

AUSTRALIAN PRODUCT INFORMATION

ALPHAPRESS

hydralazine hydrochloride film coated tablet



1 NAME OF THE MEDICINE

Hydralazine hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ALPHAPRESS tablet contains either 25 mg and 50 mg of hydralazine hydrochloride as the active ingredient.

Excipients of known effect: lactose monohydrate (50 mg only) and traces of sulfites.

For the full list of excipients, see section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

ALPHAPRESS 25: flat bevelled edged cream tablet with score mark on one side.

ALPHAPRESS 50: pink film coated normal convex tablet marked HE 50 on one side, G on reverse.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypertension (drug resistant, moderate to severe)

As *supplementary medication* for use together with other antihypertensives such as beta-blockers and diuretics; the complementary mechanisms of action of such combined therapy enable the drugs to exert their antihypertensive effects at low doses; in addition, unwanted accompanying effects of the individual substances are either partially offset or even cancelled out.

4.2 DOSE AND METHOD OF ADMINISTRATION

The dosage must always be adjusted to the individual requirements of the patient and the following recommendations adhered to.

Adults

Treatment should begin with low doses of ALPHAPRESS, which, depending on the patient's response, should be increased stepwise in order to achieve an optimal therapeutic effect and to avoid unwanted effects as far as possible.

Give ALPHAPRESS in a twice daily regimen; the usual starting dosage of 25 mg twice daily is generally sufficient. This dosage can be increased as required within the effective maintenance dosage range of 50 to 200 mg daily. However, the dose should not be increased above 100 mg daily without determining the acetylator phenotype (see section 4.4 Special Warnings and Precautions for Use).

Children

Safety and efficacy of hydralazine have not been established in children.

4.3 CONTRAINDICATIONS

- Known hypersensitivity to hydralazine or dihydralazine
- Idiopathic systemic lupus erythematosus (SLE) and related diseases
- Severe tachycardia and heart failure with a high cardiac output (e.g. in thyrotoxicosis)

- Myocardial insufficiency due to mechanical obstruction (e.g. in the presence of aortic or mitral stenosis or constrictive pericarditis)
- Isolated right ventricular heart failure due to pulmonary hypertension (cor pulmonale)
- Dissecting aortic aneurysm
- Porphyria

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cardiac Dysfunction

The overall hyperdynamic state of the circulation induced by hydralazine may accentuate certain clinical conditions. Myocardial stimulation may provoke or aggravate angina pectoris or provoke myocardial infarction. Hydralazine can cause anginal attacks and ECG changes indicative of myocardial ischaemia. Therefore, it must be used with caution in patients with suspected coronary artery disease. Patients with suspected or confirmed coronary artery disease should therefore be given ALPHAPRESS only under cover of a beta-blocker or in combination with other suitable sympatholytic agents. It is important that the beta-blocker medication should be commenced a few days before the start of treatment with ALPHAPRESS.

Patients who have survived a myocardial infarction should not receive ALPHAPRESS until a post-infarction stabilisation phase has been achieved. Hydralazine should not be used in heart failure.

SLE-like Syndrome with Long-term Use of Oral Hydralazine

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

Since such reactions tend to occur more frequently the higher the dosage and the longer the duration of the medication, and since they are also more common in slow acetylators, it is recommended that for maintenance therapy the lowest dosage that still proves effective should be used. If 100 mg daily fails to elicit an adequate clinical effect, the patient's acetylator status should be evaluated.

Slow acetylators and women run a greater risk of developing an SLE-like syndrome. In such patients every effort should therefore be made not to exceed a dosage of 100 mg daily; a careful watch should also be kept for clinical signs and symptoms suggestive of an SLE-like syndrome.

Rapid acetylators, by contrast, often respond inadequately even to dosages of 100 mg daily. In these patients, the dosage can be raised with only a slightly increased risk of an SLE-like syndrome.

During long-term treatment with ALPHAPRESS it is advisable to determine the antinuclear factors (ANF) and to carry out full blood count and urine analyses at intervals of approximately 6 months. Microhaematuria and/or proteinuria, in particular together with positive titres of ANF, may be initial signs of immune complex glomerulonephritis associated with the SLE-like syndrome. A positive ANF titre requires that the physician carefully weighs the implications of the test results against the benefits of continued therapy with hydralazine. If overt clinical signs and symptoms develop, the drug should be withdrawn at once. 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 are also applicable if the patient develops arthralgia, fever, chest pain, persistent malaise, or other unexplained signs or symptoms.

Treatment with hydralazine may induce systemic vasculitis, including ANCA (anti-neutrophil cytoplasm antibody)-positive vasculitis, leading to pulmonary renal syndrome which is a combination of diffuse

alveolar haemorrhage and rapidly progressive glomerulonephritis. Patients may present with severe respiratory and/or renal failure and require treatment in an intensive care unit. The syndrome is characterised by a fulminant course if left untreated and may sometimes be fatal.

Nervous System

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

Cerebrovascular Disease

Like all potent antihypertensives, ALPHAPRESS should be used with caution in patients suffering from cerebrovascular disease, since it can cause ischaemia.

Haematological effects

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

Skin

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

Use During Surgery

When undergoing surgery, patients treated with ALPHAPRESS 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.

Use in Hepatic or Renal Impairment

In patients with renal impairment (creatinine clearance less than 30 mL/minute or serum creatinine concentration greater than 2.5 mg/100 mL or 221 micromol/L) and in patients with hepatic dysfunction, the dose or the dosing interval must be adapted according to the clinical response, in order to avoid accumulation of the 'apparent' active substance.

Use in the Elderly

No studies in the elderly have been performed. Concurrent hepatic and renal insufficiency should be taken into account (see section 4.4 Special Warnings and Precautions for Use – Use in Renal or Hepatic Impairment).

Paediatric Use

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

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The effects of hydralazine are potentiated by other antihypertensives medicines (including vasodilators, calcium antagonists, ACE inhibitors, diuretics), tricyclic antidepressants, anaesthetics and major tranquillisers, as well as the consumption of alcohol, or any medicine exerting a central depressant action.

Administration of ALPHAPRESS shortly before or after diazoxide may give rise to marked hypotension.

Monoamine oxidase inhibitors (MAOIs) should be used with caution in patients receiving ALPHAPRESS.

Concurrent administration of ALPHAPRESS with beta-blockers, such as propranolol, metoprolol and other beta-blockers subject to a strong first-pass effect, may increase their bioavailability. Downward dosage adjustment of these drugs may be required when they are given concomitantly with ALPHAPRESS.

Adrenaline (epinephrine) enhances the cardiac accelerating effects of hydralazine. Patients taking ALPHAPRESS who develop hypotension should not be treated with sympathomimetics, e.g. adrenaline (epinephrine), as ALPHAPRESS can cause tachycardia, and sympathomimetics could enhance this (see section 4.4 Special Warnings and Precautions for Use – Use During Surgery).

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

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

Use in Pregnancy

Pregnancy Category: C

Animal experiments have shown hydralazine, causing cleft palate and malformations of facial and cranial bones, is teratogenic in mice at oral doses equal to or greater than 20 mg/kg/day; a 'no effect' dose has not been clearly established. Hydralazine was teratogenic in rabbits where oral doses equal to and greater than 75 mg/kg/day caused phalangeal defects. Hydralazine was not teratogenic in rats at oral doses up to 180 mg/kg/day. Embryoletality was observed in mice at doses equal to or greater than 20 mg/kg/day. Hydralazine was, however, not embryoletal in rats and rabbits at oral doses up to 180 and 60 mg/kg/day, respectively. Delayed ossification was observed in mice and rats at maternotoxic doses greater than 20 and 60 mg/kg/day, respectively, and reduced fetal weight was seen in mice at doses greater than 20 mg/kg/day.

Hydralazine crosses the placenta and following intravenous administration has been associated with fetal distress and fetal cardiac arrhythmia in the last trimester of pregnancy. In view of the possible teratogenic potential in humans, use of ALPHAPRESS in pregnancy before the third trimester should be avoided. The drug should only be given in the third trimester after weighing the needs of the mother against the risk to the foetus.

Use in Lactation

Hydralazine passes into human breast milk. Alternatives to hydralazine should be considered in breastfeeding women unless the benefits are considered to outweigh the risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ALPHAPRESS, especially at the start of treatment, may impair the patient's reactions. Dizziness or hypotension may occur due to the established mechanism of action (see section 4.8 Adverse Effects (Undesirable Effects)), it is therefore advisable to exercise caution when driving or operating machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The unwanted effects listed below are derived from the use of both oral and parenteral hydralazine.

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.

Frequency Estimates:

Very Common: ≥10%

Rare: ≥0.01% to <0.1%

<i>Common:</i>	≥1 to <10%	<i>Very Rare:</i>	<0.01%
<i>Uncommon:</i>	≥0.1% to <1%	<i>Not known:</i>	Cannot be estimated from the available data.

Blood and Lymphatic System Disorders

<i>Uncommon</i>	Anaemia, leucopenia, neutropenia, thrombocytopenia with or without purpura.
<i>Very Rare</i>	Haemolytic anaemia, leucocytosis, lymphadenopathy, pancytopenia, splenomegaly; agranulocytosis.

Cardiac Disorders

<i>Very Common</i>	Tachycardia, palpitation.
<i>Common</i>	Flushing, hypotension, angina pectoris, anginal symptoms.
<i>Uncommon</i>	Oedema, congestive heart failure.
<i>Very Rare</i>	Paradoxical pressor responses.

Eye Disorders

<i>Uncommon</i>	Increased lacrimation, conjunctivitis.
<i>Very Rare</i>	Exophthalmos

Gastrointestinal Disorders

<i>Common</i>	Gastrointestinal disorder, diarrhoea, nausea, vomiting.
<i>Very Rare</i>	Paralytic ileus, retroperitoneal fibrosis.

General Disorders and Administration Site Conditions

<i>Uncommon</i>	Pyrexia, malaise, oedema.
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Hepatobiliary Disorders

<i>Uncommon</i>	Jaundice, hepatomegaly, abnormal hepatic function sometimes in association with hepatitis.
<i>Not known</i>	Hepatosplenomegaly (usually associated with SLE-like symptoms).

Immune System Disorders

<i>Common</i>	Positive test for ANF (see section 4.4 Special Warnings and Precautions for Use - SLE-like Syndrome with Long-term Use of Oral Hydralazine), hypersensitivity reactions
<i>Uncommon</i>	SLE-like syndrome (see section 4.4 Special Warnings and Precautions for Use - SLE-like Syndrome with Long-term Use of Oral Hydralazine), hypersensitivity reactions such as pruritus, urticaria, vasculitis including pulmonary renal syndrome, eosinophilia, hepatitis.

Investigations

<i>Uncommon</i>	Weight decrease.
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Musculoskeletal and Connective Tissue Disorders

<i>Common</i>	Arthralgia, joint swelling, myalgia.
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Central and Peripheral Nervous System

<i>Very Common</i>	Headache.
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Uncommon Dizziness.

Very Rare Peripheral neuropathy, polyneuropathy, paraesthesiae (these unwanted effects may be reversed by administration of pyridoxine), tremor.

Psychiatric Disorders

Uncommon Agitation, anorexia nervosa, anxiety.

Very Rare Depression, hallucinations.

Renal and Urinary Disorders

Uncommon Proteinuria, increased plasma creatinine, haematuria sometimes in association with glomerulonephritis.

Very Rare Acute renal failure, urinary retention.

Respiratory, Thoracic and Mediastinal Disorders

Uncommon Dyspnoea, pleural pain nasal congestion.

Skin and Subcutaneous Tissue Disorders

Uncommon Rash.

Miscellaneous

Uncommon Fever.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

The chief manifestations are cardiovascular disorders such as pronounced tachycardia and hypotension, which are accompanied by nausea, dizziness, and sweating, 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 and coma.

Treatment

Activated charcoal may be administered. Treatment is supportive and symptomatic care. Severe hypotension may respond to placing the patient in the supine position with the feet raised. The effects of gross overdosage may be treated by the infusion of plasma expanders.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Hydralazine exerts its peripheral vasodilating effect through a direct relaxation of smooth muscle tissue in vascular resistance vessels, predominantly in the arterioles. The cellular mechanism of action responsible for this effect is not fully understood.

In hypertension, this effect results in decreased arterial blood pressure (diastolic more than systolic). A reflex action by the sympathetic nervous system compensates for this fall in blood pressure by increasing heart rate, stroke volume, and cardiac output. Up to 75% of the therapeutic effect of hydralazine can be lost by this reflex action. To counteract the reflex action, hydralazine is often given in conjunction with a β -blocker.

The preferential dilatation of arterioles, as compared with veins, minimises postural hypotension and promotes the increase in cardiac output. The peripheral vasodilatation is widespread but not uniform.

Splanchnic, coronary, cerebral, and renal blood flow increases unless the fall in blood pressure is very marked. Vascular resistance in the cutaneous and muscle beds is not consistently affected.

The use of 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.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Distribution

Hydralazine is rapidly and 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. 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. Peak plasma concentrations are reached within 1 hour in most cases.

Orally administered hydralazine undergoes a dose dependent first-pass effect (systemic availability: 26 to 55%), this first-pass effect being dependent on the individual's acetylator status. In response to the same dose, slow acetylators show higher 'apparent' plasma hydralazine levels than rapid acetylators.

Hydralazine becomes bound to plasma proteins (chiefly albumin) to the extent of 88 to 90%. It is rapidly distributed in the body and displays a specific affinity for muscle tissue in the arterial walls. It crosses the placental barrier and also passes into human milk.

Metabolism

The pattern of the metabolites depends on the subject's acetylator and presumably hydroxylator status. Urinary excretion of NAc-HPZ (N-acetyl-hydralazine-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. Hydralazine persists for longer periods at its site of action, arteriolar smooth muscle, which enables twice daily dosing. In patients with impaired renal function, the plasma half-life is prolonged to up to 16 hours at creatinine clearance of less than 20 mL/minute. Renal elimination may be impaired in patients of advanced age.

Excretion

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Hydralazine induces gene mutations, chromosomal aberrations and DNA damage in mammalian cells *in vitro*, as well as gene mutations in bacteria, yeast and *Drosophila*. The potential for similar effects *in vivo* has not been adequately reported.

Carcinogenicity

Carcinogenicity studies in Swiss mice showed an increased incidence of pulmonary adenomas and adenocarcinomas when hydralazine was administered in the drinking water at concentrations of 312 to 1,250 ppm (approximately 50 to 200 mg/kg/day); a 'no effect' dose has not been established. A carcinogenicity study in rats dosed by gavage at 15, 30 and 60 mg/kg/day showed increases in the incidence of hepatic neoplasms in both sexes and Leydig cell tumours in males.

In the absence of adequate information on the genotoxic activity of hydralazine in *in vivo* studies, the possibility that the carcinogenic effects of hydralazine may be related to its genotoxic activity cannot be ruled out. The extent to which these findings indicate a risk to humans is uncertain. While long-term clinical observation has not suggested that human cancer is associated with hydralazine use, epidemiological studies have so far been insufficient to arrive at any conclusions.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets contain the following inactive ingredients: colloidal anhydrous silica, disodium edetate, magnesium stearate, microcrystalline cellulose, pregelatinized maize starch, purified talc, sodium starch glycolate and Opadry Pink OY-LS-34902 (Proprietary Ingredient Number: 2948) (50 mg strength only).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: bottle (HDPE)

Pack sizes: 60 (25 mg only), 90 and 100 tablets

Some strengths, pack sizes and/or pack types may not be marketed.

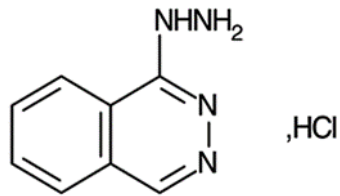
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

A white or almost white, crystalline powder, soluble in water, slightly soluble in alcohol, very slightly soluble in methylene chloride. It melts at about 275°C, with decomposition.



Chemical name: 1-hydrazinophthalazine hydrochloride

Molecular formula: C₈H₈N₄,HCl

Molecular weight: 196.6

CAS Number

304-20-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Limited

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Millers Point NSW 2000

www.mylan.com.au

9 DATE OF FIRST APPROVAL

23/08/2005

10 DATE OF REVISION

05/09/2019

Summary Table of Changes

Section Changed	Summary of New Information
All	Reformat of PI
2; 4.1; 4.2; 4.3; 4.4; 4.5; 4.6; 4.7; 4.8; 6.1; 9; 10	Editorial changes
4.5	Inclusion of 'epinephrine' when referencing adrenaline due to international harmonisation

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