Felodipine Versant®-XR

10 mg Extended-Release Tablet
CALCIUM CHANNEL BLOCKER / ANTIHYPERTENSIVE

FORMULATION

Each extended-release tablet contains:
Felodipine..... 10 mg

PRODUCT DESCRIPTIONS

10 mg Extended-release Tablet: Red, round, biconvex, film-coated tablet, 11/32" in diameter, plain on both sides

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Felodipine is a member of the dihydropyridine class of calcium channel antagonists (calcium channel blockers). Felodipine's predominant pharmacodynamic feature is its pronounced vascular versus myocardial selectivity. Smooth muscles in arterial resistance vessels are particularly sensitive to felodipine. It inhibits electrical and contractile activity of vascular smooth muscle cells via an effect on the calcium channels in cell membranes.

Felodipine's effect on blood pressure is a result of a dose-related decrease of peripheral vascular resistance, with a modest reflex increase in heart rate. With the exception of a mild diuretic effect seen in animals and man, felodipine's effects are due to its effects on 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. It is not associated with orthostatic hypotension since there is no effect on venous smooth muscle or adrenergic vasomotor control.

Felodipine has a mild natriuretic/diuretic effect due to decreased tubular reabsorption of filtered sodium. This counteracts the salt and water retention observed with other vasodilators. It does not affect daily potassium excretion. It decreases renal vascular resistance while glomerular filtration rate is unchanged. The glomerular filtration rate may increase in patients with impaired renal function. Felodipine decreases blood pressure and improves renal blood flow and glomerular filtration rate in renal transplant patients. It may also improve early renal graft function.

Felodipine is effective in all grades of hypertension. It decreases both systolic and diastolic blood pressure and may be used in isolated systolic hypertension. It may be used as monotherapy or in combination with other antihypertensive agents to achieve increased antihypertensive effect. Felodipine maintains its antihypertensive effect during concomitant therapy with nonsteroidal anti-inflammatory drugs (NSAIDs).

Felodipine has anti-anginal and anti-ischemic effects due to improved myocardial oxygen supply-demand balance. Due to dilatation of epicardial arteries and arterioles, felodipine decreases coronary vascular resistance and increases coronary blood flow and myocardial oxygen supply. Felodipine effectively counteracts coronary vasospasm. It decreases systemic blood pressure resulting in decreased left ventricular afterload and myocardial oxygen demand.

Felodipine favorably affects left ventricular function, as assessed by ejection fraction and stroke volume, and does not cause neurohormonal activation. However, felodipine does not seem to affect survival. Thus, it may be used in patients with hypertension or angina pectoris who also have impaired left ventricular function. Felodipine treatment is associated with significant regression of pre-existing left ventricular hypertrophy.

Felodipine improves exercise tolerance and decreases anginal attacks in patients with stable effort-induced angina pectoris. It decreases symptomatic and silent myocardial ischemia in patients with vasospastic angina. Felodipine may be used as monotherapy or in combination with beta-blockers in patients with stable angina pectoris.

Felodipine is effective and well tolerated in adult patients irrespective of age and race and is also well tolerated in the presence of concomitant diseases such as congestive heart failure, asthma and other obstructive pulmonary disease, impaired renal function, diabetes mellitus, gout, hyperlipidemia, Raynaud's disease, and in renal transplant recipients. Felodipine has no effect on blood glucose levels or lipid profile.

PHARMACOKINETICS

Felodipine, administered as extended-release tablets, is completely absorbed in the gastrointestinal tract. The systemic bioavailability of felodipine is about 15% and is independent of dose in the therapeutic range. Mean peak concentrations (C_{max}) are reached in 2.5 to 5 hours after oral administration of the extended-release tablet. Felodipine is about 99% bound to plasma proteins, mainly to albumin.

After multiple oral administration of a 10 mg extended-release tablet once daily for six days to healthy volunteers, mean peak felodipine plasma concentration (C_{max}) at steady state was 2.712 ± 1.363 ng/mL achieved in 3.563 ± 1.378 hours (T_{max}). The area under the plasma concentration-time curve (AUC) at steady state was 37.18 ± 14.188 ng•hr/mL.

After oral administration of felodipine to hypertensive patients, mean peak plasma concentrations at steady state are about 20% higher than after a single dose. Blood pressure response is correlated with plasma felodipine concentration.

Felodipine's bioavailability is influenced by the presence of food. When administered either with a high fat or high carbohydrate diet, C_{max} is increased by about 60%; AUC is unchanged. When felodipine was administered after a light meal (orange juice, toast, and cereal), however, there was no effect on felodipine's pharmacokinetics. Felodipine's bioavailability was increased approximately two-fold when taken with grapefruit juice. Orange juice does not appear to modify felodipine's kinetics. A similar finding has been seen with other dihydropyridine calcium antagonists, but to a lesser extent than that seen with felodipine.

Felodipine's systemic plasma clearance in young healthy subjects is about 0.8 L/min and the apparent volume of distribution is about 10 L/kg.

Felodipine is extensively metabolized in the liver by cytochrome P450 3A4 (CYP3A4) and all identified metabolites are inactive. Concurrent administration with CYP3A4 inhibitors may result in increased plasma felodipine levels, either due to increased bioavailability or decreased metabolism. Increases in concentration may lead to lower blood pressure and increased heart rate.

Felodipine is a high clearance agent with an average blood clearance of 1200 mL/min. Felodipine's average half-life in the terminal phase is 24 hours. There is no significant 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 feces. Less than 0.5% of a dose is recovered unchanged in urine.

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

INDICATIONS

- Hypertension, either alone or with other antihypertensive agents
- Chronic stable angina pectoris, either alone or with other antianginal agents

DOSAGE AND ADMINISTRATION

General Dosing Recommendations:
- Dosing must be individualized and adjusted according to patient response.
- Felodipine extended-release tablet should be swallowed whole with a glass of water. Do not divide, chew or crush the extended-release tablet since this may cause inappropriate release and absorption of the drug. Mild gingival hyperplasia (gum swelling) has been observed in patients taking felodipine. Good dental hygiene decreases its incidence and severity.
- Should be taken in the morning, either without food or with a light meal not rich in fat or carbohydrate
- May be used together with beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, or diuretics. The effects on blood pressure are likely to be additive and combination therapy will enhance the antihypertensive effect. Care should be taken to avoid hypotension.

INDICATIONS	RECOMMENDED ORAL FELODIPINE DOSE
Hypertension	***Usual Initial Adult Dose:*** 5 mg once daily - Adjust dosage according to patient's response. - Dose may be decreased to 2.5 mg once daily, increased to 10 mg once daily, or another antihypertensive agent added. - Dose adjustments should occur generally at intervals of not less than 2 weeks. ***Usual Maintenance Dose:*** 5 to 10 mg once daily ***Recommended Dose Range:*** 2.5 to 10 mg once daily ***Initial Dose in Elderly (>65 years old):*** 2.5 mg once daily - Closely monitor blood pressure during dosage adjustment
Angina pectoris	***Usual Initial Adult Dose:*** 5 mg once daily - If needed, dose may be increased to 10 mg once daily. ***Initial Dose in Elderly:*** 5 mg once daily - Consider alternative treatment if the 5 mg dose is not well tolerated.
	Or, as prescribed by a physician.

Dosage in Hepatic Impairment: Orally, 2.5 mg once daily
- Closely monitor blood pressure during dosage adjustment

CONTRAINDICATIONS

- Hypersensitivity to felodipine or any component of the product
- History of previous allergic reaction to other dihydropyridine calcium channel blockers because of theoretical risk of cross-reactivity
- Clinically significant aortic stenosis
- Uncompensated heart failure
- Acute myocardial infarction
- Unstable angina pectoris
- As with other calcium channel blockers, felodipine should be discontinued in patients who develop cardiogenic shock
- Pregnancy

WARNINGS AND PRECAUTIONS

Hypotension: Felodipine, like other calcium antagonists, may occasionally precipitate significant hypotension and, rarely, syncope. It may lead to reflex tachycardia which, in susceptible individuals, may precipitate angina pectoris.

Heart Failure: Although acute hemodynamic studies in a small number of patients with NYHA Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects, the safety of felodipine in patients with heart failure has not been established. Thus, exercise caution when using felodipine in patients with heart failure or compromised ventricular function, particularly in combination with a beta-blocker.

Peripheral Edema: The most common adverse effect associated with felodipine in clinical studies is peripheral edema (generally mild and not associated with generalized fluid retention) (see **Clinical Pharmacology, Pharmacodynamics**). The incidence of peripheral edema was both dose and age dependent. This adverse effect generally occurs within 2 to 3 weeks after initiation of felodipine treatment.

INTERACTIONS WITH OTHER MEDICAMENTS

Beta-blockers (e.g., metoprolol): Increased AUC and C_{max} of metoprolol

CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, erythromycin, cimetidine): May increase plasma felodipine levels (see **Clinical Pharmacology, Pharmacokinetics**)

Anticonvulsants and other enzyme inducers (e.g., phenytoin, carbamazepine, phenobarbital): May decrease plasma felodipine concentration

Digoxin: The pharmacokinetics of digoxin in patients with heart failure were not significantly altered

Tacrolimus: May increase tacrolimus blood concentration. When coadministered with felodipine, the tacrolimus blood concentration should be followed and the tacrolimus dose may need to be adjusted.

Grapefruit Juice: Taking grapefruit juice together with felodipine 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. Thus, grapefruit juice should not be taken with felodipine.

Others:
- There were no clinically significant interactions when felodipine was given concomitantly with indomethacin or spironolactone in healthy subjects.
- Felodipine does not affect plasma ciclosporin concentrations
- Felodipine does not appear to affect the unbound fraction of other extensively plasma protein bound drugs such as warfarin.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy: **Pregnancy Category C.** There are no adequate or well-controlled studies in pregnant women. Felodipine should not be given during pregnancy.

Teratogenic Effects: In animal studies, pregnant rabbits given felodipine 0.46, 1.2, 2.3, and 4.6 mg/kg/day (0.8 to 8 times** the maximum recommended human dose on a mg/m^2 basis) showed digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. The frequency and severity of the changes appeared dose related and were observed even at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Similar fetal anomalies were not observed in rats given felodipine.

In cynomolgus monkeys, no reduction in size of the terminal phalanges was reported, but an abnormal position of the distal phalanges was seen in about 40% of the fetuses.

Nonteratogenic Effects: A prolongation of parturition with difficult labor and an increased frequency of fetal and early postnatal deaths were observed in rats given felodipine 9.6 mg/kg/day (8 times** the maximum human dose on a mg/m^2 basis) and above.

** Based on patient weight of 50 kg
(2.1 times the maximum human dose on a mg/m^2 basis). This effect occurred only in pregnant rabbits and regressed during lactation.

Significant enlargement of the mammary glands, in excess of the normal enlargement for pregnant rabbits, was observed with doses greater than or equal to 1.2 mg/kg/day.

Lactation: Felodipine has been detected in breast milk, but it is unknown whether it has harmful effects on the newborn. A decision should therefore be made whether to discontinue breastfeeding or to discontinue felodipine, taking into consideration the importance of the drug to the mother.

Elderly: Clinical studies on felodipine did not include sufficient numbers of subjects 65 years and older to determine whether they respond differently from younger subjects. General caution must be observed in dosing for an elderly since felodipine plasma levels appear to be higher in older patients.

Children: The safety and efficacy of felodipine in children have not been established.

UNDESIRABLE EFFECTS

Body as a Whole: Peripheral edema, asthenia, warm sensation, chest pain, edema (facial, ankle), flu-like illness, fatigue, fever

Cardiovascular: Palpitation, myocardial infarction, hypotension, syncope, angina pectoris, arrhythmia, tachycardia, premature beats

Endocrine/Metabolic: Gynecomastia, increased liver enzymes/alanine aminotransferase (ALT)

Gastrointestinal: Nausea, dyspepsia, constipation, abdominal pain, diarrhea, vomiting, dry mouth, flatulence, acid regurgitation, mild gingival hyperplasia, gingivitis

Hematologic: Anemia, epistaxis

Musculoskeletal: Arthralgia, myalgia, muscle cramps, pain (back, arm, knee, hip, leg, foot), ankle edema

Nervous System: Headache, dizziness, paresthesia, insomnia, depression, anxiety disorders, irritability, nervousness, somnolence, decreased libido, impotence, sexual dysfunction

Respiratory: Upper respiratory infection, cough, rhinorrhea, sneezing, dyspnea, pharyngitis, bronchitis, influenza, sinusitis, respiratory infection

Skin: Flushing, rash, pruritus, contusion, erythema, photosensitivity reactions, leukocytoclastic vasculitis, hypersensitivity reactions (e.g., angioedema, urticaria)

Special Senses: Vision disturbances

Urogenital: Urinary frequency/pollakisuria, urinary urgency, dysuria, polyuria

OVERDOSE AND TREATMENT

Symptoms of felodipine overdose include peripheral vasodilatation with marked hypotension and bradycardia.

Activated charcoal, induction of vomiting or gastric lavage, if necessary.

Institute symptomatic treatment if severe hypotension occurs. Place the patient in supine position with legs elevated. In case of bradycardia, administer intravenous atropine 0.5 to 1 mg IV. If this is not sufficient, increase plasma volume by infusion of glucose, saline or dextran. Sympathomimetic agents with predominant effect on the α_1-adrenoceptor may be given if the above mentioned measures are insufficient.

It has not been established whether felodipine can be removed by hemodialysis.

STORAGE CONDITION

Store at temperatures not exceeding 30°C.
Keep the product out of sight and reach of children.

AVAILABILITY

Felodipine (Versant®-XR) 10 mg Extended-Release Tablet, in strip foil x 4s (box of 100s)

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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