NEW ZEALAND DATA SHEET

REGITINE® (phentolamine mesilate)

10 mg Aqueous solution for injection in 1ml Ampoules

Trade name

REGITINE® 10 mg aqueous solution for injection in 1 ml ampoules

Description and composition

Pharmaceutical form(s)

Aqueous solution for injection in ampoules.

Active substance

1 ml Regitine ampoule contains 10 mg phentolamine mesilate

Active moiety

(Phentolamine).

Excipients

Ampoules: 0.5 mg sodium metabisulphite, 35.0 mg glucose, anhydrous and water for injection up to 1 mL.

Sodium metabislphite [E223] as antioxidant.

Information might differ in some countries.

Indications

- Therapeutic: Management of hypertensive episodes that may occur in patients with phaeochromocytoma, during preoperative preparation and surgical manipulation.
- Diagnostic: Diagnosis of phaeochromocytoma by Regitine® blocking test if other more specific tests are not available (see Warnings and precautions).
- Preventive: Prevention of dermal necrosis and sloughing after extravasation of noradrenaline.

Dosage and administration

Dosage

General target population

- **Management of hypertensive episodes in patients with phaeochromocytoma**

For the management of hypertensive crises that arise before surgery or during induction of anaesthesia, intubation, or surgical removal of tumour, 2-5 mg of Regitine is injected intravenously (i.v) and repeated if necessary, monitoring the blood pressure response.

- **Diagnosis of phaeochromocytoma - Regitine blocking test**

The test is most reliable in detecting phaeochromocytoma in patients with sustained hypertension and least reliable in those with paroxysmal hypertension. False-positive tests may occur in patients with hypertension without phaeochromocytoma.

Preparation for the test:

Sedatives, analgesics, and all other medications except those that might be deemed essential (such as digitalis and insulin) are withheld for at least 24 hours, and preferably 48-72 hours, prior to the test. Antihypertensive drugs are withheld until blood pressure returns to the untreated, hypertensive level. This test is not performed on a patient who is normotensive.

Intravenous Regitine blocking test

Procedure: The patient is kept at rest in the supine position throughout the test, preferably in a quiet, darkened room. Injection of Regitine is delayed until blood pressure is stabilised, as evidenced by blood pressure readings taken every 10 minutes for at least 30 minutes.

The dose for adults is 5 mg. The syringe needle is inserted into the vein, and injection is delayed until pressor response to venepuncture has subsided.

Regitine is injected rapidly. Blood pressure is recorded immediately after injection, at 30-second intervals for the first 3 minutes, and at 60-second intervals for the next 7 minutes.

Interpretation: A positive response, suggestive of phaeochromocytoma, is indicated when the blood pressure is reduced by more than 35 mm Hg systolic and by 25 mm Hg diastolic. A typical positive response is a reduction in pressure of 60 mm Hg systolic and 25 mm Hg diastolic. Usually, the maximal effect is evident within 2 minutes after injection. A return to preinjection pressure commonly occurs within 15-30 minutes but may occur more rapidly.

If blood pressure decreases to a dangerous level, the patient should be treated as outlined under "Overdose" (see Overdosage).

A negative response is indicated when the blood pressure is elevated, unchanged, or reduced by less than 35 mm Hg systolic and by 25 mm Hg diastolic after injection of Regitine. A negative response to this test does not exclude the diagnosis of phaeochromocytoma, especially in patients with paroxysmal hypertension in whom the incidence of false-negative responses is high.

Intramuscular Regitine blocking test

The dose for adults is 5 mg intramuscularly (i.m). Blood pressure is recorded every 5 minutes for 30-45 minutes following injection. A positive response is defined as a reduction in blood pressure by 35 mm Hg systolic and by 25 mm Hg diastolic, or more, within 20 minutes following injection.

- **Prevention of dermal necrosis and sloughing after extravasation of noradrenaline**

5-10 mg of Regitine in 10 mL of saline is injected subcutaneously into the area of extravasation within 12 hours.

Special populations

Renal Impairment

No pharmacokinetic studies with Regitine have been performed in patients with renal impairment. Regitine should be administered with caution in these patients (see section 6 Warnings and precautions).

Hepatic Impairment

No studies with Regitine have been performed in hepatically impaired patients.

Geriatrics (65 years and above)

No studies with Regitine have been performed in geriatric population (patients 65 years or above).

Paediatrics

Management of hypertensive episodes in patients with phaeochromocytoma

0.05-0.1mg/kg/dose is given i.m or i.v 1-2 hours before surgery, and should be repeated as needed every 2-4 hours. The maximum recommended single dose is 5mg.

Regitine blocking test (Intramuscular or Intravenous)

0.05-0.1mg/kg/dose is given i.m or i.v. The maximum recommended single dose is 5mg. The testing procedure and interpretation of results are the same as in adults.

Prevention of dermal necrosis and sloughing after extravasation of noradrenaline

A small amount (e.g 1 ml) of diluted solution (5-10 mg of Regitine in 10 ml of normal saline) is injected subcutaneously into the area of extravasation within 12 hours. The maximum recommended dose should not exceed 0.1-0.2mg/kg (5mg total).

Contraindications

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

Warnings and precautions

Cardiovascular

Tachycardia and cardiac arrhythmias may occur with the use of Regitine.

Monitoring of the blood pressure is necessary for appropriate selection of patient, dosage, and duration of therapy. Myocardial infarction, cerebrovascular spasm, and cerebrovascular occlusion have been reported to occur following the administration of Regitine, usually in association with marked hypotensive episodes.

Gastrointestinal

Due to its stimulatory effect on the gastrointestinal tract, including gastric secretion, Regitine should be used with caution in patients with gastritis and peptic ulcer.

Renal Impairment

Since no pharmacokinetic studies with Regitine have been performed in patients with renal impairment, use caution in administering Regitine to these patients.

Hypersensitivity to sulfites

The presence of sulfites in Regitine ampoules can, especially in patients with bronchial asthma, lead to isolated hypersensitivity reactions, which may become manifest as an acute asthma attack, or shock, or clouding of consciousness.

Screening test

For screening tests in patients with hypertension, the generally available urinary assay of catecholamines or other biochemical assays have largely replaced the Regitine and other pharmacological tests for reasons of accuracy and safety. Therefore, the Regitine blocking test is not the procedure of choice and should be used only when these other specific tests are not available.

Adverse drug reactions

The following adverse drug reactions (Table 1) are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Frequency estimates: very common ≥ 10%, common ≥ 1% to < 10%, uncommon ≥ 0.1% to < 1%, rare ≥ 0.01% to < 0.1%, very rare < 0.01%

Table 1 Adverse drug reactions

Nervous system disorders

Common: Dizziness

Cardiac disorders

Very common: Tachycardia

Uncommon: Angina pectoris, arrhythmias

Vascular disorders

Very common: Orthostatic hypotension

Common: Acute or prolonged hypotensive episodes (Myocardial infarction, cerebrospasm, and cerebrovascular occlusion may occur), flushing

Respiratory, thoracic and mediastinal disorders

Common: Nasal congestion

Gastrointestinal disorders

Common: Nausea, vomiting, diarrhoea

General disorders and administration site conditions

Common: Asthenia

Uncommon: Chest pain

Interactions

Anticipated interactions to be considered

Agents causing lowering of blood-pressure

Regitine may augment the hypotensive effect of other antihypertensive agents. Antipsychotics may enhance the hypotensive effect of alpha-adrenergic blocking agents.

Nonselective beta-agonists

Due to blockade of vasoconstrictor alpha receptors by phentolamine, concurrent use of agents with nonselective beta-agonist properties (i.e. adrenaline, isoprenaline) can produce additive lowering of blood pressure.

Women of child-bearing potential, pregnancy, breast-feeding and fertility

Women of child-bearing potential

No information is available about the effect of phentolamine on women of child-bearing potential.

Pregnancy

Experience with Regitine in pregnant women is very limited. When using Regitine during pregnancy, the risk-benefit relationship must be carefully considered and the therapy should only be used if clearly indicated.

While phentolamine was not teratogenic in animal experiments, it did show embryotoxicity in certain species (see section 13 Non-clinical safety data).

Breast-feeding

No information is available as to whether phentolamine passes into breast milk. As cautionary measure, Regitine should be avoided during breast feeding.

Fertility

No fertility data is available from animals or humans.

Overdosage

Signs and symptoms

The main clinical manifestations of overdosage with Regitine are arterial hypotension, reflex tachycardia, cardiac stimulation, arrhythmia, increase of systemic venous capacity, and possibly shock. These effects may, be accompanied by headache, hyperexcitability and disturbances of vision, sweating, increased gastric motility, vomiting and diarrhoea, hypoglycaemia.

Treatment

There is no specific antidote available for phentolamine overdose. Symptomatic treatment should be prescribed as per clinical condition of the patient and the physician’s assessment.

Clinical pharmacology

Pharmacotherapeutic group, ATC code

Alpha-adrenergic receptor blocker, C04A B01

Mechanism of action (MOA)

Phentolamine, the active substance of Regitine, is a competitive non-selective alpha-$_1$ and alpha-$_2$ adrenergic receptor blocker of relatively short duration of action.

Pharmacodynamics (PD)

Phentolamine causes vasodilatation and a fall in blood pressure resulting from the blockade of both post-junctional vascular alpha-$_1$ and alpha-$_2$adrenoceptors. It also antagonises the vasoconstrictor response to noradrenaline and adrenaline infusions. Enhanced neural release of noradrenaline due to presynaptic alpha-$_2$blockade may contribute to the positive inotropic and chronotropic effects of Regitine on cardiac muscle.

The administration of Regitine intravenously to man produces transient declines in mean systemic vascular resistance and mean systemic arterial pressure as a result of dilatation in the arterial as well as in the venous vascular bed. These effects of Regitine are accompanied by tachycardia, triggered by the baroreceptor reflex system and the autonomic nervous system.

Pharmacokinetics (PK)

Absorption

During intravenous infusion of 10 mg of ^{14}C-labelled phentolamine mesilate over a period of 45 minutes, both the peak blood concentrations of total radioactivity (0.11 microgram/mL) and of unchanged drug (0.09 microgram/mL) are attained at 30 minutes.

Distribution

Phentolamine is bound to an extent of 54% to proteins of human serum in the concentration range of 0.02 to 109 microgram/mL.

Biotransformation/Metabolism

Phentolamine is extensively metabolised in humans after intravenous infusion; the unchanged drug in urine covered about 13% of the dose, at an average. A prominent metabolite is the carboxyphenyl derivative, constituting 17%; conjugates of both compounds are of minor importance after intravenous administration. The metabolism of phentolamine is more pronounced after oral than after intravenous dosing of the drug.

Elimination

The elimination of phentolamine from blood is rapid and does not follow first-order kinetics; already after 2-4 hours the concentration has dropped to about 15% of the peak value. The elimination half-life of phentolamine is 19 min after 30 mg intravenous bolus injection. After intravenous infusion of phentolamine mesilate (10 mg), urinary excretion of drug and metabolites accounts for 70% of the dose within the first 24 hours; another 3% is found in the faeces. At the end of the observation period of 3 days, the excretory balance is not complete, amounting to 79% of the dose.

Clinical studies

Regitine is an established drug. No new clinical studies.

Non-clinical safety data

Teratogenicity

Regitine was embryotoxic to mice at oral doses as low as 60 mg/kg and to rats at oral doses as low as 120 mg/kg; however, it was not teratogenic at any dose tested in mice, rats, or rabbits (see section 9 Women of child-bearing potential, pregnancy, breast-feeding and fertility).

Mutagenicity

An extensive battery of in vitro and in vivo genotoxicity tests have indicated that Regitine does not display mutagenic or genotoxic potential.

Carcinogenicity

The weight of evidence suggests that Regitine is negative for carcinogenicity following oral administration.

Pharmaceutical information

Incompatibilities

Alkaline solutions.

Special precautions for storage

Store at 2°-8°C. Do not freeze.

Protect from light.

Regitine must be kept out of the reach and sight of children.

Information might differ in some countries.

Nature and contents of container

5 ampoules per pack

Medicine classification

Prescription Medicine

Name and address

Novartis New Zealand Limited
Private Bag 65904
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14 October 2011