1. Name of the Medicinal Product

1.1 Name of the Medicinal Product

APREDIN INJECTION (Hydralazine Hydrochloride Injection USP)

1.2. Strength

20 mg/ml

1.3. Pharmaceutical Dosage Form

Liquid Injection

2. Qualitative And Quantitative Composition

Qualitative Declaration

APREDIN Injection contains. Hydralazine Hydrochloride USP

Quantitative Declaration

Each ml contains:

Hydralazine Hydrochloride USP	20 mg/ml
Water for injection BP	q.s.

3. Pharmaceutical Form

Liquid Injection

4. Clinical Particulars

4.1 Therapeutic Indications

Apredin injection is indicated in the treatment of hypertensive emergencies particularly those associated with pre eclampsia and toxaemia of pregnancy. Treatment of hypertension with renal complication.

4.2 Posology and Method of Administration

When there is urgent need, therapy in the hospitalized patient may be initiated intramuscularly or as a rapid intravenous bolus injection directly into the vein. Hydralazine hydrochloride injection should be used only when the drug cannot be given orally. The usual dose is 20 to 40 mg, repeated as necessary.

Certain patients (especially those with marked renal damage) may require a lower dose. Blood pressure should be checked frequently. It may begin to fall within a few minutes after injection, with the average maximal decrease occurring in 10 to 80 minutes. In cases where there has been increased intracranial pressure, lowering the blood pressure may increase cerebral

ischemia. Most patients can be transferred to oral hydralazine hydrochloride within 24 to 48 hours.

The product should be used immediately after the vial is opened. It should not be added to infusion solutions. Hydralazine hydrochloride injection may discolor upon contact with metal; discolored solutions should be discarded.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit

Dosage: For slow IV use only.

4.3 Contraindications

Hypersensitivity to hydralazine; coronary artery disease; mitral valvular rheumatic heart disease.

4.4 Special Warning and Precautions for Use

In a few patients hydralazine may produce a clinical picture simulating systemic lupus erythematosus including glomerulonephritis. In such patients hydralazine should be discontinued unless the benefit-to-risk determination requires continued antihypertensive therapy with this drug. Symptoms and signs usually regress when the drug is discontinued but residua have been detected many years later. Long-term treatment with steroids may be necessary

General: Myocardial stimulation produced by hydralazine can cause anginal attacks and ECG changes of myocardial ischemia. The drug has been implicated in the production of myocardial infarction. It must, therefore, be used with caution in patients with suspected coronary artery disease.

The “hyperdynamic” circulation caused by hydralazine may accentuate specific cardiovascular inadequacies. For example, hydralazine may increase pulmonary artery pressure in patients with mitral valvular disease. The drug may reduce the pressor responses to epinephrine. Postural hypotension may result from hydralazine but is less common than with ganglionic blocking agents. It should be used with caution in patients with cerebral vascular accidents.

In hypertensive patients with normal kidneys who are treated with hydralazine, there is evidence of increased renal blood flow and maintenance of glomerular filtration rate. In some instances where control values were below normal, improved renal function has been noted after administration of hydralazine. However, as with any antihypertensive agent, hydralazine should be used with caution in patients with advanced renal damage.

Peripheral neuritis, evidenced by paresthesia, numbness, and tingling, has been observed. Published evidence suggests an antipyridoxine effect, and that pyridoxine should be added to the regimen if symptoms develop.

Laboratory Tests: Complete blood counts and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy with hydralazine even though the patient is asymptomatic. These studies are also indicated if the patient develops arthralgia, fever, chest pain, continued malaise, or other unexplained signs or symptoms.

A positive antinuclear antibody titer requires that the physician carefully weigh the implications of the test results against the benefits to be derived from antihypertensive therapy with hydralazine hydrochloride.

Blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura, have been reported. If such abnormalities develop, therapy should be discontinued.

Drug Interactions: MAO inhibitors should be used with caution in patients receiving hydralazine.

When other potent parenteral antihypertensive drugs, such as diazoxide, are used in combination with hydralazine, patients should be continuously observed for several hours for any excessive fall in blood pressure. Profound hypotensive episodes may occur when diazoxide injection and hydralazine injection are used concomitantly.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established in controlled clinical trials, although there is experience with the use of hydralazine hydrochloride in children. The usual recommended parenteral dosage, administered intramuscularly or intravenously, is 1.7 to 3.5 mg/kg of body weight daily, divided into four to six doses.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Interactions resulting in a concomitant use not recommended

Potentiation of effects: Concurrent therapy with other antihypertensive (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 Fertility, pregnancy and lactation

Pregnancy

Pregnancy: Teratogenic effects. Pregnancy Category C: Animal studies indicate that hydralazine is teratogenic in mice at 20 to 30 times the maximum daily human dose of 200 to 300 mg and possibly in rabbits at 10 to 15 times the maximum daily human dose, but that it is nonteratogenic in rats. Teratogenic effects observed were cleft palate and malformations of facial and cranial bones.

There are no adequate and well-controlled studies in pregnant women. Although clinical experience does not include any positive evidence of adverse effects on the human fetus, hydralazine should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

Breastfeeding

Nursing Mothers: Hydralazine has been shown to be excreted in breast milk.

Fertility

In a lifetime study in Swiss albino mice, there was a statistically significant increase in the incidence of lung tumors (adenomas and adenocarcinomas) of both male and female mice given hydralazine continuously in their drinking water at a dosage of about 250 mg/kg per day (about 80 times the maximum recommended human dose). In a 2-year carcinogenicity study of rats given hydralazine by gavage at dose levels of 15, 30, and 60 mg/kg/day (approximately 5 to 20 times the recommended human daily dosage), microscopic examination of the liver revealed a small, but statistically significant, increase in benign neoplastic nodules in male and female rats from the high-dose group and in female rats from the intermediate-dose group. Benign interstitial cell tumors of the testes were also significantly increased in male rats from the high-dose group. The tumors observed are common in aged rats and a significantly increased incidence was not observed until 18 months of treatment. Hydralazine was shown to be mutagenic in bacterial systems (Gene Mutation and DNA Repair) and in one of two rats and one rabbit hepatocyte in vitro DNA repair studies. Additional in vivo and in vitro studies using lymphoma cells, germinal cells, and fibroblasts from mice, bone marrow cells from chinese hamsters and fibroblasts from human cell lines did not demonstrate any mutagenic potential for hydralazine.

The extent to which these findings indicate a risk to man is uncertain. While long-term clinical observation has not suggested that human cancer is associated with hydralazine use, epidemiologic studies have so far been insufficient to arrive at any conclusions.

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

Adverse reactions with hydralazine hydrochloride are usually reversible when dosage is reduced. However, in some cases it may be necessary to discontinue the drug.

The following adverse reactions have been observed, but there has not been enough systematic collection of data to support an estimate of their frequency.

Common:	Headache, anorexia, nausea, vomiting, diarrhea, palpitations, tachycardia, angina pectoris.
Less Frequent:	Digestive: constipation, paralytic ileus.
	Cardiovascular: hypotension, paradoxical pressor response, edema.
	Respiratory: dyspnea.
	Neurologic: peripheral neuritis, evidenced by paresthesia, numbness, and tingling; dizziness; tremors; muscle cramps; psychotic reactions characterized by depression, disorientation, or anxiety.
	Genitourinary: difficulty in urination.
	Hematologic: blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, purpura; lymphadenopathy; splenomegaly.
	Hypersensitive Reactions: rash, urticaria, pruritus, fever, chills, arthralgia, eosinophilia, and, rarely, hepatitis.
	Other: nasal congestion, flushing, lacrimation, conjunctivitis.

4.9 Overdose

Acute Toxicity:	No deaths due to acute poisoning have been reported.
	Highest known dose survived: adults, 10 g orally.
	Oral LD50 in rats: 173 and 187 mg/kg

Signs and Symptoms: Signs and symptoms of overdosage include hypotension, tachycardia, headache, and generalized skin flushing.

Complications can include myocardial ischemia and subsequent myocardial infarction, cardiac arrhythmia, and profound shock.

Treatment: There is no specific antidote.

Support of the cardiovascular system is of primary importance. Shock should be treated with plasma expanders. If possible, vasopressors should not be given, but if a vasopressor is required, care should be taken not to precipitate or aggravate cardiac arrhythmia. Tachycardia responds to beta blockers. Digitalization may be necessary, and renal function should be monitored and supported as required.

No experience has been reported with extracorporeal or peritoneal dialysis.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

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

ATC code: C02DB02

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.

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

Water for injections BP

Macrogols-400 BP

Propylene glycol BP

Benzyl alcohol BP

6.2 Incompatibilities

Dextrose infusion solutions are not compatible because contact between hydralazine and glucose causes hydralazine to be rapidly broken down.

6.3 Shelf Life

3 years.

6.4 Special Precautions for Storage

Store at temperature below 25° C. protect from light.

Keep all medicines out of the reach of children.

6.5 Nature and Contents of Container

10 x 2 ml amber coloured glass ampoules packed in tray in a unit carton along with patient information leaflet.

6.6 Special Precautions for Disposal and Other Handling

None

7. Registrant/Sole Agnet

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9. Date of Revision of Text

To be given after approval of product.