Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Apresoline Ampoules 20 mg Powder for concentrate for solution for injection or infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Apresoline Ampoules contain 20 mg Hydralazine Hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for injection or infusion. (Powder for sterile concentrate)
2 ml, Type 1, Ph. Eur. clear glass ampoules containing a yellowish crystalline powder for reconstitution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the treatment of hypertensive emergencies, including pre-eclampsia and toxaemia of pregnancy, and in hypertension with renal complications.

4.2 Posology and method of administration

Posology:
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.

Paediatric population
Not recommended

Use in the elderly
Clinical evidence would indicate that no special dosage regimen is necessary but concurrent hepatic and renal insufficiency should be taken into account.

Method of administration:
Parenteral: 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 mm Hg. The contents of the vial should be reconstituted by dissolving in 1ml of Water for Injection. This should then be further diluted with 10 ml of Sodium Chloride Injection 0.9% and be administered by slow intravenous injection. The injection must be given immediately and any remainder discarded.

Apresoline may also be given by continuous intravenous infusion, beginning with a flow rate of 200-300 microgram/minute. Maintenance flow rates must be determined individually and are usually within the range 50-150 microgram/minute. The product reconstituted as for direct iv injection may be added via the infusion container to 500 millilitre of Sodium Chloride Injection 0.9% and given by continuous infusion. The addition should be made immediately before administration and the mixture should not be stored. Apresoline for infusion can also be used with 5% sorbitol solution or isotonic inorganic infusion solutions such as Ringer's solution.

4.3 Contraindications

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

Severe tachycardia and heart failure with a high cardiac output (e.g. in thyroxicosis).

Myocardial insufficiency due to mechanical obstruction (e.g. aortic or mitral stenosis or constrictive pericarditis).

Idiopathic systemic lupus erythematosus (SLE) and related diseases.

Isolated right ventricular failure due to pulmonary hypertension (cor pulmonale).

Dissecting aortic aneurysm.

4.4 Special warnings and precautions for use

Warnings
The overall state of the circulation induced by hydralazine may accentuate certain clinical conditions. Myocardial stimulation may provoke or aggravate uncontrolled or untreated angina pectoris. Therefore, Apresoline should only be given to patients with suspected or confirmed coronary artery disease who are already being treated with a ß–blocker, or in combination with other suitable sympatholytic agents. It is important that the ß–blocker medication should be commenced a few days before the start of treatment with Apresoline.

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

Prolonged treatment with hydralazine (ie, 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; whereas nervous system and renal involvement are more rare than in idiopathic lupus),. Early detection and a timely diagnosis with appropriate therapy (i.e. treatment discontinuation and possibly long-term treatment with corticosteroids) are of utmost importance in this life-threatening illness to prevent more severe complications, which may sometimes be fatal.

In particular, renal symptoms are less frequent than in idiopathic SLE and pleuro-pulmonary symptoms, as well as pericarditis, are more frequent.

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 a 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 a SLE-like syndrome.

During long-term treatment with Apresoline it is advisable to determine the antinuclear factors (ANF) and to carry out urine analyses at intervals of approx. 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 and symptoms develop, the drug should be withdrawn at once.

Precautions
Isolated cases of peripheral neuritis have been reported. Published evidence suggests an antipyridoxine effect, which may respond to pyridoxine administration or drug withdrawal.

Laboratory tests: 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.

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

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.

In patients with moderate to severe renal impairment (creatinine clearance < 30 ml/min or serum creatinine concentrations > 2.5 mg/100 ml or 221micromol/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 (see 4.2 Posology and method of administration, and 4.3 Contraindications).

Like all potent antihypertensives, Apresoline should be used with caution in patients with coronary artery disease or acute cerebrovascular disease, since it enhances the cardiac-enhancing effects of hydralazine.

In patients undergoing surgery whilst being treated with Apresoline a fall in blood pressure may occur. Adrenaline should not be used to correct the hypertension as it enhances the cardiac-accelerating effects of hydralazine

Treatment with hydralazine may induce systemic vasculitis, including ANCA(+) 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 characterized by a fulminant course if left untreated, and may sometimes be fatal.

Oral forms only
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 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 Interaction with other medicinal products and other forms of interaction

The effects of this preparation are potentiated by other anti-hypertensive drugs, diuretics, alcohol, anaesthetics, tricyclic antidepressants, major tranquilisers or drugs exerting a central depressant action. This should be borne in mind when relevant concomitant therapy is being considered.

This product should be used with caution in patients taking MAO inhibitors.

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

Concurrent administration of Apresoline 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
No serious adverse effects in human pregnancy have been observed to date with Apresoline, although experience in the third trimester is extensive. However, animal experiments have shown teratogenic potential in mice but not in other animal species. Hydralazine crosses the placenta. 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, eg pre-eclampsia and/or eclampsia.

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 Apresoline proves 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 has minor influence on the ability to drive and use machines.
Apresoline may impair the patient's reactions, especially at the start of treatment and the patient should be warned of the hazard when driving or operating machinery.

4.8 Undesirable effects

The information below lists reported adverse reactions, ranked using the following frequency classification: 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), not known (cannot be estimated from the available data).

Some of the adverse effects listed below e.g. tachycardia, palpitation, anginal 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.

System Organ Class	***Frequency***	***Adverse effects***
Blood and lymphatic system disorder	*Uncomman*	anaemia, leucopenia, neutropenia, thrombocytopenia with or without purpura.
	Very rare	haemolytic anaemia, leucocytosis, lymphadenopathy, pancytopenia, splenomegaly, agranulocytosis.
Immune system disorders	Not known	vasculitis including pulmonary renal syndrome.
	Common	SLE-like syndrome (sometimes resulting in a fatal outcome - see 4.4 Special warnings and precautions for use).
	Uncommon	hypersensitivity reactions such as pruritus, urticaria, vasculitis, eosinophilia, hepatitis.
Psychiatric disorders	Uncommon	agitation, anorexia, anxiety.

	Very rare	depression, hallucinations.
Nervous system disorders	Very common	headache.
	Uncommon	dizziness.
	Very rare	peripheral neuritis, polyneuritis, paraesthesiae, (these unwanted effects may be reversed by administering pyridoxine), and tremor.
Eye disorders	Uncommon	increased lacrimation, conjunctivitis.
	Very rare	exophthalmos.
Cardiac disorders	Very common	tachycardia, palpitation.
	Common	flushing, hypotension, anginal symptoms.
	Uncommon	oedema, congestive heart failure.
	Very rare	paradoxical pressor responses.
Respiratory, thoracic and mediastinal disorders	Uncommon	dyspnoea, pleural pain, nasal congestion.
Gastrointestinal disorders	Common	gastro-intestinal disturbances, diarrhoea, nausea, vomiting.
	Uncommon	jaundice, liver enlargement, abnormal liver function sometimes in association with hepatitis.
	Very rare	paralytic ileus.
Skin and subcutaneous tissue disorders	Uncommon	rash.
Musculoskeletal and connective tissue disorders	Common	arthralgia, joint swelling, myalgia.
Renal and urinary disorders	Uncommon	proteinuria, increased plasma creatinine, haematuria sometimes in association with glomerulonephritis.
	Very rare	acute renal failure, urinary retention.
General disorders and administration site conditions	Uncommon	fever, weight decrease, malaise

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: HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2. Tel: +353 1 6764971; Fax: +353 1 6762517; Website:

www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms:
Symptoms include hypotension, tachycardia, myocardial ischaemia, dysrrhythmias and coma. Supportive measures, including intravenous fluids are indicated.

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: vasodilator and antihypertensive agent, 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:
Local arteriolar vasodilator, well absorbed and subject to a dose-dependant first pass effect (bioavailability 26-55%) depending on individual acetylator status.

Distribution:
Peak plasma concentrations are attained after 0.5 to 1.5 hours. Plasma T ½ averages 2-3 hours but is prolonged up to 16 hours in severe renal failure (creatinine clearance less than 20 ml/min) and is shortened to approximately 45 mins in rapid acetylator. Apresoline is rapidly distributed in the body and displays a particular affinity for the blood-vessel walls. Plasma protein binding is in the order of 90%.

Biotransformation:
Apresoline appears in the plasma chiefly in the form of a readily hydrolysable conjugate with pyruvic acid.

Elimination:
Excretion is mainly through kidney as acetylated and hydroxylated metabolites, some of which are conjugated with glucuronic acid.

5.3 Preclinical safety data

In lifetime carcinogenicity studies, hydralazine caused small but statistically significant increases in lung tumours in mice and hepatic and testicular tumours in rats, towards the end of the experiments.

A mutagenic potential in bacterial test systems was noted, but the significance of this is unclear. Many years of

international use have not implied an association of hydralazine with human cancer.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

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.
The product should be used immediately after reconstitution.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container in order to protect from light.

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

6.5 Nature and contents of container

2 ml, Type I, Ph. Eur., clear glass ampoules. 1 pack contains 5 ampoules.

6.6 Special precautions for disposal and other handling

The product should be used immediately after reconstitution.

For single use only.

The contents of the vial should be reconstituted by dissolving in 1ml of Water for Injection. After reconstitution the product is a clear, colourless to slightly yellowish solution. This should then be further diluted with 10ml of Sodium Chloride Injection 0.9% for administration by slow intravenous injection.
The diluted solution may be added to 500 milliliter of Sodium Chloride Injection 0.9% for administration by continuous infusion. The addition should be made immediately before administration and the mixture should not be stored. Apresoline for infusion can also be used with 5% sorbitol solution or isotonic inorganic infusion solutions such as Ringer's solution.
The product should be used immediately after reconstitution. Single use only. Any unused medicinal product should be disposed of in accordance with local requirements. See section 4.2 for further information

7 MARKETING AUTHORISATION HOLDER

Amdipharm Limited
Temple Chambers
3 Burlington Road
Dublin 4
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1142/015/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 01 April 2009

10 DATE OF REVISION OF THE TEXT

February 2016