SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Apresoline Tablets 25 mg
Hydralazine 25 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is 1-hydrazinophthalazine hydrochloride (hydralazine hydrochloride).
One coated tablet contains 25 mg hydralazine hydrochloride B.P.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Sugar-coated tablets.

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 Apresoline 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 Apresoline 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.

**Children:**
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.

4.3. **Contra-indications**

Known hypersensitivity to hydralazine or dihydralazine 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 failure due to pulmonary hypertension. 
Porphyria
4.4. Special Warnings and Special 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 Apresoline/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 Apresoline/Hydralazine Tablets.

Patients who have survived a myocardial infarction should not receive Apresoline/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, 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 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 Apresoline/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.

Apresoline//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 Apresoline/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, Apresoline/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.

4.5. Interactions 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 Apresoline/Hydralazine Tablets shortly before or after diazoxide may give rise to marked hypotension.

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

Concurrent administration of Apresoline/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 Apresoline/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. Pregnancy and Lactation

Use of Apresoline 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 Apresoline, although experience in the third trimester is extensive.

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

4.7. Effects on Ability to Drive and Use Machines

Apresoline 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 gastrointestinal 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: frequent > 10%, occasional 1-10%, rare 0.001-1%, isolated cases < 0.001%)

**Cardiovascular system:**
Frequently: tachycardia, palpitations.
Occasionally: flushing, hypotension, anginal symptoms.
Rarely: oedema, heart failure.
Isolated cases: paradoxical pressor responses.

**Central and peripheral nervous system:**
Frequently: headache.
Rarely: dizziness.
Isolated cases: peripheral neuritis, polyneuritis, paraesthesiae (these unwanted effects may be reversed by administering pyridoxine).

**Musculo-skeletal system:**
Occasionally: arthralgia, joint swelling, myalgia.

**Skin and appendages:**
Rarely: rash.

**Urogenital system:**
Rarely: proteinuria, increased plasma creatinine, haematuria sometimes in association with glomerulonephritis.
Isolated cases: acute renal failure, urinary retention.

**Gastrointestinal tract:**
Occasionally: gastro-intestinal disturbances, diarrhoea, nausea, vomiting.
Rarely: jaundice, liver enlargement, abnormal liver function sometimes in association with hepatitis.
Isolated cases: paralytic ileus.

**Blood:**
Rarely: anaemia, leucopenia, neutropenia, thrombocytopenia with or without purpura.
Isolated cases: haemolytic anaemia, leucocytosis, lymphadenopathy, pancytopenia, splenomegaly, agranulocytosis.

**Psychiatric reactions:**
Rarely: agitation, anorexia, anxiety.
Isolated cases: depression, hallucinations.
Sense organs:
Rarely: increased lacrimation, conjunctivitis, nasal congestion.

Hypersensitivity reactions:
Occasionally: SLE-like syndrome (sometimes resulting in a fatal outcome see section 4.4 Special warnings and precautions for use).
Rarely: hypersensitivity reactions such as pruritus, urticaria, vasculitis, eosinophilia, hepatitis.

Respiratory tract:
Rarely: dyspnoea, pleural pain.

Miscellaneous:
Rarely: fever, weight decrease, malaise.
Isolated cases: exophthalmos.

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.

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. 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 Apresoline 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

Apresoline 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

Apresoline 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/min) 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 glucoronic acid.

Characteristics in patients

None relevant.

5.3. Pre-clinical 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

Sugar-coated tablets of 25 mg contain silicon dioxide, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, maize starch, hydroxypropylmethylcellulose, povidone, talc, titanium dioxide, polyethylene glycol, sucrose, yellow iron oxide, water, shellac glaze, black iron oxide (E172) and propylene glycol (E1520), Red iron oxide (E172), Ammonium Hydroxide (E527).

6.2. Incompatibilities

None.

6.3. Shelf life

4 years.

6.4. Special precautions for storage

Protect from moisture and heat. Store below 30°C.
6.5. **Nature and Contents of Container**

Securitainers of 84 or 56 or 100 tablets.

6.6 **Special precautions for disposal**

None.

7 **MARKETING AUTHORISATION HOLDER**

Amdipharm UK Limited
Regency House
Miles Gray Road
Basildon
Essex
SS14 3AF
United Kingdom.

8. **MARKETING AUTHORISATION NUMBER(S)**

PL 20072/0026

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

30th March 2005

10 **DATE OF REVISION OF THE TEXT**

10/09/2013