

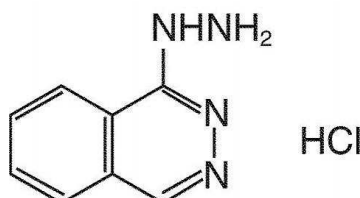
PRODUCT INFORMATION

APRESOLINE[®]

(hydralazine hydrochloride 20 mg powder for injection ampoule)

NAME OF THE MEDICINE

Hydralazine hydrochloride



1-Hydrazinophthalazine hydrochloride (C₈H₈N₄·HCl)

Molecular weight of 196.64

CAS No: 304-20-1

DESCRIPTION

Hydralazine hydrochloride is a white to yellowish odourless crystalline powder with a bitter saline taste. It is soluble 1 in 25 of water and 1 in 500 of alcohol; very slightly soluble in ether. A 2% solution in water has a pH of 3 to 4.

PHARMACOLOGY

Pharmacodynamics

Hydralazine exerts its peripheral vasodilating effect through a direct relaxation of smooth muscle tissue in vascular resistance vessels, predominantly in the arterioles. The cellular mechanism of action responsible for this effect is not fully understood.

In hypertension, this effect results in decreased arterial blood pressure (diastolic more than systolic). A reflex action by the sympathetic nervous system compensates for this fall in blood pressure by increasing heart rate, stroke volume, and cardiac output. Up to 75% of the therapeutic effect of hydralazine can be lost by this reflex action. To counteract the reflex action, hydralazine is often given in conjunction with a β -blocker.

The preferential dilatation of arterioles, as compared with veins, minimises postural hypotension and promotes the increase in cardiac output. The peripheral vasodilatation is widespread but not uniform.

Splanchnic, coronary, cerebral, and renal blood flow increases unless the fall in blood pressure is very marked. Vascular resistance in the cutaneous and muscle beds is not consistently affected.

The use of hydralazine can result in sodium and fluid retention, producing oedema and reduced urinary volume. These unwanted effects are best prevented by concomitant administration of a diuretic.

Pharmacokinetics

Distribution:

After intravenous administration of hydralazine no first-pass effect occurs; acetylator status therefore has no influence on the plasma levels. In the plasma only small amounts of the free drug can be traced, the bulk circulating in conjugated form, i.e. mainly as pyruvic acid hydrazone. Only the so-called "apparent" hydralazine, i.e. the sum of the free and conjugated hydralazine, can be measured reliably.

Hydralazine becomes bound to plasma proteins (chiefly albumin) to the extent of 88 to 90%. Hydralazine is rapidly distributed in the body and displays a specific affinity for muscle tissue in the arterial walls. Hydralazine crosses the placental barrier and also passes into the human milk.

Metabolism and elimination:

The pattern of the metabolites depends on the subject's acetylator and presumably hydroxylator status. Urinary excretion of NAc-HPZ (N-acetyl-hydrazine-phthalazinone), the main metabolite from the acetylation pathway, may be used to determine acetylator phenotype.

The plasma half-life generally ranges from 2 to 3 hours, but in rapid acetylators it is shorter, averaging 45 minutes. In patients with impaired renal function, the plasma half-life is prolonged to up to 16 hours at a creatinine clearance of <20 mL/min. Renal elimination may be impaired in patients of advanced age.

Hydralazine and its metabolites are rapidly excreted by the kidney. The bulk of the hydralazine excreted is in the form of acetylated and hydroxylated metabolites, some of which are conjugated with glucuronic acid; 2 to 14% is excreted as "apparent" hydralazine.

INDICATIONS

Hypertensive crises, especially during late pregnancy (pre-eclampsia and eclampsia).

CONTRAINDICATIONS

- Known hypersensitivity to hydralazine or 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 constrictive pericarditis).
- Isolated right-ventricular heart failure due to pulmonary hypertension (cor pulmonale).
- Dissecting aortic aneurysm.

PRECAUTIONS

Cardiac dysfunction:

The overall "hyperdynamic" state of the circulation induced by hydralazine may accentuate certain clinical conditions. Myocardial stimulation may provoke or aggravate angina pectoris or provoke myocardial infarction. Hydralazine can cause anginal attacks and ECG changes indicative of myocardial ischaemia. Therefore, it must be used with caution in patients with suspected coronary artery disease. Patients with suspected or confirmed coronary artery disease should be given Apresoline only under cover of a beta-blocker 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 Apresoline.

Patients who have survived a myocardial infarction should not receive Apresoline until a post-infarction stabilisation phase has been achieved. Hydralazine should not be used in heart failure.

Cerebrovascular disease:

Like all potent antihypertensives, Apresoline should be used with caution in patients suffering from cerebrovascular disease, since it can increase ischaemia.

Renal or hepatic impairment:

In patients with renal impairment (creatinine clearance <30 mL/min or serum creatinine concentration >2.5 mg/100 mL or 221 µmol/L) and in patients with hepatic dysfunction, the dose or the dosing interval has to be adapted according to the clinical response, in order to avoid accumulation of the "apparent" active substance.

Use during surgery:

When undergoing surgery, patients treated with Apresoline 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.

Effects on ability to drive or use machines:

Apresoline, especially at the start of treatment, may impair the patient's reactions, e.g. when driving or operating machines.

SLE-like syndrome with long-term use of oral hydralazine:

Prolonged treatment with hydralazine (i.e. usually treatment for more than 6 months) may provoke a systemic lupus erythematosus (SLE)-like syndrome, especially where dosages exceeding 100 mg daily are prescribed. In its mild form this syndrome is reminiscent of rheumatoid arthritis (arthralgia, sometimes associated with fever and skin rash) and proves reversible after withdrawal of the drug. In its more severe form it resembles acute SLE, and long-term treatment with corticosteroids may be required to reverse it completely. Since such reactions tend to occur more frequently the higher the dosage and the longer the duration of the medication, and since they are also more common in slow acetylators, it is recommended

that for maintenance therapy the lowest dosage that still proves effective 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 a greater risk of developing an SLE-like syndrome. In such patients every effort should therefore be made not to exceed a dosage of 100 mg daily; a careful watch should also be kept for clinical signs and symptoms suggestive of an SLE-like syndrome. Rapid acetylators, by contrast, often respond inadequately even to dosages of 100 mg daily. In these patients, the dosage can be raised with only a slightly increased risk of an SLE-like syndrome.

During long-term treatment with Apresoline it is advisable to determine the antinuclear factors (ANF) and to carry out urine analyses 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 and symptoms develop, the drug should be withdrawn at once. A complete blood count and ANF titer determination is indicated before and periodically during prolonged therapy with hydralazine even if the patient is asymptomatic.

Carcinogenicity / mutagenicity:

Hydralazine induces gene mutations, chromosomal aberrations and DNA damage in mammalian cells *in vitro*, as well as gene mutations in bacteria, yeast and *Drosophila*. The potential for similar effects *in vivo* has not been adequately reported. Carcinogenicity studies in Swiss mice showed an increased incidence of pulmonary adenomas and adenocarcinomas when hydralazine was administered in the drinking water at concentrations of 312-1250 ppm (approximately 50-200 mg/kg/day); a "no effect" dose has not been established. A carcinogenicity study in rats dosed by gavage at 15, 30 and 60 mg/kg/day showed increases in the incidences of hepatic neoplasms in both sexes and of Leydig cell tumours in males.

In the absence of adequate information on the genotoxic activity of hydralazine in *in vivo* studies, the possibility that the carcinogenic effects of hydralazine may be related to its genotoxic activity cannot be ruled out. The extent to which these findings indicate a risk to humans is uncertain. While long term clinical observation has not suggested that human cancer is associated with hydralazine use, epidemiological studies have so far been insufficient to arrive at any conclusions.

Use in pregnancy (Category C)

Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

Animal experiments have shown hydralazine, causing cleft palate and malformations of facial and cranial bones, is teratogenic in mice at oral doses equal to or greater than

20 mg/kg/day; a "no effect" dose has not been clearly established. Hydralazine was teratogenic in rabbits where oral doses equal to and greater than 75 mg/kg/day caused phalangeal defects. Hydralazine was not teratogenic in rats at oral doses up to 180 mg/kg/day. Embryo lethality was observed in mice at doses equal to or greater than 20 mg/kg/day. Hydralazine was, however, not embryo lethal in rats and rabbits at oral doses up to 180 and 60 mg/kg/day, respectively. Delayed ossification was observed in mice and rats at maternotoxic doses greater than 20 and 60 mg/kg/day, respectively, and reduced foetal weight was seen in mice at doses greater than 20 mg/kg/day.

Hydralazine is known to cross the placenta following intravenous administration and has been associated with foetal distress and foetal cardiac arrhythmia in the last trimester of pregnancy. In view of the possible teratogenic potential in humans, use of Apresoline in pregnancy before the third trimester should be avoided. The drug should only be given in the third trimester after weighing the needs of the mother against the risk to the foetus.

Use in lactation

Hydralazine passes into the breast milk. Alternatives to hydralazine should be considered in nursing mothers unless the benefits are considered to outweigh the risks.

Interactions with other drugs

Concomitant treatment with other vasodilators, calcium antagonists, ACE inhibitors, diuretics, antihypertensives, tricyclic antidepressants, and major tranquillisers, as well as the consumption of alcohol, may potentiate the blood pressure lowering effect of Apresoline. In particular, administration of Apresoline shortly before or after diazoxide may give rise to marked hypotension. MAO inhibitors should be used with caution in patients receiving Apresoline.

Concurrent administration of Apresoline with beta-blockers, such as propranolol, metoprolol and other beta-blockers subject to a strong first-pass effect, may increase their bioavailability. Downward dosage adjustment of these drugs may be required when they are given concomitantly with Apresoline.

Glucose infusion solutions are not compatible with Apresoline in ampoules because contact between hydralazine and glucose causes the active substance to be rapidly broken down.

Adrenaline enhances the cardiac-accelerating effects of hydralazine (see **PRECAUTIONS - Use during surgery**).

ADVERSE EFFECTS

The unwanted effects listed below are derived from the use of both oral and parenteral hydralazine. Some of the unwanted effects such as tachycardia, palpitation, anginal symptoms, flushing, headache, dizziness, nasal congestion and gastro-intestinal disturbances are

commonly seen at the start of treatment, especially if the dosage is raised rapidly. However, such reactions generally subside in the further course of treatment.

Frequency estimates: very common: $\geq 10\%$; common: $\geq 1\%$ to $< 10\%$; uncommon: $\geq 0.1\%$ to $< 1\%$; rare: $\geq 0.01\%$ to $< 0.1\%$; very rare: $< 0.01\%$.

Cardiovascular system:

Very common: tachycardia, palpitation

Common: flushing, hypotension, anginal symptoms

Uncommon: oedema, heart failure

Very rare: paradoxical pressor responses

Central and peripheral nervous system:

Very common: headache

Uncommon: dizziness

Very rare: peripheral neuritis, polyneuritis, paraesthesiae (these unwanted effects may be reversed by administering pyridoxine), tremor

Musculoskeletal system:

Common: arthralgia, joint swelling, myalgia

Skin and appendages:

Uncommon: rash

Urogenital system:

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

Very rare: acute renal failure, urinary retention

Gastrointestinal tract:

Common: gastrointestinal disturbances, diarrhoea, nausea, vomiting

Uncommon: jaundice, liver enlargement, abnormal liver function sometimes in association with hepatitis

Very rare: paralytic ileus

Blood:

Uncommon: anaemia, leucopenia, neutropenia, thrombocytopenia with or without purpura

Very rare: haemolytic anaemia, leucocytosis, lymphadenopathy, pancytopenia, splenomegaly; agranulocytosis

Psyche:

Uncommon: agitation, anorexia, anxiety

Very rare: depression, hallucinations

Sense organs:

Uncommon: increased lacrimation, conjunctivitis, nasal congestion

Immune system disorders:

Common: Positive test for ANF (see **PRECAUTIONS - SLE-like syndrome with long-term use of oral hydralazine**)

Hypersensitivity reactions:

Uncommon: SLE-like syndrome (see **PRECAUTIONS - Long-term use of oral hydralazine**); hypersensitivity reactions such as pruritus, urticaria, vasculitis, eosinophilia, hepatitis

Respiratory tract:

Uncommon: dyspnoea, pleural pain

Miscellaneous:

Uncommon: fever, weight decrease, malaise

Very rare: exophthalmos, retroperitoneal fibrosis

DOSAGE AND ADMINISTRATION

Injection treatment with Apresoline should always be carried out cautiously and under strict medical surveillance (if possible in hospital).

Adult dosage:

The initial dose is 5 to 10 mg, administered by slow intravenous injection in order to avoid precipitous decreases in mean arterial pressure with a critical reduction in cerebral or utero-placental perfusion. If it is necessary to repeat the injection, this should be done after an interval of 20 to 30 minutes, throughout which the blood pressure and heart rate should be monitored. A satisfactory response can be defined as a decrease in diastolic blood pressure to 90 to 100 mm Hg.

Apresoline may also be given by continuous intravenous infusion, beginning with a flow rate of 200 to 300 µg/min. Maintenance flow rates must be determined individually and are usually within the range of 50 to 150 µg/min.

Instructions for use:

Prior to each injection, the dry active substance should be completely dissolved in 1 mL water for injections. The freshly prepared solution should be used immediately. For the preparation of infusion solutions, this fresh solution should be diluted with sodium chloride intravenous infusion 9 mg/mL. Glucose infusion solutions are not compatible because contact between hydralazine and glucose causes the active substance to be rapidly broken down.

The ampoule contains no antimicrobial preservative. Infusion of the reconstituted injection and of admixtures of the injection should be commenced as soon as possible after preparation in order to reduce microbiological hazards. Both the reconstituted injection and admixtures of the injection should be stored at 2 to 8°C. Preparations not used within 24 hours of reconstitution should be discarded.

Use in children:

Safety and efficacy of hydralazine have not been established in children.

OVERDOSAGE

Signs and symptoms:

The chief manifestations are cardiovascular disorders such as pronounced tachycardia and hypotension, which are accompanied by nausea, dizziness, and sweating, and which can result in circulatory collapse; also possible are myocardial ischaemia with angina pectoris and cardiac arrhythmias. Further signs and symptoms may include impairment of consciousness, headache, and vomiting, as well as possibly tremor, convulsions, oliguria, and hypothermia.

Management:

Severe hypotension may respond to placing the patient in the supine position with the feet raised. The effects of gross overdosage may be treated by the infusion of plasma expanders. Contact Poison Information Centre on 131 126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Injection 20 mg dry powder/2 mL ampoules; 5 ampoules.

Store below 25°C, protected from light.

NAME AND ADDRESS OF THE SPONSOR

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AFT Pharmaceuticals Ltd.
Auckland

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF APPROVAL

Date of TGA approval

27 March 2005

Date of most recent amendment

9 April 2009

Version 01