Fiolax (USP type 1) glass ampoule with yellow OPC dot.

Pack size: 1 or 10 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Intravenous infusion

RUSLOPAM (only the ampoule with the active substance) can be diluted for infusion with the

following media in a ratio of 1 ampoule (1 mg) to at least 85 mL (e.g. 3 ampoules in 250 mL) to avoid precipitation: sodium chloride 0,9 %; sodium chloride 0,45 % plus glucose 2,5 %; glucose 5 % and glucose 10 %. These mixtures are stable for 24 hours at room temperature.

The active ingredient can be absorbed on polyvinyl chloride (PVC). It is therefore, recommended that either glass containers be used or, if PVC bags are employed, that the mixture be infused immediately and usually within 4 hours. The infusion time should not exceed 8 hours.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

LeBasi Pharmaceuticals (Pty) Ltd

San Domenico Building, Unit 6, Ground floor

10 Church Street

Durbanville

7550

Tel: 087 551 3245

8. REGISTRATION NUMBER

59/2.5/0126

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT