SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Apresoline 20 mg Ampoules
Hydralazine 20mg Powder for Concentrate for Solution for Injection/Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is 1-hydralainophthalazine hydrochloride (hydralazine hydrochloride). Each 2 ml ampoule contains 20mg hydralazine hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Clear glass ampoules containing powder for concentrate for solution for injection/infusion.

White to yellow lyophilisate (pellet).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Apresoline is indicated in adults for the treatment of hypertensive emergencies, particularly those associated with pre-eclampsia and toxaemia of pregnancy.
2. Apresoline is indicated in adults for the treatment of hypertension with renal complications.

4.2 Posology and method of administration

Posology

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.

Adults:
Initially 5 to 10 mg by slow intravenous injection, to avoid precipitous decreases in arterial pressure with a critical reduction in cerebral or utero-placental perfusion. If necessary, a repeat injection can be given after an interval of 20-30 minutes, throughout which blood pressure and heart rate should be monitored. A satisfactory response can be defined as a decrease in diastolic blood pressure to 90/100 mmHg.

Method of Administration
The contents of the vial should be reconstituted by dissolving in 1 ml of water for injection BP. This should then be further diluted with 10 ml of Sodium Chloride injection BP 0.9% and be administered by slow intravenous injection. The injection must be given immediately, and any remainder discarded. Hydralazine may also be given by continuous intravenous infusion, beginning with a flow rate of 200-300µg/min. Maintenance flow rates must be determined individually and are usually within the range 50-150µg/min. The product reconstituted as for direct iv injection may be added via the infusion container to 500 ml of Sodium Chloride Injection BP 0.9% and given by continuous infusion. The addition should be made immediately before administration and the mixture should not be stored. Hydralazine for infusion can also be used with 5% sorbitol solution or isotonic inorganic infusion solutions such as Ringers solution.

Paediatric population:
The safety and efficacy of Apresoline 20 mg Ampoules / Hydralazine 20mg Powder for Concentrate for Solution for Injection/Infusion in children have not yet been established.

Method of administration
For Intravenous use only.

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 μ mol/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).

4.3 Contraindications

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

Known hypersensitivity to 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 failure due to pulmonary hypertension (cor pulmonale).

Dissecting aortic aneurysm.

Porphyria

4.4 Special warnings and precautions for use

Cardiovascular system
The overall 'hyperdynamic' state of the circulation induced by hydralazine may accentuate certain clinical conditions. Myocardial stimulation may provoke or aggravate angina pectoris. Hydralazine can cause anginal attacks and ECG changes indicative of myocardial ischaemia. It must therefore be used with caution in patients with suspected coronary artery disease or with cerebrovascular disease. 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.

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

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 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.

Immune system
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 SLE-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.

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 studies are also indicated if the patient develops arthralgia, fever, chest pain, persistent malaise, or other unexplained signs or symptoms. A positive ANF titre requires that the physician carefully weighs the implications of the test results against the benefits of continued therapy with hydralazine.

Nervous system
Isolated cases of Peripheral neuritis in the form of paraesthesia has been reported, and may respond to pyridoxine administration or drug withdrawal.

Renal and hepatic impairment
In patients with moderate to severe renal impairment (creatinine clearance < 30 mL/min or serum creatinine concentration > 2.5 mg/100 mL or 221 □mol/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 4.2).

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

Genetic effects
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.

Skin
Skin rash, febrile reactions and change in blood count occur rarely and drug should be withdrawn.

Driving and using machines
Dizziness or hypotension may occur with Apresoline with established mechanism of action, it is therefore advisable to exercise caution when driving or operating machinery.

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, [1]nitrates or drugs exerting central depressant actions (including alcohol).

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

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

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

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

4.6 Fertility, pregnancy and lactation

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

Pregnancy
Use of Hydralazine in pregnancy, before the third trimester should be avoided but the drug maybe 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 proves

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

Fertility
No data available.

4.7 Effects on ability to drive and use machines

Dizziness or hypotension may occur with Apresoline, it is therefore advisable to exercise caution when driving or operating machinery.

4.8 Undesirable effects

Adverse drug reactions from multiple sources including clinical trials and spontaneous reports are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), isolated cases (< 0.001%), not known (cannot be estimated from the available data).

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	**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	Anorexia
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).
	Not known:	Tremor
Eye disorders	Rare	Conjunctivitis, lacrimation increased
	Isolated cases	Exophthalmos
Cardiac disorders	Very common:	Tachycardia, palpitations

	Common	Anginal pectoris
	Rare	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 functio sometimes in association with hepatitis.
	Not known	Hepatosplenomegaly (more common when associated with SLE-like symptoms
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, Oedema.
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 Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

Management
Since no specific antidote is known, - in addition to attempts to eliminate the drug from the gastrointestinal tract (early induction of vomiting, later gastric lavage; administration of activated charcoal and possibly laxatives) - treatment should be supportive including use of a plasma expander or intravenous fluids as 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: 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
After intravenous administration of hydralazine, there was no first pass effect observed and acetylator status has no influence on the plasma levels.

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
None stated.

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.

Characteristics in patients
None stated.

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 20-120mg/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 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid

Water for injection
Nitrogen, pure 99.99%

6.2 Incompatibilities

Dextrose infusion solutions are not compatible because contact between hydralazine and glucose causes hydralazine to be rapidly broken down.

6.3 Shelf life

5 years.

Use immediately after reconstitution.

6.4 Special precautions for storage

Store in original package in order to protect from light. Store below 25°C.

For single use only.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Colourless Type I glass 2ml ampoule. Five ampoules are packed in a cardboard printed carton.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 20072/0230

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