PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

HYPOPRESS 10 mg/ml (solution for injection or infusion)

HYPOPRESS 10 mg/ml can only be administered via IV after dilution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

HYPOPRESS 10 mg/ml contains 10 mg/ml phenylephrine hydrochloride. One ampoule of 1 ml contains 10 mg of phenylephrine hydrochloride.

1 ampoule of 1 ml contains 0,103 mmol (or 2,36 mg) sodium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion.

A clear colourless solution.

pH 3,0 – 5,0

Osmolarity: 270 – 300 mOsm/l.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HYPOPRESS 10 mg/ml is indicated for increasing blood pressure in adults with clinically significant hypotension resulting primarily from vasodilation in such settings as septic shock and anaesthesia.

Submission date: May 2024
Implemented: 10 May 2024

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

4.2 Posology and method of administration

HYPOPRESS 10 mg/ml can only be administered via IV after dilution.

HYPOPRESS 10 mg/ml should only be administered by healthcare professionals with appropriate training and relevant experience in the safe administration of phenylephrine preparations. HYPOPRESS 10 mg/ml should be administered in the lowest effective dosage for the shortest possible time. When possible, small doses should be injected initially and subsequent doses determined by pressor response.

Patients receiving HYPOPRESS 10 mg/ml should be closely monitored. Treatment with HYPOPRESS 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.

Posology

Adults

Intravenous bolus injection:

10 mg of phenylephrine (1 ml of HYPOPRESS 10 mg/ml) must be diluted to 200 ml of glucose 5 % injection or sodium chloride 0,9 % injection prior to bolus intravenous injection. This dilution yields 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.

- 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.

Continuous infusion:

10 mg of phenylephrine (1 ml of HYPOPRESS 10 mg/ml) must be diluted in 500 ml of glucose 5 % injection or sodium chloride 0,9 % injection prior to administration via intravenous infusion:

- Dosing for Perioperative Setting

  In adult patients undergoing surgical procedures with either neuraxial anaesthesia or general anaesthesia: 0,5 µg/kg/min to 1,4 µg/kg/min by intravenous continuous infusion, titrated to blood pressure goal.

- Dosing for septic shock

  In adult patients with septic 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.

Special populations

Patients with renal impairment:

Lower doses of HYPOPRESS 10 mg/ml may be required in patients with renal impairment.

Patients with hepatic impairment:

Higher doses of HYPOPRESS 10 mg/ml may be needed in patients with liver cirrhosis.

Elderly patients:

Treatment of the elderly should be made with caution.

Paediatric population:

HYPOPRESS 10 mg/ml should not be administered to paediatric patients (see Section 4.3). The safety and efficacy of HYPOPRESS 10 mg/ml in children have not been established. No data are available.

Method of administration:

HYPOPRESS 10 mg/ml should be administered by slow intravenous bolus injection or continuous intravenous infusion, after dilution.

When discontinuing therapy, the dosage should be reduced gradually, since sudden cessation of therapy may result in severe hypotension, intravascular fluid should be administered if necessary to avoid hypotension.

4.3 Contraindications

Hypersensitivity to phenylephrine hydrochloride, or to any of the excipients (see section 6.1).

Paediatric use.

HYPOPRESS 10 mg/ml is contraindicated in the presence of severe:

- Uncontrolled hypertension or peripheral vascular disease due to the risk of ischaemic gangrene or vascular thrombosis.
- Hyperthyroidism.
- Heart-block with or without bradycardia.
- Uncontrolled cardiac failure.
- Bradycardia (less than 50 bpm).
- Seriously impaired coronary arterial circulation.

HYPOPRESS 10 mg/ml should not be used in combination with indirectly acting sympathomimetic medicines (ephedrine, methylphenidate, pseudoephedrine): risk of vasoconstriction and / or hypertensive crisis.

HYPOPRESS 10 mg/ml should not be used in combination with alpha-sympathomimetic medicines (oral and / or nasal use) (etilefrine, midodrine, naphazoline, oxymetazoline, synephrine, tetryzoline, tuaminoheptane, tymazoline): risk of vasoconstriction and / or hypertensive crisis.

HYPOPRESS 10 mg/ml should not be used in combination with non-selective monoamine oxidase inhibitors (MAOs) (or within 2 weeks of their withdrawal), due to risk of paroxysmal arterial hypertension and possibly fatal hyperthermia (see section 4.5).

4.4 Special warnings and precautions for use

Sustained IV infusion may result in diminished efficacy.

Arterial blood pressure should be monitored during treatment.

HYPOPRESS 10 mg/ml should be given with caution to patients with:

- Diabetes.
- Arterial hypertension.
- Aneurysm.
- Uncontrolled hyperthyroidism.
- Coronary heart disease and chronic heart disease.
- Bradycardia.
- Tachycardia.
- Dysrhythmia.
- Angina pectoris (phenylephrine can precipitate or exacerbate angina in patients with coronary artery disease and history of angina).
- Non-severe peripheral vascular insufficiency.
- Closed angle glaucoma.

Concurrent use of a halogenated volatile anaesthetic (e.g., desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane) with HYPOPRESS 10 mg/ml may increase the risk of perioperative hypertensive crisis and dysrhythmia (see section 4.5).

HYPOPRESS 10 mg/ml may cause severe bradycardia and decreased cardiac output. 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 increase pulmonary arterial pressure.

In patients with severe heart failure or cardiogenic shock, HYPOPRESS 10 mg/ml may cause a worsening of heart failure as a result of the induced vasoconstriction (increased afterload).

Therefore, it should be administered with extreme caution in patients with atherosclerosis, in the elderly and in patients with impaired cerebral or coronary arterial circulation.

Patients with medical conditions such as decreased cardiac output or peripheral or coronary artery disease should have frequent monitoring of vital body functions and lower systemic blood pressure boundary should be considered as a criterion for dose reduction or discontinuation of HYPOPRESS 10 mg/ml.

Particular attention should be paid during injection to avoid extravasation, since this may cause tissue necrosis.

Lower doses may be required in patients with renal impairment.

Higher doses may be required in patients with liver cirrhosis.

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

The administration of HYPOPRESS 10 mg/ml simultaneously with the following medicines is not recommended, because of the risk of vasoconstriction and / or hypertensive crisis associated with its indirect sympathomimetic effect (see section 4.5):

- dopaminergic ergot alkaloids (bromocriptine, carbergoline, lisuride or pergolide) or vasoconstrictors (dihydroergotamine, ergotamine, or methysergide, methylergometrine).
- in combination with linezolid.

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.

HYPOPRESS 10 mg/ml contains 2,36 mg sodium per ml, equivalent to 0,1 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

Combinations that are contraindicated (see section 4.3):

- Non-selective monoamine oxidase inhibitors (MAOIs) (iproniazid, nialamide, phenelzine): increased risk of paroxysmal hypertension, hyperthermia possibly fatal. Due to the long duration of action of MAOIs, this interaction is still possible 15 days after discontinuation of the MAOIs.
- Indirect sympathomimetics medicines (ephedrine, methylphenidate, pseudoephedrine): increased risk of vasoconstriction and / or hypertensive crisis.
- Alpha sympathomimetic medicines (oral and/or nasal use) (etilefrine, midodrine, naphazoline, oxymetazoline, synephrine, tetryzoline, tuaminoheptane, tymazoline): increased risk of vasoconstriction and / or hypertensive crisis.

Combinations not recommended (see section 4.4):

- Dopaminergic ergot alkaloids (bromocriptine, cabergoline, lisuride and pergolide): increased risk of vasoconstriction and/or hypertensive crisis.
- Vasoconstrictor ergot alkaloids (dihydroergotamine, ergotamine, methylergometrine, methysergide): increased risk of vasoconstriction and/or hypertensive crisis.
- Linezolid: increased risk of vasoconstriction and/or hypertensive crisis.
- Tricyclic antidepressants (desipramine, imipramine, nortriptyline): increased risk of paroxysmal hypertension with possibility of dysrhythmia (inhibition of adrenaline or noradrenaline entry in sympathetic fibres).
- Noradrenergic-serotoninergic antidepressants (venlafaxine): increased risk of paroxysmal arterial hypertension with possibility of dysrhythmias (inhibition of adrenaline or noradrenaline entry in sympathetic fibres).
- Selective monoamine oxidase inhibitors (MAOs) (moclobemide, pargyline, selegiline, toloxatan): risk of vasoconstriction and/or hypertensive crisis.
- Guanethidine and related products: 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 lower doses of sympathomimetic medicines.

- Digoxin, quinidine: increased risk of dysrhythmias.
- Halogenated volatile anaesthetics (desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane): risk of perioperative hypertensive crisis and dysrhythmia.
- The effect of antihypertensive and diuretic medicines used as antihypertensives may be reduced when used concurrently with HYPOPRESS 10 mg/ml; the patient should be carefully monitored to confirm the desired effect is obtained.
- Beta-adrenoceptor-blocking medicines, systemic or ophthalmic - concurrent use of HYPOPRESS 10 mg/ml may result in an exaggeration of the vasoconstriction effects and profound bradycardia.
- Reserpine and other sympatholytic medicines - concomitant use with HYPOPRESS 10 mg/ml causes a substantial increase in blood pressure. If the combination cannot be avoided, use with caution.
- The pressor effect of HYPOPRESS 10 mg/ml is increased in patients receiving atropine sulphate.

Combinations requiring caution:

- Oxytocic medicines: The effect of presso-active sympathomimetic amines is potentiated. Thus, some oxytocic medicines may cause severe persistent hypertension and strokes can occur during post-partum period.
- Digoxin: HYPOPRESS 10 mg/ml may be used with digoxin for therapeutic advantage; caution and close electrocardiographic monitoring are recommended during concurrent use.

- Alpha-adrenoceptor-blocking medicines (doxazosin, labetalol, prazosin, haloperidol, phenothiazines): concurrent use may antagonise the peripheral vasoconstriction effect of HYPOPRESS 10 mg/ml.

4.6 Fertility, pregnancy and lactation

Fertility

There are no data available regarding fertility, following treatment with HYPOPRESS 10 mg/ml (see section 5.3).

Pregnancy

The safety of HYPOPRESS 10 mg/ml during pregnancy has not been established. Animal studies are insufficient with respect to effects on pregnancy, embryonal / foetal development, parturition or postnatal development. The potential risk for humans is unknown.

Breastfeeding

The safety of HYPOPRESS 10 mg/ml during breastfeeding has not been established. Small amounts of phenylephrine are excreted in human milk. The administration of vasoconstrictors to the mother puts the child at risk for cardiovascular and neurological effects. HYPOPRESS 10 mg/ml should not be used during lactation.

4.7 Effects on ability to drive and use machines

HYPOPRESS 10 mg/ml can cause undesirable effects (including hypotension with dizziness, fainting, dyspnoea, muscular weakness), which may affect the ability to drive and use machines.

Patients should be advised not to engage in driving or using machines until they know how HYPOPRESS 10 mg/ml might affect them.

4.8 Undesirable effects

Most of the adverse events of phenylephrine are dose-dependent and a consequence of the expected pharmacodynamic profile.

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

System Organ Class	**Undesirable effects**	**Frequency**
Immune system disorders	Hypersensivity	Less frequent
Metabolism and nutrition disorders	Glucose metabolism abnormal	Not known*
Psychiatric disorders	Euphoria, agitation, anxiety, psychotic states, confusion	Less frequent
Nervous system disorders	Headache	Frequent
	Tingling, fullness head, nervousness or restlessness, insomnia, paraesthesia, tremor	Less frequent

Eye disorders	Mydriasis, aggravation of pre-existing angle-closure glaucoma	Less frequent
Cardiac disorders	Anginal pain, reflex bradycardia, tachycardia, ventricular dysrhythmias	Less frequent
	Dysrhythmia, cardiac arrest, palpitations, myocardial ischemia	Not known*
Vascular disorders	Cerebral haemorrhage, hypertension, hypotension with dizziness, hypertensive crisis, pallor	Less frequent
	Fainting, flushing, coldness of skin	Not known*
Respiratory, thoracic and mediastinal disorders	Dyspnoea, pulmonary oedema	Less frequent
Gastrointestinal disorders	Vomiting, nausea	Less frequent
	Hypersalivation	Not known*
Skin and subcutaneous tissue disorders	Piloerection, sweating, skin blanching	Less frequent
	Diaphoresis	Not known*
Musculoskeletal and connective tissue disorders	Muscular weakness	Less frequent
Renal and urinary disorders	Difficulty in micturition, urinary retention	Less frequent

General disorders and administration site conditions	Extravasation necrosis at injection site	Less frequent

* Frequency cannot be estimated from available data.

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. Healthcare 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 of overdosage include headache, nausea, vomiting, hypertension (which may be severe), palpitations and reflex bradycardia and other cardiac dysrhythmias (ventricular extra systoles and short paroxysms of ventricular tachycardia). Treatment should consist of symptomatic and supportive measures.

Should an excessive elevation of blood pressure occur, the administration of HYPOPRESS 10 mg/ml should be reduced or temporarily discontinued until blood pressure is decreased. If these measures fail to lower the blood pressure, a short acting alpha adrenoceptor blocking medicine (e.g. phentolamine, 5 to 60 mg i.v. over 10 – 30 minutes, repeated as necessary) may be administered.

Reflex bradycardia may be expected with a significant increase in blood pressure.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: 6.1 Cardiac stimulants

Pharmacotherapeutic group: Cardiac stimulants, excluding cardiac glycosides

ATC code: C01C A06

Mechanism of action

Phenylephrine acts predominantly by direct stimulation of alpha1-adrenergic receptors. In therapeutic doses, it has no substantial stimulant effect on the beta-adrenergic receptors of the heart (beta1-adrenergic receptors), but substantial activation of these receptors may occur when larger doses are given. Phenylephrine does not stimulate beta-adrenergic receptors of the bronchi or peripheral blood vessels (beta2-adrenergic receptors). It is believed that alpha1-adrenergic effects result from the inhibition of the production of cyclic adenosine-3',5'-monophosphate (cAMP) by inhibition of the enzyme adenyl cyclase, whereas beta-adrenergic effects result from stimulation of adenyl cyclase activity. Phenylephrine also has an indirect effect by releasing norepinephrine from its storage sites.

Pharmacodynamic effects

The predominant actions of phenylephrine are on the cardiovascular system. Parenteral administration causes a rise in systolic and diastolic pressures. Accompanying the pressor response to phenylephrine is a marked reflex bradycardia that can be blocked by atropine; after atropine, large doses of the medicine increase the heart rate only slightly. Cardiac output is slightly decreased and peripheral resistance is considerably increased. Circulation time is slightly prolonged, and venous pressure is slightly increased; venous constriction is not marked. Most vascular beds are constricted; renal splanchnic, cutaneous and limb blood flows are reduced but coronary blood flow is increased. Pulmonary vessels are constricted, and pulmonary arterial pressure is raised.

Clinical efficacy and safety

Phenylephrine is a potent vasoconstrictor that acts almost exclusively through stimulation of alpha 1-adrenergic receptors. Such arterial vasoconstriction, also accompanied by venous vasoconstriction, provides an increase in blood pressure and bradycardia reflex and its pressor activity is weaker than that of noradrenaline but of longer duration. It is used parenterally in the treatment of hypotensive states, such as those encountered during circulatory failure, general or spinal anaesthesia or medicine induced hypotension. In many published clinical studies phenylephrine was used in low-risk pregnant women undergoing spinal anaesthesia during Caesarean delivery.

Phenylephrine allowed to maintain maternal blood pressure near to baseline reduced the incidence of nausea and vomiting without causing foetal acidosis.

Actually in therapeutic doses, it produces little if any stimulation of either the spinal cord or cerebrum. A singular advantage of this medicine is the fact that repeated injections produce comparable effects.

The potent arterial vasoconstriction resulting in an increase in the resistance of ventricular ejection fraction (increased afterload). Which results in a reduction of cardiac output, this is less pronounced in healthy people but can be exacerbated in the case of previous heart failure.

5.2 Pharmacokinetic properties

Absorption

After intravenous (IV) administration, a pressor effect occurs almost immediately and persists for 15 – 20 minutes. After intramuscular (IM) administration, a pressor effect occurs within 10 – 15 minutes and persists for 30 minutes to 1 or 2 hours.

Distribution

Phenylephrine undergoes rapid distribution into peripheral tissues; there is some evidence that it may be stored in certain organ compartments. Plasma protein binding is unknown. The volume of distribution is 340 litres, after a single dose, exceeded the body volume by a factor of 5, suggesting a high distribution into certain organ compartments. The pharmacologic effects of phenylephrine are terminated at least partially by uptake into tissues. Penetration of phenylephrine into the central nervous system (CNS) appears to be minimal. Phenylephrine does not appear to be distributed to any great extent into breast milk. The average total serum clearance (2095 ml/min) was close to one-third of the cardiac output.

Metabolism and Elimination

Phenylephrine undergoes extensive metabolism in the intestinal wall and in the liver, with only 12 % of the dose excreted unchanged in the urine. The principal routes of metabolism involve sulphate conjugation (primarily in the intestinal wall) and oxidative deamination by monoamine oxidase (MAO) resulting in the formation of the major metabolite (m-hydroxymandelic acid) which accounts for 57 % of the total administered dose; glucuronidation also occurs to a lesser extent. The elimination of phenylephrine is primarily urinary and elimination via the renal route seems to be similar between the IV and per oral routes; 86 % and 80 % of the administered dose, respectively. The short duration of action of phenylephrine (about 20 minutes after IV injection) suggests a rapid distribution, metabolism and elimination from the body.

Pharmacokinetics in Special Populations

There are no data available on the pharmacokinetics in special populations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid, sodium chloride and water for injections.

6.2 Incompatibilities

HYPOPRESS 10 mg/ml is not compatible with alkaline solutions, iron salts and other metals, phenytoin sodium and oxidising medicines.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30 °C in the outer carton.

Do not refrigerate or freeze.

Use immediately after opening.

Maintain strict aseptic standards during dilution for administration by intravenous infusion.

6.5 Nature and contents of container

HYPOPRESS 10 mg/ml is presented in 2 ml (1 ml fill) one point cut clear Type I glass ampoules. Ampoules are packed into outer cardboard cartons in pack sizes of 10.

6.6 Special precautions for disposal and other handling

HYPOPRESS 10 mg/ml must be diluted prior to bolus intravenous injection or intravenous infusion.

Bolus intravenous injection:

1 ml of HYPOPRESS 10 mg/ml can be diluted to 200 ml of glucose 5 % injection or sodium chloride 0,9 % injection.

Intravenous infusion:

1 ml of HYPOPRESS 10 mg/ml can be diluted in 500 ml of glucose 5 % solution or sodium chloride 0,9 % solution.

For single use only.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Umsebe Healthcare

506 Sunclare Building

21 Dreyer Street, Claremont

Cape Town

7708

South Africa

Name of Manufacturer: Sintetica SA

8. REGISTRATION NUMBER

55/6.1/0353

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

9 November 2021

10. DATE OF REVISION OF THE TEXT

10 May 2024

NAMIBIA:

Reg. No.: 21/7.2/0003 NS2