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Professional information for PHENYLEPHRINE HYDROCHLORIDE INJECTION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PHENYLEPHRINE HYDROCHLORIDE INJECTION (10 mg/mL solution for injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL ampoule contains 10 mg of phenylephrine hydrochloride.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Colourless, sterile, aqueous solution, practically free from extraneous material, for parenteral administration, packed in ampoules containing 1 mL of solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PHENYLEPHRINE HYDROCHLORIDE INJECTION 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.

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4.2 Posology and method of administration

General dosing information

Patients receiving **PHENYLEPHRINE HYDROCHLORIDE INJECTION** should be closely monitored.

Treatment with **PHENYLEPHRINE HYDROCHLORIDE INJECTION** 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 hydrochloride.

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 **PHENYLEPHRINE HYDROCHLORIDE INJECTION** 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.

PHENYLEPHRINE HYDROCHLORIDE INJECTION 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.

Posology

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PHENYLEPHRINE HYDROCHLORIDE INJECTION 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.

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 **PHENYLEPHRINE HYDROCHLORIDE INJECTION** 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 **PHENYLEPHRINE HYDROCHLORIDE INJECTION** and add to 500 mL of 5 % dextrose injection or 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.

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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.

4.3 Contraindications

Hypersensitivity to phenylephrine hydrochloride or any of the excipients of **PHENYLEPHRINE HYDROCHLORIDE INJECTION** (see section 6.1).

Paediatric use.

PHENYLEPHRINE HYDROCHLORIDE INJECTION is contraindicated in the presence of severe:

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

PHENYLEPHRINE HYDROCHLORIDE INJECTION should not be used in combination with non-selective monoamine oxidase inhibitors (MAOs) (or within two weeks of their withdrawal) due to the risk of paroxymal 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.

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The arterial blood pressure should be monitored during treatment.

PHENYLEPHRINE HYDROCHLORIDE INJECTION should be administered with care to patients with:

- diabetes mellitus;
- tachycardia;
- dysrhythmias;
- angina pectoris (**PHENYLEPHRINE HYDROCHLORIDE INJECTION** can precipitate or exacerbate angina in patients with coronary artery disease and history of angina);
- aneurysma;
- closed angle glaucoma.

Concurrent use of a halogenated volatile anaesthetic (e.g. desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane) with **PHENYLEPHRINE HYDROCHLORIDE INJECTION** may increase the risk of perioperative hypertensive crisis and dysrhythmia (see section 4.5).

Cardiovascular effects: 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 increase pulmonary arterial pressure. In patients with serious heart failure or cardiogenic shock, **PHENYLEPHRINE HYDROCHLORIDE**

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INJECTION may cause deterioration in the heart failure as a consequence of the induced vasoconstriction (increase in afterload) (see section 4.3).

Therefore, care should be exercised in administering **PHENYLEPHRINE HYDROCHLORIDE INJECTION** to patients with arteriosclerosis, the elderly and to patients with impaired cerebral circulation. 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.

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

Endocrine and metabolic effects: Use extreme caution in patients with hyperthyroidism.

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).

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

Neurologic effects: Blood pressure response to **PHENYLEPHRINE HYDROCHLORIDE INJECTION** may be increased in patients with autonomic dysfunction.

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Renal Toxicity: PHENYLEPHRINE HYDROCHLORIDE INJECTION can increase the need for renal replacement therapy in patients with septic shock. Monitor renal function.

4.5 Interaction with other medicines and other forms of interaction

Contraindicated combinations

- Non-selective monoamine oxidase inhibitors (MAOIs) (e.g. iproniazid, nialamide, linezolid, phenelzine) – concurrent use with **PHENYLEPHRINE HYDROCHLORIDE INJECTION** may cause paroxysmal hypertension and possibly fatal hyperthermia. Due to the long duration of action of MOAIs, this interaction is still possible 15 days after discontinuation of the MOAI.

Inadvisable combinations

- Dopaminergic and vasoconstrictor ergot alkaloids such as bromocriptine, lisuride, cabergoline, pergolide dihydroergotamine, ergotamine, methylergometrine, methylsergide – concurrent use with **PHENYLEPHRINE HYDROCHLORIDE INJECTION** increases the risk of vasoconstriction and/or hypertensive crisis.
- Tricyclic antidepressants (e.g. imipramine) and noradrenergic-serotoninergic antidepressants (minalcipram, venlafaxine) – concomitant use with **PHENYLEPHRINE HYDROCHLORIDE INJECTION** causes paroxysmal hypertension with possibility of dysrhythmias due to the inhibition of epinephrine (adrenaline) or norepinephrine (noradrenaline) entry in sympathetic fibers.
- Selective type A monoamine oxidase inhibitors (e.g. moclobemide, toloxatone) – concurrent use with **PHENYLEPHRINE HYDROCHLORIDE INJECTION** may lead to a risk of vasoconstriction and/or hypertensive crisis. This interaction is still possible 15 days after discontinuation of monoamine oxidase inhibitors.

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- Selective type B monoamine oxidase inhibitors (e.g. selegiline, pargyline) – concurrent use with **PHENYLEPHRINE HYDROCHLORIDE INJECTION** may prolong and intensify cardiac stimulation and vasopressor effects (see section 4.4). This interaction is still possible 15 days after discontinuation of monoamine oxidase inhibitors.
- Linezolid – concurrent use with **PHENYLEPHRIN HYDROCHLORIDE INJECTION** may lead to a risk of vasoconstriction and/or hypertensive crisis.
- Guanethidine and related products – concurrent use with **PHENYLEPHRINE HYDROCHLORIDE INJECTION** may cause a substantial increase in blood pressure (hyper reactivity linked to the reduction in sympathetic tone and/or to the inhibition of adrenaline or noradrenaline entry in sympathetic fibers). If the combination cannot be avoided, use with caution lower doses of sympathomimetic medicines due to the increase in cardiovascular effects and the potential for side effects.
- Reserpine and other sympatholytic medicines – concomitant use with **PHENYLEPHRINE HYDROCHLORIDE INJECTION** 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 fibers). If the combination cannot be avoided, use with caution.
- Cardiac glycosides, quinidine – concurrent use with **PHENYLEPHRINE HYDROCHLORIDE INJECTION** may increase the risk of cardiac dysrhythmias.
- Halogenated volatile anaesthetics (desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane) – concurrent use with **PHENYLEPHRINE HYDROCHLORIDE INJECTION** may lead to a risk of perioperative hypertensive crisis and dysrhythmia.
- Alpha-adrenergic blocking medicines (e.g. doxazosin, labetalol, prazosin, haloperidol, phenothiazines) – concurrent use may antagonise the peripheral vasoconstriction effect of **PHENYLEPHRINE HYDROCHLORIDE INJECTION**.

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- The effect of antihypertensive and diuretic medicines used as antihypertensives may be reduced when used concurrently with **PHENYLEPHRINE HYDROCHLORIDE INJECTION**; the patient should be carefully monitored to confirm the desired effect is obtained.
- Beta-adrenergic blocking medicines, systemic or ophthalmic – concurrent use of **PHENYLEPHRINE HYDROCHLORIDE INJECTION** in the presence of beta-adrenergic medicines (systemic or ophthalmic) may result in an exaggeration of the vasoconstriction effects and profound bradycardia.
- The pressor effect of **PHENYLEPHRINE HYDROCHLORIDE INJECTION** is increased in patients receiving atropine sulfate.

Combinations requiring precautions for use

- Oxytocic medicines – concomitant use with **PHENYLEPHRINE HYDROCHLORIDE INJECTION** potentiates the vasopressor-active effects of sympathomimetic amines. Thus, some oxytocic medicines may cause severe persistent hypertension and strokes can occur during post-partum period.
- Digoxin – **PHENYLEPHRINE HYDROCHLORIDE INJECTION** may be used with digoxin for therapeutic advantage; caution and close electrocardiographic monitoring are recommended during concurrent use.

4.6 Fertility, pregnancy and lactation

Pregnancy

Administration of **PHENYLEPHRINE HYDROCHLORIDE INJECTION** in late pregnancy or labour may potentially cause fetal hypoxia and bradycardia. **PHENYLEPHRINE HYDROCHLORIDE INJECTION** is not recommended during pregnancy.

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The combination with some oxytocic medicines can cause severe hypertension (see section 4.5).

Breastfeeding

Small quantities of **PHENYLEPHRINE HYDROCHLORIDE INJECTION** are excreted into human breast milk and oral bioavailability may be low. Administering vasoconstrictors to the mother exposes the infant to a theoretical risk of cardiovascular and neurological effects.

However, in the event of a single bolus administration during childbirth, breastfeeding is possible.

Fertility

There is no available data concerning fertility after exposure to **PHEYLEPHRINE HYDROCHLORIDE INJECTION**.

4.7 Effects on ability to drive and use machines

PHENYLEPHRINE HYDROCHLORIDE INJECTION has no or negligible influence on the mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects

PHENYLEPHRINE HYDROCHLORIDE INJECTION can cause side effects.

PHENYLEPHRINE HYDROCHLORIDE INJECTION 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 **PHENYLEPHRINE HYDROCHLORIDE INJECTION** in high doses or low doses in the presence of peripheral vascular disease.

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Summary of the safety profile

The most frequent adverse events of **PHENYLEPHRINE HYDROCHLORIDE INJECTION** reported in literature are bradycardia, hypertensive episodes, nausea and vomiting. Most undesired effects of **PHENYLEPHRINE HYDROCHLORIDE INJECTION** are dose dependent.

Structured listing of adverse reactions

Immune system disorders:

Less frequent: hypersensitivity

Psychiatric disorders:

Less frequent: anxiety, excitability, agitation, psychotic states, confusion

Nervous system disorders:

Frequent: headache

Less frequent: nervousness or restlessness, insomnia, paresthaesia, tremor

Eye disorders:

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

Cardiac disorders:

Less frequent: angina, bradycardia, hypertension, hypotension, tachycardia, and ventricular dysrhythmias

Frequency unknown: reflex bradycardia, palpitations, dysrhythmia, myocardial ischemia

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Vascular disorders:

Less frequent: cerebral haemorrhage, hypertensive crisis

Respiratory, thoracic and mediastinal disorders:

Less frequent: dyspnoea, pulmonary oedema

Gastrointestinal disorders:

Less frequent: nausea, vomiting

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 and urinary retention

Description of selected adverse reactions

As **PHENYLEPHRINE HYDROCHLORIDE INJECTION** has been frequently used in the critical care setting in patients with hypotension and shock, some of the reported serious adverse events and deaths are probably related to the underlying disease and not related to the use of **PHENYLEPHRINE HYDROCHLORIDE INJECTION**.

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Other special population

Elderly: risk for phenylephrine toxicity is increased in elderly patients (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of **PHENYLEPHRINE HYDROCHLORIDE INJECTION** is important. It allows continued monitoring of the benefit/risk balance of **PHENYLEPHRINE HYDROCHLORIDE INJECTION**. 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 overdose include headache, nausea, vomiting, paranoid psychosis, hallucinations, hypertension (which may be severe), palpitations and reflex bradycardia. Cardiac dysrhythmia such as ventricular extra-systoles and short paroxysmal episodes of ventricular tachycardia may occur.

Treatment

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, such as phentolamine, may be administered.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: 7.2 Vasoconstrictors, pressor medicines.

Pharmacotherapeutic group: Adrenergic- and dopaminergic drugs.

ATC code: C01C A06.

Mechanism of action

Phenylephrine hydrochloride is a potent vasoconstrictor that acts almost exclusively by stimulation of alpha-1-adrenergic receptors. Arterial vasoconstriction is accompanied by venous vasoconstriction which gives an increase in blood pressure and reflex bradycardia. The potent arterial vasoconstriction results in an increase in the resistance which results in reduction of the cardiac output. This is less pronounced in healthy people, but can be exacerbated in the case of previous heart failure. Beta-1-adrenergic effects are insignificant.

5.2 Pharmacokinetic properties

Following an intravenous infusion of phenylephrine hydrochloride, the effective half-life was approximately 5 minutes. Plasma protein binding is unknown.

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 and elimination

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

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A mass balance study showed that phenylephrine hydrochloride 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid

Nitrogen

Sodium hydroxide

Water for injection.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from sunlight.

Keep out of reach of children.

Keep covered in carton until time of use.

For single use only. Discard unused portion.

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6.5 Nature and contents of container

5 x 1 mL amber colour, type I glass open ampoules, with snap-off neck packed in a tray and cardboard carton.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Abbott Laboratories S.A. (Pty) Ltd

Abbott Place, 219 Golf Club Terrace

Constantia Kloof, 1709

South Africa

8. REGISTRATION NUMBER

H630 (Act 101 of 1965)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 August 1976

10. DATE OF REVISION OF THE TEXT

05 October 2022

NAME AND ADDRESS OF THE MANUFACTURER OF THE MEDICINE

Alfasigma S.p.A

Via Enrico Fermi, 1

65020 Alanno (PE)

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Italy

Country	Registration number	Category of Distribution
Botswana	B9301910	S2
Namibia	90/3.1/0051	NS1