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1 PRODUCT NAME

Metaraminol Phebra 0.5mg/mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of Metaraminol Phebra solution for injection contains metaraminol (as tartrate) 0.5 mg.

Each 6mL vial contains 3.0mg metaraminol (as tartrate). Each 10mL vial contains 5.0mg metaraminol (as tartrate).

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention and treatment of the acute hypotensive state occurring with spinal anaesthesia; adjunctive treatment of hypotension due to haemorrhage, reactions to medications, surgical complications, and shock associated with brain damage due to tumour or trauma.

It may also be useful as an adjunct in the treatment of hypotension due to cardiogenic shock or septicaemia.

4.2 Dose and method of administration

Metaraminol Phebra injection is for intravenous administration only (injection or infusion) and should be used in one patient on one occasion only. It contains no antimicrobial preservative. Unused solution should be discarded.

Because the maximum effect is not immediately apparent, at least ten minutes should elapse before increasing the dosage. As the effect tapers off when the vasopressor is discontinued, the patient should be carefully observed so that therapy can be reinitiated promptly if the blood pressure falls too rapidly. Patients with coexistent shock and acidosis may show a poor response to vasopressors. Established methods of shock management, such as blood or fluid replacement when indicated, and other measures directed to the specific cause of the shock also should be used.

Direct intravenous injection

In severe shock, when time is of great importance, it may be desirable to administer Metaraminol Phebra injection by direct intravenous injection. The suggested dose is 0.5 to 5 mg (1 to 10 mL), followed by an infusion of 15 to 95 mg in a diluent made up to a total volume of 500 mL. Extreme care must be exercised to give the proper dose.

Intravenous infusion. (For adjunctive treatment of hypotension.)

The recommended dose is 15 to 100 mg (30 to 200 mL) in sodium chloride injection or glucose injection 5% to make up a total volume of 500 mL infusion, adjusting the rate of infusion to maintain the blood pressure at the desired level.

Higher concentrations of metaraminol tartrate (150 to 500 mg/500 mL of infusion fluid) have been used. However Metaraminol Phebra is not suitable for use at these doses. A higher strength product should be used in these circumstances.

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If the patient needs additional saline or glucose solution at a rate of flow that would provide an excessive dose of the vasopressor, the recommended volume (500 mL) of infusion fluid should be increased accordingly. Conversely, if a smaller volume of infusion fluid is desirable, the required dose of metaraminol tartrate may be added to less than 500 mL of diluent.

4.3 Contraindications

Use with cyclopropane or halothane anaesthesia should be avoided, unless clinical circumstances demand such use.

Hypersensitivity to any component of this product including sulfites. In particular, Metaraminol Phebra injection is contraindicated in patients who are hypersensitive to sodium metabisulfite.

4.4 Special warnings and precautions for use

Metaraminol Phebra solution for injection contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

Caution should be exercised to avoid an excessive blood pressure response. Rapidly induced hypertensive responses have been reported to cause acute pulmonary oedema, cardiac arrhythmias and arrest. Patients with cirrhosis should be treated with caution, with adequate restoration of electrolytes if diuresis ensues. A fatal ventricular arrhythmia has been reported in a patient with Laennec's cirrhosis while receiving metaraminol tartrate. In several instances, ventricular extrasystoles that appeared during infusion subsided promptly when the rate of flow was reduced.

With the prolonged action of this drug, a cumulative effect is possible, and with an excessive vasopressor response there may be a prolonged elevation of blood pressure even when therapy with metaraminol tartrate is discontinued.

Because of its vasoconstrictor effect, metaraminol tartrate should be given with caution in the presence of heart or thyroid disease, hypertension, or diabetes. Sympathomimetic amines may provoke a relapse in patients with a history of malaria.

When vasopressor amines are used for long periods, the resulting vasoconstriction may prevent adequate expansion of the circulating volume and may cause perpetuation of the shock state. There is evidence that plasma volume may be reduced in all types of shock, and that the measurement of central venous pressure is useful in assessing the adequacy of the circulating blood volume. Therefore, blood or plasma volume expanders should be employed when the principal reason for hypotension or shock is decreased circulating volume.

In choosing the site of injection, it is important to avoid those areas recognised as unsuitable for the use of any pressor agent, and to discontinue the infusion immediately if infiltration or thrombosis occurs. Although the urgent nature of the patient's condition may force the choice of an unsuitable injection site, the preferred areas of injection should be used when possible. The larger veins of the antecubital fossa or thigh are preferred to the veins in the ankle or the dorsum of the hand, particularly in patients with peripheral vascular disease, diabetes mellitus, Buerger's disease, or conditions with coexistent hypercoagulability.

The effect of therapy with Metaraminol Phebra injection in children has not been established.

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4.5 Interaction with other medicines and other forms of interaction

Metaraminol Phebra injection should be used with caution in digitalised patients, since the combination of digitalis and sympathomimetic amines is capable of causing ectopic arrhythmic activity.

MAOIs and tricyclic antidepressants have been reported to potentiate the action of sympathomimetic amines.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy

There are no well controlled studies in pregnant women. Metaraminol Phebra injection may cause fetal hypoxia by constricting the uterine vessels thereby limiting placental perfusion.

Metaraminol Phebra injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Lactation

It is not known whether Metaraminol Phebra injection is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised if Metaraminol Phebra injection is given to a breastfeeding woman.

4.7 Effects on ability to drive and use machines

None

4.8 Undesirable effects

Abscess formation, tissue necrosis or sloughing and anaphylactic reaction rarely follow the use of metaraminol tartrate.

Sympathomimetic amines, including metaraminol tartrate, may cause sinus or ventricular tachycardia or other arrhythmias, especially in patients with myocardial infarction.

Reporting of suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Overdosage may result in severe hypertension accompanied by headache, constricting sensation in the chest, nausea, vomiting, euphoria, diaphoresis, pulmonary oedema, tachycardia, bradycardia, sinus arrhythmia, atrial or ventricular arrhythmias, myocardial infarction, cardiac arrest or convulsions.

Should an excessive elevation of blood pressure occur, it may be immediately relieved by a sympatholytic agent, e.g. phentolamine. An appropriate antiarrhythmic agent may also be required.

The oral LD₅₀ in the rat and mouse is 240 mg/kg and 99 mg/kg, respectively.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Metaraminol is a potent sympathomimetic amine that increases both systolic and diastolic blood pressure. The pressor effect begins one to two minutes after intravenous injection, about ten minutes after intramuscular injection, 5 to 20 minutes after subcutaneous injection, and lasts about 20 minutes to one hour. Metaraminol has a positive inotropic effect on the heart and has a peripheral vasoconstrictor action.

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Renal, coronary, and cerebral blood flow are a function of perfusion pressure and regional resistance. In most instances of cardiogenic shock, the beneficial effect of sympathomimetic amines is attributable to their positive inotropic effect. In patients with insufficient or failing vasoconstriction, there is additional advantage to the peripheral action of metaraminol, but in most patients with shock, vasoconstriction is adequate and any further increase is unnecessary. Therefore, blood flow to vital organs may decrease with metaraminol if regional resistance increases excessively.

The pressor effect of metaraminol is decreased but not reversed by alpha-adrenergic blocking agents. A primary or secondary fall in blood pressure and a tachyphylactic response to repeated use are uncommon.

5.2 Pharmacokinetic properties

None

5.3 Preclinical safety data

None

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

3mg/6mL presentation: Each 6mL contains sodium chloride 54mg, sodium metabisulfite 7.2mg and water for injections to 6mL. Tartaric acid and/or sodium hydroxide are added for pH adjustment.

5mg/10mL presentation: Each 10mL contains sodium chloride 90mg, sodium metabisulfite 12mg and water for injections to 10mL. Tartaric acid and/or sodium hydroxide are added for pH adjustment.

6.2 Incompatibilities

None

6.3 Shelf life

Prior to first use: 15 months

6.4 Special precautions for storage

Prior to first use: Store below 25°C Protect from light.

In use: In addition to sodium chloride injection and glucose injection 5%, Ringer's injection and lactated Ringer's injection were found physically and chemically compatible with Metaraminol Phebra injection when 15 mg – 100 mg of metaraminol (30 mL – 200 mL Metaraminol Phebra injection) was diluted to a total volume of 498 and 530 mL respectively.

When Metaraminol Phebra injection is mixed with an infusion solution, sterile precautions should be observed. To reduce microbiological hazard, use as soon as practicable after preparation. If storage is necessary, hold at 2-8°C for not more than 24 hours. Do not freeze.

6.5 Nature and contents of container

3mg/6mL presentation: 6 mL solution in a 7 mL clear type I glass vial with a rubber stopper and flip off seal in packs of 5 vials.

5mg/10mL presentation: 10 mL solution in a 10 mL clear type I glass vial with a rubber stopper and flip off seal in packs of 5 vials.

6.6 Special precautions for disposal

The injection solution contains no antimicrobial preservative and is for single use in one patient only. Discard any residue.

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7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

16 August 2018

10 DATE OF REVISION OF THE TEXT

28 November 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
n/a	New
6.1, 8	Added excipients tartaric acid and sodium hydroxide for pH adjustment and changed NZ sponsor