Apresoline®

Peripheral Vasodilator

Composition
Active Substance
1-Hydrazinophthalazine hydrochloride (=hydralazine, hydrochloric,)
Hydralazine is a phthalazine derivative.

Pharmaceutical forms and quantity of active substance per unit.
Coated tablets of 25 mg
Dry substance for injection: 20 mg per ampoule of 1 mL.

Appearance of the product:

Tablet: Pale yellow round sugar coated tablets marked GF on one side. This presentation is not currently marketed in New Zealand.

Injection: White to yellowish lyophilisate.

Uses

Actions
Pharmacotherapeutic group: Peripheral vasodilator.
ATC code C02DB02.

Mechanism of Action
Hydralazine hydrochloride is a peripheral vasodilator. It 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.

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.

In hypertension, this effect results in decreased arterial blood pressure (diastolic more than systolic) and in an increased heart rate, stroke volume, and cardiac output.

Since hydralazine exhibits no cardiodepressant or sympatholytic properties, reflex regulatory mechanisms producing an increase in stroke volume and heart rate continue to operate. Reflex-induced tachycardia, which may occur as an accompanying effect, can be counteracted by concomitant treatment with a beta-blocker or any substance that inhibits sympathetic function.

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.
In chronic congestive heart failure hydralazine, through its primary action as an arteriolar dilator, reduces afterload; this leads to a decrease in the work which the left ventricle has to perform, coupled with an increase in stroke volume, renal blood flow, and cardiac output with blood pressure being well maintained or falling only slightly.

**Pharmacokinetics**

**Absorption and plasma concentrations**

After intravenous administration of hydralazine no first-pass effect occurs; acetylator status therefore has no influence on the plasma levels.

Hydralazine is rapidly and completely absorbed after oral administration from the gastrointestinal tract and the absorption is variable according to the acetylation status of the individual. The maximum serum concentration of hydralazine after single oral administration of 50 mg Apresoline Tablets was found to be 229 ± 20 ng/mL and 148 ± 15 ng/mL in slow and fast acetylators, respectively.

Concurrent intake of food has been found to decrease the bioavailability of hydralazine and also to reduce vasodilator effect.

Orally administered hydralazine undergoes a dose-dependent first-pass effect (systemic bioavailability: 26-55%), this first-pass effect being dependent on the individual’s acetylator status. Hydralazine exhibits non-linear pharmacokinetics and it is attributed to the saturable first pass effects.

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 apparent hydralazine i.e. the sum of the free and conjugated hydralazine, can be reliably measured. Peak plasma levels are reached within one hour in most cases.

**Distribution**

Hydralazine is primarily present as hydrazone conjugate with pyruvic acid in plasma. Hydralazine becomes bound to plasma proteins (chiefly albumin) to the extent of 88-90%. The volume of distribution of hydralazine was determined as 1.5 ± 1.0 L/kg. Hydralazine is rapidly distributed in the body and displays a specific affinity for muscle tissue of the arterial walls. Hydralazine crosses the placental barrier and also passes into the breast milk.

**Metabolism**

Orally administered hydralazine undergoes a first-pass effect (systemic availability 26-55%) – this first pass effect can depend on the individual’s acetylator status. In response to the same dose, slow acetylators show higher apparent hydralazine levels than rapid acetylators. Systemic metabolism in the liver is by hydroxylation of the ring system and conjugation with glucuronic acid and acetylator status does not affect elimination. The major metabolites are the acetylation product (3-methyl-1,2,4-triazolo-(3,4a) phthalazine) hydralazine pyruvic acid hydrazone, which is the major plasma metabolite; and NAc-HPZ (4-(2-ethylhydrazino) phthalazine-1-one, N-AcHPZ (4-(2-ethylhydrazino) which is mostly found in the urine and was found to be the relevant indicator for the drug-related phenotype.

**Elimination**
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.

Hydralazine and its metabolites are rapidly excreted by the kidney. Within 24 hours after an oral dose, approx. 80% of the dose can be recovered in the urine. The bulk of the hydralazine excreted is in the form of acetylated and hydroxylated metabolites, some of which are conjugated with glucuronic acid; 2-14% is excreted as “apparent” hydralazine.

Advancing age does not affect either the blood concentration or the systemic clearance of “apparent” hydralazine. Renal elimination may however be affected insofar as kidney function diminishes with age.

**Indications**

- Hypertensive crisis, especially during late pregnancy (pre-eclampsia and eclampsia) (Ampoules)
- For the treatment of moderate to severe hypertension as an adjunct to other anti-hypertensive agents e.g. beta-blockers and diuretics (Tablets)
- For the treatment of chronic congestive heart failure as adjunct to long-acting nitrates, digitalis and other positive-inotropic agents and/or diuretics

**Dosage and Administration**

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

**Adults**

The initial dose is 5-10 mg, administered by slow intravenous injection in order to avoid precipitous fall 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 20-30 min, 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 90-100 mmHg.

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

Prior to injection, the powdered active substance should be completely dissolved in 1 mL distilled water for injection and the freshly prepared solution should be used immediately. For the preparation of infusion solutions, this fresh solution should be diluted with physiological saline or with 5% sorbitol solution.

**Children**

In the rare cases where rapid treatment proves indispensable in a child, Apresoline ampoules should be used with extreme caution.

The initial dose is 0.1-0.5 mg/kg body weight administered intravenously over 1-2 min with repeat
doses every 30-90 min as required, up to a maximum daily dose of 3.5 mg/kg body weight.

Tablets (Tablets are not currently marketed in New Zealand). The dose should be adjusted to the individual needs of the patient.

**Adults**

**Hypertension**

Treatment should begin with low doses which should be increased stepwise to achieve an optimal effect while minimising unwanted effects. Apresoline tablets are usually given twice daily with the usual starting dose being 25 mg b.i.d. This dosage may be increased as required up to 200 mg per day. However the dose should not be increased above 100 mg per day without determining the patient's acetylator status.

**Congestive Heart Failure**

Doses vary according to individual patients' needs and are generally higher than those used for treating hypertension. After dose titration the effective maintenance dose is typically 50-75 mg every 6 hours or 100 mg 2-3 times daily.

**Children**

**Hypertension**

The recommended starting dose is 0.75 mg/kg body weight daily. The dosage may be increased to obtain the desired response up to a maximum daily dose of 3.5 mg/kg body weight.

**Congestive Heart Failure**

Therapy may be started with a dosage of 0.75-1 mg/kg body weight in 4 divided doses given every 6 hours gradually increasing to 4.0 mg/kg body weight daily.

**Contraindications**

- Known hypersensitivity to hydralazine or dihydralazine or to any of the excipients.
- 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.
- Porphyria

**Warnings and Precautions**

In other autoimmune diseases than SLE, blood dyscrasias, pronounced arteriosclerosis, severe myocardial disease and hepatic impairment. In patients with severe renal insufficiency (creatinine clearance <10 mL/min/1.73 m²), or serum creatinine concentration >2.5 mg/100 mL or 221 µmol/L) and in patients with disorders of hepatic function, dose reduction or extension of the dose interval should be implemented, given the risk of accumulation.

**Cardiovascular system**

In heart failure with hypotension, special caution is indicated. Apresoline therapy for heart
failure should be initiated in hospital and limited for the present to clinics having special experience with heart disease. If possible, a haemodynamic evaluation is recommended; accordingly it is primarily patients with low cardiac output and normal or moderately elevated filling pressure in the left ventricle that are recommended for treatment with Apresoline.

The overall state of the circulation induced by hydralazine may accentuate certain clinical conditions. Myocardial stimulation may provoke or aggravate uncontrolled or untreated angina pectoris. Hydralazine can cause anginal attacks and ECG changes indicative of myocardial ischaemia. It must therefore be used with caution in patients with suspected coronary artery disease or with cerebrovascular disease. Therefore, Apresoline should only be given to patients with suspected or confirmed coronary artery disease who are already being treated with a β-blocker, or in combination with other suitable sympatholytic agents. It is important that the β-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.

When initiating oral therapy in heart failure, particular caution should be exercised and the patient kept under careful surveillance and/or haemodynamic monitoring for early detection of postural hypotension or tachycardia. Where discontinuation of therapy in heart failure is indicated, Apresoline Tablets should be withdrawn gradually (except in serious situations, such as an SLE-like syndrome or blood dyscrasias), in order to avoid precipitation and/or exacerbation of heart failure.

Like all potent antihypertensives, Apresoline should be used with caution in patients with coronary artery disease or acute cerebrovascular disease, since it can increase ischaemia. 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.

**Immune system**

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, anaemia, leucopenia, thrombocytopenia and skin rash) and proves 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; whereas nervous system and renal involvement are more rare than in idiopathic lupus), long-term treatment with corticosteroids may be required to reverse it completely. Early detection and a timely diagnosis with appropriate therapy (i.e. treatment discontinuation and possibly long-term treatment with corticosteroids) are of utmost importance in this lifethreatening illness to prevent more severe complications, which may sometimes be fatal.

In particular, renal symptoms are less frequent than in idiopathic SLE and pleuro-pulmonary symptoms, as well as pericarditis, are more frequent. 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 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 approx. 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.

Treatment with hydralazine may induce systemic vasculitis, including ANCA(+) 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 characterized by a fulminant course if left untreated, and may sometimes be fatal.

**Nervous system**
Isolated cases of peripheral neuritis have been reported. Published evidence suggests an antipyridoxine effect. Peripheral neuropathy secondary to an influence on the metabolism of vitamin B6 (pyridoxine) may occur which may respond to pyridoxine administration or drug withdrawal.

**Laboratory tests**
A complete blood count and ANF titre determination is indicated before and periodically during prolonged therapy with hydralazine 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. A positive ANF titre requires that the physician carefully weighs the implications of the test results against the benefits of continued therapy with hydralazine.

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

**Renal and hepatic impairment**
In patients with moderate to severe renal impairment (creatinine clearance < 30 mL/min or serum creatinine concentration > 2.5 mg/100 mL or 221 μmol/L) or hepatic dysfunction, the dosage or the dosing interval must be adapted according to the clinical response to avoid accumulation of the “apparent” active substance.

**Skin**
Skin rash, febrile reactions and change in blood count occur rarely and drug should be withdrawn.

**Apresoline 25 mg Tablets contain sucrose**

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

**Preclinical safety data**

**Fertility and Teratogenicity**
No significant effects upon fertility or other reproductive parameters in rats were noted. Hydralazine is teratogenic in mice, causing cleft palate and malformations of the facial and cranial bones at doses 20-30 times the maximum human daily dose of 200-300 mg. It is not teratogenic in rats or rabbits, and perinatal and postnatal growth of the rats’ offspring is not affected.

**Mutagenicity**
Hydralazine, in cyto-toxic concentrations, induces gene mutations in bacteria, yeasts and Drosophila, and in mammalian cells in vitro. No clear mutagenic effects including chromosomal aberrations have been detected in vivo in a large number of test systems.

Under in vitro conditions, the formation of reactive metabolites/intermediates is favoured, so that DNA damage may occur. In vivo, however, i.e. under normal metabolic conditions, there is intense detoxification of potentially toxic intermediates. Consequently, the genotoxic/mutagenic risk for man is estimated to be very low.

**Carcinogenicity**
Hydralazine, in carcinogenicity studies in mice and rats caused small but statistically significant increases in some types of tumours, but these also occur spontaneously with fairly high frequency in aged rodents.

Studies of the carcinogenic potential of hydralazine in rodents do not suggest a specific carcinogenic risk at therapeutic doses.

In a 2-year carcinogenicity study in rats, microscopic examination of the liver revealed some increase in the incidence of benign neoplastic nodules at oral doses (gavage) of 30 and 60 mg/kg. No such nodules were found at 15 mg/kg. The results of 3 other carcinogenicity studies (2 in mice, 1 in rats) are considered inconclusive with respect to increases in the frequency of compound-related neoplastic changes. The males of the 60 mg/kg dose group also showed benign tumours of testicular interstitial cells.

In carcinogenicity studies in mice and rats, hydralazine has caused statistically significant increases in individual types of tumours. These tumours also occur spontaneously to a relatively great extent in ageing rodents.

The frequency of neoplastic changes has been studied in three other carcinogenicity studies (two in mice, one in rats). However, the results of these studies have been contradictory.

Studies of the carcinogenic potential of hydralazine in rats do not suggest a specific carcinogenic risk
at therapeutic doses. Moreover, many years of clinical experience have not suggested that hydralazine use is associated with human cancer.

**Use during Pregnancy and Lactation**

Category C
Women of child-bearing potential
Women planning to become pregnant should not take Apresoline Tablets. When pregnancy is confirmed in women taking Apresoline Tablets, the treatment should be discontinued immediately.

**Pregnancy**
No serious adverse effects in human pregnancy have been observed to date with Apresoline, although experience in the third trimester is extensive. However, animal experiments have shown teratogenic potential in mice but not in other animal species. Hydralazine crosses the placenta. Use of Apresoline in pregnancy, before the third trimester should be avoided, but the drug may be 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.

**Breast-feeding**
Hydralazine passes into breast milk, but reports available so far do not suggest an adverse effect on the infant. Mothers taking Apresoline may breast-feed their infant, provided that the infant is observed for possible unexpected adverse effects.

**Fertility**
No significant effects upon fertility or other reproductive parameters in rats were noted. The effects of Apresoline Tablets on fertility in humans are not known.

**Effects on ability to drive and use machines**

Apresoline, especially at the start of treatment, may impair the patient’s reactions when driving or operating machines. Dizziness or hypotension may occur with Apresoline Tablets, it is therefore advisable to exercise caution when driving or operating machinery.

**Adverse Effects**

Adverse drug reactions from multiple sources including clinical trials and spontaneous reports are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions 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%, not known (cannot be estimated from the available data).

Some of the unwanted effects listed below 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.
**Blood and lymphatic system disorders**
Uncommon: anaemia, leucopenia, neutropenia, eosinophilia, thrombocytopenia with or without purpura.
Very rare: haemolytic anaemia, leucocytosis, lymphadenopathy, pancytopenia, splenomegaly, agranulocytosis.

**Immune system disorders**
Uncommon: hypersensitivity.

**Metabolism and nutrition disorders**
Uncommon: decreased appetite

**Psychiatric disorders**
Uncommon: agitation, anorexia nervosa, anxiety.
Very rare: depression, hallucinations.

**Nervous system disorders**
Very common: headache.
Uncommon: dizziness.
Very rare: peripheral neuropathy, polyneuropathy, paraesthesia (these may be reversed by giving pyridoxine), and tremor.

**Eye disorders**
Uncommon: lacrimation increased, conjunctivitis.
Very rare: exophthalmos

**Cardiac disorders**
Very common: tachycardia, palpitation.
Common: angina pectoris.
Uncommon: cardiac failure congestive.

**Vascular disorders**
Common: flushing, hypotension
Very Rare: Paradoxical pressor response
Not known: vasculitis, orthostatic hypotension.

**Respiratory, thoracic and mediastinal disorders**
Uncommon: dyspnoea, pleuritic pain, nasal congestion.

**Gastrointestinal disorders**

**Hepatobiliary disorders**
Uncommon: jaundice, hepatomegaly, hepatitis.
Not known: hepatosplenomegaly (more common when associated with SLE-like symptoms).

**Skin and subcutaneous tissue disorders**
Uncommon: rash, pruritus, urticaria.
Musculoskeletal and connective tissue disorders
Common: arthralgia, joint swelling, myalgia, SLE-like syndrome.

Renal and Urinary disorders
Uncommon: proteinuria, haematuria, sometimes in association with glomerulonephritis.
Very rare: acute glomerulonephritis, acute renal failure, urinary retention.
Not known: pulmonary renal syndrome.

General disorders and administration site conditions
Uncommon: pyrexia, malaise, oedema.

Investigations
Uncommon: weight decreased, blood creatinine increased, liver function test abnormal.

During long-term treatment (usually more than 6 months) Apresoline may induce a condition similar to lupus erythematosus, especially if daily doses above 100 mg are used. In its milder form, the syndrome may resemble rheumatoid illness with joint pain, fever and rash, which are reversible upon discontinuation of the drug. In its more severe form, the condition resembles acute SLE and prolonged treatment with corticosteroids may be needed for complete recovery. The risk of these reactions increases with increasing dose and duration of treatment. It is therefore important that the lowest effective maintenance dose is used.

Interactions
Concomitant treatment with other antihypertensives (vasodilators e.g. minoxidil, calcium antagonists e.g. nifedipine or amlodipine, ACE inhibitors e.g. enalapril or ramipril, diuretics e.g. furosemide or hydrochlorothiazide), tricyclic antidepressants e.g. imipramine or clomipramine, levodopa, anaesthetics, nitrates, major tranquillisers e.g. haloperidol or promethazine, as well as drugs exerting central depressant actions (including 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 (e.g., selegiline or isoniazid) should be used with caution in patients receiving Apresoline Tablets.

Concurrent administration of Apresoline Tablets with 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 Tablets.

Concurrent intake of food has been found to decrease the bioavailability of hydralazine and also to reduce vasodilator effect.

There is potential for the hypotensive effect of hydralazine to be antagonised when used concomitantly with non-steroidal anti-inflammatory drugs (NSAIDs) (e.g. ibuprofen or diclofenac), oestrogens or corticosteroids (e.g. hydrocortisone or prednisolone), and a dosage
adjustment may be required. Concurrent administration of indometacin can reduce hypotensive effect of hydralazine. Combination with indomethacin may require dosage adjustments.

Patients taking hydralazine who develop hypotension should not be treated with sympathomimetics (e.g. epinephrine). As hydralazine can cause tachycardia, and sympathomimetics could enhance this.

**Overdosage**

**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.

**Treatment**
Since no specific antidote is known, - in addition to attempts to eliminate the drug from the gastrointestinal tract (early induction of vomiting, later gastric lavage; administration of activated charcoal and possibly laxatives) - treatment should be supportive including use of a plasma expander or intravenous fluids as indicated. If hypotension is present, an attempt should be made to raise the blood pressure without increasing the tachycardia. Adrenaline should therefore be avoided.

**Pharmaceutical Precautions**
Protect from light and heat and store below 30ºC.
Ampoules: Store the reconstituted solution below 25ºC and use within 24 hours. Apresoline should be kept out of the reach of children.

**Incompatibilities**
Hydralazine hydrochloride can form complexes with various types of metal ions, causing discolouration of the solution. If possible the solution should be prepared using a non-metallic filter and contact with metal parts should be minimised. If not used immediately, the reconstituted solution should not be stored in a container with metal parts. Glucose infusion solutions are not compatible because contact between hydralazine and glucose causes the active substance to be rapidly broken down.

**Medicines Classification**
Prescription Medicine

**Package Quantities**
Ampoules: Box of 5 ampoules
Tablets: Bottles of 100 tablets

**Further Information**
Nil

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Date of Preparation
14 Sept 2016

2047794 U17