| | | |
|---|---|---|
| Applicant/HCR | : | Umsebe Healthcare V4 (31.01.2022) |
| Product name, strength and dosage form | : | Hypopress 0,1 mg/ml (solution for injection or infusion)<br>Hypopress 10 mg/ml (solution for injection or infusion) |

# PROFESSIONAL INFORMATION

**SCHEDULING STATUS S4**

## 1. NAME OF THE MEDICINE

HYPOPRESS 0,1 mg/ml (solution for injection or infusion)

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 0,1 mg/ml contains 0,1 mg/ml (100 µg/ml) phenylephrine hydrochloride. One ampoule of 5 ml contains 0,5 mg of phenylephrine hydrochloride.

1 ampoule of 5 ml contains 0,77 mmol (or 17,7 mg) sodium.

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

HYPOPRESS 0,1 mg/ml:

Solution for injection or infusion.

A clear colourless solution.

pH 3,0 – 5,0



Submission date: January 2022
Implemented: 31 January 2022

Osmolarity: 270 – 300 mOsm/l.

HYPOPRESS 10 mg/ml:

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

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 should only be administered by healthcare professionals with appropriate training and relevant experience in the safe administration of phenylephrine preparations. HYPOPRESS 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 should be closely monitored. Treatment with HYPOPRESS 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***

HYPOPRESS 0,1 mg/ml:

*Intravenous bolus injection:*

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:*

- 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.

HYPOPRESS 10 mg/ml:

*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 may be required in patients with renal impairment.

***Patients with hepatic impairment:***

Higher doses of HYPOPRESS 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 HYPOPRESS in children have not been established. No data are available.

**Method of administration:**

HYPOPRESS 0,1 mg/ml should be administered by slow intravenous bolus injection or continuous intravenous infusion.

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).
- Patients with severe hypertension.
- Patients with peripheral vascular disease, as it can lead to ischaemia with a risk of gangrene or vascular thrombosis.

- Patients with heart-block with or without bradycardia, uncontrolled cardiac failure, bradycardia less than 50 bpm or seriously impaired coronary arterial circulation.
- In combination with indirectly acting sympathomimetic medicines (ephedrine, methylphenidate, pseudoephedrine): risk of vasoconstriction and / or hypertensive crisis.
- 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.
- 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).
- Patients with severe hyperthyroidism.

**4.4 Special warnings and precautions for use**

Arterial blood pressure should be monitored during treatment.

HYPOPRESS should be given with caution to patients with:

- Diabetes.
- Arterial hypertension.
- Aneurysm.
- Uncontrolled hyperthyroidism.
- Coronary heart disease and chronic heart disease.
- Bradycardia.
- Heart block.
- 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.
- Peripheral vascular diseases e.g. Raynaud's phenomenon.
- Closed angle glaucoma.

HYPOPRESS may induce a decrease in cardiac output. 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.

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

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.

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.

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

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

The administration of HYPOPRESS 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 0,1 mg/ml contains 3,54 mg sodium per ml, equivalent to 0,2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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; the patient should be carefully monitored to confirm the desired effect is obtained.
- Beta-adrenoceptor-blocking medicines, systemic or ophthalmic - concurrent use of HYPOPRESS may result in an exaggeration of the vasoconstriction effects and profound bradycardia.
- Reserpine and other sympatholytic medicines - concomitant use with HYPOPRESS causes a substantial increase in blood pressure. If the combination cannot be avoided, use with caution.
- The pressor effect of HYPOPRESS 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 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.

**4.6 Fertility, pregnancy and lactation**

**Fertility**

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

**Pregnancy**

The safety of HYPOPRESS 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 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 should not be used during lactation.

**4.7 Effects on ability to drive and use machines**

No studies done.

**4.8 Undesirable effects**

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

HYPOPRESS 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 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 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 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 0,1 mg/ml is presented in 5 ml one point cut clear Type I glass ampoules. Ampoules are packed into outer cardboard cartons in pack sizes of 10.

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**

The dilution before intravenous infusion of HYPOPRESS 0,1 mg/ml is not necessary.

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

Unit 20, Sunclare Building, 3rd Floor

21 Dreyer Street, Claremont

Cape Town

7708

South Africa

**Name of Manufacturer:** Sintetica SA

## 8. REGISTRATION NUMBERS

HYPOPRESS 0,1 mg/ml: 55/6.1/0352

HYPOPRESS 10 mg/ml: 55/6.1/0353

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

9 November 2021

## 10. DATE OF REVISION OF THE TEXT

31 January 2022

**NAMIBIA:**

HYPOPRESS 0,1 mg/ml: Reg. No.: 21/7.2/0002 NS2

HYPOPRESS 10 mg/ml: Reg. No.: 21/7.2/0003 NS2