1. NAME OF THE MEDICINAL PRODUCT

HYDRALAZINE 50mg TABLETS BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50mg Hydralazine Hydrochloride.

Excipient with known effect:
Each tablet contains carmoisine aluminium lake azorubine (E122).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pink, circular, biconvex, film-coated tablets impressed “C” on one face and the identifying letters “HZ” on the reverse

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hydralazine is indicated for:

1) 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.

2) 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

Posology

Older people (over 65 years)
No studies in the elderly have been performed. The safety and efficacy of Hydralazine is not established in the elderly population.

Elderly
Clinical evidence indicates 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.

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 50mg once daily. This can be increased gradually to a dose not exceeding 200mg daily.

The dose should not be increased beyond 100mg daily without first checking the patient's acetylator status. The maximum dose in women should not exceed 100 mg (see section 4.4).

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 50mg twice daily increasing every second day) the maintenance dosage averages 50-75mg four times a day.

Paediatric population
Not recommended for this age group.

Special Populations
Renal impairment and hepatic impairment (all indications)
In patients with moderate to severe renal impairment (creatinine clearance < 30 mL/min or serum creatinine concentration > 2.5 mg/100 mL or 221 Lmol/L) or hepatic dysfunction, the dosage or the dosing interval must be adapted according to the clinical response to avoid accumulation of the "apparent" active substance (see section 4.4).

Method of administration
For oral administration.

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
- 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 (*i.e.* cor pulmonale).
- Dissecting aortic aneurysm.
- 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 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 hydralazine.

Patients who have survived a myocardial infarction should not receive hydralazine until a post-infarction stabilisation phase has been achieved.

Prolonged treatment with hydralazine may provoke a systemic lupus erythematosus (SLE)-like syndrome. First symptoms are likely to be similar to rheumatoid arthritis (arthralgia, sometimes associated with fever, anaemia, leucopenia, 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 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 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.

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.

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 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 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.

Treatment with hydralazine may induce systemic vasculitis. There have also been a small number of reported cases of suspected antineutrophil cytoplasmic antibody ANCA(+) vasculitis in some patients also receiving hydralazine, 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 early diagnosis, discontinuation of the medicine and prompt hospital treatment. The syndrome is characterised by a fulminant course if left untreated and may sometimes be fatal.

Excipients
Hydralazine 50mg tablets contain carmoisine aluminium lake azorubine (E122) which may cause allergic reactions.

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), muscle relaxants (baclofen and tizanidine), anaesthetics,

tricyclic antidepressants, major tranquillisers, nitrates or drugs exerting central depressant actions (including alcohol).

Administration of Hydralazine 50mg Tablets BP shortly before or after diazoxide may give rise to marked hypotension.

MAO inhibitors should be used with caution in patients receiving Hydralazine 50mg Tablets BP.

Concurrent administration of Hydralazine 50mg Tablets BP 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 50mg Tablets BP.

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

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

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential
Women planning to become pregnant should not take Hydralazine Tablets. When pregnancy is confirmed in women taking Hydralazine Tablets, the treatment should be discontinued immediately (see subsection Pregnancy).

Pregnancy
Use of Hydralazine Tablets 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, although experience in the third trimester is extensive. However, studies have shown teratogenic potential in mice but not in other animal species. Hydralazine crosses the placenta.

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 Tablets is unavoidable may breast feed their infant provided that the infant is observed for possible adverse effects.

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

4.7 Effects on ability to drive and use machines

Dizziness or hypotension may occur with Hydralazine Tablets, it is therefore advisable to exercise caution 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.

System organ class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Rare (≥1/10,000 to <1/1,000)**	**Very rare (<1/10,000)**	**Frequency not known (cannot be estimated from the available data).**
Blood and lymphatic system disorders			anaemia, leucopenia, neutropenia, thrombocytopenia with or without purpura, eosinophilia	haemolytic anaemia, leucocytosis, lymphadenopathy, pancytopenia, splenomegaly, agranulocytosis	
Immune system disorders					vasculitis including pulmonary renal syndrome
Metabolism and nutrition disorders			anorexia		
Psychiatric disorders			agitation, anxiety	depression, hallucinations	
Nervous system disorder	headache		dizziness	peripheral neuritis, polyneuritis, paraesthesiae (these unwanted effects may be reversed by administering pyridoxine)	
Eye disorders			increased lacrimation, conjunctivitis		
Cardiac disorders	tachycardia, palpitations	anginal symptoms	oedema, heart failure		
Vascular disorders		flushing, hypotensio		paradoxical pressor responses	

		n			
Respiratory, thoracic and mediastinal disorders			nasal congestion, dyspnoea, pleuritic pain		
Gastrointestinal disorders		gastro-intestinal disturbances, diarrhoea, nausea, vomiting		paralytic ileus	
Hepatobiliary disorders			jaundice, hepatomegaly, abnormal liver function sometimes in association with hepatitis		
Skin and subcutaneous tissue disorders		SLE-like syndrome (sometimes resulting in a fatal outcome, see section 4.4)	hypersensitivity reactions such as pruritus, urticaria, rash		
Musculoskeletal and connective tissue disorders		arthralgia, joint swelling, myalgia			
Renal and Urinary disorders			proteinuria, blood creatinine increased, haematuria sometimes in association with glomerulonephritis	acute renal failure, urinary retention,	
General disorders and administration site conditions			pyrexia, malaise	exophthalmos	
Investigations			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 Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Symptoms including hypotension, tachycardia, myocardial ischaemia, dysrrhythmias and coma.

Management
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. Adrenaline should therefore be avoided.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hydrazinophthalazine derivatives; ATC code: C02D B02

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

Hydralazine given orally is rapidly and completely absorbed from the gastrointestinal tract and the absorption is variable according to the acetylation status of the individual. The maximum serum concentration of hydralazine after single oral administration of 50 mg hydralazine was found to be 229 ± 20 ng/mL and 148 ± 15 ng/mL in slow and fast acetylators, respectively. Peak plasma concentrations are reached within 1 hour in most cases.

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

Orally administered hydralazine undergoes a dose-dependent first-pass effect (systemic bioavailability: 26-55%), this first-pass effect being dependent on the individual's acetylator status. Hydralazine exhibits non-linear pharmacokinetics and it is attributed to the saturable first pass effects.

Distribution
Hydralazine is primarily present as hydrazone conjugate with pyruvic acid in plasma. Hydralazine becomes bound to plasma proteins (chiefly albumin) to the extent of 88- 90%. The volume of distribution of hydralazine was determined as 1.5 ± 1.0 L/kg. Hydralazine is rapidly distributed in the body and displays a specific affinity for muscle tissue of the arterial walls. Hydralazine crosses the placental barrier and also passes into the breast milk.

Biotransformation
After oral administration the pattern of metabolites depends mainly on the subject's acetylator status.

Systemic metabolism in the liver is by hydroxylation of the ring system and conjugation with glucuronic acid and acetylator status does not affect elimination. The major metabolites are the acetylation product (3-methyl-1,2,4-triazolo-(3,4a)phthalazine) hydralazine piruvic acid hydrazone, which is the major plasma metabolite; and NAc-HPZ (4-(2-aetylhydrazino) phtalazin-1-one, N-AcHPZ (4-(2-aetylhydrazino) which is mostly found in the urine and was found to be the relevant indicator for the drug-related phenotype.

Elimination
The plasma half-life generally ranges from 2 to 3 hours, but in rapid acetylators it is shorter, averaging 45 minutes. In patients with impaired renal function, the plasma half- life is prolonged to up to 16 hours at a creatinine clearance of < 20 mL/min.

Hydralazine and its metabolites are rapidly excreted by the kidney. Within 24 hours after an oral dose, approx. 80% of the dose 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; 2-14% is excreted as "apparent" hydralazine. Advancing age does not affect either the blood concentration or the systemic clearance of "apparent" hydralazine. Renal elimination may however be affected insofar as kidney function diminishes with age.

5.3 Preclinical safety data

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.

Hydralazine in lifetime carcinogenicity studies caused, towards the end of the studies, 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.

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.

6.1. List of excipients

The tablet core contains: polyvidone, disodium edetate, microcrystalline cellulose (E460), magnesium stearate.

The coating contains: hypromellose (E464), titanium dioxide (E171), polyethylene glycol, carmoisine aluminium lake azorubine (E122).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4 Special precautions for storage

Polypropylene containers
Do not store above 25°C. Store in the original container.
Blister packs
Do not store above 25°C. Keep container in the outer carton.

6.5 Nature and contents of container

The product containers are rigid injection moulded polypropylene containers and snap-on polyethylene lids.

The product may also be supplied in blister packs and cartons:

a) Carton: Printed carton manufactured from white folding box board.

b) Blister pack: 250µm white rigid PVC. Surface printed 20µm hard temper aluminium foil with 5-6g/M² PVC and PVdC compatible heat seal lacquer on the reverse side.

Pack sizes: 28s, 30s, 56s, 60s, 84s, 90s, 100s, 112s, 120s, 168s, 180s, 250s, 500s, 1000s.

6.6. Special precautions for disposal and other handling

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

8 MARKETING AUTHORISATION NUMBER

PL 00142/0500

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/03/2001 / 19/03/2009

10 DATE OF REVISION OF THE TEXT

20/11/2024