PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr APRESOLINE®

hydralazine hydrochloride injection

Solution, 20 mg / mL, Intravenous

Manufacturer's Standard

Antihypertensive Agent

SteriMax Inc.
2770 Portland Drive,
Oakville, ON
L6H 6R4

Date of Initial Authorization:
May 24, 2012

Date of Revision:
September 13, 2022

Control # 263009

RECENT MAJOR LABEL CHANGES

None at the time of the most recent authorization.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

APRESOLINE (hydralazine hydrochloride Injection Mfr. Std) is indicated for the emergency treatment of severe essential hypertension when the drug cannot be given orally or when there is an urgent need to lower blood pressure (e.g. toxemia of pregnancy or pre-eclampsia).

1.1 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatric patients or patients with marked renal damage may require a lower dosage.

2 CONTRAINDICATIONS

- Hypersensitivity to hydralazine or dihydrazine, 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).
- Acute dissecting aneurysm of the aorta.
- Coronary artery disease.
- Porphyria

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Hydralazine can cause anginal attacks and ECG changes indicative of myocardial ischemia. Myocardial stimulation may provoke or aggravate angina pectoris, congestive heart failure or myocardial infarction.
- Patients with suspected or confirmed coronary artery disease should therefore be given APRESOLINE only under beta-blocker cover 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.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- The dose of APRESOLINE (hydralazine hydrochloride - injection) must always be individualized and adjusted according to the patient's blood pressure response.
- Patients should be hospitalized. The parenteral administration of APRESOLINE should always be carried out cautiously and under strict medical supervision.
- Blood pressure and heart rate should be checked frequently (i.e., every 5 minutes). Blood pressure levels may begin to fall within a few minutes after injection, with an average maximal decrease occurring in 10 to 80 minutes. In cases where there has been increased intracranial pressure, lowering the blood pressure may increase cerebral ischemia. A satisfactory response can be defined as a decrease in diastolic blood pressure to 90 to 100 mmHg.

4.2 Recommended Dose and Dosage Adjustment

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. Geriatric patients or patients with marked renal damage may require a lower dosage. In hypertensive crises other than pre-eclampsia/eclampsia, usual doses of 20 - 40 mg have been used, repeated as necessary. If it is necessary to repeat the injection, this should be done after an interval of 20 to 30 minutes, throughout which blood pressure and heart rate should be monitored.

Most patients can be transferred to an oral anti-hypertensive within 24 to 48 hours.

4.3 Reconstitution

Parenteral Products: The injection solution should be used immediately after the vial is opened. It should not be added to infusion solutions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

4.4 Administration

Patients should be hospitalized. The parenteral administration of APRESOLINE should always be carried out cautiously and under strict medical supervision.

Blood pressure and heart rate should be checked frequently (i.e., every 5 minutes). Blood pressure levels may begin to fall within a few minutes after injection, with an average maximal decrease occurring in 10 to 80 minutes. In cases where there has been increased intracranial pressure, lowering the blood pressure may increase cerebral ischemia. A satisfactory response can be defined as a decrease in diastolic blood pressure to 90 to 100 mmHg.

Direct Injection
Administer the solution by slow intravenous injection. For ease of administration the solution may be further diluted with physiological saline.

5 OVERDOSAGE

Signs and Symptoms of Overdosage
Symptoms include hypotension, tachycardia, accompanied by headache, generalized skin flushing, sweating, nausea and dizziness. Also possible are myocardial ischemia with angina pectoris, and cardiac arrhythmia. Further signs may include impairment of consciousness, headache and vomiting, as well as possible tremor, convulsions, oliguria, hypothermia, profound shock and coma.

Treatment for Overdosage
There is no known specific antidote. Supportive measures including intravenous fluids are also indicated. If hypotension is present, an attempt should be made to raise the blood pressure without increasing the tachycardia. Adrenaline should not be used to correct the hypotension, since it enhances the cardiac-accelerating effects of hydralazine.

Support of the cardiovascular system is of primary importance. Shock should be treated with plasma expanders. If possible, vasopressors should not be given, but if a vasopressor is required, care should be taken not to precipitate or aggravate cardiac arrhythmia. The ECG should be monitored while the vasopressors are being administered. Tachycardia responds to beta blockers. Digitalization may be necessary, and renal function should be monitored and supported as required. The use of dopamine to elevate systolic blood pressure to 90 mmHg may be considered in an emergency.
No experience has been reported with extracorporeal or peritoneal dialysis.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Solution, 20 mg/mL hydralazine hydrochloride	Hydrochloric acid, propylene glycol, sodium hydroxide, and water for injection

1 mL clear glass vials containing clear to pale yellow sterile solution, available in cartons of 10 vials.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Cardiovascular

The overall "hyperdynamic" state of the circulation induced by hydralazine may accentuate certain clinical conditions. Hydralazine can cause anginal attacks and ECG changes indicative of myocardial ischemia. Myocardial stimulation may provoke or aggravate angina pectoris, congestive heart failure or myocardial infarction.

Patients with suspected or confirmed coronary artery disease should therefore be given APRESOLINE only under beta-blocker cover 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 post-infarction stabilization has been achieved. APRESOLINE should not be used in heart failure.

Postural hypotension may result from APRESOLINE (hydralazine hydrochloride injection), but is less common than with ganglionic blocking agents. The drug should be used with caution in patients with cerebral vascular disease since abrupt decreases in blood pressure should be avoided in these patients.

Cerebrovascular disease

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

APRESOLINE (hydralazine hydrochloride injection) may provoke in a few patients a clinical picture simulating systemic lupus erythematosus (SLE) including glomerulonephritis. In its mild form this syndrome is reminiscent of rheumatoid arthritis (arthralgia, sometimes associated with fever and skin rash). When fully developed a syndrome resembling disseminated lupus erythematosus occurs.

Should this SLE-like syndrome develop, treatment should be discontinued immediately. Symptoms and signs usually regress when the drug is discontinued but residua have been detected many years later. Long-term treatment with adrenocorticosteroids may be necessary.

The frequency of these untoward effects increases with dosage and duration of exposure to the drug and is higher in slow than in fast acetylators. When treated with the same dosage, slow acetylators have higher serum concentrations than fast acetylators. The lowest effective dosage should therefore be used for maintenance therapy. Rapid acetylators, often respond

inadequately even to doses of 100 mg daily. In these patients, the dosage can be raised with only a slightly increased risk of a SLE-like syndrome. 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 this SLE-like syndrome. In such cases dosage should be kept below 100 mg daily and the patients carefully monitored for clinical signs and symptoms suggestive of this syndrome.

Complete blood counts, examination of lupus erythematosus cell preparations, antinuclear antibody titer determinations and urine analysis are indicated before and periodically (e.g. every 6 months) during prolonged therapy with hydralazine even though the patient is asymptomatic. Microhaematuria and/or proteinuria, in particular together with positive titres of anti-nuclear factors (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 tests are also indicated if the patient develops arthralgia, fever, chest pain, continued malaise or other unexplained signs or symptoms. If the results of these tests are abnormal, treatment should be discontinued.

Antinuclear antibodies may be found in the blood of as many as 50 percent of patients receiving hydralazine who remain asymptomatic. A positive antinuclear antibody titer requires that the physician carefully weigh the implications of the test results against the benefits to be derived from antihypertensive therapy with APRESOLINE.

Driving and Operating Machinery

A pronounced lowering of the blood pressure may adversely affect the patient's reactions (e.g. as in driving or operating machinery).

Hematologic

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

Hepatic/Biliary/Pancreatic

In patients with hepatic dysfunction, serum levels of hydralazine increased as compared to those in patients with normal hepatic function, therefore the dose or the dosing interval should be adjusted according to the clinical response, in order to avoid accumulation of the "apparent"

active substance.

Neurologic

Peripheral neuritis, evidenced by paresthesias, numbness and tingling in the extremities has been observed. Published evidence suggests an antipyridoxine effect and the addition of pyridoxine to the regimen or medicine withdrawal if symptoms develop.

Peri-Operative Considerations

When undergoing surgery, patients treated with Hydralazine 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 hydrochloride.

Renal

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

In patients with renal impairment (creatinine clearance < 30 mL/min or serum creatinine > 2.5 mg/100 mL or 221 µmol/L), serum levels of hydralazine increased as compared to those in patients with normal renal function, therefore the dose or the interval between doses should be adjusted according to the clinical response, in order to avoid accumulation of the "apparent" active substance.

Reproductive Health: Female and Male Potential

- **Fertility**

  No data exists on effects of the drug on fertility.

- **Function**

  No data exists on effects of the drug on sexual function.

- **Teratogenic Risk**

Usage in Pregnancy (Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on human fetus or neonate without causing malformations). These effects may be reversible.

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. Teratogenic effects observed in humans included the cleft palate and malformations of facial and cranial bones. 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 if the expected benefit justifies the potential risk to the fetus.

Animal experiments have shown hydralazine 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 embryolethal 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.

Respiratory

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 aggressive 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.

Skin

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

7.1 Special Populations

7.1.1 Pregnant Women

Usage in Pregnancy (Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on human fetus or neonate without causing malformations. These effects may be reversible.

7.1.2 Breast-feeding

Hydralazine passes into breast milk. Alternatives to hydralazine should be considered in nursing mothers.

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

The elderly may be more sensitive to the hypotensive effects. In addition, the risk of hydralazine-induced hypothermia may be increased in elderly patients. Concurrent hepatic and renal insufficiency should be taken into account.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse reactions are tachycardia, palpitation, anginal symptoms, flushing, headache, dizziness, nasal congestion and gastrointestinal disturbances. These are more frequent at the start of treatment, especially if the dosage is raised rapidly. However, such reactions generally subside in the further course of treatment or following a reduction of dosage. Isolated cases of peripheral neuritis, polyneuritis and paraesthesia have also been reported.

The most severe reactions are neuropathy, blood dyscrasias, and an acute rheumatoid state resulting in a syndrome resembling disseminated lupus erythematosus (see 7 Warnings and Precautions).

8.2 Clinical Trial Adverse Reactions

This information is not available for this drug.

8.3 Less common clinical trial adverse reactions

This information is not available for this drug.

8.4 Abnormal laboratory findings: hematologic, clinical chemistry and other quantitative data

This information is not available for this drug product.

8.5 Post-market adverse reactions

Cardiovascular System

Tachycardia, palpitations, flushing, hypotension, anginal symptoms, edema, heart failure, paradoxical pressor responses.

Central and Peripheral Nervous System

Headache, dizziness, peripheral neuritis evidenced by paresthesia numbness and tingling, tremor.

Musculo-Skeletal System

Arthralgia, joint swelling, myalgia, muscle cramps.

Skin and Appendages

Rash.

Urogenital System

Proteinuria, increased plasma creatinine, hematuria sometimes in association with glomerulonephritis, acute renal failure, urinary retention, difficulty in micturition

Gastrointestinal Tract

Gastrointestinal disturbances, diarrhea, constipation, nausea, vomiting, jaundice, liver enlargement, abnormal liver function sometimes in association with hepatitis, paralytic ileus.

Blood

Anemia, leukopenia, neutropenia, thrombocytopenia with or without purpura, hemolytic anemia, leucocytosis, lymphadenopathy, pancytopenia, splenomegaly, agranulocytosis, antinuclear antibodies.

Psychiatric reactions

Agitation, anorexia, anxiety, depression, hallucinations, disorientation, sleep disturbances

Sense Organs

Increased lacrimation, conjunctivitis, nasal congestion, blurred vision.

Hypersensitivity Reactions

Systematic lupus erythematosus like syndrome (sometimes resulting in a fatal outcome; see 7 WARNINGS AND PRECAUTIONS), chills, eosinophilia, hypersensitivity reactions such as pruritus, urticaria, vasculitis, hepatitis.

Respiratory Tract

Dyspnea, pleural pain.

Miscellaneous

Rare: Fever, weight decrease, malaise, exophthalmos, decreased libido, pancreatitis; hyperuricemia, hyperglycemia and hypokalemia

9 DRUG INTERACTIONS

9.1 Drug Interactions Overview

Concomitant treatment with other vasodilators, calcium antagonists, ACE inhibitors, diuretics, antihypertensives, anaesthetics, tricyclic antidepressants and major tranquilizers, nitrates or drugs exerting central depressant actions (including alcohol), may potentiate the hypotensive effect of APRESOLINE.

9.2 Drug-Behavioural Interactions

Interactions between the drug and behavioural risks such as alcohol consumption, sexual activity, and smoking have not been studied.

9.3 Drug-Drug Interactions

The drugs listed in Table 3 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Table 3 Established or Potential Drug-Drug interactions with APRESOLINE

Proper/Common name	Source of Evidence	Effect	Clinical comment
Beta blockers (e.g. acebutolol, atenolol, metaprolol, propranolol)	T	Concurrent administration of APRESOLINE with beta blockers subject to a strong first pass effect (e.g. propanolol) may increase their bioavailability.	Download adjustment of these drugs may be required when they are given concomitantly with hydralazine hydrochloride.
Diazoxide (Anti-hypertensive)	T	Administration of APRESOLINE shortly before or after	Patients should be continuously observed for several hours for any

		diazoxide may lead to marked hypotension	excessive fall in blood pressure
Other antihypertensives (vasodilators, calcium antagonists, ACE inhibitors, diuretics), anaesthetics, tricyclic antidepressants, major tranquillisers, nitrates or drugs exerting central depressant actions (including alcohol)	T	There is potential for the hypotensive effect of hydralazine to be antagonised.	Patients should be continuously observed for several hours for any excessive fall in blood pressure.
Epinephrine	T	Hydralazine hydrochloride may reduce the pressor responses to epinephrine	Caution is warranted
MAO inhibitors (e.g. moclobemide, phenelzine, procarbazine, tranylcypromine)	T		MAO inhibitors should be used with caution in patients receiving hydralazine
NSAIDS (e.g. celecoxib, diclofenac, ibuprofen, indomethacin, naproxen)	T	There is potential for the hypotensive effect of hydralazine to be antagonised.	Patients should be continuously observed for several hours for any excessive fall in blood pressure.
Oestrogens	T	There is potential for the hypotensive effect of hydralazine to be antagonised.	Patients should be continuously observed for several hours for any excessive fall in blood pressure.

T = Theoretical

9.4 Drug-Food Interactions

Interactions with food have not been established.

9.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.6 Drug-Laboratory Test Interactions
Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action
Although the precise mechanism of action of hydralazine hydrochloride injection is not fully understood, the major effects are on the cardiovascular system. Hydralazine apparently lowers blood pressure by exerting a peripheral vasodilating effect through a direct relaxation of vascular smooth muscle. Hydralazine, by altering cellular calcium metabolism, interferes with the calcium movements within the vascular smooth muscle that are responsible for initiating or maintaining the contractile state.

The peripheral vasodilating effect of hydralazine results in decreased arterial blood pressure (diastolic more than systolic); decreased peripheral vascular resistance; and an increased heart rate, stroke volume, and cardiac output. The vasodilating effect is much greater on arterioles than on veins and vascular resistance decreases more in the coronary, cerebral, splanchnic and renal circulations than in skin and muscle.

Hydralazine usually increases renin activity in plasma, presumably as a result of increased secretion of renin by the renal juxtaglomerular cells in response to reflex sympathetic discharge. This increase in renin activity leads to the production of angiotensin II, which then causes stimulation of aldosterone and consequent sodium reabsorption and fluid retention.

Sodium retention and excessive sympathetic stimulation of the heart caused by hydralazine may be precluded by co-administration of a thiazide diuretic and a beta-blocker. Beta-adrenergic blocking drugs and APRESOLINE are complementary in their pharmacologic effects, a beta-adrenergic blocking agent minimizes hydralazine-induced increases in cardiac rate and output, and hydralazine prevents the reflex increase in peripheral resistance induced by beta-blockers.

APRESOLINE (hydralazine hydrochloride injection) acts directly on peripheral arterioles, where it has a relaxing effect on the smooth muscle of the vessel wall, with a resultant decrease in arteriolar resistance, decreasing arterial blood pressure, diastolic often more than systolic. Hydralazine exerts no direct actions on the heart. When the drug decreases arterial pressure and thereby activating the baroreceptors, cardiovascular reflexes result in increased sympathetic discharge. Since APRESOLINE does not increase venous capacitance or depress cardiac function, sympathetic stimulation increases heart rate, left ventricular velocity, stroke volume and cardiac output.

10.2 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 -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 breast 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.

Elimination

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

11 STORAGE, STABILITY AND DISPOSAL

Protect vials from heat (store at 15ºC to 30ºC) and light.
Discard unused portion.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions applicable to this drug.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

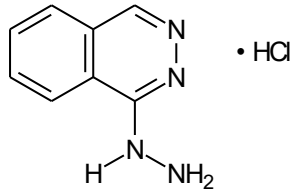
Drug Substance

Proper name: Hydralazine Hydrochloride

Chemical name: 1-Hydrazinophthalazine monohydrochloride.

Molecular formula and molecular mass: $C_8H_8N_4 \cdot HCl$, 196.64 g/mol

Structural formula:



Pharmaceutical standard: USP

Product Characteristics:

Description: White, odourless, crystalline powder.

Melting Point: 270-280°C.

Solubility: 1 g dissolves in about 25 mL water and in about 500 mL alcohol. It is very slightly soluble in ether.

pH: 3.5 to 4.2 (2% solution).

14 CLINICAL TRIALS

Clinical trial data is not available for this drug.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity
Rats: The acute toxicity of hydralazine, as determined intravenously in female white rats is comparatively low: the LD_{50} is 34 mg/kg.
Dogs: Single doses of 20 mg/kg intravenously and 200 mg/kg orally were tolerated. The test animals manifested tachycardia, depression, and emesis. Vomiting occurred at doses of 8 and 16 mg/kg and central nervous system stimulation at 32 and 64 mg/kg.

Sub-acute Toxicity
Dogs: Hydralazine in oral doses of 30 mg/kg given 5 days per week for 3 months was well tolerated.
Long-term Toxicity
Mice: Doses of 7.4 mg/day to males and 5.4 mg/day to females administered orally throughout the lifespan resulted in increased incidence of lung tumours (classified as adenomas and adenocarcinomas).
Dogs: Hydralazine was given in oral doses of 1, 3 and 10 mg/kg per day for 6 months. Heinz bodies were detected in the erythrocytes of the high dosage group. Other changes observed included: reversible elevations and depressions of the ST-segment; dose¬-related tachycardia; dose-related conjunctivitis and in one animal conjunctivitis sicca with pannus formation; in one intermediate dose animal, a small area of subendocardial fibrosis was observed histologically.

Teratogenicity
Mice: Doses of 20, 60, 120 and 150 mg/kg were used. Somnolence and dyspnea, as well as death, at the highest doses indicate that maximum tolerated doses had been exceeded. A dose-related increase in the incidence of cleft palate, agnathia, and hypognathia was observed.
Rats: Doses of 20, 60 and 180 mg/kg were used. Maximum tolerated doses were again exceeded, but teratogenic manifestations were not observed, although there was a delay in ossification characterized by unossified calcanei, sternebrae and phalangeal nuclei.
Rabbits: Doses of 10, 30 and 60 mg/kg were used. At the high dose level, some somnolence, as well as one apparent drug-related death, indicated that doses were in the maximum tolerated range.
In the 60 mg/kg dose group one out of 84 fetuses showed mandibular aplasia (agnathia inferior). This malformation is considered to be of spontaneous origin, however, a drug related effect cannot be entirely discounted.

Hydralazine was teratogenic in rabbits where oral doses equal to and greater than 75 mg/kg/day caused phalangeal defects.

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.

Mice: In a lifetime study in Swiss albino mice, there was a statistically significant increase in the incidence of lung tumours (adenomas and adenocarcinomas) of both male and female mice given hydralazine hydrochloride continuously in their drinking water at a dosage of about 50-200 mg/kg/day; a “no effect” dose has not been established.

Rat: In a 2-year carcinogenicity study of Sprague-Dawley albino rats given hydralazine

hydrochloride by gavage at dose levels of 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. Benign interstitial (Leydig) cell tumours of the testes were also significantly increased in male rats from the high-dose group. The tumours observed are common in aged rats and the increased incidence was not observed until 18 months of treatment.

Mutagenicity:

Hydralazine was shown to be mutagenic in bacterial systems (Gene Mutation and DNA Repair) and in one of two rat and one rabbit hepatocyte in-vitro DNA repair studies. In the latter study the effect was evident in cells from slow acetylator rabbits but not from fast acetylators. Additional in-vivo and in-vitro studies using lymphoma cells, germinal cells, and fibroblasts from mice, bone marrow cells from Chinese hamsters and fibroblasts from human cell lines did not demonstrate any mutagenic potential for hydralazine.

Hydralazine hydrochloride in chronic toxicity studies has been shown to increase the incidence of some tumours in aging rodents. A mutagenic potential was observed in some but not all mutagenicity tests. The extent to which these findings indicate a risk to man is uncertain. While long-term clinical observations have not suggested that human cancer is associated with hydralazine use, epidemiologic studies have so far been insufficient to arrive at any conclusion.

17 SUPPORTING PRODUCT MONOGRAPHS

APRESOLINE Solution, 20 mg / mL, Control # 227648, Product Monograph, SteriMax Inc., August 15, 2019

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]APRESOLINE
hydralazine hydrochloride injection

Read this carefully before you start taking **APRESOLINE**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APRESOLINE**.

Serious Warnings and Precautions

Serious Heart Problems:

- APRESOLINE can cause chest pain and reduce blood flow to the heart. These conditions can lead to **heart failure** or **heart attack**. See the **Serious side effects and what to do about them** table, below, for information on these and other serious side effects.
- If you have or may have heart disease APRESOLINE should be given with beta-blocker medications or other similar medications.

What is APRESOLINE used for?

APRESOLINE is used in adults in:

- the emergency treatment of severe high blood pressure when the oral form of the drug cannot be given.
- medical situations where there is an urgent need to lower blood pressure.

How does APRESOLINE work?

APRESOLINE works to lower blood pressure by widening blood vessels. It does this by interfering with the movement of calcium in the blood vessels. This reduces blood vessel contraction.

What are the ingredients in APRESOLINE?

Medicinal ingredients: hydralazine hydrochloride

Non-medicinal ingredients: hydrochloric acid, propylene glycol, sodium hydroxide, and water for injection

APRESOLINE comes in the following dosage forms:

Solution, 20 mg / mL

Do not use APRESOLINE if:

- you are allergic to hydralazine or dihydrazine, or any of the non-medicinal ingredients in APRESOLINE (See **What are the ingredients in APRESOLINE?**).
- you have lupus, an autoimmune disease, or a related disease.
- you have a high heart rate or heart failure.
- you have a blockage in your heart such as a narrowing of the valves or blood vessels.
- you have isolated heart failure in the right side of the heart which affects your blood pressure.
- you have a tear in your main artery (the aorta).
- you have coronary artery disease.
- you have porphyria, a genetic blood disorder.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APRESOLINE. Talk about any health conditions or problems you may have, including if you:

- have heart disease or have survived a heart attack.
- have cerebrovascular disease, a condition that affects blood flow in the brain.
- have liver or kidney problems.
- are pregnant.
- are breastfeeding. APRESOLINE passes into breastmilk.

Other warnings you should know about:

Pulmonary renal syndrome: Treatment with APRESOLINE may cause inflammation of arteries and veins in the lungs and kidneys which can lead to respiratory or kidney failure. These symptoms can be sudden and severe and can sometimes be fatal. See the **Serious side effects and what to do about them** table, below, for information on this and other serious side effects.

Driving and operating machines: Give yourself time after being given APRESOLINE to see how you feel before driving a vehicle or using machinery.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APRESOLINE:

- Other medications used to lower blood pressure such as:
    - vasodilators
    - calcium channel blockers
    - ACE inhibitors
    - diuretics

    - beta blockers, e.g. acebutolol, atenolol, metaprolol, propranolol
    - diazoxide
- anaesthetics, used during medical procedures to keep you from feeling pain
- medicines used to treat depression, such as monoamine oxidase inhibitors (MAOIs), e.g. moclobemide, phenelzine, procarbazine, tranylcypromine and tricyclic antidepressants
- nitrates, used to treat chest pain
- epinephrine, used to treat severe allergic reactions
- non-steroidal anti-inflammatory drugs (NSAIDs) used to treat pain and inflammation, e.g. celecoxib, diclofenac, ibuprofen, indomethacin, naproxen
- medicines that contain estrogens, such as hormonal birth control and hormone replacement therapy
- medicines that depress the nervous system, including alcohol

How to take APRESOLINE:

- APRESOLINE will be given to you by a healthcare professional in a healthcare setting.
- It will be given by an injection directly into your vein.

Usual dose:

Your healthcare professional will decide on the dose that is right for you according to your individual needs and based on your blood pressure.

Overdose:

If you think you, or a person you are caring for, have been given too much APRESOLINE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using APRESOLINE?

These are not all the possible side effects you may have when taking APRESOLINE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- flushing
- headache
- dizziness
- stuffy nose
- pink eye, eye inflammation, eye tearing
- blurred vision

- diarrhea or constipation
- nausea, vomiting
- loss of appetite
- weight loss
- muscle pain, muscle cramps
- joint pain, joint swelling
- rash
- anxiety, agitation

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
Allergic reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, fever, chills, cough, stomach pain, weakness, confusion			√
Blood problems (low levels of red or white blood cells or platelets): fatigue, weakness, pale skin, shortness of breath, skin rash with purple spots, bleeding for longer than usual when you cut yourself, nose bleeds, symptoms of infections (fever, chills, sore throat, mouth sores, body aches)		√	
Edema: unusual swelling of the arms, hands, legs, feet and ankles, face or airway passages		√	
Heart attack: sudden chest pain, discomfort, pressure or heaviness, sensation of squeezing or fullness in the shoulder, chest, arm or below the breastbone, feeling of being full, having indigestion or choking, sweating, nausea, vomiting, dizziness, weakness,			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
anxiety, shortness of breath, rapid or irregular heartbeat			
Heart failure (heart does not pump blood as well as it should): shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise			√
Heart problems: irregular heartbeat, palpitations, fast heartbeat, chest pain or discomfort		√	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		√	
Liver problems: yellowing of the skin or eyes, dark urine, pale stool, abdominal pain, nausea, vomiting, loss of appetite		√	
Lupus-like syndrome: butterfly shaped skin rash typically on the face, skin sensitivity to sunlight, fever, joint pain, swelling or stiffness			√
Neuropathy (nerve damage): numbness, tingling, muscle weakness, pain		√	
Pulmonary renal syndrome (lung and kidney failure): cough, shortness of breath, coughing up blood, fever, reduced or lack of urination, blood in the urine, swelling of			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
the extremities, nausea, vomiting			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at 15ºC to 30ºC. Protect vials from heat and light.

Keep out of reach and sight of children.

If you want more information about APRESOLINE:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.sterimaxinc.com, or by calling 1-800-881-3550.

This leaflet was prepared by SteriMax Inc.

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