PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

PHENPRESSOR 10 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 10 mg/ml phenylephrine hydrochloride.

Contains sodium hydroxide: q.s. to pH adjustment

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

A clear colourless solution with a pH range of 3,5 to 5,0.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PHENPRESSOR 10 mg/ml 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

Posology

Patients receiving PHENPRESSOR 10 mg/ml should be closely monitored.

Treatment with PHENPRESSOR 10 mg/ml 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 phenylephrine.

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.

Dosing for perioperative setting

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

- 50 µg to 250 µg by intravenous bolus administration. The most frequently reported initial bolus dose is 50 µg or 100 µg.
- 0,5 µg/kg/min to 1,4 µg/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 µg/kg/min to 6 µg/kg/min by intravenous continuous infusion, titrated to blood pressure goal. Doses above 6 µg/kg/min do not show significant incremental increase in blood pressure.

Method of administration

PHENPRESSOR 10 mg/ml is not for intramuscular or subcutaneous use.

Caution is recommended to avoid extravasation, which may cause tissue necrosis and sloughing of surrounded 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.

PHENPRESSOR 10 mg/ml must be diluted before administration as slow

intravenous bolus injection or intravenous infusion or continuous intravenous infusion.

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. Infusion of PHENPRESSOR 10 mg/ml 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. The diluted solution should not be kept for more than 4 hours at room temperature or for more than 24 hours under refrigerated conditions. Discard any unused portion.

For preparation of the solution for injection, see section 6.6.

4.3 Contraindications

- Hypersensitivity to phenylephrine or to any of the excipients of PHENPRESSOR 10 mg/ml (see section 6.1).
- Patients taking monoamine oxidase inhibitors, or within 14~~-5~~ days of ceasing such treatment (see section 4.4 and 4.5).
- Paediatric use.
- Severe uncontrolled hypertension.
- Severe hyperthyroidism.
- Severe heart-block with or without bradycardia.
- Severe bradycardia (less than 50 bpm).
- Uncontrolled cardiac failure.
- Severe impaired coronary circulation.
- Prostatic enlargement.

4.4 Special warnings and precautions for use

Sustained IV infusion may result in diminished effect.

Cardiovascular effects

Great care should be exercised in administering PHENPRESSOR 10 mg/ml to patients with pre-existing cardiovascular disease such as ischaemic heart disease, dysrhythmias, occlusive vascular disease including arteriosclerosis, hypertension or aneurysms.

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. Increased blood pressure may occur and precipitate underlying heart failure, angina in patients with severe arteriosclerosis or past history of angina and increased pulmonary arterial pressure.

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.

Dermatological effects

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

Endocrine and metabolic effects

Use extreme caution in patients with hyperthyroidism. Care is also required when given to patients with diabetes mellitus.

Monoamine oxidase (MAO) inhibitors

Concurrent use 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 (see section 4.3 and 4.5).

Immunologic effects

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

Neurologic effects

Blood pressure response to PHENPRESSOR 10 mg/ml may be increased in patients with autonomic disfunction.

Renal toxicity

PHENPRESSOR 10 mg/ml can increase the need for renal therapy in patients with septic shock. Monitor renal function.

Effects on the eye

Care is required when given to patients with closed angle glaucoma.

4.5 Interaction with other medicines and other forms of interaction

Phenylephrine may interact with cyclopropane and halothane and other halogenated inhalational anaesthetics, to induce ventricular fibrillation.

An increased risk of dysrhythmias may also occur if phenylephrine injection is given to patients receiving cardiac glycosides (such as digoxin), quinidine or tricyclic antidepressants (such as imipramine) and nor adrenergic-serotonergic antidepressants (such as minalcipram, venlafaxine).

Phenylephrine is a hypertensive medicine and may consequently reverse the action of many antihypertensive and diuretic medicines. The patient should be carefully monitored to confirm the desired effect is obtained.

Interactions of phenylephrine with alpha and beta receptor blocking medicines may be complex. Medicines which have an effect on α1 adrenoceptors could potentiate (such as clonidine) the vasopressive action of phenylephrine and may result in profound bradycardia, or inhibit (such as doxazosin, labetalol, prazosin, haloperidol, phenothiazines) the vasopressive action of phenylephrine.

Caution should be applied when administering atomoxetine concurrently, as there is potential for synergistic pharmacological effects.

Severe hypertension may occur following the use of phenylephrine and atropine or other antimuscarinics.

The pressor effects of phenylephrine may be slightly reduced by lithium carbonate.

The effects of phenylephrine may be potentiated by the use of monoamine oxidase inhibitors (such as selegiline, moclobemide, linezolid, nialamide, pargyline, phenelzine) or reversible inhibitors of monoamine oxidase (see section 4.3 and 4.4). This interaction is still possible 15 days after discontinuation of the MAO.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of PHENPRESSOR 10 mg/ml during pregnancy has not been established. Due to the vasoconstrictive properties of phenylephrine, PHENPRESSOR 10 mg/ml should be used with caution in patients with a history of pre-eclampsia. Administration of PHENPRESSOR 10 mg/ml in late pregnancy or labour may cause foetal hypoxia and bradycardia.

Breastfeeding

The safety of PHENPRESSOR 10 mg/ml during lactation has not been established. Excretion of phenylephrine in breast milk appears to be minimal.

Fertility

No data is available on fertility.

4.7 Effects on ability to drive and use machines

No adverse effects known.

4.8 Undesirable effects

a. Summary of the safety profile

A tabulated list of undesirable effects is outlined below:

The undesirable effects are listed according to organ systems and following frequency: Frequent, Less frequent, Frequency unknown (cannot be estimated from the available data).

b. Tabulated summary of adverse reactions

MedDRA system organ class	Frequency	Adverse reactions
Immune system disorders	Less frequent	Hypersensitivity
Metabolism and nutrition disorders	Frequency unknown	Metabolic disorders
Psychiatric disorders	Less frequent	Nervousness, insomnia, anxiety, excitability, agitation, psychotic states, confusion
Nervous system disorders	Frequent	Headache
	Less frequent	Paraesthesia, tremor
	Frequency unknown	Cerebral haemorrhage
Eye disorders	Less frequent	Mydriasis, angle-closure glaucoma
Cardiac disorders	Less frequent	Bradycardia, tachycardia, ventricular dysrhythmia, angina pectoris
	Frequency unknown	Palpitations, cardiac arrest

MedDRA system organ class	Frequency	Adverse reactions
Vascular disorders	Less frequent	Hypotension, hypertension, cerebral haemorrhage, hypertensive crisis
	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 disorder	Less frequent	Sweating, pallor or skin blanching, piloerection, skin necrosis with extravasation
Musculoskeletal disorders	Less frequent	Muscle weakness
Renal and urinary disorders	Less frequent	Dysuria, urinary retention
General disorders and administration site conditions	Frequency unknown	Extravasation, infusion site necrosis, hyperhidrosis
Investigations	Frequency unknown	Increased blood pressure, abnormal blood glucose

c. Description of selected adverse reactions

Phenylephrine is without significant stimulating effects on the central nervous system at usual doses.

PHENPRESSOR 10 mg/ml 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 PHENPRESSOR 10 mg/ml in high doses or low doses in the presence of peripheral vascular disease.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. 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, vomiting, hypertension 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 medicine temporarily discontinued until the blood pressure is decreased. If the

measures fail to lower the blood pressure, a short acting alpha-adrenergic blocking medicine may be administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: adrenergic and dopaminergic medicine. ATC code: C01CA6.

Pharmacological classification: 7.2 Vasoconstrictors, pressor medicines.

Phenylephrine is an alpha 1 adrenergic receptor agonist. After injection phenylephrine produces peripheral vasoconstriction and an increase in arterial pressure; it also produces reflex bradycardia. Beta 1 adrenergic effects are insignificant.

5.2 Pharmacokinetic properties

Distribution

Following intravenous infusion of phenylephrine hydrochloride, the effective half-life is approximately 5 minutes. The steady-state volume of distribution (340 l) exceeds the body volume by a factor of 5, suggesting a high distribution into certain organ compartments. The average total serum clearance (2 095 ml/min) is close to one-third of the cardiac output.

Metabolism and elimination

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 monoamine 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.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate (E330)

Hydrochloric acid (for pH adjustment) (E507)

Sodium chloride

Sodium citrate dihydrate (E331)

Sodium hydroxide (for pH adjustment) (E524)

Sodium metabisulfite (E223)

Water for injection

6.2 Incompatibilities

PHENPRESSOR 10 mg/ml has been stated to be incompatible with alkalies, ferric salts, phenytoin sodium and oxidising medicines.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

After dilution with 5 % Dextrose Injection or 0,9 % Sodium Chloride Injection, the diluted solution can be stored at or below 25 °C for 4 hours or at 2 – 8 °C for 24 hours.

6.5 Nature and contents of container

5 ml USP Type-I Clear glass tubular vial closed with 20 mm grey chlorobutyl rubber stoppers and 20 mm aluminium flip-off seals with blue colour button.

10 ml USP Type-I Clear glass tubular vial closed with 20 mm grey chlorobutyl rubber stoppers and 20 mm aluminium flip-off seals with orange colour button.

6.6 Special precautions for disposal and other handling

Preparing a 50 µg/ml solution of bolus intravenous administration

For bolus intravenous administration, add 10 mg (1 ml of a 10 mg/ml concentration) of PHENPRESSOR 10 mg/ml to 200 ml of 5 % Dextrose Injection or 0,9 % Sodium Chloride Injection. This will yield a final concentration of 50 µg/ml. Withdraw an appropriate dose from the 50 µg/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 PHENPRESSOR 10 mg/ml and add 500 ml of 5 % Dextrose Injection or 0,9 % Sodium Chloride Injection (providing a final concentration of 20 µg/ml).

7 HOLDER OF CERTIFICATE OF REGISTRATION

Kahma Biotech (Pty) Ltd

106, 16th Road

Midrand, 1686

Gauteng

South Africa

8 REGISTRATION NUMBER

550361

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 April 2023

10 DATE OF REVISION OF THE TEXT