AUSTRALIAN PRODUCT INFORMATION – METARAMINOL PHEBRA (METARAMINOL) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

metaraminol (as tartrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Metaraminol Phebra 3 mg in 6 mL injection: Each vial contains 3 mg of metaraminol (as tartrate) in 6 mL of solution.

Metaraminol Phebra 5 mg in 10 mL injection: Each vial contains 5 mg of metaraminol (as tartrate) in 10 mL of solution.

Metaraminol Phebra 10 mg in 20 mL injection: Each vial contains 10 mg of metaraminol (as tartrate) in 20 mL of solution.

Excipient with known effect: contains sulfites.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

METARAMINOL PHEBRA is a clear, colourless, sterile solution for injection, practically free of any visible particles.

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 is for intravenous administration only (injection or infusion) and should be used in one patient on one occasion only. The injection solution 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 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.

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.

Compatibility
In addition to sodium chloride injection and glucose injection 5%, Ringer's injection and lactated Ringer's injection were found to be physically and chemically compatible with Metaraminol Phebra when 15 mg – 100 mg of metaraminol (30 mL – 200 mL Metaraminol Phebra) was diluted to a total volume of 498 and 530 mL respectively. Compatibility with Dextran 6% with saline has not been tested.

When Metaraminol Phebra 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.

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

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 is contraindicated. In particular, Metaraminol Phebra solution for injection is contraindicated in patients who are hypersensitive to sodium metabisulfite (see Section 4.4 Special warnings and precautions for use).

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.

Use in the elderly
No data available.

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

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Metaraminol Phebra 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

Effects on fertility
No data available.

Use in pregnancy (Category C)
There are no well controlled studies in pregnant women. Metaraminol Phebra may cause fetal hypoxia by constricting the uterine vessels thereby limiting placental perfusion.

Metaraminol Phebra 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 is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised if Metaraminol Phebra is given to a breastfeeding woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (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 suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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 LD_{50} in the rat and mouse is 240 mg/kg and 99 mg/kg, respectively.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
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.

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.

Clinical trials
No data available.

5.2 PHARMACOKINETIC PROPERTIES

No relevant data.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
No data available.

Carcinogenicity
No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride, sodium metabisulfite, water for injections. Tartaric acid and/or sodium hydroxide are added for pH adjustment.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: colourless glass type 1 vials with a chlorobutyl rubber stopper.

Pack sizes:
Metaraminol Phebra 3 mg in 6 mL: pack of 5 x 6 mL vials
Metaraminol Phebra 5 mg in 10 mL: pack of 5 x 10 mL vials
Metaraminol Phebra 10 mg in 20 mL: pack of 5 x 20 mL vials

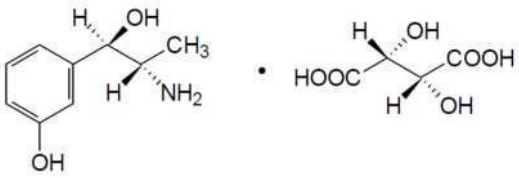
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Metaraminol tartrate is a white, crystalline powder, which is freely soluble in water, slightly soluble in alcohol and practically insoluble in chloroform and in ether.

Chemical structure



Chemical name: (1R,2S)-2-amino-1-(3-hydroxyphenyl)propan-1-ol hydrogen (2R,3R)-tartrate

Molecular formula: $C_9H_{13}NO_2.C_4H_6O_6$.

Molecular weight: 317.29

CAS number
33402-03-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Phebra Pty Ltd
17 - 19 Orion Road
Lane Cove West, NSW 2066
Australia.
Telephone: 1800 720 020

9 DATE OF FIRST APPROVAL

30 November 2016

10 DATE OF REVISION

23 September 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
ALL	PI reformat
6.5	Inclusion of an additional volume of fill.