PRODUCT MONOGRAPH

APRESOLINE®
(Hydralazine Hydrochloride)

10 mg, 25 mg and 50 mg Tablets
20 mg lyophilized powder in Ampoules

Antihypertensive Agent

Sterimax Inc.
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Kingston ON
K7M 8N1

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Control # 089991

Product Monograph

PrAPRESOLINE®

(hydralazine hydrochloride)

10 mg, 25 mg and 50 mg tablets

20 mg lyophilized powder in ampoules

USP Standard

Therapeutic Classification

Antihypertensive Agent

Actions and Clinical Pharmacology

Although the precise mechanism of action of APRESOLINE (hydralazine hydrochloride) 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.

Pharmacokinetics:

Hydralazine is rapidly and fairly completely absorbed after oral administration. In the plasma only small amounts of the free drug can be traced, the bulk circulating in conjugated form, i.e. pyruvic acid hydrazone. Peak serum concentrations are reached within one to two hours after a dose.

Plasma levels of hydralazine vary widely among individuals. Orally administered hydralazine undergoes extensive, saturable first-pass metabolism (systemic availability: 26 - 55%), this first-pass effect being dependent on the individual's acetylator status. In response to the same oral dose, slow-acetylators show higher "apparent" plasma hydralazine levels than rapid acetylators and ranges require lower doses to maintain control of blood pressure.

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

Hydralazine is widely distributed in the body. The apparent volume of distribution of hydralazine is approximately 50% body weight. Binding to plasma proteins (chiefly albumin) is 88 - 90%.

Hydralazine crosses the placental barrier and is excreted in the breast milk.

The pattern of the metabolites depends on the subject's acetylator and presumably hydroxylator status. The main metabolite, NAc-HPZ (N-acetyl-hydrazine-phthalazinone), was found to be the relevant indicator for the drug-related phenotype.

The plasma half-life generally ranges between 1.7 and 3.0 hours in most subjects, but in rapid acetylators it is shorter, averaging 45 minutes.

Hydralazine and its metabolites are rapidly excreted by the kidney and 80% of the oral dose appears in the urine within 48 hours. 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.

Indications

APRESOLINE (hydralazine hydrochloride) Oral: Essential hypertension.

APRESOLINE is used in conjunction with other antihypertensives such as beta-blockers and diuretics.

APRESOLINE Parenteral: Severe hypertension when the drug cannot be given orally or when there is an urgent need to lower blood pressure (e.g. toxemia of pregnancy).

Contraindications

1) Hypersensitivity to hydralazine or other hydrazino-phthalazine derivatives.

2) Idiopathic systemic lupus erythematosus (SLE) and related diseases.

3) Severe tachycardia and heart failure with a high cardiac output (e.g., in thyrotoxicosis).

4) Myocardial insufficiency due to mechanical obstruction (e.g., in the presence of aortic or mitral stenosis or constrictive pericarditis).

5) Isolated right-ventricular heart failure due to pulmonary hypertension (cor pulmonale).

6) Acute dissecting aneurysm of the aorta.

7) Coronary artery disease.

Warnings

1) APRESOLINE (hydralazine hydrochloride) 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. 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. 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 antibody 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 hydralazine.

   Microhematuria and/or proteinuria, in particular together with positive titres of antinuclear antibodies, may be initial signs of immune-complex glomerulonephritis associated with the SLE-like syndrome.

2) The chronotropic and inotropic effects of hydralazine increase myocardial oxygen requirements. It can cause electrocardiographic changes of myocardial ischemia, and in patients with coronary artery disease may precipitate angina pectoris or congestive heart failure. Hydralazine has been implicated in the production of myocardial infarction.

APRESOLINE must therefore be used with caution in patients with suspected coronary artery disease. It should be given only in combination with a beta-blocker or other suitable sympatholytic agents. 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.

The "hyperdynamic" circulation caused by APRESOLINE may accentuate specific cardiovascular inadequacies (e.g. APRESOLINE may increase pulmonary artery pressure in patients with mitral valvular disease).

3) Usage in Pregnancy

Animal studies indicate that high doses of hydralazine are teratogenic in mice, possibly in rabbits, but not in rats (**See Toxicology**). Teratogenic effects observed were cleft palate and malformation of facial and cranial bones. There are no adequate and well-controlled studies in pregnant women. Although clinical experience does not include any positive evidence of adverse effects on the human fetus, hydralazine should be used during pregnancy only if the benefit clearly justifies the potential risk to the fetus.

Precautions

Postural hypotension may result from APRESOLINE (hydralazine hydrochloride), 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.

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

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, serum levels of hydralazine increased as compared to those in patients with normal renal function, therefore the dose or the dosing interval has to be adapted according to the clinical response, in order to avoid accumulation of the "apparent" active substance.

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 has to be adapted according to the clinical response, in order to avoid accumulation of the "apparent" active substance.

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 if symptoms develop.

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.

Tumorigenicity and Mutagenicity

Hydralazine hydrochloride in chronic toxicity studies has been shown to increase the incidence of some tumors in aging rodents. A mutagenic potential was observed in some but not all mutagenicity tests (**See Toxicology**). 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 (**See Toxicology**).

Lactation

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

Use in the Elderly

The elderly may be more sensitive to the hypotensive effects. In addition the risk of hydralazine-induced hypothermia may be increased in elderly patients.

Use in Children

Although there is some experience with the use of hydralazine hydrochloride in children, controlled clinical trials to establish safety and effectiveness in this age group have not been conducted.

Drug Interactions

Concomitant treatment with other vasodilators, calcium antagonists, ACE inhibitors, diuretics, antihypertensives, tricyclic antidepressants and major tranquilizers, as well as the consumption of alcohol, may potentiate the hypotensive effect of APRESOLINE.

Administration of APRESOLINE shortly before or after diazoxide may lead to marked hypotension. When potent antihypertensive drugs, such as diazoxide, are used in combination with APRESOLINE, patients should be continuously observed for several hours for any excessive fall in blood pressure.

Concurrent administration of APRESOLINE with beta-blockers subject to a strong first-pass effect (e.g. propranolol) may increase their bioavailability. Downward dosage adjustment of these drugs may be required when they are given concomitantly.

MAO inhibitors should be used with caution in patients receiving hydralazine.

Hydralazine may reduce the pressor responses to epinephrine.

Adverse Reactions

The most common adverse reactions are tachycardia, palpitation, anginal symptoms, flushing, headache, 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.

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

Cardiovascular System

Tachycardia, palpitation, 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, polyneuritis, tremor, agitation, anorexia, anxiety, depression, hallucinations, disorientation, sleep disturbances.

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.

Sense Organs

Increased lacrimation, conjunctivitis, nasal congestion, blurred vision.

Hypersensitivity Reactions

SLE-like syndrome (**See Warnings**), chills, eosinophilia, hypersensitivity reactions such as pruritus, urticaria, vasculitis, hepatitis.

Respiratory Tract

Dyspnea, pleural pain.

Miscellaneous

Fever, weight decrease, malaise, exophthalmos, decreased libido, pancreatitis.

Hyperuricemia, hyperglycemia and hypokalemia have been reported.

Symptoms And Treatment Of Overdosage

Symptoms

Hypotension, tachycardia, headache, generalized skin flushing, sweating, nausea and dizziness. Myocardial ischemia with angina pectoris, cardiac arrhythmia, and profound shock can develop.

Further signs may include impairment of consciousness, vomiting, tremor, convulsions, oliguria, and hypothermia.

Treatment

There is no known specific antidote.

Evacuate gastric contents by induction of emesis or gastric lavage, taking adequate precautions against aspiration and for protection of the airway. If general conditions permit, administer activated charcoal slurry and possibly an osmotic cathartic. These procedures may have to be omitted or carried out after cardiovascular status has been stabilized, since they might precipitate cardiac arrhythmias or increase the depth of shock.

Support of the cardiovascular system is of primary importance. Shock should be treated with volume expanders without resorting to use of vasopressors. The use of dopamine to elevate systolic blood pressure to 90 mmHg may be considered in an emergency. If a vasopressor is required, a type that is least likely to precipitate or aggravate cardiac arrhythmia should be used, and the ECG should be monitored while they are being administered. Digitalization may be necessary. Renal function must be monitored and supported as required.

No experience has been reported with extracorporeal or peritoneal dialysis.

Dosage And Administration

The dose of APRESOLINE (hydralazine hydrochloride) must always be individualized and adjusted according to the patient's blood pressure response.

Orally

Initially, one 10 mg tablet 4 times daily for the first 2 to 4 days. The dose is increased to 25 mg 4 times daily for the remainder of the first week. Dosage is then increased to 50 mg 4 times daily for the second and subsequent weeks of treatment.

For maintenance, adjust dosage to lowest effective levels. The incidence of toxic reactions, particularly the lupus erythematosus syndrome, is highest in the group of patients receiving large doses of hydralazine.

The usual effective maintenance daily dose from 50 to 200 mg. However, the dose should not be increased above 100 mg per day without determining the acetylator phenotype.

After the titration period, some patients may be maintained on a twice daily schedule.

The influence of food on the bioavailability of hydralazine is uncertain. Contradictory results have been obtained.

Note:

Geriatric patients may be more sensitive to the effects of the usual adult dose. Response should be monitored and the dosage adjusted accordingly to lowest effective levels.

In patients with renal impairment the dose or the dosing interval should be adapted according to the clinical response, in order to avoid accumulation of the "apparent" active substance.

In patients with hepatic dysfunction the dose or the dosing interval should be adapted according to the clinical response, in order to avoid accumulation of the "apparent" active substance.

Parenterally

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 (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. A satisfactory response can be defined as a decrease in diastolic blood pressure to 90 to 100 mmHg.

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. In hypertensive crises other than pre-eclampsia/eclampsia, initial doses of up to 40 mg have been used. If necessary, the dose can be repeated after an interval of 20 to 30 minutes.

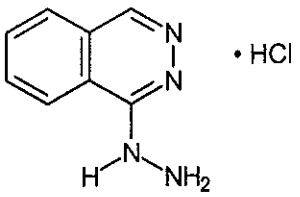
APRESOLINE may also be given by continuous intravenous infusion, beginning with a flow rate of 200 - 300 :g/min. Maintenance flow rates must be determined individually and are usually within the range of 50 - 150 :g/min.

Patients with marked renal damage may require a lower dosage. In cases where there is a previously existing increased intracranial pressure, lowering the blood pressure may increase cerebral ischemia.

Most patients can be transferred to oral APRESOLINE within 24 to 48 hours.

Pharmaceutical Information

Drug Substance



Hydralazine Hydrochloride

Molecular Formula:	$C_8H_8N_4 \cdot HCl$
Molecular Weight:	196.64
Chemical Name:	1-Hydrazinophthalazine monohydrochloride.
Description:	White, odorless, 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).

Composition

APRESOLINE (hydralazine hydrochloride) 10 mg Tablets

Each tablet contains the medicinal ingredient hydralazine hydrochloride (10 mg) and the non-medicinal ingredients; colloidal silicon dioxide, corn starch, edetate disodium, magnesium stearate, mannitol, talc, and tartrazine (FD&C Yellow No. 5).

APRESOLINE (hydralazine hydrochloride) 25 mg Tablets

Each tablet contains the medicinal ingredient hydralazine hydrochloride (25 mg) and the non-medicinal ingredients; acacia powder, brilliant blue (FD&C Blue No. 1), carnauba wax, corn starch, hydroxypropylmethylcellulose, gelatin, lactose, magnesium stearate, polyethylene glycol, povidone, sucrose, talc and titanium dioxide.

APRESOLINE (hydralazine hydrochloride) 50 mg Tablets

Each tablet contains the medicinal ingredient hydralazine hydrochloride (50 mg) and the non-medicinal ingredients; acacia, carnauba wax, corn starch, erythrosine (FD&C Red No.3), gelatin, hydroxypropylmethylcellulose, lactose, magnesium stearate, polyethylene glycol, povidone, sucrose, talc, and titanium dioxide.

APRESOLINE (hydralazine hydrochloride for injection) 20 mg Ampoules

Each glass ampoule of sterile lyophilized powder contains the medicinal ingredient hydralazine hydrochloride (20 mg).

Stability and Storage Recommendations

Protect tablets from heat (store below 30°C) and humidity.

Protect ampoules from heat (store below 30°C) and light.

Ampoules - Reconstitution

Vial Size	Diluent Volume Added to Ampoule	Approximate Available Volume	Concentration on Reconstitution
20 mg	1 mL sterile water for injection	1.0 mL	approximately 19.7 mg/mL

The freshly prepared solution should be used immediately and any remainder discarded.

Direct Injection

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

Intravenous Infusion

For administration by intravenous infusion, freshly reconstituted APRESOLINE ampoule(s) should be further diluted by the addition of physiological saline, 5% sorbitol solution or Ringer solution. Such admixtures should be used within 24 hours because of the risk of microbial contamination during preparation.

Glucose solution is not suitable for further dilution.

Dilution and Administration Table

Each mL reconstituted solution contains approximately 19.7 mg hydralazine hydrochloride.

To 500 mL Add	Final Concentration	Flow Rate (mL/hr)			
		60	65	70	75
		Dosage Delivered (:g/min)			
1 mL	39 :g/mL	39	42	45	49
2 mL	79 :g/mL	79	86	92	99
3 mL	118 :g/mL	118	128	138	148
4 mL	158 :g/mL	158	171	184	198
5 mL	197 :g/mL	197	213	230	246
6 mL	236 :g/mL	236	256	275	295

Availability

[Pr]APRESOLINE® (hydralazine hydrochloride) 10 mg Tablet:

Yellow, round, flat-faced, bevel-edged tablets, imprinted CIBA on one side and FA with bisect on the other.

[Pr]APRESOLINE® (hydralazine hydrochloride) 25 mg Tablet:

Blue, round, biconvex, sugar coated tablets.

[Pr]APRESOLINE® (hydralazine hydrochloride) 50 mg Tablet:

Dark-pink, round, biconvex, sugar coated tablets.

[Pr]APRESOLINE® (hydralazine hydrochloride for injection) 20 mg Ampoules:

Colorless glass ampoules containing white to yellowish sterile lyophilized powder.

Tablets available in bottles of 100.

Ampoules available in cartons of 10 ampoules.

Pharmacology

APRESOLINE (hydralazine hydrochloride) 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.

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 tumors (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.

Carcinogenicity

Mice: In a lifetime study in Swiss albino mice, there was a statistically significant increase in the incidence of lung tumors (adenomas and adenocarcinomas) of both male and female mice given hydralazine hydrochloride continuously in their drinking water at a dosage of about 250 mg/kg.

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, microscopic examination of the liver revealed a small but statistically significant increase in benign neoplastic nodules in male and female high-dose rats and in female rats from the intermediate dose group. Benign interstitial (Leydig) cell tumors of the testes were also significantly increased in male rats from the high-dose group. The tumors 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.

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