1.3

Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

HYDRALAZINE INJECTION

(Hydralazine Hydrochloride Injection USP 20mg/ml)

2. Qualitative and quantitative composition

Each ml contains:

Hydralazine Hydrochloride USP 20mg
Methyl Paraben USP 0.65mg
Propyl Paraben USP 0.35mg

3. Pharmaceutical form

Injection

4. Clinical particulars

4.1 Therapeutic indications

Treatment of hypertensive emergencies, particularly those associated with pre-eclampsia and toxaemia of pregnancy. Treatment of hypertension with renal complications.

4.2 Posology and method of administration

Adults:

Initially 5 to 10 mg by slow intravenous injection, to avoid precipitous decreases in arterial pressure with a critical reduction in cerebral or utero-placental perfusion. If necessary a repeat injection can be given after an interval of 20-30 minutes, throughout which blood pressure and heart rate should be monitored. A satisfactory response can be defined as a decrease in diastyloic blood pressure to 90/100 mmHg. The contents of the vial should be reconstituted by dissolving in 1 ml of water for injection BP. This should then be further diluted with 10 ml of Sodium Chloride injection BP 0.9% and be administered by slow intravenous injection. The injection must be given immediately and any remainder discarded. Hydralazine may also be given by continuous intravenous infusion, beginning with a flow rate of 200-300µg/min. Maintenance flow rates must be determined individually and are usually within the range 50-150µg/min. The product reconstituted as for direct iv injection may be added via the infusion container to 500 ml of Sodium Chloride Injection BP 0.9% and given by continuous infusion. The addition should be made immediately before administration and the mixture should not be stored. Hydralazine for infusion can also be used with 5% sorbitol solution or isotonic inorganic infusion solutions such as Ringers solution.

Children:

Not recommended

Elderly:

Clinical evidence would indicate that no special dosage regime is necessary. Advancing age does not affect either blood concentration or systemic clearance. Renal elimination may however be affected in so far as kidney function diminishes with age.

4.3 Contraindications

Known hypersensitivity to hydralazine of dihydralazine.

Idiopathic systemic lupus erythematosus (SLE) and related diseases.

Severe tachycardia and heart failure with a high cardiac output (e.g. in thyrotoxicosis).

Myocardial insufficiency due to mechanical obstruction (e.g. in the presence of aortic or mitral stenosis or constructive pericarditis).

Isolated right ventricular failure due to pulmonary hypertension (cor pulmonale).

Dissecting aortic aneurysm.

4.4 Special warnings and precautions for use

Warnings

The overall 'hyperdynamic' state of the circulation induced by hydralazine may accentuate certain clinical conditions. Myocardial stimulation may provoke or aggravate angina pectoris. Patients with suspected or confirmed coronary artery disease should therefore be given Hydralazine only under beta-blocker cover or in combination with other suitable sympatholytic agents. It is important that the beta-blocker medication should be commenced a few days before the start of treatment with Hydralazine.

Patients who have survived a myocardial infarction should not receive Hydralazine until a post-infarction stabilisation phase has been achieved.

Prolonged treatment with hydralazine may provoke a systemic lupus erythematosus (SLE)-like syndrome. First symptoms are likely to be similar to rheumatoid arthritis (arthralgia, sometimes associated with fever, anaemia, leucopenia, thrombocytopenia and rash) and are reversible after withdrawal of the drug. In its more severe form it resembles acute SLE (similar manifestations as the milder form plus pleurisy, pleural effusions and pericarditis), and in rare cases renal and ocular involvement have been reported. Early detection and a timely diagnosis with appropriate therapy (i.e. treatment discontinuation and possibly long-term treatment with corticosteroids may be required to reverse these changes) are of utmost

importance in this life-threatening illness to prevent more sever complications, which may sometimes be fatal.

Since such reactions tend to occur more frequently the higher the dose and the longer its duration, and since they are more common in slow acetylators, it is recommended that for maintenance therapy the lowest effective dose should be used. If 100 mg daily fails to elicit an adequate clinical effect, the patient's acetylator status should be evaluated. Slow acetylators and women run greater risk of developing the LE like syndrome and every effort should therefore be made to keep the dosage below 100 mg daily and a careful watch kept for signs and symptoms suggestive of this syndrome. If such symptoms do develop the drug should be gradually withdrawn. Rapid acetylators often respond inadequately even to doses of 100 mg daily and therefore the dose can be raised with only a slightly increased risk of an LE-like syndrome.

During long term treatment with Hydralazine it is advisable to determine the antinuclear factors and conduct urine analysis at intervals of approximately 6 months. Microhaematuria and / or proteinuria, in particular together with positive titres of ANF, may be initial signs of immune-complex glomerulonephritis associated with the SLE like syndrome. If overt clinical signs or symptoms develop, the drug should be withdrawn immediately.

Skin rash, febrile reactions and change in blood count occur rarely and drug should be withdrawn. Peripheral neuritis in the form of paraesthesia has been reported and may respond to pyridoxine administration or drug withdrawal.

In high (cyto-) toxic concentrations, hydralazine induces gene mutations in single cell organisms and in mammalian cells in vitro. No unequivocally mutagenic effects have been detected in vivo in a great number of test systems.

Hydralazine in lifetime carcinogenicity studies, caused, towards the end of the experiments, small but statistically significant increases in lung tumours in mice and in hepatic and testicular tumours in rats. These tumours also occur spontaneously with fairly high frequency in aged rodents.

With due consideration of these animals and in-vitro toxicological findings, hydralazine in therapeutic doses does not appear to bear risk that would necessitate a limitation of its administration. Many years of clinical experience have not suggested that human cancer is associated with hydralazine use.

Precautions

In patients with renal impairment (creatine clearance < 30 ml/min or serum creatinine concentrations> 2.5 mg / 100 ml or 221 µmol / l) and in patients with hepatic dysfunction the

dose or interval between doses should be adjusted according to clinical response, in order to avoid accumulation of the 'apparent' active substance.

Hydralazine should be used with caution in patients with coronary artery disease (since it may increase angina) or cerebrovascular disease.

When undergoing surgery, patients treated with Hydralazine may show a fall in blood pressure, in which case one should not use adrenaline to correct the hypotension, since it enhances the cardiac-accelerating effects of hydralazine.

4.5 Interaction with other medicinal products and other forms of interaction

Potentiation of effects: Concurrent therapy with other antihypertensives (vasodilators, calcium antagonists, ACE inhibitors, diuretics), anaesthetics, tricyclic antidepressants, major tranquillisers, 2nitrates or drugs exerting central depressant actions (including alcohol).

Administration of Hydralazine shortly before or after diazoxide may give rise to marked hypotension.

MAO inhibitors should be used with caution in patients receiving Hydralazine.

Concurrent administration of Hydralazine with beta-blockers subject to a strong first pass effect (e.g. propranolol) may increase their bioavailability. Download adjustment of these drugs may be required when they are given concomitantly with Hydralazine.

There is potential for the hypotensive effect of hydralazine to be antagonised when used concomitantly with oestrogens or non-steroidal anti-inflammatory drugs.

4.6. Pregnancy and lactation

Use of Hydralazine in pregnancy, before the third trimester should be avoided but the drug maybe employed in later pregnancy if there is no safer alternative or when the disease itself carries serious risks for the mother or child e.g. pre-eclampsia and /or eclampsia.

No serious adverse effects in human pregnancy have been reported to date with Hydralazine, although experience in the third trimester is extensive.

Hydralazine passes into breast milk but reports available so far have not shown adverse effects on the infant. Mothers in whom use of Hydralazine proves unavoidable may breast feed their infant provided that the infant is observed for possible adverse effects.

4.7 Effects on ability to drive and use machines

Hydralazine may impair the patient's reactions especially at the start of the treatment. The patient should be warned of the hazard when driving or operating machinery.

4.8 Undesirable effects

Some of the adverse effects listed below e.g. tachycardia, palpitations, angina symptoms, flushing, headache, dizziness, nasal congestion and gastro-intestinal disturbances are commonly seen at the start of treatment, especially if the dose is raised quickly. However such effects generally subside in the further course of treatment.

(The following frequency estimates are used: frequent> 10 %, occasional 1-10% rare 0.001-1% isolated cases < 0.001%)

Cardiovascular system:

Frequently: tachycardia, palpitations.

Occasionally: flushing, hypotension, anginal symptoms.

Rarely: oedema, heart failure.

Isolated cases: paradoxical pressor responses.

Central and peripheral nervous system:

Frequently: headache.

Rarely: dizziness.

Isolated cases: peripheral neuritis, polyneuritis, paraesthesia (these unwanted effects may be reversed by administering pyridoxine).

Musculo-skeletal system:

Occasionally: arthralgia, joint swelling, myalgia.

Skin and appendages:

Rarely: rash.

Urogenital system:

Rarely: proteinuria, increased plasma creatinine, haematuria sometimes in association with glomerulonephritis.

Isolated cases: acute renal failure, urinary retention.

Gastrointestinal tract:

Occasionally: gastrointestinal disturbances, diarrhoea, nausea, vomiting. Rarely: jaundice, liver enlargement, abnormal liver function sometimes in association with hepatitis.

Isolated cases: paralytic ileus.

Blood:

Rarely: anaemia, leucopenia, neutropenia, thrombocytopenia with or without purpura.

Isolated cases: haemolytic anaemia, leucocytosis, lymphadenopathy, pancytopenia, splenomegaly, agranulocytosis.

Psychiatric reactions:

Rarely: agitation, anorexia, anxiety.

Isolated cases: depression, hallucinations.

Sense organs:

Rarely: increased lacrimination, conjunctivitis, nasal congestion.

Hypersensitivity reactions:

Occasionally: SLE-like syndrome (sometimes resulting in a fatal outcome see section 4.4 Special warnings and precautions for use)

Rarely: hypersensitivity reactions such as pruritus, urticaria, vasculitis, eosinophilia, hepatitis.

Respiratory tract:

Rarely: dyspnoea, pleural pain.

Miscellaneous:

Rarely: fever, weight decrease, malaise.

Isolated cases: exophthalmos.

4.9 Overdose

Signs and symptoms

Symptoms include hypotension, tachycardia, myocardial ischaemia dysrhythmias and coma.

Treatment

Supportive measures including intravenous fluids are also indicated. If hypotension is present, an attempt should be made to raise the blood pressure without increasing the tachycardia. Adrenaline should therefore be avoided.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Hydralazine is a peripheral vasodilator.

Mechanism of action

Hydralazine is a direct acting vasodilator which exerts its effects principally on the arterioles. Its precise mode of action is not known. Administration of hydralazine produces a fall in peripheral resistance and a decrease in arterial blood pressure, effects which induce reflux sympathetic cardiovascular responses. The concomitant use of a beta-blocker will reduce these reflex effects and enhance the anti-hypertensive effect. The use of hydralazine can result in sodium and fluid retention, producing oedema and reduced urinary volume. These effects can be prevented by concomitant administration of a diuretic.

5.2 Pharmacokinetic properties

Absorption

None stated

Distribution

Hydralazine is rapidly distributed in the body and displays a particular affinity for the blood-vessel walls. Plasma protein binding is of the order of 90%.

Biotransformation

None stated

Elimination

Plasma half-life averages 2-3 hours but is prolonged up to 16 hours in severe renal failure (creatinine clearance less than 20 ml / min) and shortened to approximately 45 minutes in rapid acetylators.

Characteristics in patients

None stated

5.3 Preclinical safety data

Hydralazine has been found to be teratogenic in mice producing a small incidence of cleft palate and certain other bony malformations, in oral doses ranging from 20-120 mg / kg i.e. 20-30 times the maximum human daily dose. It was not teratogenic in rats or rabbits.

6. Pharmaceutical particulars

6.1 List of excipients

Methyl Paraben USP
Propyl Paraben USP
Propylene Glycol USP
Water for injection USP

6.2 Shelf life

36 months.

6.3 Special precautions for storage

Store at a temperature not exceeding 30 ^{0}C. Protect from light.

Keep medicines out of reach of children.

6.4 Nature and contents of container

Clear colourless solution filled in amber coloured sealed ampoules with blue dot at constriction.

7. Marketing authorisation holder

Alpa Laboratories Limited

33/2 A.B Road, Pigdamber, Indore (MP)

Pin Code- 453446

+91 731 4294567

+91 731 4294444

8. Marketing authorisation number(s)

To be allocated

9. Date of first authorisation/renewal of the authorisation

To be allocated

10. Date of revision of the text

To be allocated