SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metaraminol 0.5 mg/ml Solution for Injection/Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 0.5 mg metaraminol (as tartrate).

Each vial of 6 ml contains 3 mg metaraminol (as tartrate)

Each vial of 10 ml contains 5 mg metaraminol (as tartrate)

Excipient(s) with known effect:

Sodium chloride

Sodium metabisulfite

Each 1 ml of solution contains 1.2 mg sodium metabisulfite and 0.166 mmol sodium (equivalent to 3.83 mg).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection/Infusion.

Each glass vial contains a clear colourless solution with a pH of 3.2 – 4.5 and osmolarity of 312 mOsm/L.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of acute hypotension due to loss of vasoconstrictor tone as may occur during spinal anaesthesia and as an adjunct to accepted remedial procedures.

4.2 Posology and method of administration

Posology

Direct intravenous injection in grave emergencies: 0.5 – 5 mg (1 – 10 ml), which may be followed by an infusion of 15 – 100 mg (30 - 200 ml of metaraminol 0.5 mg/ml Solution for Injection/Infusion) titrated to clinical effect.

Intravenous infusion: The recommended dose is 15-100 mg (30 – 200 ml of metaraminol 0.5 mg/ml Solution for Injection/Infusion) titrated to clinical effect, adjusting the rate of infusion to maintain the blood pressure at the desired level.

In the event of escalating vasopressor requirement, the more concentrated metaraminol 10mg/ml solution for injection or infusion can be administered as 15 – 100mg in a diluent, made up to a total volume of 500 ml. When vasoactive drug support is no longer indicated, the infusion should be gradually decreased. Abrupt

withdrawal can result in acute hypotension.

As 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.

Use in Children:

Metaraminol should not be used in children under 12 years of age. The safety and efficacy of Metaraminol 0.5 mg/ml Solution for Injection/Infusion in children under 12 years of age has not been established. No data are available.

Use in the Elderly:

The dosage may not require modification for elderly patients; however geriatric patients may be more sensitive to sympathomimetic agents, therefore particular caution should be taken in this group.

Method of administration

For intravenous use. Metaraminol 0.5 mg/ml Solution for Injection/Infusion should not be diluted before use: it is supplied ready to use.

Each vial is intended for single use only. If only part of a vial is used, the remainder must be discarded.

4.3 Contraindications

- Metaraminol should not be used concurrently with cyclopropane or halothane anaesthesia, unless clinical circumstances demand it.
- Hypotension due to blood volume deficit (hypovolaemia).
- Metaraminol is contraindicated in patients who are hypersensitive to the active substance, sulfites or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

There is insufficient data to recommend use in children under 12 years of age.

Metaraminol solution contains sodium metabisulfite which is associated with circulatory or respiratory collapse and depression of the CNS in certain susceptible individuals, particularly in those with asthma.

Caution should be exercised to avoid excessive blood pressure changes since response to metaraminol is very variable and the ensuing control of blood pressure may prove difficult.

Rapidly induced hypertensive responses have been reported to cause acute pulmonary oedema, cardiac arrhythmias and arrest. Metaraminol should be used with caution in patients with cirrhosis; electrolyte levels should be adequately restored if a diuresis ensues. A fatal ventricular arrhythmia was reported in a patient with Laennec's cirrhosis while receiving metaraminol. In several instances ventricular extrasystoles that appeared during infusion of metaraminol promptly subsided when the rate of flow was reduced.

With the prolonged action of metaraminol, a cumulative effect is possible. An excessive vasopressor response may cause a prolonged elevation of blood pressure, even after discontinuation of therapy. Metaraminol should be used with caution in patients with heart disease, hypertension, thyroid disease or diabetes mellitus because of the vasoconstrictor action.

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 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. Blood or plasma volume expanders should therefore be employed when the principal reason for hypotension or shock is decreased circulating volume.

In choosing the site for injection, it is important to avoid those areas generally recognised as being unsuitable for the use of pressor agents and to discontinue the infusion immediately if infiltration of 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 whenever possible. The larger veins of the antecubital fossa or thigh are preferred to the veins in the ankle or dorsum of the hand, particularly in patients with peripheral vascular disease, diabetes mellitus, Buerger's disease or conditions with coexistent hypercoagulability.

Extravasation risk

The infusion site should be checked frequently for free flow. Care should be taken to avoid extravasation that would cause a necrosis of the tissues surrounding the vein used for injection. Because of the vasoconstriction of the vein wall with increased permeability, there might be some leakage of metaraminol in the tissues surrounding the infused vein causing a blanching of the tissues which is not due to an obvious extravasation. Therefore, if blanching occurs, consideration should be given to changing the site of infusion to allow the effects of local vasoconstriction to subside.

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per 1 ml vial, that is to say essentially "sodium free". If the maximum recommended dose of 100 mg metaraminol is to be given, the administered dose will contain 38.3 mg sodium per 10 ml of metaraminol solution. This is equivalent to 1.9% of the WHO recommended maximum daily dietary intake of 2 g sodium for an adult.

This medicine also contains 1.2 mg/ml sodium metabisulfite which may rarely cause severe hypersensitivity reactions and bronchospasm.

Accidental spillage of metaraminol solution on the skin can cause dermatitic reactions linked to the presence of the agent's preservatives.

4.5 Interaction with other medicinal products and other forms of interaction

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

Monoamine oxidase inhibitors have been reported to potentiate the action of sympathomimetic amines. The pressor effect of metaraminol is decreased but not reversed by alpha-adrenergic blocking agents.

Oxytocin may enhance the vasopressor and vasoconstrictor effects of metaraminol.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no well-controlled studies in pregnant women. Metaraminol should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

Breastfeeding

It is not known whether metaraminol is excreted in human milk. Caution should be exercised if metaraminol is given to a breast-feeding mother.

Fertility

There are no fertility data available.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

The frequency of adverse events with metaraminol has not been firmly established. Excessive therapeutic effect leading to hypertension, quickly reversible by reducing the rate of infusion, and headaches are very common. Adverse reactions listed below are classified according to frequency and system organ class (SOC). The frequencies of adverse reactions are ranked according to the following convention: Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

System Organ Class	**Undesirable Effect**
Nervous system disorders	Very common: Headache
Cardiac disorders	Not known: Palpitations; sinus tachycardia; bradycardia; ventricular tachycardia; other cardiac arrhythmias (especially in patients with myocardial infarction); fatal ventricular arrhythmia reported in Laennec's cirrhosis.
Vascular disorders	Very common: Hypertension Not known: Peripheral ischaemia
Skin and subcutaneous tissue disorders	Rare: Abscess formation, tissue necrosis, sloughing
Gastrointestinal disorders	Not known: Nausea

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Metaraminol is rapidly acting. The major therapeutic effects are complete within an hour of parenteral administration. 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.

If the drug has been ingested, induce emesis or perform gastric lavage. If Metaraminol solution has been administered by subcutaneous or intramuscular injection, local ice packs may be applied to delay absorption. Intravenous infusion should be stopped immediately but reinstated if hypotension occurs. If needed, an alpha-adrenergic blocking agent such as phenoxybenzamine may be used to reduce hypertension. Intravenous beta-adrenergic blocking agents may also be useful for reducing hypertension and may have a beneficial effect on cardiac arrhythmia, if present. Parenteral diazepam may be given for convulsions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergic and dopaminergic agent, ATC code: C01CA09.

Metaraminol is a sympathomimetic agent with direct and indirect effects on adrenergic receptors. It has both alpha- and beta-adrenergic activity, the former being predominant.

Metaraminol increases the force of myocardial contraction as well as having a peripheral vasoconstrictor action. It increases both systolic and diastolic blood pressures. The vasoconstrictor effect of metaraminol is not affected by depletion of the tissue stores of noradrenaline.

Metaraminol is highly effective in displacing and replacing noradrenaline from the stores in adrenergic neurones and competitively inhibits noradrenaline uptake. The metaraminol that is taken up by the adrenergic neurones then acts as a false transmitter.

The overall effects of metaraminol are similar to those of noradrenaline but it is much less potent and has a more prolonged action. It can cause pulmonary vasoconstriction, and pulmonary BP is elevated when cardiac output is reduced.

5.2 Pharmacokinetic properties

The pressor effect of a single dose of metaraminol lasts from about twenty minutes up to one hour. The onset of action is around one or two minutes after direct intravenous injection.

The vasopressor effects taper off when therapy is stopped.

5.3 Preclinical safety data

No relevant information.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulfite (E223)

Sodium chloride

Water for injection

Sodium hydroxide (pH adjuster)

Tartaric acid (pH adjuster)

6.2 Incompatibilities

Metaraminol 0.5 mg/ml Solution for Injection/Infusion must not be mixed with other medicinal products.

6.3 Shelf life

6 ml presentation: 18 months

10 ml presentation: 2 years

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

Store vials in the outer carton in order to protect from light.

6.5 Nature and contents of container

6 ml presentation: 7 ml Type I clear glass vial.

10 ml presentation: 10 ml Type I clear glass vial.

Pack sizes: Each carton contains 10 vials.

6.6 Special precautions for disposal

Metaraminol 0.5 mg/ml Solution for Injection/Infusion is already diluted and ready to use. It should be used without prior dilution.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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