SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Neofel XL 5 mg Prolonged Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Neofel XL 5 mg Prolonged Release Tablets contain 5mg of felodipine.

3 PHARMACEUTICAL FORM

Light pink, round, biconvex, film coated prolonged-release tablets with imprint 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

The tablets should be taken in the morning and be swallowed with water. In order to keep the prolonged release properties, the tablets must not be divided, crushed or chewed. The tablets can be administered without food or following a light meal not rich in fat or carbohydrate.

Hypertension
The dose should be adjusted individually. Treatment can be started with 5 mg once daily. Depending on the patient’s response, the dosage can, where applicable, be decreased to 2.5 mg or increased to 10 mg daily. If necessary

another antihypertensive agent may be added. The standard maintenance dose is 5 mg once daily.

Angina pectoris
The dose should be adjusted individually. Treatment should be initiated with 5 mg once daily and, if needed, increased to 10 mg once daily.

Elderly population
Initial treatment with lowest available dose should be considered.

Renal Impairment
Dose adjustment is not needed in patients with impaired renal function.

Hepatic Impairment
Patients with impaired hepatic function may have elevated plasma concentrations of felodipine and may respond to lower doses (see section 4.4 Special warnings and precautions for use).

Paediatric Population
There is limited clinical trial experience of the use of felodipine in hypertensive paediatric patients, see sections 5.1 and 5.2.

Neofel XL 5 mg Prolonged Release Tablets can be used in combination with -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. In patients with severely impaired liver function the dose of felodipine should be low. The pharmacokinetics are not significantly affected in patients with impaired renal function.

4.3 Contraindications

- Pregnancy
- Hypersensitivity to felodipine or any of the excipients listed in section 6.1
- Decompensated heart failure
- Acute myocardial infarction
- Unstable angina pectoris
- Haemodynamically significant cardiac valvular obstruction
- Dynamic cardiac outflow obstruction

4.4 Special warnings and precautions for use

The efficacy and safety of felodipine in the treatment of hypertensive emergencies has not been studied.

Felodipine may cause significant hypotension with subsequent tachycardia.

This may lead to myocardial ischaemia in susceptible patients.

Felodipine is cleared by the liver. Consequently can higher therapeutic concentrations and response be expected in patients with clearly reduced liver function (see also section 4.2 Posology and method of administration).

Concomitant administration of drugs that strongly induce or inhibit CYP 3A4 enzymes result in extensively decreased or increased plasma levels of felodipine, respectively. Therefore, such combinations should be avoided (see section 4.5).

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Felodipine is metabolised in the liver by cytochrome P450 3A4 (CYP 3A4). Concomitant administration of substances which interfere with CYP3A4 enzyme system may affect plasma concentrations of felodipine.

Enzyme interactions
Enzyme inhibiting and enzyme inducing substances of cytochrome P450 isoenzyme 3A4 may exert an influence on the plasma level of felodipine.

Interactions leading to increased plasma concentration of felodipine CYP 3A4 enzyme inhibitors have been shown to cause an increase in
felodipine plasma concentrations. Felodipine Cmax and AUC increased 8-fold and 6-fold, respectively, when felodipine was co-administered with the strong

CYP3A4 inhibitor itraconazole. When felodipine and erythromycin were co- administered, the Cmax and AUC of felodipine were increased by about 2.5- fold. Cimetidine increased the felodipine Cmax and AUC by approximately 55%. The combination with strong CYP3A4 inhibitors should be avoided.

In case of clinically significant adverse events due to elevated felodipine exposure when combined with strong CYP 3A4 inhibitors, adjustment of felodipine dose and/or discontinuation of the CYP 3A4 inhibitor should be considered. Examples:
• Cimetidine
• Erythromycin
• Itraconazole
• Ketoconazole
• Anti HIV/protease inhibitors (e.g.ritonavir)
• Certain flavonoids present in grapefruit juice

Neofel XL 5 mg Prolonged Release Tablets should not be taken together with grapefruit juice.

<u>Interactions leading to decreased plasma concentration of felodipine</u>
Enzyme inducers of the cytochrome P450 3A4 system have been shown to
cause a decrease in plasma concentrations of felodipine. When felodipine was co-administered with carbamazepine, phenytoin or phenobarbital, the Cmax and AUC of felodipine were decreased by 82% and 96% respectively. The combination with strong CYP 3A4 inducers should be avoided.

In case of lack of efficacy due to decreased felodipine exposure when combined with potent inducers of CYP 3A4, adjustment of felodipine dose and/ or discontinuation of the CYP 3A4 inducer should be considered.
Examples:
• Phenytoin
• Carbamazepine
• Rifampicin
• Barbiturates
• Efavirenz
• Nevirapine
• Hypericum Perforatum (Saint John’s wort)

Additional interactions
Tacrolimus: Felodipine may increase the concentration of tacrolimus. When used together, the tacrolimus serum concentration should be followed and the tacrolimus dose may need to be adjusted.

Cyclosporin: Felodipine does not affect plasma concentrations of cyclosporin.

4.6 Fertility, pregnancy and lactation Pregnancy

Pregnancy

Felodipine should not be given during pregnancy.

In non-clinical reproductive toxicity studies there were foetal development effects, which are considered to be due to the pharmacological action of felodipine.

Breastfeeding

Felodipine has been detected in breast milk and due to insufficient data on potential effect on the infant, treatment is not recommended during breast-feeding.

Fertility

Data on fertility in patients are missing (see also section 5.3). In a non-clinical reproductive study in the rat, there were effects on foetal development but no effect on fertility at doses approximating to therapeutic.

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, ability to react may be impaired. Caution is recommended, especially at the start of treatment.

4.8 Undesirable effects

Felodipine can cause flushing, headache, palpitations, dizziness and fatigue. Most of these reactions are dose-dependent and appear at the start of treatment or after a dose increase. Should such reactions occur, they are usually transient and diminish with time.

Dose-dependent ankle swelling can occur in patients treated with felodipine. This results from precapillary vasodilatation and is not related to any generalised fluid retention.

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

Tabulated list of adverse reactions
The adverse reactions listed below have been identified from clinical trials and from Post Marketing Surveillance.

The following definitions of frequencies are used: Very common (>1/10); Common (>1/100, <1/10); Uncommon (>1/1,000, <1/100); Rare (>1/10,000, <1/1,000), Very rare (<1/10,000)

Table 1 Undesirable effects

System Organ Class	**Frequency**	**Adverse Drug Reaction**
Nervous system disorders	Common	Headache
	Uncommon	Dizziness, paraesthesia
Cardiac disorders	Uncommon	Tachycardia, palpitations
Vascular disorders	Common	Flush
	Uncommon	Hypotension
	Rare	Syncope
Gastrointestinal disorders	Uncommon	Nausea, abdominal pain
	Rare	Vomiting
	Very Rare	Gingival hyperplasia, gingivitis
Hepatobiliary disorders	Very rare	Increased liver enzymes
Skin and subcutaneous tissue disorders	Uncommon	Rash, pruritus
	Rare	Urticaria
	Very rare	Photosensitivity reactions,

		leucocytoclastic 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

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed on this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Symptoms
Overdosage may cause excessive peripheral vasodilatation with marked hypotension and sometimes bradycardia.

Management
If justified: activated charcoal. If necessary, gastric lavage when performed within one hour after ingestion.
If severe hypotension occurs, symptomatic treatment should be instituted. The patient should be placed supine with the legs elevated. In case of accompanying bradycardia, atropine 0.5-1 mg should be administered intravenously. 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 if the abovementioned measures are insufficient.

5.1 Pharmacodynamic properties

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

Mechanism of action

Felodipine is a vascular selective calcium antagonist, which lowers arterial blood pressure by decreasing peripheral vascular resistance. 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. Because there is no effect on venous smooth muscle or adrenergic vasomotor control, felodipine is not associated with orthostatic hypotension.

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

Pharmacodynamic effects

Felodipine is effective in all grades of hypertension. It can be used as monotherapy or in combination with other antihypertensive drugs, e.g. -adrenoreceptor 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.

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 and myocardial oxygen demand.

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 -receptor blockers in patients with stable angina pectoris.

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, generally 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 are positively correlated to the decrease in total peripheral resistance and blood pressure.

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 due to reduced tubular reabsorption of filtered sodium. Felodipine does not affect daily potassium excretion. The renal vascular resistance is decreased by felodipine. Felodipine does not influence urinary albumin excretion. In cyclosporintreated renal transplant recipients, felodipine reduces blood pressure and improves both the renal blood flow and the glomerular filtration rate. Felodipine may also improve early renal graft function.

<u>Clinical efficacy:</u>
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.

Paediatric population
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 2.5 mg (n=33), 5 mg (n=33) and 10 mg (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 (see section 4.2).

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.

5.2 Pharmacokinetic properties

Absorption:
Felodipine is administered as extended-release tablets, from which it is completely absorbed from the gastrointestinal tract. The systemic availability of felodipine is approximately 15% in man and is independent of dose in the therapeutic dose range. The extended-release tablets the absorption phase is prolonged. This results in even felodipine plasma concentrations within the therapeutic range for 24 hours. Maximum blood plasma levels (t_{max}) are achieved with the prolonged release form after 3 to 5 hours. The rate, but not the extent, of absorption of felodipine is increased when taken simultaneously with food with a high fat content.

Distribution:

The plasma protein binding of felodipine is approximately 99%. It is bound predominantly to the albumin fraction.Volume of distribution at steady state is 10 L/kg.

Biotransformation:
Felodipine is extensively metabolised by the liver by cytochrome P450 3A4 (CYP 3A4) and all identified metabolites are inactive. Felodipine is a high clearance medicinal product with an average blood clearance of 1200ml/min. There is no significant accumulation during long-term treatment.

Elderly patients and patients with reduced liver function have an average higher plasma concentration of felodipine than younger patients. The pharmacokinetics of felodipine are not changed in patients with renal impairment, including those treated with haemodialysis.

Elimination:
The average half-life of felodipine in the elimination phase is 25 hours and the steady state is reached after 5 days. There is no risk of accumulation during long-term treatment. 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.

Linearity/non-linearity:
Plasma concentrations are directly proportional to dose with therapeutic range 2.5-10mg.

Paediatric population:
In a single dose (felodipine prolonged release 5 mg) 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, C_{max} or half-life of felodipine.

5.3 Preclinical safety data

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), Ferric oxide red (E172), Titanium dioxide (E171), Talc, Propylene glycol.

6.2 Incompatibilities

None stated.

6.3 Shelf life

48 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

None stated.

7 MARKETING AUTHORISATION HOLDER

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England, TN23 1FB

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