PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

TACYPHEN (solution for injection).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each ml contains: Phenylephrine hydrochloride 10 mg.

Sugar free.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Solution for injection.

Clear, colourless sterile solution for injection.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

TACYPHEN 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:

Patients receiving TACYPHEN should be closely monitored.

Treatment with TACYPHEN 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.

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 TACYPHEN 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 (see **section 6.3**).

TACYPHEN 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 and method of administration:

TACYPHEN 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.

For instructions on dilution of the product before administration, see **section 6.6**.

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.

4.3 Contraindications:

- Hypersensitivity to phenylephrine or to any of the excipients mentioned in **section 6.1**
- patients on treatment with monoamine oxidase (MAO) inhibitors or who have stopped this treatment within 14 days (see **section 4.4** and **4.5**)
- 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
- paediatric use.

4.4 Special warnings and precautions for use:

Sustained IV infusion may result in diminished efficacy.

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 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 (see **section 4.3**).

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.

Immunologic effects:

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

Neurologic effects:

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

Renal toxicity:

TACYPHEN can increase the need for renal replacement therapy in patients with septic shock. Monitor renal function.

Other:

TACYPHEN should be avoided in patients with prostatic enlargement.

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

4.5 Interaction with other medicines and other forms of interaction:

- TACYPHEN may interact with cyclopropane and halothane and other halogenated inhalational anaesthetics, to induce ventricular fibrillation.
- Alpha-adrenergic blocking medicines - concurrent use may antagonise the peripheral vasoconstriction effect of TACYPHEN. Examples: doxazosin, labetalol, granisetron, prazosin, haloperidol, phenothiazines.
- The effect of antihypertensive and diuretic medicines used as antihypertensives may be reduced when used concomitantly with TACYPHEN; the patient should be carefully monitored to confirm the desired effect is obtained.

- Beta-adrenergic blocking medicines, systemic or ophthalmic – concomitant use of TACYPHEN in the presence of beta-adrenergic medicines (systemic or ophthalmic) may result in an exaggeration of the vasoconstriction effects and profound bradycardia.
- Digoxin – TACYPHEN may be used with digoxin for therapeutic advantage; caution and close electrocardiographic monitoring are recommended during concomitant use.
- Other sympathomimetic medicines - concomitant use with TACYPHEN may increase cardiovascular effects and the potential for side effects.
- Monoamine oxidase (MAO) inhibitors such as selegiline, moclobemide, linezolid, nialamide, pargyline, phenelzine - concomitant use may prolong and intensify cardiac stimulation and vasopressor effects (see **section 4.3**). This interaction is still possible 15 days after discontinuation of MAO (see **section 4.3**).
- Ergot alkaloids such as bromocriptine, lisuride, carbergoline, pergolide dihydroergotamine, ergotamine, methylergometrine, and methylsergide - concomitant use with TACYPHEN increases the risk of vasoconstriction and/or hypertensive crisis.
- Tricyclic antidepressants (e.g. imipramine) and noradrenergic-serotoninergic antidepressants (minalcipran, venlafaxine) - concomitant use with TACYPHEN causes paroxysmal hypertension with possibility of dysrhythmias due to the inhibition of epinephrine (adrenaline) or norepinephrine (noradrenaline) entry in sympathetic fibres.
- Quinidine - concurrent use with TACYPHEN may increase the risk of cardiac dysrhythmias.
- Oxytocic medicines - concomitant use with TACYPHEN potentiates the vasopressor-active effects. Thus, some oxytocic medicines may cause severe persistent hypertension and strokes can occur during post-partum period.
- Reserpine and other sympatholytic medicines - concomitant use with TACYPHEN 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.
- The pressor effect of TACYPHEN is increased in patients receiving atropine sulphate.
- The pressor effects of phenylephrine may be slightly reduced by lithium carbonate.
- Caution should be applied when administering atomoxetine concurrently, as there is potential for synergistic pharmacological effects.

4.6 Fertility, pregnancy and lactation:

Pregnancy:

Safety during pregnancy and breastfeeding has not been established. Due to the vasoconstrictive properties of phenylephrine, TACYPHEN should be used with caution in patients with a history of pre-eclampsia. The administration of phenylephrine as contained in TACYPHEN at the end of pregnancy or during delivery may cause foetal hypoxia and bradycardia.

Breastfeeding:

Safety during breastfeeding has not been established.

4.7 Effects on ability to drive and use machines:

No adverse effects on the ability to drive or use machines are known.

4.8 Undesirable effects:

MedDRA SOC	Frequency	Description
Immune system disorders	*Less frequent*	Hypersensitivity.
Metabolism and nutrition disorders	*Less frequent*	Metabolic disorders.
Psychiatric disorders	*Less frequent*	Nervousness, insomnia, anxiety, excitability, agitation, psychotic states, confusion.
Nervous system disorders	*Frequent*	Headache.
	Less frequent	Cerebral haemorrhage, paraesthesia, tremor.
Eye disorders	*Less frequent*	Mydriasis, angle-closure glaucoma.
Cardiac disorders	*Less frequent*	Bradycardia, tachycardia, dysrhythmia, angina pectoris, palpitations, cardiac arrest.
Vascular disorders	*Less frequent*	Hypotension, hypertension, dizziness, syncope, flushing.
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Dyspnoea, pulmonary oedema.
Skin and subcutaneous tissue disorders	*Less frequent*	Sweating, pallor or skin blanching, piloerection.
Gastrointestinal disorders	*Less frequent*	Nausea, vomiting, salivary hypersecretion.
Renal and urinary disorders	*Less frequent*	Dysuria, urinary retention.
Musculoskeletal and connective tissue disorders	*Less frequent*	Muscular weakness.

General disorders and administration site conditions	*Frequency unknown*	Extravasation, infusion site necrosis, hyperhidrosis.
Investigations	*Frequency unknown*	Increased blood pressure, abnormal blood glucose.

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 over dosage include headache, nausea, vomiting, hypertension which may be severe reflex bradycardia and other cardiac dysrhythmias. In severe cases confusion, hallucinations and seizures may occur.

Treatment should consist of symptomatic and supportive measures.

For excessive hypertensive effects, the administration should be reduced or the medicine 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:

7.2 Vasoconstrictors, pressor medicines

Pharmacotherapeutic group: Cardiac stimulants, excluding cardiac glycosides, adrenergic and dopaminergic agents.

ATC Code: C01CA06.

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:

Following an intravenous infusion of phenylephrine hydrochloride, the effective half-life was approximately 5 minutes. 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. The average total serum clearance (2095 ml/min) was close to one-third of the cardiac output.

Phenylephrine is metabolised in the liver by monoamine oxidase. The metabolites, their route and rate of excretion have not been identified. 12 % of the phenylephrine dose is 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.

5.3 Preclinical safety data:

Phenylephrine has been used to induce cardiac myocyte hypertrophy in cultures of rat neonatal mycocytes at doses of 100 µM and 10 µM. There have been no human studies associating therapeutic phenylephrine use with the development of cardiac myocyte hypertrophy.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Hydrochloric acid (to adjust pH)
Sodium hydroxide (to adjust pH)
Water for injection.

6.2 Incompatibilities:

This medicine must not be mixed with other medicines except those mentioned in **section 6.6**.

6.3 Shelf life:

36 months.
From a microbiological point of view, the product should be used immediately.
Discard any unused portion (see **section 6.4**).

6.4 Special precautions for storage:

Store at or below 25 °C.
Store in the original package.
For single use only, discard any unused medicine (see **section 6.3**).

6.5. Nature and contents of container:

TACYPHEN is packaged in amber-coloured glass ampoules (Type I). The ampoules are placed in trays holding 5 or 10 ampoules; these are packed into a cardboard packet with the corresponding professional information.

6.6 Special precautions for disposal and other handling:

Any unused medicine or material that has been in contact with it should be disposed of in accordance with local requirements.

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 TACYPHEN 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 TACYPHEN 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:

Teva Pharmaceuticals (Pty) Ltd.
Maxwell Office Park., Magwa Crescent West
Waterfall City, Midrand, Gauteng
2090

8. REGISTRATION NUMBER(S):

49/7.2/0153

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

06 July 2021