

New Zealand Data Sheet

1 APRESOLINE® (20 mg/mL powder for injection)

APRESOLINE® 20 mg/mL powder for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Hydralazine hydrochloride 20 mg/mL

3 PHARMACEUTICAL FORM

White to yellowish lyophilisate

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of administration

Dose

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.

Method of administration

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

4.3 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.

4.4 Special warnings and precautions for use

Hydralazine should be used with caution 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 μ mol/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.

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 life-threatening 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.

4.5 Interaction with other medicines and other forms of interaction

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.

Concurrent administration of Apresoline 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.

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.

4.6 Fertility, pregnancy and lactation

Category C

Women of child-bearing potential

Women planning to become pregnant should not take Apresoline. When pregnancy is confirmed in women taking Apresoline, 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.

Breastfeeding

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 on fertility in humans are not known.

4.7 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, it is therefore advisable to exercise caution when driving or operating machinery.

4.8 Undesirable 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 $\geq 1/10$, 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).

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

Common: gastrointestinal disorder, diarrhoea, nausea, vomiting

Very rare: ileus paralytic

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, urticarial

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 **Overdose**

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Pharmacotherapeutic group: Peripheral vasodilator, ATC code: C02DB02

Mechanism of action

Properties:

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.

5.2 **Pharmacokinetic properties**

Absorption

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

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

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.

Biotransformation

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-acetylhydrazino) phthalazine-1-one, N-AcHPZ (4-(2-acetylhydrazino) 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. 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.

5.3 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 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.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Protect from light and heat and store below 30°C.

Store the reconstituted solution below 25°C and use within 24 hours. Apresoline should be kept out of the reach of children.

6.5 Nature and contents of container

Box of 5 ampoules

6.6 Special precautions for disposal

No special requirements

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

Name and address of the sponsor in New Zealand

AFT Pharmaceuticals Ltd.,

PO Box 33.203

Takapuna

Auckland

Email:customer.service@aftpharm.com

For and on behalf of Amdipharm Ltd, Temple Chambers, 3 Burlington Road, Dublin 4, Ireland

Name and address of the Marketing authorization holder in Singapore

A. Menarini Singapore Pte Ltd

30 Pasir Panjang Road, #08-32

Mapletree Business City

Singapore 117440

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
31 December 1969

10 DATE OF REVISION OF TEXT

20 November 2018

Summary table of changes

Section changed	Summary of new information
All	Datasheet updated in line with the SPC-style format
All	Reference to the tablet formulation has been removed as this license has been cancelled.