SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Phentolamine mesilate 10 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 10 mg phentolamine mesilate in 1 ml solution equivalent to 7.45 mg/ml phentolamine.

Excipient with known effect

Each 1 ml of solution contains 0.5 mg sodium metabisulphite.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Single use, ready-to-use, sterile, clear colourless solution practically free from visible matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Reversal of paroxysmal hypertension in pheochromocytoma before and during surgical treatment.
- Diagnostic phentolamine test for the identification of pheochromocytoma when other more specific tests cannot be used or have not provided sufficient results.

4.2 Posology and method of administration

Posology

- Reversal of paroxysmal hypertension in phaeochromocytoma

Administer 2-5 mg of phentolamine mesilate intravenously for the treatment of hypertensive crises occurring before surgery or during the induction of anesthesia, intubation, or surgical tumor removal. This administration is repeated if necessary, while monitoring blood pressure. For children over 8 years old, the minimum effective dose is 1 mg. The dosage should be further adjusted based on the clinical condition.

During surgical tumor removal as part of the treatment of phaeochromocytoma, a hypertensive crisis may occasionally occur, even if the patient has received phentolamine as premedication. In such cases, beta-blockade may be indicated. Use a β1-selective beta blocker, such as metoprolol, administered as a slow IV injection.

- Diagnostic use in phaeochromocytoma

Preparation for the test

Do not administer sedatives, analgesics or other medications for 24 hours and preferably not even for 48-72 hours prior to testing, except for essential medications (such as digitalis and insulin). Do not administer antihypertensive drugs after the test until the blood pressure has returned to the untreated elevated blood pressure level. The test should not be conducted on patients with normal blood pressure.

Intravenous test

Procedure:

1. Keep the patient in a reclining position throughout the entire test, preferably in a quiet darkened room. First wait until the blood pressure has stabilized (measure the blood pressure every ten minutes for at least half an hour).

2. The dosage for adults is 5 mg (0.5 ml) and for children, 1 mg (0.1 ml).

3. Insert the injection needle into the vein and wait until the effect of venipuncture on blood pressure has passed before administering the injection.

4. Then administer the injection quickly and measure the blood pressure immediately after the injection with time intervals of 30 seconds for the first 3 minutes and 60 second intervals for the next 7 minutes.

Interpretation of the test

The test is most reliable in the determination of phaeochromocytoma in patients with persistent hypertension and least reliable in patients with paroxysmal hypertension. False positive results can occur in hypertensive patients without phaeochromocytoma.

The test is positive and possibly indicates a phaeochromocytoma if the blood pressure drops by more than 35 mm Hg systolic and 25 mm Hg diastolic. A typical positive response for pheochromocytoma is a decrease of 60 mm Hg systolic and 25 mm Hg diastolic. The maximum effect is usually visible within 2 minutes after the injection. Blood pressure usually returns to pre-test levels within 15-30 minutes, but this can occur more quickly. If the blood pressure is reduced excessively, the patient should be treated as indicated in section 4.9.

The result is considered negative if blood pressure after injection increases, remains the same or decreases by less than 35 mm Hg systolic and 25 mm Hg diastolic. However, a negative test result does not preclude the diagnosis of phaeochromocytoma, especially in patients with paroxysmal hypertension, where false negative results are common.

Intramuscular test

The dose for adults is 5 mg (0.5 ml) and for children 3 mg (0.3 ml).

Measure blood pressure every 5 minutes for 30-45 minutes after intramuscular injection. A positive result for phaeochromocytoma is defined as a decrease in blood pressure of 35 mm Hg systolic and 25 mm Hg diastolic, or more, within 20 minutes of administration.

Special populations

Renal impairment

No pharmacokinetic studies have been performed with phentolamine mesilate in patients with renal impairment. Caution is advised when administering phentolamine mesilate to these patients (see section 4.4).

Method of administration

This medicinal product is administered intravenously or intramuscularly.

4.3 Contraindications

- Hypersensitivity to phentolamine and related compounds.
- Hypersensitivity to sulphites.
- Hypotension.
- Myocardial infarction, history of myocardial infarction, coronary insufficiency, angina, or other evidence of coronary artery disease.

4.4 Special warnings and precautions for use

Tachycardia and cardiac arrhythmias may occur with the use of phentolamine mesilate. Blood pressure should be monitored regularly to ensure that dosage and duration of therapy are carefully adjusted to the patient. In case of overdose (manifesting as a significant drop in blood pressure and tachycardia), treatment should be symptomatic based on the patient's clinical condition and the physician's judgment (see section 4.9).

Myocardial infarction, cerebrovascular spasms, and cerebrovascular occlusion have been reported after the administration of phentolamine mesilate, usually in association with severe hypotensive episodes.

The use of phentolamine mesilate as a screening test in hypertensive patients has largely been replaced by the commonly available urinalysis of catecholamines or other biochemical tests due to their accuracy and safety. Therefore, the diagnostic use of phentolamine mesilate is not the first choice and should only be used if the other specific tests are not available.

Due to its stimulating effect on the gastrointestinal tract, including gastric acid secretion, phentolamine mesilate should be used with caution in patients with gastritis and peptic ulcers.

Since no pharmacokinetic studies have been conducted in patients with renal impairment, phentolamine mesilate should be used with caution in these patients.

Sodium metabisulphite

This medicinal product contains 0.5 mg sodium metabisulphite in each 1 ml of solution which may rarely cause severe hypersensitivity reactions and bronchospasm.

This medicinal product contains less than 1 mmol sodium (23 mg) per 1 ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Phentolamine mesilate may potentiate the hypotensive effect of other antihypertensive agents. Antipsychotics may potentiate the hypotensive effect of alpha-blockers.

Non-selective beta-agonists

Concomitant use of non-selective beta-agonists such as epinephrine and isoprenaline may lead to additional lowering of blood pressure. This is because adrenaline, when co-administered with phentolamine, has an effect only on the beta receptors due to blockade of the alpha receptors by phentolamine.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is very limited data on the use of phentolamine in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). Phentolamine mesilate is not recommended during pregnancy.

Breast-feeding
It is not known whether phentolamine is excreted in human milk. As a precautionary measure, breastfeeding should be discontinued during treatment with phentolamine mesilate.

Fertility
There are no available data on the effect of phentolamine on fertility in animals or humans.

4.7 Effects on ability to drive and use machines

Phentolamine mesilate may affect the central nervous system (see section 4.8) which may adversely affect the patients' reaction times. Therefore, patients should be advised to exercise caution when driving and using machines.

4.8 Undesirable effects

Adverse reactions are listed according to MedDRA system organ class. Within each system organ class, adverse reactions are presented in order of decreasing seriousness. Frequency categories: very common (≥ 1/10); 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); frequency not known (cannot be estimated from the available data).

System Organ Class	**Very Common (≥ 1/10)**	**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 established from the available data)**
Nervous system disorders		Dizziness				
Cardiac disorders	Tachycardia		Angina pectoris, arrhythmias			
Vascular disorders	Orthostatic hypotension	Acute or prolonged hypotensive episodes (myocardial infarction, cerebrovascular spasm and cerebrovascular occlusion may occur), flushing.				
Respiratory, thoracic and mediastinal disorders		Nasal congestion				
Gastrointestinal disorders		Nausea, vomiting, diarrhoea.				
General disorders and administration site conditions		Asthenia	Chest pain			

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

Signs and complaints

The main clinical manifestations of an overdose with phentolamine mesilate are arterial hypotension, reflex tachycardia, arrhythmias and possibly shock. These effects may be accompanied by headache, hyperexcitability and visual disturbances, sweating, vomiting and diarrhoea as well as hypoglycaemia.

Treatment

There is no specific antidote available for phentolamine overdose. It should be treated symptomatically according to the clinical condition of the patient and the judgment of the physician.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: alpha-adrenergic receptor antagonist, ATC code: C04AB01

Phentolamine, the active ingredient of Phentolamine mesilate 10 mg/ml solution for injection, is a competitive, non-selective α1 and α2-adrenergic receptor antagonist of relatively short duration. Phentolamine causes vasodilation and a decrease in blood pressure due to the blockade of the postsynaptic vascular α1 and α2 adrenoceptors.

Increased neuronal release of noradrenaline due to presynaptic α2- adrenergic receptor blockade may contribute to the positive inotropic and chronotropic effects of phentolamine mesilate on the cardiac muscle.

The decrease in systemic vascular resistance and blood pressure after administration of phentolamine mesilate is accompanied by tachycardia, caused by activation of the baroreceptors and the autonomic nervous system.

5.2 Pharmacokinetic properties

Absorption
During a 45-minute intravenous infusion of 10 mg C^{14}-labeled phentolamine mesilate, maximum blood levels (measured as total radioactivity) are reached after 30 minutes for both the total amount of drug (0.11 micrograms/ml) and for the unchanged drug (0.09 micrograms/ml).

Distribution
Phentolamine is 54% bound to human serum proteins in the concentration range of 0.02 to 109 micrograms/ml.

Biotransformation
Phentolamine is extensively metabolized in humans after intravenous administration; the unchanged drug excreted in the urine amounts to an average of 13% of the dose. A major metabolite is the carboxyphenyl derivative, which accounts for 17% of the dose; conjugates of both substances have minimal significance.

Elimination
The elimination of phentolamine from the blood is rapid and does not follow first-order kinetics. After 2-4 hours, the concentration is reduced to approximately 15% of the peak value. The elimination half-life of phentolamine is 19 minutes after a 30 mg intravenous bolus injection. Following intravenous infusion of phentolamine mesilate (10 mg), 70% of the dose is excreted in the urine within 24 hours as unchanged drug and metabolites, with an additional 3% found in the feces. By the end of the 3-day observation period, not the entire dose has been recovered, but only 79%.

5.3 Preclinical safety data

Preclinical data do not indicate a special risk for humans based on studies on repeated dose toxicity, genotoxicity, and carcinogenicity.

Phentolamine mesilate was embryotoxic in mice at high oral doses. However, it was not teratogenic in mice, rats, and rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulphite (E223)

Glucose monohydrate

Water for injections

6.2 Incompatibilities

Incompatible with alkaline solutions.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store in the original package in order to protect from light.

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep this medicine out of the sight and reach of children.

6.5 Nature and contents of container

Clear, type I glass One Point Cut (OPC) ampoules of 1 ml nominal capacity, suitable for pharmaceutical use. Each ampoule is filled with 1 ml solution for injection.

Each pack contains 5 single use ampoules.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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