Professional Information for RUSAINE 10 mg/mL

SCHEDULING STATUS

S1

1. NAME OF THE MEDICINE

RUSAINE 10 mg/mL solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL contains 10 mg phenylephrine hydrochloride.

Excipients with known effect:

Contains sodium metabisulphite (2 mg per 1 mL).

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion.

A clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RUSAINE is indicated for increasing the blood pressure in adults with clinically significant hypotension resulting primarily from vasodilation, in such settings as septic shock or anaesthesia.

The duration of action is short-lived (minutes) and repeat injections are frequently required.

4.2 Posology and method of administration

General dosing information

Patients receiving RUSAINE should be closely monitored. Treatment with RUSAINE is not a substitute for replacement of blood, plasma, fluids and/or electrolytes.

Prior to administration of therapy, hypovolaemia should be corrected. Acidosis may reduce the effectiveness of RUSAINE. An infusion pump or other suitable metering device should be used to control the rate of infusion in order to avoid unintended administration of a bolus dose. Infusions of RUSAINE should be given into a large vein, or preferably, directly into the central venous line.

Inspect the solution for particulate matter and discolouration prior to administration. Discard any unused portion.

RUSAINE is not for intramuscular or subcutaneous use.

Caution is recommended to avoid extravasation, which may cause tissue necrosis and sloughing of surrounding tissues (see section 4.4). When discontinuing therapy, the dosage should be reduced gradually, since sudden cessation of therapy may result in severe hypotension.

Intravascular fluid should be replaced if necessary, to avoid hypotension.

RUSAINE must be diluted before administration as bolus intravenous infusion or continuous intravenous infusion. Dosage must be adjusted to meet the individual requirements of each patient, on the basis of clinical response. Some patients may need higher than usual recommended doses for a time.

Posology

Adults

Preparing a 50 mcg/mL solution of bolus intravenous administration

For bolus intravenous administration, add 10 mg (1 mL of a 10 mg/mL concentration) of RUSAINE to 200 mL of 5 % dextrose injection or 0,9 % sodium chloride injection. This will yield a final concentration of 50 mcg/mL. Withdraw an appropriate dose from the 50 mcg/mL solution prior to bolus intravenous administration of the diluted solution.

Preparing a solution for continuous intravenous infusion

For continuous intravenous infusion, withdraw 10 mg (1 mL of 10 mg/mL concentration) of RUSAINE and add 500 mL of 5 % dextrose injection of 0,9 % sodium chloride injection (providing a final concentration of 20 mcg/mL).

Dosing for perioperative setting

In adult patients undergoing surgical procedures with either neuraxial anaesthesia or general anaesthesia:

- 50 mcg to 250 mcg by intravenous bolus administration. The most frequently reported initial bolus dose is 50 mcg or 100 mcg.
- 0,5 mcg/kg/min to 1,4 mcg/kg/min by intravenous continuous infusion, titrated to blood pressure goal.

Dosing for septic or other vasodilatory shock

In adult patients with septic or other vasodilatory shock:

- 0,5 mcg/kg/min to 6 mcg/kg/min by intravenous continuous infusion, titrated to blood pressure goal. Doses above 6 mcg/kg/min do not show significant incremental increase in blood pressure.

Special populations

Patients with renal impairment

Lower doses of RUSAINE may be required in patients with renal impairment.

Patients with hepatic impairment

Higher doses of RUSAINE may be needed in patients with liver cirrhosis.

Elderly patients

Treatment of the elderly should be made with caution.

Paediatric population

The safety and efficacy of RUSAINE in children have not been established. No data are available.

Method of administration

For intravenous use.

RUSAINE should be administered by slow intravenous bolus injection or continuous intravenous infusion, after dilution.

4.3 Contraindications

- Hypersensitivity to phenylephrine hydrochloride or to any of the excipients of RUSAINE (see section 6.1).
- Paediatric use.
- Severe uncontrolled hypertension.
- Severe hyperthyroidism.
- Severe heart-block with or without bradycardia.
- Severe uncontrolled cardiac failure.
- Severe bradycardia (less than 50 bpm).
- Seriously impaired coronary circulation.

4.4 Special warnings and precautions for use

Sustained intravenous (IV) infusion may result in diminished efficacy.

Great care should be exercised in administering RUSAINE to patients with pre-existing cardiovascular disease, such as ischaemic heart disease, dysrhythmias, occlusive vascular disease including arteriosclerosis, hypertension or aneurysms. Increased blood pressure may occur and precipitate underlying heart failure, angina in patients with severe arteriosclerosis or past history of angina and increase pulmonary arterial pressure. Anginal pain may be precipitated in

patients with angina pectoris.

Severe bradycardia and decreased cardiac output may occur.

Excessive peripheral and visceral vasoconstriction with ischaemia to vital organs may occur, especially in patients with extensive peripheral vascular disease e.g. Raynaud's phenomenon.

In patients with reduced cardiac output or coronary vascular disease, vital organ functions should be closely monitored and dose reduction should be considered when systemic blood pressure is near the lower end of the target range.

Care is also required when given to patients with diabetes mellitus, or closed angle glaucoma.

Avoid extravasation as this can cause necrosis or sloughing of tissue.

Use extreme caution in patients with hyperthyroidism.

Concurrent use with monoamine oxidase (MAO) inhibitors may prolong and intensify cardiac stimulation and vasopressor effects because of the release of catecholamines which accumulate in intraneuronal

storage sites during MAO inhibitor therapy; this may result in headache, cardiac dysrhythmias, vomiting or sudden and severe hypertensive or hyper-pyretic crises. For patients who have been receiving MAO inhibitors 2 to 3 weeks prior to administration of sympathomimetic medicines, the initial dosage should be reduced to be no more than one-tenth of the usual dose.

Allergic reactions, including anaphylactic symptoms, may occur in patients with sulphite-sensitivity.

Blood pressure response to RUSAINE may be increased in patients with autonomic dysfunction.

RUSAINE can increase the need for renal replacement therapy in patients with septic shock.

Monitor renal function.

RUSAINE contains sodium metabisulphite

RUSAINE contains sodium metabisulphite which may rarely cause severe hypersensitivity reactions and bronchospasm.

4.5 Interaction with other medicines and other forms of interaction

RUSAINE may interact with cyclopropane and halothane and other halogenated inhalational anaesthetics, to induce ventricular fibrillation. An increased risk of dysrhythmias may also occur if RUSAINE is given to patients receiving cardiac glycosides, quinidine, tricyclic antidepressants (e.g. imipramine) and noradrenergic-serotoninergic antidepressants (venlafaxine).

RUSAINE is a hypertensive medicine and may consequently reverse the action of many antihypertensive medicines. The patient should be carefully monitored to confirm the desired effect is obtained.
Interactions of RUSAINE with alpha and beta receptor blocking medicines may be complex.

Medicines which have an effect on alpha1-adrenoceptors could potentiate (such as clonidine) or inhibit (such as doxazosin, labetalol, prazosin, haloperidol, phenothiazines) the vasopressive action of RUSAINE.
Concurrent use with beta-adrenergic blocking medicines (systemic or ophthalmic) may result in an exaggeration of the vasoconstriction effects and profound bradycardia.

Concomitant use of oxytocic medicines with RUSAINE potentiates the vasopressor-active effects. Thus, some oxytocic medicines may cause severe persistent hypertension and strokes can occur during post-partum period.

Caution should be applied when administering atomoxetine concurrently with RUSAINE, as there is potential for synergistic pharmacological effects.
Severe hypertension may occur following the use of RUSAINE and atropine or other

antimuscarinics.

The pressor effects of RUSAINE may be slightly reduced by lithium carbonate.
The cardiac stimulation and vasopressor effects of RUSAINE may be potentiated by the use of monoamine oxidase inhibitors or reversible inhibitors of monoamine oxidase, such as selegiline, moclobemide, linezolid, nialamide, pargyline, phenelzine (see section 4.4). This interaction is still possible 15 days after discontinuation of MAO inhibitor.

Concurrent use with ergot alkaloids, such as bromocriptine, lisuride, cabergoline, pergolide, dihydroergotamine, methylergometrine, methysergide and ergotamine increases the risk of vasoconstriction and/or hypertensive crisis.

Concomitant use of reserpine and other sympatholytic medicines with RUSAINE causes a substantial increase in blood pressure (hyperreactivity linked to the reduction in sympathetic tone and/or to the inhibition of adrenaline or noradrenaline entry in sympathetic fibres). If the combination cannot be avoided, use with caution.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of RUSAINE during pregnancy has not been established. Due to the vasoconstrictive properties of RUSAINE, the product should be used with caution in patients with a history of pre-eclampsia. Administration of RUSAINE in late pregnancy or labour may cause foetal hypoxia and bradycardia.

Breastfeeding

The safety of RUSAINE during lactation has not been established. Excretion of phenylephrine in breast milk appears to be minimal.

Fertility

There are no data available regarding fertility.

4.7 Effects on ability to drive and use machines

It is not known if RUSAINE has an effect on the ability to drive or use machines. Caution is advised before driving a vehicle or operating machinery until the effects of RUSAINE are known.

4.8 Undesirable effects

RUSAINE may cause a transient tingling and coolness of the skin and a temporary sensation of fullness in the head. Extravasation of the injection may cause local necrosis (see section 4.4). Peripheral vasoconstriction, possibly leading to necrosis or gangrene, may occur with prolonged use of RUSAINE in high doses or low doses in the presence of peripheral vascular disease.

Immune system disorders

Less frequent:	hypersensitivity
Frequency unknown:	metabolism and nutrition disorders, metabolic disorders

Psychiatric disorders

Less frequent:	anxiety, excitability, agitation, psychotic states, confusion
Frequency unknown:	nervousness or restlessness, insomnia

Nervous system disorders

Frequent:	headache
Less frequent:	paraesthesia, tremor

Eye disorders

Less frequent:	mydriasis, aggravation of pre-existing angle-closure glaucoma

Cardiac disorders

Less frequent: angina pectoris, bradycardia, tachycardia, ventricular dysrhythmias

Frequency unknown: palpitations, cardiac arrest

Vascular disorders

Less frequent: cerebral haemorrhage, hypertensive crisis, hypertension, hypotension

Frequency unknown: dizziness, syncope, flushing

Respiratory, thoracic and mediastinal disorders

Less frequent: dyspnoea, pulmonary oedema

Gastrointestinal disorders

Less frequent: nausea, vomiting

Frequency unknown: salivary hypersecretion

Skin and subcutaneous tissue disorders

Less frequent: sweating, pallor or skin blanching, piloerection, skin necrosis with extravasation

Musculoskeletal and connective tissue disorders

Less frequent: muscular weakness

Renal and urinary disorders

Less frequent: difficulty in micturition, urinary retention

Frequency unknown: dysuria

General disorders and administration site conditions

Less frequent: extravasation

Frequency unknown: infusion site necrosis, hyperhidrosis

Investigations

Frequency unknown: abnormal blood glucose

RUSAINE 10 mg/mL is without significant stimulating effects on the central nervous system at usual doses.

Reporting of suspected adverse reactions

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

Symptoms

Symptoms of overdosage include headache, nausea, vomiting, palpitations, hypertension (which may be severe) and reflex bradycardia and other cardiac dysrhythmias. In severe cases confusion, hallucinations and seizures may occur.

Management

Treatment should consist of symptomatic and supportive measures. For excessive hypertensive effects, the administration should be reduced or the medication temporarily discontinued until blood pressure is

decreased. If these measures fail to lower the blood pressure, a short acting alpha-adrenergic

blocking medicine may be administered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.2 Vasoconstrictors, pressor medicines.

Pharmacotherapeutic group: Adrenergic and dopaminergic agent.

ATC code: C01CA

Phenylephrine is an alpha 1 adrenergic receptor agonist.

Phenylephrine hydrochloride is a sympathomimetic medicine with mainly direct effects on adrenergic receptors. It has predominantly alpha-adrenergic activity and is without significant stimulating effects on the central nervous system at usual doses.

Mechanism of action

After injection, it produces peripheral vasoconstriction and increased arterial pressure; it also causes reflex bradycardia. Beta 1 adrenergic effects are insignificant.

5.2 Pharmacokinetic properties

Absorption

When injected subcutaneously or intramuscularly, phenylephrine takes 10 to 15 minutes to act. Subcutaneous and intramuscular injections are effective for up to about one and up to about two hours respectively. Intravenous injections are effective for up to about 20 minutes.

Following an intravenous infusion of phenylephrine hydrochloride, the effective half-life was approximately 5 minutes.

Distribution

The steady-state volume of distribution (340 L) exceeded the body volume by a factor of 5, suggesting a high distribution into certain organ compartments.

Biotransformation

A mass balance study showed that phenylephrine is extensively metabolised by the liver with only 12 % of the dose excreted unchanged in the urine. Deamination by monoamino oxidase is the primary metabolic pathway resulting in the formation of the major metabolite (m-hydroxymandelic acid) which accounts for 57 % of the total administered dose.

Elimination

The average total serum clearance (2095 mL/min) was close to one-third of the cardiac output.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate (for pH-adjustment)

Sodium chloride

Sodium citrate dihydrate (for pH-adjustment)

Sodium metabisulphite (E223)

Water for injection.

6.2 Incompatibilities

Phenylephrine injection has been stated to be incompatible with alkalies, ferric salts, phenytoin sodium and oxidising agents.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

1 mL clear Fiolax ampoule (USP Type I) with a pink OPC dot.

1 mL clear NEG ampoule (USP Type I) with a black OPC dot.

5 or 10 ampoules are placed in a plastic tray and packed in an outer carton.

6.6 Special precautions for disposal and other handling

None.

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

56/7.2/0060

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 06 June 2023

10. DATE OF REVISION OF THE TEXT