Felodipine Versant®-XR

5 mg Extended-Release Tablet

Calcium Channel Blocker / Antihypertensive

FORMULATION

Each extended-release tablet contains :
Felodipine .....5 mg

PRODUCT DESCRIPTION

Pink, round, biconvex, film-coated tablet, 11 mm 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 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 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 identical 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. Tha pharmacokinetics of felodipine is not changed in patients with renal impairment, including those treated with hemodialysis.

Bioequivalence Study

Felodipine (Versant-XR)10 mg extended-release tablet was shown to be bioequivalent to the reference product (innovator) in adults under fed conditions. The following are important pharmacokinetic parameters of felodipine in adult volunteers who received extended-release felodipine (Versant-XR) 10 mg tablet (one 10 mg tablet given once a day for six days) under fed conditions at steady state:

Pharmacokinetic Parameters	Felodipine 10 mg Extended-relea Tablet given once a day for six days	90% Confidence Interval
$T_{max,ss}$(hr)	3.563 ± 1.378	
$C_{max,ss}$ ± S.D. (ng/mL)	2.712 ± 1.363	81.50 - 108.39
$C_{ave,ss}$± SD. (ng/mL)	1.549 ± 0.591	98.15 - 115.29
$AUC_{0\rightarrow\tau,ss}$ ± S.D. (hr-ng/mL)	37.180 ± 14.188	98.15 - 115.19

$T_{max,ss}$ = time the drug reached its maximum concentration in blood at steady state
$C_{ave,ss}$ = average plasma concentration at steady state
$C_{max,ss}$ = maximum plasma concentration at steady state
$AUC_{0\rightarrow\tau,ss}$ =area under the concentration-time curve at steady state for one dosing interval

INDICATIONS

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

DOSAGE AND MODE OF 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 a day ⇨Adjust dosage according to patient's response. ⇨Dose may be decreased to 2.5 mg once a day, increased to 10 mg once a day, 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 a day Recommended Dose Range: 2.5 to 10 mg once a day Initial Dose in Elderly (>65 years old): 2.5 mg once a day ⇨Closely monitor blood pressure during dosage adjustment
Angina pectoris	Usual Initial Adult Dose: 5 mg once a day ⇨If needed, dose may be increased to 10 mg once day. Initial Dose in Elderly: 5 mg once a day ⇨Consider alternative treatment if the 5 mg dose is not well tolerated.
	Or, as prescribed by the physician.

Dosage in Patients with Hepatic Impairment: Orally, 2.5 mg once a day
⇨Closely monitor blood pressure during dosage adjustment

Dosage in Patients with Renal Impairment: No dosage adjustment is necessary

CONTRAINDICATIONS

- Hypersensitivity to felodipine, other dihydropyridines, or any component of the product
- Uncompensated heart failure
- Acute myocardial infarction
- Unstable angina pectoris
- Hemodynamically significant cardiac valvular obstruction
- Dynamic cardiac outflow obstruction
- 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.

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

Effects on Ability to Drive and Use Machines
Felodipine has minor or moderate influence on the ability to drive and use machines. If patients experience headache, nausea, dizziness or fatigue, their ability to react may be impaired. Patients should exercise caution particularly at the start of 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, ritonavir): May increase plasma felodipine levels (see Clinical Pharmacology, Pharmacokinetics)
Anticonvulsants and other CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, rifampicin, efavirenz, nevirapine, St. John's Wort): 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: Certain flavonoids present in grapefruit juice may increase plasma felodipine concentration. 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 and well-controlled studies in pregnant women. Felodipine should not be given during pregnancy.

In animal studies, after administration of felodipine to pregnant dams during the period of organogenesis, morphological abnormalities of the phalanges were observed in the rabbit fetus.

In rats, oral doses of felodipine 3.8 mg/kg or higher, caused prolongation of labor.

Lactation: Felodipine has been detected in human milk. However, there is insufficient data on its potential effect to the infant. 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 pediatric patients have not been established.

UNDESIRABLE EFFECTS

The most frequently reported adverse effects with felodipine include peripheral edema and headache. Felodipine may also cause flushing, palpitations, dizziness, and fatigue. Most of these adverse effects are dose- dependent and occur during initiation of treatment or after an increase in dose. These adverse effects are usually transient and diminish with time.

Blood and lymphatic system disorders: Anemia
Immune system disorders: Hypersensitivity reactions (e.g., angioedema, fever)
Psychiatric disorders: Anxiety disorders, decreased libido, depression, insomnia, irritability, nervousness
Nervous system disorders: Paresthesia, somnolence, stroke, vertigo
Eye disorders: Visual disturbances
Cardiac disorders: Angina pectoris, arrhythmia, bradycardia, chest pain, myocardial infarction, premature beats, second degree atrio-ventricular block (rare), tachycardia
Vascular disorders: Hypotension, syncope
Respiratory, thoracic and mediastinal disorders: Bronchitis, cough, dyspnea, epistaxis, influenza, pharyngitis, rhinorrhea, sinusitis, sneezing, upper respiratory infection/ respiratory infection
Gastrointestinal disorders: Abdominal pain, acid regurgitation, constipation, diarrhea, dry mouth, dyspepsia, flatulence, gingival hyperplasia, gingivitis, nausea, vomiting
Hepatobiliary disorders: Increased liver enzymes [e.g., alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST)]
Skin and subcutaneous tissue disorders: Erythema, leukocytoclastic vasculitis, photosensitivity reactions, pruritus, rash, urticaria
Musculoskeletal and connective tissue disorders: Arthralgia, muscle cramps, myalgia, pain (back, arm, knee, hip, leg, foot)
Renal and urinary disorders: Dysuria, pollakiuria/urinary frequency, polyuria, urinary urgency
Reproductive system and breast disorders: Gynecomastia, impotence/sexual dysfunction
General disorders and administration site conditions: Asthenia, cold sensation, edema (facial, ankle), flu-like illness, warm sensation
Investigations: Increased thrombocyte count
Injury, poisoning and procedural complications: Contusion

OVERDOSE AND TREATMENT

Symptoms of felodipine overdose include peripheral vasodilation 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 CONDITIONS

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

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

AVAILABILITY
Felodipine (VERSANT-XR) 5 mg Extended-Release Tablet, in blister pack x 10's (box of 100's).

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph.
By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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Reg. IPOPHIL

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