

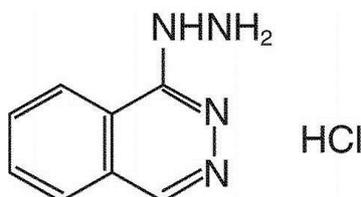
PRODUCT INFORMATION

APRESOLINE®

(hydralazine hydrochloride 20 mg powder for injection ampoule)

NAME OF THE MEDICINE

Hydralazine hydrochloride



1-Hydrazinophthalazine hydrochloride (C₈H₈N₄·HCl)

Molecular weight: 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 parts of water and 1 in 500 parts 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 beta-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 Apresoline 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 Apresoline 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%. It is rapidly distributed in the body and displays a specific affinity for muscle tissue in the arterial walls. It crosses the placental barrier and also passes into the human milk.

Metabolism

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.

Excretion

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. Renal elimination may be impaired in patients of advanced age.

INDICATIONS

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

CONTRAINDICATIONS

- 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
- Porphyrria.

PRECAUTIONS

Cardiovascular system

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, Apresoline 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. Apresoline 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.

Immune system

Prolonged treatment with Apresoline (i.e. usually treatment for more than 6 months) may provoke an 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, anaemia, leucopenia, thrombocytopenia and skin rash) and proves reversible after withdrawal of the medicine. In its more severe form, it resembles acute SLE (similar manifestations as the milder form, plus pleurisy, pleural effusions and pericarditis; nervous system and renal involvement are rarer than in idiopathic lupus). Early

detection and a timely diagnosis with appropriate therapy (treatment discontinuation and possibly long-term treatment with corticosteroids may be required to reverse the effects) are of utmost importance in this life-threatening illness to prevent more severe complications, which may sometimes be fatal.

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 full blood count and 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. A positive ANF titre requires that the physician carefully weighs the implications of the test results against the benefits of continued therapy with Apresoline. If overt clinical signs and symptoms develop, the medicine should be withdrawn at once. A complete blood count and ANF titre determination is indicated before and periodically during prolonged therapy with Apresoline even if the patient is asymptomatic. These studies are also indicated if the patient develops arthralgia, fever, chest pain, persistent malaise, or other unexplained signs or symptoms.

Treatment with Apresoline may induce systemic vasculitis, including ANCA (anti-neutrophil cytoplasm antibody)-positive vasculitis, leading to pulmonary renal syndrome which is a combination of diffuse alveolar haemorrhage and rapidly progressive glomerulonephritis. Patients may present with severe respiratory and/or renal failure and require treatment in an intensive care unit. The syndrome is characterised by a fulminant course if left untreated, and may sometimes be fatal.

Nervous system

Isolated cases of peripheral neuritis in the form of paraesthesia have been reported, which may respond to pyridoxine administration or medicine withdrawal.

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 (see DOSAGE AND ADMINISTRATION).

Haematological effects

Adverse haematological effects, such as a reduction in haemoglobin and red cell count, leucopenia, agranulocytosis and purpura, have been reported. If such abnormalities develop, therapy should be discontinued.

Skin

Skin rash, febrile reactions and change in blood count occur rarely, in which case the medicine should be withdrawn.

Use during surgery

Patients treated with Apresoline may show a fall in blood pressure when undergoing surgery. In such cases, one should not use adrenaline (epinephrine) to correct the hypotension, since it enhances the cardiac-accelerating effects of hydralazine.

Effects on fertility

The effects of hydralazine on fertility in humans are not known.

Use in pregnancy (Category C)

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 fetal 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 fetal distress and fetal 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 medicine should only be given in the third trimester after weighing the needs of the mother against the risk to the fetus.

Use in lactation

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

Paediatric use

Safety and efficacy of hydralazine have not been established in children. Apresoline is not recommended for paediatric use.

Use in the elderly

No studies in the elderly have been performed. Concurrent hepatic and renal insufficiency should be taken into account (see PRECAUTIONS, Renal or hepatic impairment).

Genotoxicity

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

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.

Effects on ability to drive or use machines

Apresoline may impair the patient's reactions especially at the start of treatment. Dizziness or hypotension may occur due to the established mechanism of action (see ADVERSE EFFECTS). It is therefore advisable to exercise caution when driving or operating machinery.

INTERACTIONS WITH OTHER MEDICINES

The effects of Apresoline are potentiated by other antihypertensive medicines (including vasodilators, calcium antagonists, ACE inhibitors, diuretics), tricyclic antidepressants, alcohol, anaesthetics, major tranquillisers, or any medicine exerting a central depressant action. 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 medicines may be required when they are given concomitantly with Apresoline.

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

Adrenaline (epinephrine) enhances the cardiac-accelerating effects of hydralazine. Patients taking Apresoline who develop hypotension should not be treated with sympathomimetics, e.g. adrenaline (epinephrine), as Apresoline can cause tachycardia, and sympathomimetics could enhance this (see PRECAUTIONS, Use during surgery).

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

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 gastrointestinal 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: $\geq 1/10$; common: $\geq 1/100$ to $< 1/10$; uncommon: $\geq 1/1,000$ to $< 1/100$; rare: $\geq 1/10,000$ to $< 1/1,000$; very rare: $< 1/10,000$; not known: cannot be estimated from the available data.

Adverse drug reactions from multiple sources including clinical trials and spontaneous reports:

Blood and lymphatic system disorders

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

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

Cardiac disorders

Very common: tachycardia, palpitation

Common: angina pectoris, anginal symptoms

Uncommon: congestive heart failure

Eye disorders

Uncommon: increased lacrimation, conjunctivitis

Very rare: exophthalmos

Gastrointestinal disorders

Common: gastrointestinal disorder, diarrhoea, nausea, vomiting

Very rare: paralytic ileus, retroperitoneal fibrosis

General disorders and administration site conditions

Uncommon: pyrexia, malaise, oedema

Hepatobiliary disorders

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

Not known: hepatosplenomegaly (usually associated with SLE-like symptoms)

Immune system disorders

Common: positive test for ANF (see PRECAUTIONS, Immune system)

Uncommon: SLE-like syndrome (see PRECAUTIONS, Immune system); hypersensitivity reactions such as pruritus, urticaria, vasculitis including pulmonary renal syndrome, eosinophilia, hepatitis

Investigations

Uncommon: weight decrease

Musculoskeletal and connective tissue disorders

Common: arthralgia, joint swelling, myalgia

Nervous system disorders

Very common: headache

Uncommon: dizziness

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

Psychiatric disorders

Uncommon: agitation, anorexia nervosa, anxiety

Very rare: depression, hallucinations

Renal and urinary disorders

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

Very rare: acute renal failure, urinary retention

Respiratory, thoracic and mediastinal disorders

Uncommon: dyspnoea, pleural pain, nasal congestion

Skin and subcutaneous tissue disorders

Uncommon: rash

Vascular disorders

Common: flushing, hypotension

Very rare: paradoxical pressor responses

DOSAGE AND ADMINISTRATION

Treatment with Apresoline for injection should always be carried out with caution 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 micrograms/min. Maintenance flow rates must be determined individually and are usually within the range of 50 to 150 micrograms/min.

Instructions for use

Prior to each injection, the contents of the ampoule 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 product 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°C to 8°C. Preparations not used within 24 hours of reconstitution should be discarded. Each vial is intended for single use in one patient only. Discard any unused portion.

Use in children

Safety and efficacy of hydralazine have not been established in children. Apresoline is not recommended for paediatric use.

Renal and 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), or in patients with hepatic dysfunction, the dosage or the dosing interval must be adapted according to the clinical response to avoid accumulation of the “apparent” active substance.

OVERDOSAGE

Signs and symptoms

The chief manifestations of overdosage 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, hypothermia and coma.

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 the Poison Information Centre on 131 126 for advice on management of overdose.

PRESENTATION AND STORAGE CONDITIONS

Powder for Injection 20 mg in glass ampoules; 5 ampoules per pack.

Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Amdipharm Mercury (Australia) Pty Ltd
Level 9, 76 Berry Street
North Sydney, NSW 2060

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine – Schedule 4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

15 February 1993

DATE OF MOST RECENT AMENDMENT

03 April 2017

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