SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cardioplen XL 2.5 mg Prolonged Release Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cardioplen XL 2.5mg Prolonged Release Tablets contain 2.5mg of felodipine.

Cardioplen XL 2.5mg Prolonged Release Tablets contain 25.20mg of lactose monohydrate/prolonged release tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Yellow, round, biconvex, film coated prolonged-release tablets with imprint 2.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In the management of hypertension and prophylaxis of chronic stable angina pectoris.

4.2 Posology and method of administration

For oral administration

Hypertension:
Adults (including older people): The dose should be adjusted to the individual requirements of the patient. The recommended starting dose is 5mg once daily. If necessary the dose may be further increased or another antihypertensive agent added. The usual maintenance dose is 5-10mg once daily. Doses higher than 20mg daily are not usually needed. In older patients an initial treatment with 2.5mg daily should be considered.

Angina pectoris:
Adults: The dose should be adjusted individually. Treatment should be started with 5mg once daily and if needed be increased to 10mg once daily.
Elderly population: Initial treatment with lowest available dose should be considered.

Administration: The tablets should regularly be taken in the morning without food or with a light meal. Cardioplen XL 2.5mg Prolonged Release Tablets

must not be chewed or crushed. They should be swallowed whole with half a glass of water.

Paediatric Population: The safety and efficacy of Cardioplen XL 2.5mg Prolonged Release Tablets in children has not been established.

Cardioplen XL 2.5mg Prolonged Release Tablets can be used in combination with β-blockers, ACE inhibitors or diuretics. The effects on blood pressure are likely to be additive and combination therapy will usually enhance the antihypertensive effect. Care should be taken to avoid hypotension. Patients with impaired hepatic function may have elevated plasma concentrations of felodipine and may respond to lower doses. The pharmacokinetics are not significantly affected in patients with impaired renal function.

4.3 Contraindications

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

Unstable angina pectoris.

Pregnancy.

Patient with a previous allergic reaction to Cardioplen XL 2.5mg Prolonged Release Tablets or other dihydropyridines because of the theoretical risk of cross-reactivity.

Cardioplen XL 2.5mg Prolonged Release Tablets should not be used in patients with clinically significant aortic stenosis, and during or within one month of a myocardial infarction.

As with other calcium channel blockers, Cardioplen XL 2.5mg Prolonged Release Tablets should be discontinued in patients who develop cardiogenic shock.

Decompensated heart failure.

Haemodynamically significant cardiac valvular obstruction.

Dynamic cardiac outflow obstruction.

4.4 Special warnings and precautions for use

As with other vasodilators, Cardioplen XL 2.5mg Prolonged Release Tablets may, in rare cases, precipitate significant hypotension with tachycardia which in susceptible individuals may result in myocardial ischaemia.

There is no evidence that Cardioplen XL 2.5mg Prolonged Release Tablets are useful for secondary prevention of myocardial infarction.

The efficacy and safety of Cardioplen XL 2.5mg Prolonged Release Tablets in the treatment of malignant hypertension and hypertensive emergencies has not been studied.

Cardioplen XL 2.5mg Prolonged Release Tablets should be used with caution in patients with severe left ventricular dysfunction.

Felodipine is cleared by the liver. Consequently higher therapeutic concentrations and response can be expected in patients with clearly reduced liver function.

Concomitant administration of drugs that strongly induce or inhibit CYP3 A4 enzymes result in extensively decreased or increased plasma levels of felodipine, respectively. Therefore such combinations should be avoided (see section 4.5).

Mild gingival enlargement has been reported in patients with pronounced gingivitis/periodontitis. The enlargement can be avoided or reversed by careful oral hygiene.

Patients with rare hereditary problems of galactose intolerance, **the Lapp lactase deficiency or** glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of substances which interfere with the cytochrome P450 system may affect plasma concentrations of felodipine. Enzyme inhibitors such as cimetidine, erythromycin, itraconazole, ketoconazole and ritonavir impair the elimination of felodipine, and Cardioplen XL 2.5 mg Prolonged Release Tablets dosage may need to be reduced when drugs are given concomitantly. Conversely, powerful enzyme inducing agents such as some anticonvulsants (phenytoin, carbamazepine, phenobarbitone) can increase felodipine elimination and higher than normal Cardioplen XL 2.5 mg Prolonged Release Tablets doses may be required in patients taking the drugs.

No dosage adjustment is required when Cardioplen XL 2.5 mg Prolonged Release Tablets are given concomitantly with digoxin.

Felodipine does not appear to affect the unbound fraction of other extensively plasma protein bound drugs such as warfarin.

Felodipine may increase the concentration of tacrolimus. When used together, the tacrolimus serum concentration should be monitored and the tacrolimus dose may need to be adjusted.

Grapefruit juice results in increased peak plasma levels and bioavailability possibly due to an interaction with flavonoids in the fruit juice. This interaction has been seen with other dihydropyridine calcium antagonists and represents a class effect. Therefore grapefruit juice should not be taken together with Cardioplen XL 2.5 mg Prolonged Release Tablets.

The anti-hypertensive effect of felodipine may be enhanced by other anti-hypertensive such as alpha-blockers (e.g. prazosin) or beta-blockers (e.g. atenolol) and general anaesthetics.

4.6 Fertility, pregnancy and lactation

Felodipine should not be given during pregnancy.

In a study on fertility and general reproductive performance in rats, a prolongation of parturition resulting in difficult labour, increased foetal deaths and early postnatal deaths were observed in the medium- and high-dose groups. Reproductive studies in rabbits have shown a dose-related reversible enlargement of the mammary glands of the parent animals and dose-related digital abnormalities in the foetuses when felodipine was administered during stages of early foetal development.

Felodipine has been detected in breast milk, but it is unknown whether it has harmful effects on the new-born.

4.7 Effects on ability to drive and use machines

Felodipine has minor or moderate influence on the ability to drive and use machines. If patients taking felodipine suffer from headache, nausea, dizziness or fatigue and ability to react may be impaired. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

As with other calcium antagonists, flushing, headache, palpitations, dizziness and fatigue may occur. These reactions are usually transient and are most likely to occur at the start of treatment or after an increase in dosage.

As with other calcium antagonists ankle swelling, resulting from precapillary vasodilation, may occur. The degree of ankle swelling is dose related.

In patients with gingivitis/periodontitis, mild gingival enlargement has been reported with Cardioplen XL 2.5mg Prolonged Release Tablets, as with other calcium antagonists. The enlargement can be avoided or reversed by careful dental hygiene.

As with other dihydropyridines, aggravation of angina has been reported in a small number of individuals especially after starting treatment. This is more likely to happen in patients with symptomatic ischaemic heart disease.

The following adverse events have been reported from clinical trials and from Post Marketing Surveillance. In the great majority of cases a causal relationship between these events and treatment with felodipine has not been established.

The following definitions of frequencies are used:
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

System organ class	**Frequency**	**Adverse reaction**
Nervous system disorders	Common Uncommon	Headache Dizziness, paraesthesia
Cardiac disorders	Uncommon	Tachycardia, palpitations
Vascular disorders	Common	Flush

	Uncommon Rare	Hypotension Syncope
Gastrointestinal disorders	Uncommon Rare Very rare	Nausea, abdominal pain Vomiting Gingival hyperplasia, gingivitis
Hepatobiliary disorders	Very rare	Increased liver enzymes
Skin and subcutaneous tissue disorders	Uncommon Rare Very rare	Rash, pruritus Urticaria Photosensitivity reactions, leukocytoclastic vasculitis
Musculoskeletal and connective tissue disorders	Rare	Arthralgia, myalgia
Renal and urinary disorders	Very rare	Pollakisuria
Reproductive system and breast disorders	Rare	Impotence/sexual dysfunction
General disorders and administration site conditions	Very common Uncommon Very rare	Peripheral oedema Fatigue Hypersensitivity reactions, e.g. angio-oedema, fever

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.

4.9 Overdose

Symptoms: Overdosage may cause excessive peripheral vasodilatation with marked hypotension which may sometimes be accompanied by bradycardia.

Management: If justified: activated charcoal, gastric lavage if performed within one hour after ingestion. Severe hypotension should be treated symptomatically, with the patient placed supine and the legs elevated. Bradycardia, if present, should be treated with atropine 0.5-1mg i.v. If this is not sufficient, plasma volume should be increased by infusion of e.g. glucose, saline or dextran. Sympathomimetic drugs with predominant effect on the (α_1-adrenoceptor may be given e.g. metaraminol or phenylephrine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: calcium channel blockers, dihydropyridine derivatives
ATC code: C08CA02

Felodipine is a vascular selective calcium antagonist, which lowers arterial blood pressure by decreasing peripheral vascular residence. Due to the high degree of selectivity for smooth muscle in the arterioles, felodipine in therapeutic doses has no direct effect on cardiac contractility or conduction.

It can be used as monotherapy or in combination with other antihypertensive drugs, e.g. β-receptor blockers, diuretics or ACE-inhibitors, in order to achieve an increased antihypertensive effect. Felodipine reduces both systolic and diastolic blood pressure and can be used in isolated systolic hypertension. In a study of 12 patients, felodipine maintained its antihypertensive effect during concomitant therapy with indomethacin.

Because there is no effect on venous smooth muscle or adrenergic vasomotor control, felodipine is not associated with orthostatic hypotension.

Felodipine has anti-anginal and anti-ischaemic effects due to improved myocardial oxygen supply/ demand balance. Coronary vascular resistance is decreased and coronary blood flow as well as myocardial oxygen supply are increased by felodipine due to dilation of both epicardial arteries and arterioles. Felodipine effectively counteracts coronary vasospasm. The reduction in systemic blood pressure caused by felodipine leads to decreased left ventricular afterload.

Felodipine improves exercise tolerance and reduces anginal attacks in patients with stable effort induced angina pectoris. Both symptomatic and silent myocardial ischaemia are reduced by felodipine in patients with vasospastic angina. Felodipine can be used as monotherapy or in combination with β-receptor blockers in patients with stable angina pectoris.

Felodipine possesses a mild natriuretic/diuretic effect and generalised fluid retention does not occur.

Clinical efficacy: In the HOT (Hypertension Optimal Treatment) study, the effect on major cardiovascular events (i.e. acute myocardial infarction, stroke and cardiovascular death) was studied in relation to diastolic blood pressure targets ≤90 mmHg, ≤85 mmHg and ≤80 mmHg and achieved blood pressure, with felodipine as baseline therapy.
A total of 18,790 hypertensive patients (DBP 100-115 mmHg), aged 50-80 years were followed for a mean period of 3.8 years (range 3.3-4.9). Felodipine was given as monotherapy or in combination with a betablocker, and/or an ACE-inhibitor and/or a diuretic. The study showed benefits of lowering SBP and DBP down to 139 and 83 mmHg, respectively.
According to the STOP-2 (Swedish Trial in Old Patients with Hypertension-2 study), performed in 6614 patients, aged 70-84 years, dihydropyridine calcium antagonists (felodipine and isradipine) have shown the same preventive effect on cardiovascular mortality and morbidity as other commonly used classes of antihypertensive medicinal products – ACE inhibitors, beta-blockers and diuretics.

There is limited clinical trial experience of the use of felodipine in hypertensive paediatric patients. In a randomised, double-blind, 3-week, parallel group study in children aged 6-16 years with primary hypertension, the antihypertensive effects of once daily felodipine 2.5mg (n=33), 5mg (n=33) and 10mg (n=31) were compared with placebo (n=35). The study failed to demonstrate the efficacy of felodipine in lowering blood pressure in children aged 6-16 years.
The long term effects of felodipine on growth, puberty and general development have not been studied. The long term efficacy of antihypertensive therapy as therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood has also not been established.

Felodipine is well tolerated in patients with concomitant disease such as congestive heart failure well controlled on appropriate therapy, asthma and other obstructive pulmonary diseases, diabetes, gout, hyperlipidemia impaired renal function, renal transplant recipients and Raynaud's disease. Felodipine has no significant effect on bland glucose levels or lipid profiles.

Haemodynamic effects: The primary haemodynamic effect of felodipine is a reduction of total peripheral vascular resistance which leads to a decrease in blood pressure. These effects are dose- dependent. In patients with mild to moderate essential hypertension, a reduction in blood pressure usually occurs 2 hours after the first oral dose and lasts for at least 24 hours with a trough/peak ratio usually above 50%.
Plasma concentration of felodipine and decrease in total peripheral resistance and blood pressure are positively correlated.

Electrophysiological and other cardiac effects: Felodipine in therapeutic doses has no effect on cardiac contractility or atrioventricular conduction or refractoriness.
Antihypertensive treatment with felodipine is associated with significant regression of pre-existing left ventricular hypertrophy.

Renal effects: Felodipine has a natriuretic and diuretic effect. Studies have shown that the tubular reabsorption of filtered sodium is reduced. This counteracts the salt and water retention observed for other vasodilators. Felodipine does not affect the daily potassium excretion. The renal vascular resistance is decreased by felodipine. Normal glomerular filtration rate is unchanged. In patients with impaired renal function glomerular filtration rate may increase.

Felodipine is well tolerated in renal transplant recipients.

Site and mechanism of action: The predominant pharmacodynamic feature of felodipine is its pronounced vascular versus myocardial selectivity. Myogenically active smooth muscles in arterial resistance vessels are particularly sensitive to felodipine.

Felodipine inhibits electrical and contractile activity of vascular smooth muscle cells via an effect on the calcium channels in the cell membrane.

5.2 Pharmacokinetic properties

Absorption and distribution: Felodipine is completely absorbed from the gastrointestinal tract after administration of felodipine extended release tablets.

The systemic availability of felodipine is approximately 15% in man and is independent of dose in the therapeutic dose range.

With the extended-release tablets the absorption phase is prolonged. This results in even felodipine plasma concentrations within the therapeutic range for 24 hours.

The plasma protein binding of felodipine is approximately 99%. It is bound predominantly to the albumin fraction.

Elimination and metabolism: The average half-life of felodipine in the terminal phase is 25 hours. There is no significant accumulation during long-term treatment.

Felodipine is extensively metabolised by the liver and all identified metabolites are inactive. Elderly patients and patients with reduced liver function have an average higher plasma concentration of felodipine than younger patients.

About 70% of a given dose is excreted as metabolites in the urine; the remaining fraction is excreted in the faeces. Less than 0.5% of a dose is recovered unchanged in the urine.
The kinetics of felodipine are not changed in patients with renal impairment.

In a single dose (felodipine prolonged release 5mg) pharmacokinetic study with a limited number of children aged between 6 and 16 years (n=12) there was no apparent relationship between the age and AUC, Cmax or half-life of felodipine.

5.3 Preclinical safety data

Felodipine is a calcium antagonist and lowers arterial blood pressure by decreasing vascular resistance. In general a reduction in blood pressure is evident 2 hours after the first oral dose and at steady state lasts for at least 24 hours after dose.

Felodipine exhibits a high degree of selectivity for smooth muscles in the arterioles and in therapeutic doses has no direct effect on cardiac contractility. Felodipine does not affect venous smooth muscle and adrenergic vasomotor control.
Electrophysiological studies have shown that felodipine has no direct effect on conduction in the specialised conducting system of the heart and no effect on the AV nodal refractories.

Cardioplen XL 2.5mg Prolonged Release Tablets possess a mild natriuretic/diuretic effect and does not produce general fluid retention, nor affect daily potassium excretion. Cardioplen XL 2.5mg Prolonged Release Tablets are well tolerated in patients with congestive heart failure.

Reproduction toxicity

In a study on fertility and general reproductive performance in rats treated with felodipine, a prolongation of parturition resulting in difficult labour/increased foetal deaths and early postnatal deaths was observed in the medium and high dose groups. These effects were attributed to the inhibitory effect of felodipine in high doses on uterine contractility. No disturbances of fertility were observed when doses within the therapeutic range were given to rats.

Reproduction studies in rabbits have shown a dose-related reversible enlargement of the mammary glands of the parent animals and dose-related digital anomalies in the foetuses. The anomalies in the foetuses were induced when felodipine was administered during early foetal development (before day 15 of pregnancy). In a reproduction study in monkeys, an abnormal position of the distal phalange(s) was noticed.

There were no other pre-clinical findings considered to be of concern and the reproductive findings are considered to be related to the pharmacological action of felodipine, when given to normotensive animals. The relevance of these findings for patients receiving felopidine is unknown. However, there have been no reported clinical incidences of phalangeal changes in foetus/neonate exposed to felodipine in-utero, from the information maintained within the internal patient safety databases.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, Cellulose microcristalline, Hypromellose, Povidone, Propyl gallate, Silica colloidal anhydrous, Magnesium stearate, Ferric oxide yellow (E172), Titanium dioxide (E171), Talc, Propylene glycol.

6.2 Incompatibilities

None stated.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 25 °C. Store in the original package.

6.5 Nature and contents of container

PVC/PE/PVDC Aluminium Blisters.

A single pack contains 10, 20, 28, 30, 50, 56 or 100 tablets.

6.6 Special precautions for disposal and other handling

None stated

7 MARKETING AUTHORISATION HOLDER

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