SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Hydralazine 50 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 50 mg hydralazine hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

Yellow to light yellow, round, flat tablet with ‘C’ and ‘2’ debossed on either side of break-line on one side and plain on the other side with diameter of 8.0 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of moderate to severe hypertension as an adjunct to other anti-hypertensive agents.

Due to the complementary mechanism of action the combination of hydralazine with b-blockers and diuretics may enable antihypertensive efficacy at lower dose levels and counteract accompanying hydralazine effects such as reflex tachycardia and oedema.

As supplementary medication for use in combination with long-acting nitrates in moderate to severe chronic congestive cardiac failure in patients in whom optimal doses of conventional therapy have proved insufficient.

4.2 Posology and method of administration

See “Precautions” before use.

Adults:

Hypertension: the dose should be adjusted to the individual requirements of the patient. Treatment should begin with low doses of hydralazine which, depending on the patient's response should be increased stepwise to achieve optimal therapeutic effect whilst keeping unwanted effects to a minimum.

Initially 25 mg bid. This can be increased gradually to a dose not exceeding 200 mg daily. The dose should not be increased beyond 100 mg daily without first checking the patient's acetylator status.

Chronic congestive heart failure: Treatment with hydralazine should always be initiated in hospital, where the patient's individual haemodynamic values can be reliably determined with the help of invasive monitoring. It should then be continued in hospital until the patient has become stabilised on the requisite maintenance dose. Doses vary greatly between individual patients and are generally higher than those used for treating hypertension. After progressive titration (initially 25 mg tid or qid increasing every second day) the maintenance dosage averages 50-75 mg qid.

Paediatric population:

Not recommended

Elderly:

Clinical evidence would indicate that no special dosage regime is necessary.

Advancing age does not affect either blood concentration or systemic clearance.

Renal elimination may however be affected in so far as kidney function diminishes with age.

Method of administration

For Oral use only

The dose of hydralazine should be reduced or the dosage interval prolonged in patients with hepatic or renal impairment.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 failure due to pulmonary hypertension. Porphyria.

4.4 Special warnings and precautions for use

Warnings

The overall 'hyperdynamic' state of the circulation induced by hydralazine may accentuate certain clinical conditions. Myocardial stimulation may provoke or aggravate angina pectoris. Patients with suspected or confirmed coronary artery disease should therefore be given Hydralazine Tablets only under cover of 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 Hydralazine Tablets.

Patients who have survived a myocardial infarction should not receive Hydralazine Tablets until a post-infarction stabilisation *state* has been achieved.

Prolonged treatment with hydralazine (i.e. usually for more than 6 months) may provoke a systemic lupus erythematosus (SLE)-like syndrome, especially where doses exceed 100 mg daily. First symptoms are likely to be similar to rheumatoid arthritis (arthralgia, sometimes associated with fever, anaemia, leukopenia, thrombocytopenia and rash) and are 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), and in rare cases renal and ocular involvement have been reported. Early detection and a timely diagnosis with appropriate therapy (i.e. treatment discontinuation and possibly long-term treatment with corticosteroids may be required to reverse these changes) 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 dose and the longer its duration, and since they are also more common in slow acetylators, it is recommended that for maintenance therapy the lowest effective dose 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 greater risk of developing the SLE-like syndrome and every effort should therefore be made to keep the dosage below 100 mg daily and a careful watch kept for signs and symptoms suggestive of this syndrome. If such symptoms do develop the drug should be gradually withdrawn.

Rapid acetylators often respond inadequately even to doses of 100 mg daily and therefore the dose can be raised with only a slightly increased risk of an LE like syndrome.

During long term treatment with Hydralazine Tablets it is advisable to determine the antinuclear factors and conduct urine analysis 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. If overt clinical signs or symptoms develop, the drug should be withdrawn immediately.

Skin rash, febrile reactions and change in blood count occur rarely and drug should be withdrawn. Peripheral neuritis in the form of paraesthesia has been reported, and may respond to pyridoxine administration or drug withdrawal.

Precautions

In patients with renal impairment (creatinine clearance < 30 ml/min or serum creatinine concentrations > 2.5 mg / 100 ml or 221 μmol/l) and in patients with hepatic dysfunction the dose or interval between doses should be adjusted according to clinical response, in order to avoid accumulation of the 'apparent' active substance.

Hydralazine Tablets should be used with caution in patients with coronary artery disease (since it may increase angina) or cerebrovascular disease.

When undergoing surgery, patients treated with Hydralazine Tablets 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.

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

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Potentiation of effects: Concurrent therapy with other antihypertensives (vasodilators, calcium antagonists, ACE inhibitors, diuretics), anaesthetics, tricyclic antidepressants, major tranquillisers, nitrates or drugs exerting central depressant actions (including alcohol).

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

MAO inhibitors should be used with caution in patients receiving Hydralazine Tablets.

Concurrent administration of Hydralazine Tablets with beta-blockers subject to a strong first pass effect (e.g. propranolol) may increase their bioavailability.

Downward adjustment of these drugs may be required when they are given concomitantly with Hydralazine Tablets.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Use of hydralazine in pregnancy, before the third trimester should be avoided but the drug may be employed in later pregnancy if there is no safer alternative or when the disease itself carries serious risks for the mother or child e.g. pre-eclampsia and or eclampsia.

No serious adverse effects in human pregnancy have been reported to date with Hydralazine Tablets, although experience in the third trimester is extensive.

Breast-feeding

Hydralazine passes into breast milk but reports available so far have not shown adverse effects on the infant mothers in whom use of hydralazine is unavoidable may breast feed their infant provided that the infant is observed for possible adverse effects.

Fertility

Not data available.

4.7 Effects on ability to drive and use machines

Hydralazine may impair the patient's reactions especially at the start of the treatment.

The patient should be warned of the hazard when driving or operating machinery.

4.8 Undesirable effects

Some of the adverse effects listed below e.g. tachycardia, palpitations, angina symptoms, flushing, headache, dizziness, nasal congestion and gastro-intestinal disturbances are commonly seen at the start of treatment, especially if the dose is raised quickly. However such effects generally subside in the further course of treatment.

(The following frequency estimates are used: Very common (≥ 1/10), common (≥ 1/100, < 1/10), rare (≥ 1/10000, < 1/1000); isolated cases (< 0.001%).

System Organ Class	Frequency	Adverse effects
Blood and lymphatic system disorders	Rare	Anaemia, leucopenia, neutropenia, thrombocytopenia with or without purpura. eosinophilia
	Isolated cases	Haemolytic anaemia, leucocytosis, lymphadenopathy, pancytopenia, splenomegaly, agranulocytosis
Metabolism and nutrition disorders	Rare	Decreased appetite
Psychiatric disorders	Rare	Agitation, anxiety
	Isolated cases	Depression, hallucinations
Nervous system disorders	Very common	Headache
	Rare	Dizziness
	Isolated cases	Peripheral neuritis, polyneuritis, paraesthesia (these unwanted effects may be reversed by administering pyridoxine).
Eye disorders	Rare	Conjunctivitis, lacrimation increased
Cardiac disorders	Very common	Tachycardia, palpitations
	Common	Anginal symptoms
	Rare	Oedema, heart failure
Vascular disorder	Common	Flushing, hypotension
	Isolated cases	Paradoxical pressor responses
Respiratory, thoracic and mediastinal disorders	Rare	Nasal congestion, Dyspnoea, pleuritic pain
Gastrointestinal disorders	Common	Gastrointestinal disturbances, diarrhoea, nausea, vomiting
	Isolated cases	Paralytic ileus.
Hepatobiliary disorders	Rare	Jaundice, hepatomegaly, abnormal liver function sometimes in association with hepatitis.
Skin and subcutaneous tissue disorders	Common	SLE-like syndrome (sometimes resulting in a fatal outcome see section 4.4 Special warnings and precautions for use)
	Rare	Hypersensitivity reactions such as pruritus, urticaria, vasculitis, rash
Musculoskeletal and connective tissue disorders	Common	Arthralgia, joint swelling, myalgia
Renal and urinary disorders	Rare	Proteinuria, Blood creatinine increased, haematuria sometimes in association with glomerulonephritis.
	Isolated cases	Acute kidney failure, urinary retention.
General disorders and administration site conditions	Rare	Pyrexia, malaise.
	Isolated cases	Exophthalmos
Investigations	Rare	Weight decrease

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Signs and symptoms

Symptoms include hypotension, tachycardia, myocardial ischaemia dysrhythmias and coma.

Treatment

Gastric lavage should be instituted as soon as possible. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Hydralazine is a peripheral vasodilator.

ATC code: C02DB02

Mechanism of action

Hydralazine is a direct acting vasodilator which exerts its effects principally on the arterioles. Its precise mode of action is not known.

Pharmacodynamic effects

Administration of hydralazine produces a fall in peripheral resistance and a decrease in arterial blood pressure, effects which induce reflex sympathetic cardiovascular responses. The concomitant use of a beta-blocker will reduce these reflex effects and enhance the anti-hypertensive effect. The use of hydralazine can result in sodium and fluid retention, producing oedema and reduced urinary volume. These effects can be prevented by concomitant administration of a diuretic.

5.2 Pharmacokinetic properties

Absorption

Orally administered hydralazine is rapidly and completely absorbed but is subject to a dose dependent first pass effect (systemic bioavailability: 26-55%) which is

dependent upon the individual's acetylator status. Peak plasma concentrations are attained after 0.5 to 1.5 hours.

Distribution

Hydralazine is rapidly distributed in the body and displays a particular affinity for the blood vessel walls. Plasma protein binding is of the order of 90%. Within 24 hours after an oral dose, the quantity recovered in the urine averages 80% of the dose.

Biotransformation

Nil

Elimination

Hydralazine appears in the plasma chiefly in the form of a readily hydrolysable conjugate with pyruvic acid. Plasma half-life averages 2-3 hours but is prolonged up to 16 hours in severe renal failure (creatinine clearance less than 20 ml/mm) and shortened to approximately 45 minutes in rapid acetylators.

The bulk of the dose is excreted as acetylated and hydroxylated metabolites, some of which are conjugated with glucuronic acid.

Characteristics in patients

None relevant.

5.3 Preclinical safety data

Hydralazine has been found to be teratogenic in mice producing a small incidence of cleft palate and certain other bony malformations, in oral doses ranging from 20-120 mg / kg i.e. 20-30 times the maximum human daily dose. It was not teratogenic in rats or rabbits.

In high (cyto-) toxic concentrations, hydralazine induces gene mutations in single cell organisms and in mammalian cells in vitro. No unequivocally mutagenic effects have been detected in vivo in a great number of test systems.

Hydralazine in lifetime carcinogenicity studies, caused, towards the end of the experiments, small but statistically significant increases in lung tumours in mice and in hepatic and testicular tumours in rats. These tumours also occur spontaneously with fairly high frequency in aged rodents.

With due consideration of these animals and in-vitro toxicological findings, hydralazine in therapeutic doses does not appear to bear risk that would necessitate a limitation of its administration. Many years of clinical experience have not suggested that human cancer is associated with hydralazine use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose,

Dicalcium phosphate anhydrous,

Polyvinyl pyrrolidone,

Sodium starch glycolate,

Stearic acid,

Colloidal anhydrous silica,

Quinoline yellow aluminium lake.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25^{o}C.

6.5 Nature and contents of container

250 mm Alu/Alu cold form film with 25 micron aluminium lidding foil.

Packs of 7, 10, 14, 28, 30, 56, 60, 84, 90, 100 and 112 tablets are available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Morningside Healthcare Ltd
Unit C, Harcourt Way
Leicester, LE19 1WP, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 20117/0259

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/01/2025

10 DATE OF REVISION OF THE TEXT

21/01/2025