SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metaraminol 10mg/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 10mg of metaraminol (as tartrate).
Excipients of known effect:
Each 1 ml of solution contains 0.09 mmol (2.06 mg) sodium.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.

Clear, colourless sterile, pyrogen-free solution.

The pH of the solution is 3.2-4.5 and the osmolarity of the solution is 267.0-326.0 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

Intravenous Infusion: 15 - 100 mg (1.5 - 10.0 ml) in 500 ml Sodium Chloride Injection or Glucose 5% Injection, adjusting the rate of infusion to maintain the blood pressure at the desired level. Higher concentrations of Metaraminol have been used when appropriate to the circumstances.

Direct intravenous injection in grave emergencies: 0.5 – 5 mg (0.05 - 0.5 ml), followed by an infusion of 15 – 100 mg (1.5 – 100 ml), in a diluent, made up to a total volume of 500ml.

Particular care should be taken to use the correct dose when injecting undiluted metaraminol.

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 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 age group.

Method of administration

Metaraminol 10 mg/ml Solution may be given either by intravenous infusion after further dilution or direct intravenous injection.

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

4.3 Contraindications

Metaraminol is contraindicated in patients who are hypersensitive to the active ingredient or any of the excipients listed in section 6.1.

Metaraminol should not be used concurrently with cyclopropane or halothane anaesthesia, unless clinical circumstances demand it.

Hypotension due to blood volume deficit (hypovolaemia).

4.4 Special warnings and precautions for use

Caution should be exercised to avoid excessive blood-pressure changes since response to treatment with metaraminol is very variable and the ensuing control of the 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

tartrate. 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 cases of 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 of 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 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 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 ampoule, that is to say essentially “sodium free”. If the maximum recommended dose of 100 mg metaraminol (10 ampoules) is to be given, the administered dose will contain 20.6 mg sodium per 10 ml of metaraminol solution. This is equivalent to 1% of the WHO recommended maximum daily dietary intake of 2 g sodium for an adult.

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.

A close monitoring of blood pressure is recommended in case of co-administration with oxytocic drugs due to the risk of enhancement of metaraminol effects.

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 secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised if metaraminol is given to a breastfeeding 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 at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Metaraminol acts rapidly. 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 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, alpha-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 contractions as well as having a peripheral vasoconstrictor action. It increases both systolic and diastolic blood pressures.

The vasoconstrictor action 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 blood pressure is elevated when cardiac output is reduced.

5.2 Pharmacokinetic properties

The pressor effect of a single dose of metaraminol lasts from about 20 minutes up to one hour. Its onset 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 chloride

Citric acid monohydrate (pH adjuster)

Glacial acetic acid

Sodium acetate trihydrate

Disodium edetate

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

After dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8°C.
From a microbiological point of view, the product should be used immediately.
If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze.
Store ampoules in the outer carton in order to protect from light. .
For storage conditions after dilution of the medicinal product, see section 6.3. .

6.5 Nature and contents of container

Type 1 clear glass ampoule containing 1 ml of solution for injection.

Pack size of 5 ampoules in a cardboard carton.

6.6 Special precautions for disposal

For intravenous infusion, further dilution is required: metaraminol solution should be diluted to give 15-100 mg metaraminol in 500 ml of 0.9% Sodium Chloride Infusion or 5% Glucose Infusion (see section 4.2).

In grave emergencies, direct intravenous injection followed by an infusion of 15-100 mg metaraminol in 500 ml of 0.9% Sodium Chloride Infusion or 5% Glucose Infusion may be administered (see section 4.2).

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

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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