PRODUCT MONOGRAPH

RENEDIL®
(Felodipine)

Extended Release Tablets
2.5 mg, 5 mg, 10 mg

Antihypertensive Agent

sanofi-aventis Canada Inc.
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NAME OF DRUG

RENEDIL®

(felodipine)

Extended Release Tablets

(2.5, 5 and 10 mg)

THERAPEUTIC CLASSIFICATION

Antihypertensive Agent

ACTION AND CLINICAL PHARMACOLOGY

RENEDIL (felodipine) is a calcium ion influx inhibitor (calcium channel blocker).

Felodipine is a member of the dihydropyridine class of calcium channel blockers.

Mechanism of Action

The therapeutic effect of this group of drugs is believed to be related to their specific cellular action of selectively inhibiting transmembrane influx of calcium ions into cardiac muscle and vascular smooth muscle. The contractile processes of these tissues are dependent upon the movement of extracellular calcium into the cells through specific ion channels. Felodipine blocks transmembrane influx of calcium through the slow channel without affecting to any significant degree the transmembrane influx of sodium through the fast channel. This results in a reduction of free calcium ions available within cells of the above tissues.

Felodipine does not alter total serum calcium. *In vitro* studies show that the effects of felodipine on contractile mechanisms are selective, with greater effects on vascular smooth muscle than on cardiac muscle. Negative inotropic effects can be detected *in vitro*, but such effects have not been seen in intact animals.

The effect of felodipine on blood pressure in man is principally a consequence of a dose-related decrease in peripheral vascular resistance, with a modest reflex increase in heart rate (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacodynamics).

Pharmacokinetics

Felodipine is completely absorbed from the gastrointestinal tract after oral administration. Due to rapid biotransformation of felodipine during its first pass through the portal circulation the systemic availability is approximately 15% and is independent of the dose in the range of 5-20 mg per day. The plasma protein binding of felodipine is approximately 99%. It is bound predominately to the albumin fraction.

Felodipine is extensively metabolized in the liver, predominantly by cytochrome P-450 CYP 3A4. After 72 hours, approximately 70% of a given dose is excreted as metabolites in the urine and 10% is secreted in the feces. Less than 0.5% of a dose is recovered unchanged in the urine. Six metabolites, which account for 23% of the oral dose, have been identified: none has significant vasodilating activity.

Felodipine has been observed to have a mean blood clearance of 914 ± 355 mL/min in hypertensive patients, 606 ± 245 mL/min in elderly hypertensive patients and 1337 ± 413 mL/min in young healthy volunteers. Its mean terminal half-life was 24.5 ± 7.0 hours in hypertensive patients, 27.5 ± 8.4 hours in elderly hypertensive patients and 14.1 ± 5.6 hours in young healthy volunteers.

The extended release formulation prolongs the absorption phase of felodipine resulting in an increased time to reach peak plasma concentrations (t_{max}), and a reduced maximum plasma concentration (C_{max}). The mean t_{max} ranges from 2.5 to 5 hours. The area under the plasma concentration versus time curve and C_{max} are linearly related to the dose in the 10 to 40 mg range. Following administration of RENEDIL to hypertensive patients, mean C_{max} at steady state is approximately 20% higher after multiple doses than after a single dose. No increase in the AUC is found during multiple dosing. The inter-individual variation in C_{max} and AUC after repeated dosing is approximately threefold and indicates a need for individualized dosing.

The bioavailability of RENEDIL is not influenced by the presence of food in the gastrointestinal tract. However, the peak plasma concentration of felodipine (C_{max}) is significantly increased by 1.5 to 2 fold when RENEDIL is taken after a high fat or high carbohydrate meal versus fasting. Because the effects of felodipine on blood pressure are related to plasma levels, this increase in C_{max} may cause a clinically significant fall in blood pressure. Therefore, RENEDIL should not be administered with meals rich in carbohydrate or fat. However, the absorption characteristics of felodipine are not affected when RENEDIL is administered with a light meal low in fat and carbohydrates (i.e. 2 slices of toast with cheese, 150 mL milk with cornflakes, and 150 mL orange juice) (See DOSAGE AND ADMINISTRATION).

Studies in healthy male volunteers showed significant alterations in the pharmacokinetics of felodipine when felodipine was administered concomitantly with grapefruit juice. Following the administration of a single dose of plain felodipine 5 mg tablets with 200 mL grapefruit juice or 200 mL water AUC and C_{max} of felodipine increased about threefold as compared to administration with water. When felodipine extended release tablets were administered as RENEDIL 10 mg with 250 mL grapefruit juice, felodipine AUC and C_{max} values doubled as compared to those observed with water. When grapefruit juice was taken for up to 24 hours prior to RENEDIL administration, a significant pharmacokinetic interaction was observed (see PRECAUTIONS - Interaction with Grapefruit Juice).

Plasma concentrations of felodipine, after a single dose and at steady state, increase with age. Mean clearance of felodipine in elderly hypertensives (mean age 74 years) was only 45 percent of that in young volunteers (mean age 26 years). At steady state mean AUC for young patients was 39 percent of that for the elderly patients.

In patients with hepatic disease, the clearance of felodipine was reduced to about 60 percent of that seen in normal young volunteers.

Renal impairment does not alter the plasma concentration profile of felodipine. Although higher concentrations of the metabolites are present in the plasma due to decreased urinary excretion, these are hemodynamically inactive.

Animal studies have demonstrated that felodipine crosses the blood-brain barrier and the placenta.

Pharmacodynamics

The acute hemodynamic effect of felodipine is a reduction in total peripheral resistance which leads to a decrease in blood pressure associated with a modest reflex increase in heart rate. This reflex increase in heart rate frequently occurs during the first week of therapy and generally attenuates over time. Heart rate increases of 5-10 beats per minute may be seen during chronic administration. The effect on the heart rate is inhibited by beta-blocking agents.

Following administration of RENEDIL a reduction in blood pressure generally occurs within two to five hours.

During chronic administration, substantial blood pressure control lasts for approximately 24 hours; reductions in diastolic blood pressure at trough plasma levels were 40-60 percent of those at peak plasma levels. The antihypertensive effect is dose-dependent and correlates with the plasma concentration of felodipine.

Felodipine in therapeutic doses has no effect on conduction in the conducting system of the heart and no effect on the A-V nodal refractoriness. No direct additional effects to those registered after beta-blockade are observed when RENEDIL is given concomitantly.

Renal vascular resistance is decreased by felodipine while glomerular filtration rate remains unchanged. Mild diuresis, natriuresis and kaliuresis have been observed during the first week of therapy. No significant effects on serum electrolytes have been observed during short and long-term therapy. No general salt and water retention occurs during long-term therapy. In clinical trials increases in noradrenaline plasma levels have been observed.

INDICATIONS AND CLINICAL USE

RENEDIL (felodipine) is indicated in the treatment of mild to moderate essential hypertension. RENEDIL should normally be used in those patients in whom treatment with a diuretic or a beta blocker was found ineffective or has been associated with unacceptable adverse effects.

RENEDIL can be tried as an initial agent in those patients in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

Combination of RENEDIL with a thiazide diuretic or a beta-blocker has been found to be compatible and showed an additive antihypertensive effect. Safety and efficacy of concurrent use of RENEDIL with other antihypertensive agents has not been established.

CONTRAINDICATIONS

RENEDIL (felodipine) is contraindicated in:

1. Patients with a known hypersensitivity to felodipine or other components of RENEDIL.
2. Patients with a known hypersensitivity to other dihydropyridines.
3. In women of childbearing potential, in pregnancy, and during lactation. Fetal malformations and adverse effects on pregnancy have been reported in animals.

Teratogenic Effects

Studies in pregnant rabbits administered doses of 0.46, 1.2, 2.3 and 4.6 mg/kg/day (from 0.4 to 4 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 noted even at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class. Similar fetal anomalies were not observed in rats given felodipine.

In a teratology study in cynomolgus monkeys, no reduction in the size of the terminal phalanges was observed but an abnormal position of the distal phalanges was noted in about 40 percent of the fetuses.

Non-Teratogenic Effects

In a study on fertility and general reproductive performance in rats, prolongation of parturition with difficult labour and an increased frequency of fetal and early postnatal deaths were observed in the groups treated with doses of 9.6 mg/kg/day and above.

Significant enlargement of the mammary glands in excess of the normal enlargement for pregnant rabbits was found with doses greater than or equal to 1.2 mg/kg/day. This effect occurred only in pregnant rabbits and regressed during lactation. Similar changes in the mammary glands were not observed in rats or monkeys.

WARNINGS

Congestive Heart Failure

The safety and efficacy of RENEDIL (felodipine) in patients with heart failure has not been established. Caution should, therefore, be exercised when using RENEDIL in hypertensive patients with compromised ventricular function, particularly in combination with a beta-blocker. Acute hemodynamic studies in a small number of patients with New York Heart Association Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects.

Hypotension, Myocardial Ischemia

RENEDIL may, occasionally, precipitate symptomatic hypotension and rarely syncope. It may lead to reflex tachycardia which, particularly in patients with severe obstructive coronary artery disease, may result in myocardial ischemia. Careful monitoring of blood pressure during the initial administration and titration of felodipine is recommended.

Care should be taken to avoid hypotension especially in patients with a history of cerebrovascular insufficiency, and in those taking medications known to lower blood pressure.

Beta-Blocker Withdrawal

RENEDIL gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be a gradual reduction of the dose of beta-blockers.

Outflow Obstruction

RENEDIL should be used with caution in the presence of fixed left ventricular outflow obstruction.

Dermatologic Lesions

Along with leucocytoclastic vasculitis, other dermatologic events have been observed. These include rash and flush. All cases of dermatologic lesions should be carefully diagnosed and monitored.

PRECAUTIONS

Peripheral Edema

Mild to moderate peripheral edema was the most common adverse event in the clinical trials. The incidence of peripheral edema was dose-dependent. Frequency of peripheral edema ranged from about 10 percent in patients under 50 years of age taking 5 mg daily to about 30 percent in those over 60 years of age taking 20 mg daily. This adverse effect generally occurs within 2-3 weeks of the initiation of treatment. Care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Use in Elderly Patients

Patients over 65 years of age may have elevated plasma concentrations of felodipine and, therefore, may require lower doses of RENEDIL (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics). These patients should have their blood pressure monitored closely during initial administration and after dosage adjustment of RENEDIL. A dosage of 10 mg daily should not be exceeded (see DOSAGE AND ADMINISTRATION - Use in the Elderly).

Use in Patients with Impaired Liver Function

Patients with impaired liver function may have elevated plasma concentrations of felodipine and, therefore, may require lower doses of RENEDIL (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics). These patients should have their blood pressure monitored closely during initial administration and after dosage adjustment of RENEDIL. A dosage of 10 mg daily should not be exceeded (see DOSAGE AND ADMINISTRATION - Use in Patients with Impaired Liver Function).

Gingival Hyperplasia

RENEDIL can induce gingival enlargement in patients with pronounced gingivitis and parodontitis. However, such changes may be reversed by measures of good oral hygiene and mechanical debridement of the teeth. In very rare instances, RENEDIL has also caused gingivitis.

Pregnancy and Lactation

See CONTRAINDICATIONS.

Use in Children

RENEDIL is not recommended in children since the safety and efficacy in children have not been established.

Interaction with Grapefruit Juice

Published data show that through inhibition of cytochrome P-450, grapefruit juice can increase plasma levels and augment pharmacodynamic effects of dihydropyridine calcium channel blockers. In view of the absolute bioavailability of RENEDIL, the potential for a significant increase in pharmacodynamic effects exists (see ACTION AND CLINICAL PHARMACOLOGY- Pharmacokinetics). Therefore, consumption of grapefruit juice prior to or during treatment with RENEDIL should be avoided.

Drug Interactions

As with all drugs, care should be exercised when treating patients with multiple medications. Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P-450 system, mainly via the CYP 3A4 isoenzyme. Coadminisration of felodipine with other drugs which follow the same route of biotransformation may result in altered bioavailability of felodipine or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered felodipine to maintain optimum therapeutic blood levels.

Drugs known to be inhibitors of the cytochrome P-450 system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, warfarin.

Drugs known to be inducers of the cytochrome P-450 system include: phenobarbital, phenytoin, rifampin.

Drugs known to be biotransformed via P-450 include: benzodiazepines, flecainide, imipramine, propafenone,

terfenadine, theophylline.

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

Cytochome P-450 Enzyme Inhibitors

Cimetidine

In healthy volunteers pharmacokinetic studies showed an approximately 50 percent increase in the area under the plasma concentration time curve (AUC) as well as the C_{max} of felodipine when given concomitantly with cimetidine. It is anticipated that a clinically significant interaction may occur in some hypertensive patients. Therefore, it is recommended that low doses of RENEDIL be used when given concomitantly with cimetidine.

Erythromycin

Concomitant treatment with erythromycin has been shown to cause an increase in felodipine plasma levels.

Cytochrome P-450 Enzyme Inducers

Phenytoin, Carbamazepine and Phenobarbital

In a phamacokinetic study maximum plasma concentrations of felodipine were considerably lower in epileptic patients on long term anticonvulsant therapy (phenytoin, carbamazepine, phenobarbital) than in healthy volunteers. The mean area under the felodipine plasma concentration-time curve was also reduced in epileptic patients to approximately 6% of that observed in healthy volunteers. Since a clinically significant interaction may be anticipated, alternative antihypertensive therapy should be considered in these patients.

Alcohol

Alcohol may enhance the hemodynamic effects of felodipine.

Beta-Adrenoceptor Blocking Agents

A pharmacokinetic study of felodipine in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of felodipine. The AUC and C_{max} of metoprolol, however, were increased approximately 31 and 36 percent, respectively. In controlled clinical trials, however, beta-blockers including metoprolol were concurrently administered with felodipine and were well tolerated.

Digoxin

When given concomitantly with felodipine as conventional tablets the peak plasma concentration of digoxin was significantly increased. With the extended release formulation of felodipine there was no significant change in peak plasma levels or AUC of digoxin.

Other Concomitant Therapy

In healthy subjects there were no clinically significant interactions when felodipine was given concomitantly with indomethacin or spironolactone.

ADVERSE REACTIONS

In 861 patients with essential hypertension treated once daily with 2.5 to 10 mg RENEDIL (felodipine) as monotherapy in controlled clinical trials, the most common clinical adverse events were peripheral edema and headache.

Adverse events that occurred with an incidence of 1.5% or greater at any of the recommended doses of 2.5 mg to 10 mg once a day, without regard to causality, are listed by dose in Table 1 below. These events are reported from controlled clinical trials with patients who were randomized to either a fixed dose of RENEDIL or titrated from an initial dose of 2.5 mg or 5 mg once a day. **A dose of 20 mg once a day has been evaluated in some clinical studies. Although the antihypertensive effect of RENEDIL is increased at 20 mg once a day, there is a disproportionate increase in adverse events, especially those associated with vasodilatory effects** (see DOSAGE AND ADMINISTRATION).

Table 1. Percent of patients with adverse events in controlled trials of RENEDIL (N=861)* as monotherapy without regard to causality (incidence of discontinuations shown in parentheses).

Body System Adverse Events	Placebo n=334	2.5 mg n=255	5mg n=581	10 mg n=408
Body as a Whole				
Peripheral Edema	3.3 (0.0)	2.0 (0.0)	8.8 (2.2)	17.4 (2.5)
Asthenia	3.3 (0.0)	3.9 (0.0)	3.3 (0.0)	2.2 (0.0)
Cardiovascular				
Palpitation	2.4 (0.0)	0.4 (0.0)	1.4 (0.3)	2.5 (0.5)
Warm Sensation/Flushing	0.9 (0.3)	3.9 (0.0)	6.2 (0.9)	8.4 (1.2)
Digestive				
Nausea	1.5 (0.9)	1.2 (0.0)	1.7 (0.3)	1.0 (0.7)
Dyspepsia	1.2 (0.0)	3.9 (0.0)	0.7 (0.0)	0.5 (0.0)
Constipation	0.9 (0.0)	1.2 (0.0)	0.3 (0.0)	1.5 (0.2)
Nervous				
Headache	10.2 (0.9)	10.6 (0.4)	11.0 (1.7)	14.7 (2.0)
Dizziness	2.7 (0.3)	2.7 (0.0)	3.6 (0.5)	3.7 (0.5)
Paresthesia	1.5 (0.3)	1.6 (0.0)	1.2 (0.0)	1.2 (0.2)
Respiratory				
Upper Respiratory Infection	1.8 (0.0)	3.9 (0.0)	1.9 (0.0)	0.7 (0.0)
Cough	0.3 (0.0)	0.8 (0.0)	1.2 (0.0)	1.7 (0.0)
Skin				
Rash	0.9 (0.0)	2.0 (0.0)	0.2 (0.0)	0.2 (0.0)

* Some patients have been exposed to more than one dose level of RENEDIL.

Adverse events that occurred in 0.5 up to 1.5 percent of patients who received RENEDIL in all controlled clinical trials at the recommended dosage range of 2.5 to 10 mg once a day are listed below. These events are listed in order to decreasing severity within each category regardless of relationship to RENEDIL therapy: ***Body as a Whole:*** Chest pain, facial edema, flu-like illness, fever; ***Cardiovascular:*** Tachycardia, premature beats, postural hypotension, bradycardia; ***Gastrointestinal:*** Abdominal pain, diarrhea, vomiting, dry mouth, flatulence, acid regurgitation, cholestatic hepatitis, gingival hyperplasia, salivary gland enlargement; ***Metabolic:*** ALT (SGPT) increased; ***Musculoskeletal:*** Arthralgia, muscle cramps, myalgia; ***Nervous/Psychiatric:*** Insomnia, depression, anxiety disorders, irritability, nervousness, somnolence, decrease in libido, tremor, confusion; ***Respiratory:*** Dyspnea, epistaxis; ***Dermatologic:*** Pruritis, erythema multiforme, erythema nodosum, leucocytoclastic vasculitis, urticaria, photosensitivity reactions; ***Special Senses:*** Visual disturbances; ***Urogenital:*** Impotence/sexual dysfunction, urinary frequency, urinary urgency, dysuria, polyuria.

Serious adverse events reported from controlled clinical trials and during marketing experience (incidence <0.5 percent) were myocardial infarction, hypotension, syncope, angina pectoris, arrhythmia and anemia.

Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty.

Laboratory Tests

For the following laboratory values statistically significant decreases were observed; bilirubin, red blood count, hemoglobin, and urate. Statistically significant increases were found in erythrocyte sedimentation rate and thrombocyte count. In isolated cases, there were increased liver enzymes. None of the changes were considered to be of clinical significance.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Overdosage can cause excessive peripheral vasodilation with marked hypotension and possibly bradycardia.

Treatment

In the case of known overdosage, activated charcoal may be used. If severe hypotension occurs, symptomatic treatment should be instituted. The patient should be placed supine with the legs elevated. The intravenous administration of fluids may be used to treat hypotension. Plasma volume may be increased by infusion of a plasma volume expander. When accompanied by bradycardia, atropine 0.5-1 mg should be administered intravenously. Sympathomimetic drugs predominantly affecting the α_1-adrenoceptor may be given if the above-mentioned measures are considered insufficient. Removal of felodipine from the circulation by hemodialysis has not been established.

DOSAGE AND ADMINISTRATION

RENEDIL should be swallowed whole and not crushed or chewed. The tablets should not be administered with a meal rich in carbohydrates or fat (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics).

The usual recommended initial dose is 5 mg once daily (see DOSAGE AND ADMINISTRATION - Use in the Elderly, and - Use in Patients with Impaired Liver Function).

Depending on the patient's response, the dosage should be adjusted accordingly. Dose adjustment, if necessary, should be done at intervals of not less than two weeks.

The maintenance dosage range is 2.5 to 10 mg once daily.

In clinical trials, doses above 10 mg daily showed an increased blood pressure response but a disproportionately higher incidence of peripheral edema and other vasodilatory adverse events.

Modification of the recommended dosage is usually not required in patients with renal impairment.

Use in the Elderly

Patients over 65 years of age may develop elevated plasma concentrations of felodipine. A starting dose no higher than 2.5 mg once daily is recommended. A dosage of 10 mg daily should not be exceeded (see PRECAUTIONS - Use in Elderly Patients).

Use in Patients with Impaired Liver Function

Patients with impaired liver function may develop elevated plasma concentrations of felodipine. A starting dose no higher than 2.5 mg once daily is recommended. A dosage of 10 mg daily should not be exceeded (see PRECAUTIONS - Use in Patients with Impaired Liver Function).

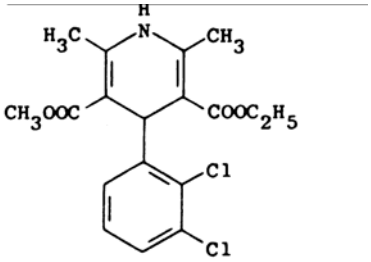
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: felodipine

Chemical Name: 3,5-pyridinedicarboxylic acid,4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-, ethyl methyl ester

Structural Formula:



Molecular Formula: $C_{18}H_{19}Cl_2NO_4$

Molecular Weight: 384.26

Description: Felodipine is a slightly yellowish, crystalline powder. It is not hygroscopic. It is soluble in acetone, dichloromethane, ethanol, heptane, methanol, n-octanol, 2-propanol, and practically insoluble in water.

Composition

	2.5 mg	5 mg	10 mg
Tablet Core		mg/tab	
felodipine	2.5	5	10
hydroxypropyl methylcellulose	100	100	100
lactose anhydrous	28	28	28
polyoxyl 40 hydrogenated castor oil			
hydroxypropyl cellulose			
propyl gallate			
aluminum silicate			
microcrystalline cellulose			
sodium stearyl fumarate			
Coating Layer			
hydroxypropyl methylcellulose			
polyethylene glycol			
titanium dioxide			
iron oxide yellow			
iron oxide red-brown			
carnauba wax			

Stability and Storage Recommendations

Store RENEDIL at 15-30ºC.

AVAILABILITY OF DOSAGE FORMS

RENEDIL tablets are extended release, film-coated tablets, containing felodipine in strengths of 2.5 mg, 5 mg and 10 mg.

RENEDIL 2.5 mg Tablet:	A yellow, circular, biconvex film-coated tablet, engraved on one side and 2.5 on the other.	H FF
RENEDIL 5 mg Tablet:	A pink, circular, biconvex film-coated tablet, engraved on one side and 5 on the other.	H FC

RENEDIL 10 mg Tablet:	A red-brown, circular, biconvex film-coated tablet, engraved on one side and 10 on the other	H FD

Each tablet strength is available in compliance packages (2 x 15).

NOTE: These extended release tablets must not be divided, crushed or chewed.

INFORMATION FOR THE CONSUMER

IMPORTANT INFORMATION YOU SHOULD KNOW ABOUT RENEDIL®
(FELODIPINE EXTENDED RELEASE TABLETS)

RENEDIL is a brand name for the drug felodipine (said as, fell-o'-di-peen). It belongs to the group of drugs called "calcium channel blockers" or "calcium antagonists".

RENEDIL is used to treat hypertension (high blood pressure). Its main action is to relax the arteries, letting the blood flow more freely; thereby lowering the blood pressure.

Read this leaflet carefully. It does not replace your doctor's or pharmacist's advice. They may have given you different instructions for your particular health condition. Be sure to follow their advice. If you have any questions, talk to your doctor or pharmacist. **Do not decide on your own how to take RENEDIL.**

BEFORE YOU START RENEDIL

Be sure you have told your doctor:

- **If you are pregnant or plan to become pregnant.**
- **If you are breast feeding.**
- About all health problems you have or have had in the past.
- About all medicines you take, including ones you can buy without a prescription.
- If you visit more than one doctor make sure that each knows about all the medicines you are taking.
- If you are allergic to "non-medicinal" substances like food products, preservatives, or dyes, which may be present in RENEDIL tablets (see RENEDIL ingredients).
- If you have ever had a bad, unusual or allergic reaction to "felodipine".

RENEDIL INGREDIENTS

Most medicines contain more ingredients than just the active drug. These ingredients are needed to keep medicines in a form that you can swallow. Check with your doctor if you think you might be allergic to any of these items (listed in alphabetical order): aluminum silicate, carnauba wax, castor oil, felodipine, hydrogen peroxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, lactose, microcrystalline

cellulose, polyethylene glycol, propyl gallate, sodium stearyl fumarate, titanium dioxide.

HOW TO USE THE RENEDIL COMPLIANCE PACK

This unique 30-day package is designed to make it easy to keep track of your medication.

Twenty-eight of the tablets are labelled with a day of the week. To start, take a tablet in the first row that matches the day you begin the pack. Then, take a tablet on each of the following days to complete the 28 labelled tablets. The 2 extra non-labelled tablets should be taken after all other tablets are gone.

Remember to get a new prescription from your doctor or a refill from your pharmacy a few days before all 30 tablets are taken.

HOW TO TAKE RENEDIL

- Take RENEDIL exactly as your doctor tells you. Do not miss doses or take extra doses, unless your doctor tells you. If you are not clear about the directions, ask your doctor or pharmacist.
- RENEDIL is taken once a day. Even if your doctor has prescribed 2 tablets a day, both should be taken at the same time, unless otherwise indicated.
- Try to take RENEDIL with something you do regularly each day; for example, upon waking or at breakfast. This will help you remember each dose.
- RENEDIL should not be taken with a meal rich in fat or carbohydrates. Breakfast foods which are rich in fat and/or carbohydrates include bacon, sausage, hash brown potatoes, and sugared cereals. RENEDIL may be taken with a light meal which is low in fat and carbohydrates (i.e. two slices of toast with cheese, cereal with milk, and orange juice).
- **Grapefruit juice increases the amount of RENEDIL in your body and should be avoided.**
- Swallow RENEDIL whole with a glass of water. Do not crush, chew, break or suck on the tablets.
- Do not transfer RENEDIL to other pill containers. To protect your RENEDIL tablets, keep them in the original Compliance Pack.

IF YOU MISS A DOSE

If you miss a dose of RENEDIL and remember within 12 hours, you should take your usual dose as soon as possible. Then go back to your regular schedule. But if it is more then 12 hours when you remember, do not take the missed dose. Just take the next dose on time.

Never take a double dose of RENEDIL to make up for missed tablets. If you are still unsure, check with your doctor or pharmacist to see what you should do.

SIDE EFFECTS TO BE AWARE OF

Along with its effects on controlling blood pressure, RENEDIL, like any medication, may include side effects.

Some side effects may occur when RENEDIL is first started or when the dose is increased. These side effects are usually mild and should go away as your body gets used to RENEDIL.

It is important that you keep your doctor informed of all side effects, especially if you experience any of the following for more than a week:

- swelling of the ankles;
- flushing or a feeling of warmth;
- dizziness;
- a racing heartbeat;
- headache;
- unusual tiredness

Medicines affect different people in different ways. Just because side effects have occurred in other patients does not mean you will get them. Discuss how you feel on RENEDIL with your doctor and pharmacist. **Do not stop taking RENEDIL on your own.**

A few patients reported mild tenderness or swelling of their gums while taking RENEDIL. This effect can be prevented with good dental care. Brush your teeth carefully and often with a soft toothbrush, and use dental floss daily.

Massaging your gums regularly with a soft toothbrush will also help. If your gums do become tender, red or swollen, be sure to tell your doctor or dentist.

Other side effects have been reported in a few cases. These include tingling in the hands, arms, feet or legs, stomach upset, diarrhea, the need to urinate frequently, and sexual problems. Again, if any of these effects bother you, be sure to tell your doctor.

You should be certain to contact your doctor immediately if you experience anything unusual.

SOME PRECAUTIONS YOU SHOULD TAKE

Keep RENEDIL out of sight and out of the reach of children. Never take medicine in front of small children as they will want to copy you.

Unused medicines which you know you will no longer need should be carefully discarded. You may wish to seek advice from your pharmacist.

The Compliance Pack protects each tablet. When you first open the package, if you find any damage to the plastic seal or foil which exposes the tablet, ask your pharmacist to check the package.

Check with your doctor if you want to drink alcohol (including wine with your meals) while you are taking RENEDIL. Drinking alcohol while on RENEDIL may make you feel dizzier than usual. Alcohol may also cause an uncomfortable drop in blood pressure.

Remember, you may not notice any signs of high blood pressure. **Therefore it is important to take RENEDIL even when you feel well.** A constant amount of drug is needed in your body to control your blood pressure. **Do not stop taking RENEDIL on your own.**

HOW TO STORE RENEDIL

Although the RENEDIL tablets are protected in this Compliance Pack, it is best to keep the package at normal room temperature and in a dry place. Do not keep RENEDIL in the bathroom. **Keep RENEDIL out of the reach of children.** Do not keep or use RENEDIL after the expiry date indicated on the Compliance Pack.

GENERAL INFORMATION

All drugs can have both helpful and harmful effects. Both depend on the person and his or her health condition. This leaflet alerts you to some of the times you should call your doctor. Other situations which cannot be predicted may arise. Nothing in this leaflet should stop you from calling your doctor or pharmacist with any questions or concerns you have about RENEDIL.

Customer Inquiries: 1-800-265-7927

PHARMACOLOGY

Animal

Pharmacodynamics

Felodipine is a selective vasodilating antihypertensive dihydropyridine which has been shown to lower arterial blood pressure in normotensive rats, cats and dogs and in rats with primary or secondary forms of hypertension.

The plasma concentration needed for 20% reduction of mean arterial pressure, in normotensive dogs and spontaneously hypertensive rats (SHR), was of the order of 15-30 nmol/L.

The oral dose of felodipine required to obtain a 20% reduction of mean arterial blood pressure in dogs (3 studies, 17 males in total) and in rats (1 study, 11 males) when given by gavage or in capsules was 1-5 μmol/kg. When felodipine was mixed in with the diet of SHR (3 studies, treatment duration ranging from 2 weeks to 6 months) daily doses of up to 85 μmol/kg had to be administered to achieve the same reduction in mean arterial pressure.

The primary effects of felodipine at plasma concentrations of 1-30 nmol/L were examined in several studies in rats and dogs given felodipine intravenously and orally. The only primary effect observed, in addition to arterial vasodilation, was diuresis-natriuresis due to a tubular action.

Felodipine exhibits a hundredfold vascular versus myocardial selectivity, based on the inhibitory potency ratios for vascular and cardiac tissues, studied *in vitro*.

Acutely, there is reflex tachycardia which may be blocked by beta-adrenoceptor antagonists and which moderates during maintained antihypertensive treatment due to baroreflex resetting.

Two different studies, in which felodipine was given to 8 male rats in a dose of 247 nmol/kg administered intravenously over 90 minutes and to 7 female rats as an oral dose of 78 μmol/kg with food for 6 months, have demonstrated that the reabsorption of filtered sodium is reduced in the distal tubules and collecting ducts in the kidney. Potassium excretion and absorption were unaffected by felodipine.

Pharmacokinetics

Felodipine is rapidly and completely absorbed after oral administration in rats and dogs. First-pass elimination reduces oral bioavailability to 20 to 30% for a dose of 5 μmol/kg. This is comparable with the 15% availability in man. Saturation of the first-pass elimination at high felodipine doses to the rat, 150 μmol/kg, results in almost 100% bioavailability.

Felodipine exhibits multiexponentially declining plasma concentration-time curves after i.v. doses. In the terminal phase distribution volumes are 10 to 20 L/kg. The binding to plasma proteins is > 99.5% in rat, dog and man. An autoradiography study with (^{14}C) felodipine in mice did not indicate any irreversible tissue binding. It was also found that the drug and/or its metabolites pass the blood-brain and placental barriers.

Elimination of felodipine was studied in single dose studies in rats (7 males) and dogs (3 females) administered drug in doses of 0.2 μmol/kg i.v. and 5 μmol/kg oral. The studies indicate that felodipine is almost exclusively eliminated as metabolites in almost equal amounts in the urine and feces of the rat and dog.

The primary step in the biotransformation of felodipine is oxidation to the corresponding pyridine analogue, which lacks vasodilating properties. Sequential metabolic processes involve ester hydrolysis and hydroxylation of pyridine methyl groups.

Eight different inactive metabolites have been identified in rat urine. The urinary metabolic pattern in mouse, rabbit, dog and man resembles in all essentials that found in the rat.

TOXICOLOGY

Acute Toxicity

Table 2.

Species	Route	Sex	No. of Animals	Dose Levels mg/kg	LD_{50} Values mg/kg	LD_{50} Values µmol/kg
Mice	p.o. p.o.	Male Female	10 10	100-700 150-750	240 (185-279) 264 (189-330)	630 (480-730) 690 (490-860)
Mice	i.v. i.v.	Male Female	10 10	6-12 5-12.5	8.6 (8.0-9.5) 10.4 (9.2-11.8)	22 (21-25) 27 (24-31)
Rats	p.o. p.o.	Male Female	6 6	1000-4500 125-4500	2390 (1710-2840) 2250 (1300-3850)	6230 (4450-7380) 5900 (3400-10000)
Rats	i.v. i.v.	Male Female	6 6	5-10 3-8	6.8 (5.9-7.5) 6.4 (4.9-7.1)	18 (15-19) 17 (13-19)

Signs of acute toxicity were sedation, convulsions, diarrhea and body weight loss.

In a single study, Beagle dogs (2 male, 2 female) were studied after single doses of 20, 40 and 80 µmol/kg felodipine given orally, and after repeated doses of 10 µmol/kg felodipine b.i.d. given orally for 7 days followed by 20 µmol/kg felodipine b.i.d. given orally for 3 days. After single administration of felodipine 80 µmol/kg, food consumption was decreased for 1 to 3 days. At all dose levels the ECGs revealed tachycardia which persisted for more than 6 hours. When the dogs received the repeated doses of felodipine there was a dose-dependent hyperemia of the mucus membranes and skin, and dose-dependent reduced food consumption. Tiredness was reported at the 20 µmol/kg b.i.d. dose level. Two dogs died at the dose level 20 µmol/kg (7.7 mg/kg) b.i.d. It is concluded that after a single oral dose of felodipine, the minimum lethal dose in dogs is higher then 80 µmol/kg. With repeated daily doses it has been shown that 20 µmol/kg (7.7 mg/kg) twice daily with four hour intervals, may be lethal to dogs.

General Toxicity After Repeated Administration

The general toxicity of felodipine has been studied after repeated oral administration in rats and dogs and repeated i.v. administration in rats.

The studies performed are summarized in Table 3.

Table 3.

Species	No. of Animals/ Sex/Group	Route of Administration	Frequency/ Duration of Dosing	Dose Groups		Deaths/ Group		Toxic Effects
				(µmol/kg)	(mg/kg)	M	F	
Rats	6	p.o.	Once daily for one month.	0 5 15 50 150 500	0 2 5.8 19.2 57.6 192	1	6	At the 150 µmol/kg dose, hyperemia manifested in redness of mucous membranes, nose and ears. Decrease in mean food intake and body weight in females during week 1. Decrease in blood glucose in females and serum potassium concentrations in males. Insignificant increase in serum protein and albumin concentrations in females. Increase in serum urea in females. Reduction in testicular weight without signs of morphological change. Elevated kidney weight values in females.
Rats	10	p.o.	Once daily for 5 weeks.	0 5 26 130 470	0 2 10 50 180	5	9	The 130 µmol/kg group showed decreased food consumption (most notable on earlier treatment days), lowered levels of plasma neutral fat, increases in liver weight and decreases in submaxillary gland weight. Male weight gain was suppressed. The 470 µmol/kg group showed decreased spontaneous locomotor activity, ptosis, loss of hair gloss, abdominal swelling, nasal bleeding, anemia and deaths from debility in cases with severe toxic symptoms. Decreases in female blood lymphocyte ratio and increase in neutrophil ratio. Increase in liver weight and decreases in submaxillary gland weight. In the dead animals, atrophy of the spleen and thymus, degenerative hematopoiesis of the bone marrow were found.
Rats	25	p.o.	Once daily for 6 months	0 5 25 125	0 2 9.6 48.0	2 3	1 1	Distinct hyperemia of the ears, lasting several hours after treatment in all 3 active groups. In mid and high dose groups, males become slightly tense and irritated after 6 weeks of treatment. The high dose group showed a clear reduction in food consumption during the first few weeks with a corresponding lag in body weight gain, most pronounced in females. Water consumption was increased in high dose males and doubled in high dose females after 3rd week. Blood glucose concentrations were decreased in all groups but most pronounced in the high dose group. The high dose group also showed a decrease in serum potassium and chloride concentrations and some decrease in osmolality of the urine. Females showed increased serum urea concentrations. Mid and high dose animals showed low-degree weight increases of several organs. High dose females had enlarged colons, often doubled. In both sexes increased ileum weight. Both mid and high dose animals showed increased activity of the zona glomerulosa of the adrenal glands. Death of the low dose female was attributed to myocarditis and the 4 deaths in the high dose group to acute circulatory insufficiency. Only the high dose deaths were attributed to felodipine.

Table 3 (continued).

Species	No. of Animals/ Sex/Group	Route of Administration	Frequency/ Duration of Dosing	Dose Groups		Deaths/ Group		Toxic Effects
				(µmol/kg)	(mg/kg)	M	F	
Rats	10	i.v.	Once daily for two weeks.	0 0 0.1 0.3 1.0	saline saline 0.04 0.12 0.38			Dose levels 0.3 and 1.0 µmol/kg produced peripheral vasodilation and apparent hyperthermia 1-3 hours after dosing. Higher liver weight gain in males. Males given 1 µmol/kg dose showed inferior body weight gain during first 4 days of treatment.
Dogs	2	p.o.	Once daily for 1 month.	0 5 10 20	0 2 3.8 9.6			Dose dependent hyperemia of the mucous membrane and abdominal skin in mid and high doses. Dose dependent tachycardia noted in all groups. High dose groups showed depression of ST-j or ST-segment. High dose group males and females showed non-significant increase of heart and kidney weights.
Dogs	5 grp 1 5 grp 2 5 grp 3 5 grp 4	p.o.	Twice daily for 12 months in grps 1-4.	0 1.0 b.i.d. 3.0 b.i.d. 6.0 b.i.d	0 0.38 b.i.d. 1.2 b.i.d. 2.3 b.i.d.			Increased heart rate throughout the study. Mid and high dose animals developed decreased heart rate before the first daily dose. Hyperemia of the mucous membranes post-dose noted in mid and high dose animals (more pronounced in the high dose). A decrease in packed cell volume hemoglobin concentration and number of red blood cells, with preponderance in males, noted in mid and high dose groups.
Dogs	3 grp 5 3 grp 6 3 grp 7 3 grp 8	p.o.	Twice daily for 6 months in grps 5-8.	0 1.0 b.i.d. 3.0 b.i.d. 6.0 b.i.d	0 0.38 b.i.d. 1.2 b.i.d. 2.3 b.i.d.	1*	1*	Decrease in osmolality of the urine in mid dose females and both sexes of the high dose group. Insignificant increase in serum glucose concentration in mid dose females. Enlargement of the gingiva observed clinically in both mid and high dose groups; pathologically, a non-inflammatory gingival hyperplasia with male high dose preponderance. Increased activity of the zona glomerulosa in mid dose animals. * The initial high dose was 10 µmol/kg. At this dose 2 dogs died after 3 days. Death was attributed to acute circulatory failure. All dogs showed tiredness post dose. After the dose was reduced, this sign was reduced.

Reproduction Studies

Please refer to Table 5.

Mutagenicity

Felodipine has not shown any mutagenic potential.

Carcinogenicity

The carcinogenic effect of felodipine has been studied in mice (50 males and 50 females/group) at doses of 40, 120 and 360 µmol/kg over 99 weeks and rats (50 males and 50 females/group) at doses of 20, 60 and 180 µmol/kg over 112 weeks. In the mouse study, the high dose group (360 µmol/kg) showed an increased incidence of hepatocellular neoplasms (carcinomas and adenomas) compared with the animals terminally sacrificed from the other groups (see Table 4).

Table 4. Incidence of hepatocellular neoplasms in mice.

Group	Sex	No. of Animals[1]/ Group[2]	Dose Level µmol/L	Total No. of Mice with Adenomas[1]	Total No. of Mice with Carcinomas[1]
1	M	93 (14)	0	3	18 (2)
2	M	41 (9)	40	3	8 (1)
3	M	42 (9)	120	1	7
4	M	39 (25)	360	0	11 (3)
1	F	94 (36)	0	1 (1)	4 (1)
2	F	46 (14)	40	1	2
3	F	48 (25)	120	2	1 (1)
4	F	42 (28)	360	2 (1)	3

[1] Number of animals entering week 54 and continuing to termination of the study.

[2] Numbers in the brackets are the number of mice that died between 54 and termination of the study.

Few neoplasms (10 in total; 6 in the treatment groups, 4 in controls) were found in animals dying before termination of the study. Because of the difference in mortality between the groups, it was necessary to analyze pre-terminal and terminal deaths together in order to evaluate the carcinogenic potential of felodipine in mice. In doing this analysis, there was no significant difference between treated and untreated groups. Although there was an increased incidence of neoplasms in the high dose group compared with animals terminally sacrificed from the other groups, the incidence of hepatic carcinomas in all groups were within the historical laboratory control range for this strain of mice.

In view of the differing survival patterns in the different dose groups, the mouse carcinogenicity study was subjected to a further statistical analysis which indicated that no significant increase in hepatic neoplasms had occurred in the felodipine treated groups. The liver slides from this study were also examined "blindly" by

another specialized pathologist who concluded that "comparisons of the incidence or mean grades or any hepatocellular proliferative lesions, or combination of lesions fail to suggest a compound-related effect".

A repeat study in male mice with felodipine in doses of 40, 90 and 180 µg/kg over 76 weeks was performed. The results of the histopathological examination of the livers showed that there was no significant increase in hepatic tumours in the felodipine treated animals at any of the dose levels.

In the rat carcinogenicity study discussed above, an increased incidence of benign interstitial cell tumours (Leydig, cell tumours) was found in the testes of the low (26% = 13/50), mid (38% = 19/49), and high (40% = 20/50) dose males when compared to controls (9% = 9/100). It is considered that these tumours have an endocrinological basis in the rat as they can be induced by various experimental interventions that increase the level of luteinizing hormone (LH) in the blood. *In vivo* and *in vitro* studies have shown effects of felodipine which indicate that there is an endocrinological mechanism behind the increased incidence of Leydig cell tumours in rats. In human studies felodipine (given as single doses of 5, 10 or 20 mg to 12 young healthy volunteers and as 10-20 mg daily for 8 weeks followed by 10 mg daily for one week to 10 hypertensive patients) has not revealed effects on testosterone levels. LH levels were also determined in the hypertensive patients and showed no abnormalities.

Treated and untreated rats in the above carcinogenicity study also differed with respect to the occurrence of bile-duct hyperplasia and squamous-cell hyperplasia in the esophageal groove of the forestomach. Bile-duct hyperplasia was found in 30% (males) and 23% (females) of the control groups and at increased incidence in medium (42% males, 24% females) and high (64% males, 46% females) dose animals. Squamous-cell hyperplasia of the esophageal groove of the forestomach was found in 0% (males) and 6% (females) of the controlled groups, and at an increased incidence in the low (40% males, 16% females), medium (46% males, 34% females) and high (56% males, 38% females) dose animals.

Table 5. Fertility and reproduction studies.

Species and Strain	No. of Animals/Group	Period of Administration	Route of Administration				
				µµmol/kg	mg/kg	Dams	Litters
Rats, Sprague Dawley	15 M 30 F	Appr. 11 weeks[1] Appr. 10 weeks[1] (Seg 1)	p.o.	0 10 25 70	 3.8 9.6 26.9	Parents Dose dependent prolongation of parturition and hard labour in the animals receiving 25 µmol/kg or 70 µmol/kg.	Dose dependently increased frequencies of late fetal deaths and early postnatal deaths in animals receiving 25 µmol/kg or 70 µmol/kg.
Rats, Sprague Dawley	20 F	Days 6-15 of gestation (Seg II)	p.o.	0 10 25 70	 3.8 9.6 26.9	70 µmol/kg Slightly lower food consumption during the dosing period and slightly reduced weight gain towards the end of the dosing period.	No signs of embryotoxic, teratogenic or fetotoxic effects related to the treatment could be detected.
Rats, Sprague Dawley	20 F	From day 15 of gestation to day 20 post part. (Seg III)	p.o.	0 3 10 30	 1.2 3.8 11.5	30 µmol/kg Slight prolongation of the gestation period, prolonged parturition and hard labour.	30 µmol/kg Increased frequencies of stillborn fetuses and early postnatal deaths.
Rabbit, New Zealand White	5 F	Days 6-19 of gestation (Seg II, pilot study)	p.o.	0 10 25 50	 3.8 9.6 19.2	One control animal and 2 high dose animals were found dead during the study. Dose dependent decrease in body weight changes and food consumption values.	In a dose dependent manner, the mean resorption values were higher than control and the mean fetal viability values were lower than control in the treated groups. The mean fetal body weights and the mean fetal lengths were less than control in all of the treated groups. These effects had an insignificant dose relation.
Rabbit, New Zealand White	15 F	Days 6-19 of gestation (Seg II)	p.o.	0 3 6 12	 1.2 2.3 4.6	3 µmol/kg Depression noted more frequently in all treated groups than in the control group. A dose-related incidence of thickening of mammary tissue was observed in all treated groups (1/15, 10/15, & 9/14, resp.) at sacrifice day 29 of gestation. 6 µmol/kg Depression, thickening of mammary tissue. Incidence of premature deliveries slightly higher than control & wt losses during days 20-29 higher than control; these effects were also observed in the animals receiving 12 µmol/kg. 12 µmol/kg Depression, body wt loss, thickening of mammary tissue, premature deliveries as above.	Dose-related skeletal anomalies were observed in the extremities of fetuses in all treated groups. 3 µmol/kg Small distal phalanges in the 4th digits of the hind feet. 6 µmol/kg Small or missing distal phalanges in the 4th digits of the hind feet. Small distal phalanges in the first digits of the fore feet. One mid dose fetus had one fore foot with the entire first digit missing. 12 µmol/kg Small or missing distal phalanges in the 4th digits of the hind feet. Small or missing distal phalanges in the first digits of the fore feet.

[1]Males were dosed for 9 weeks prior to mating and through the mating period (maximum 12 days). Females were dosed for 2 weeks prior to mating and then up to 21 days post partum. Half of the females were killed on Day 14 of pregnancy.

Table 5. (continued)

Species and Strain	No. of Animals/ Group	Period of Administration	Route of Administration				
				µµmol/kg	mg/kg	Dams	Litters
Rabbit, New Zealand White	15 F	Days 6-18 of gestation (Seg II)	p.o.	0 6 12	 2.3 4.6	6 µmol/kg Reduced food intake during first few days of dosing; this was also seen in the animals receiving 12 µmol/kg (dose related). Suppression of body wt gain during the first few days of dosing, also seen in the animals receiving 12 µmol/kg. A dose related enlargement of mammary glands; also macroscopic changes in the glands including colour darkening and no milk leakage on dissection and microscopic changes, including increased number of small acini with abundant eosinophilic secretion. 12 µmol/kg Reduced food intake and suppression of body weight gain as described above; wt loss on cessation of dosing. Cold ears (more persistent and consistent observation). Enlargement of mammary glands. Other differences from control values possibly but less certainly related to treatment: • The more persistent occurrence of nonspecific signs after initiation of dosing, particularly in animals receiving 12 µmol/kg. • A higher incidence of nonaccidental deaths and abortions after this initiation of dosing.	6 µmol/kg Digital anomalies, with a dose related trend in terms of the numbers affected and the degree of effect. The most noticeable pattern was for the greater effect on the more distal parts of the paw, particularly the hind paws, and the proportions of fetuses showing subtle reductions in the degree of claw ossification were 0, 71.4 and 100% respectively at 0, 6 and 12 µmol/kg. 12 µmol/kg Digital anomalies as observed above. Increased preimplantation loss and slight increase in early post-implantation. Reduced litter size and litter weight.

Table 5. (continued)

Species and Strain	No. of Animals/Group	Period of Administration	Route of Administration				
				(µmol/kg)	(mg/kg)	Dams	Litters
Rabbit, New Zealand White	21 F 21 F 20 F 20 F	Days 6-18 Days 6-12 Days 13-18 Days 6-28 of gestation (Seg II)	p.o.	0 12 12 12	 4.6 4.6 4.6	Days 6-12 In all treatment groups treatment was associated with an initial decline in general condition indicated by reduced food intake, low faecal output, weight loss or suppression of weight gain. Recovery was evident within days of cessation of treatment. Palpable thickening of mammary glands with a corresponding significantly increased wt at termination was associated with initiation of treatment Day 6 of pregnancy, the response being less marked for animals dosed to Day 12 than to Day 28. Days 13-18 Initial decline in general condition as described above. No significant effect on mammary glands with regard to palpable thickening or increased wt. Days 6-28 See Days 6-12. Also, increased mammary weight gain.	Days 6-12 Litter size was reduced in all treatment groups compared to the controls. In groups treated from Day 6, the reduced litter size was mainly attributed to non-significant increases in post-implantation loss in combination with slightly higher values for preimplantation loss. Mean fetal wt lower in all treatment groups, the decrease was minimal for animals dosed Days 6-12. Lower values for litter wt in all treatment groups. Increased incidence of fetuses with an extra rib associated with initiation of treatment on Day 6. Days 13-18 Lower corpora lutea count contribution to a reduced litter size. Decreased mean fetal wt and lower values for litter wt. Treatment after Day 12 was associated with anomalies of the claws of almost all fetuses. The degree of effect appeared to be greater for this period of treatment than for the longer period (Days 6-28). Days 6-28 Reduced litter size, decrease in mean fetal wt and litter wt. Increased incidence of fetuses with an extra rib and anomalies of the claws occurred.

Table 5. (continued)

Species and Strain	No. of Animals/Group	Period of Administration	Route of Administration				
				(µmol/kg)	(mg/kg)	Dams	Litters
Rabbit, New Zealand White	10 F 10 F 20 F 19 F	Days 6-18 of gestation (Seg II)	p.o.	0 0 12 12	 4.6 4.6	Reduced body wt gain from start of dosing, compensated on Day 14 and reduced food consumption during the dosing period in treated animals. Increased wts due to hyperplasia of the mammary glands, in excess of the normal gestational one, in treated animals killed on Day 29. In animals killed on Day 35, no differences were observed with respect to wt or histomorphological appearance of the mammary glands.	Increased incidence of minor skeletal anomalies: disturbed development of distal phalanges, extra center of ossification between middle and distal phalanges in one or more digits in the fetuses of treated animals.
Rabbit, New Zealand White	9 F 9 F	Day 13 Day 13-18 of gestation	p.o.	12 12	4.6	The clinical signs observed and the effects on body wt gain, food consumption and mammary glands were essentially the same as those seen in earlier performed studies in the rabbit.	N/A
Rabbit, New Zealand White	8 F not pregnant	13 days (Days 0-12)	p.o.	0 1.2 12	 0.46 4.6	Reduced food consumption and decreased body wt during the dosing period in animals receiving 12 µmol/kg. No dose or compound related lesions were seen in the mammary glands which were all within the normal variation of mammary glands in non-pregnant rabbits. The results from this study and results of the above study in pregnant rabbits indicate that pregnancy has an insignificant effect on the pharmacokinetics of felodipine.	N/A

Table 5. (continued)

Species and Strain	No. of Animals/Group	Period of Administration	Route of Administration				
				µmol/kg	mg/kg	Dams	Litters
Rabbit, New Zealand White	9 F 15 F 11 F	Days 6-18 of gestation (Seg II)	p.o.	0 1.2 12[2]	0 0.46 4.6	1.2 µmol/kg Plasma Concentration Mean plasma levels and time course were very similar to those previously seen in non-pregnant rabbits, at the same dose level. The similarity of results on Days 13 and 18 indicated that there was no accumulation of the test compound. 12 µmol/kg Signs of Maternal Toxicity Body wt gain and food consumption were decreased during the first part of the dosing period. Mammary Glands Treatment induced enlarged mammary glands. The mammary gland wts were significantly increased. The microscopic examination showed that this hyperplasia consisted of an increased volume of the glandular parenchyma due to an increased lobular size. The histologicsal architecture, however, did not differ from that of the control animals.	12 µmol/kg (Day 29 of Gestation) Fetal loss was slightly increased compared to the control group. 1.2 and 12 µmol/kg Effects on the Phalanges A dose related effect on both size and structure (reduced ossification) of the distal phalanges was seen. The most pronounced effect was on the 4th digit of the hind paws. This hypoplasia of the phalanges could be detected by external examination, but at the dose level of 12 µmol/kg only. In addition, 6 pups at 12 µmol/kg showed an extra center of ossification between the middle and distal phalanx of the pollex.
Rabbit, New Zealand White	28 F[3] 32 F[3]	Days 6-18 of gestation (Seg II)	p.o.	0 12	0 4.6	The effects on the treated dams sacrificed on Day 29 or allowed to litter were of the same type and magnitudes as in earlier studies and consisted of reduced body wt, reduced food consumption, and enlargement of the mammary glands, histologically characterized as a hyperplastic thickening due to an increased volume of the glandular parenchyma, in excess of the normal gestational hyperplasia. Changes in mammary glands were still present, although less marked in the dose group on Day 32 post parturition. The mean wts of the mammary glands were significantly increased for the treated dams on Days 29 and 32 post parturition. Since no disturbance of the post natal group of the pups was observed, the conclusion was drawn that there was no functional impairment of the mammary glands.	The findings in the fetuses were mainly disturbances of the development of the distal parts of the digits. The effects may be characterized as disturbances of the differentiation of the distal phalanges observed as decreased size of the distal phalanges and fusion of the outer phalanges in some digits. These anomalies of the digits could still be seen on Day 32 post parturition, and in addition, extra centres of ossification were also observed in some pups. The histological examination of the distal phalanges indicated a disturbed differentiation of the cartilaginous rudiments as a possible explanation of the observed effects. A slightly increased incidence of wavy ribs, an increased incidence of fetuses with an extra rib, and a decreased frequency of fetuses with variant sternebra among fetuses with normal number of ribs were observed in the dose group fetuses examined on Day 29. A few pups with gross malformations and visceral anomalies were also found in the treated group.

[2] The dose level of 12 µmol/kg had been used as the highest dose in several previous segment II studies in the rabbit, and was known to cause maternal toxicity, enlargement of the mammary glands and minor skeletal effects in the offspring.

[3] Each group was divided into two subgroups. The animals in one of the subgroups were killed on Day 29 of pregnancy. The animals in the other one were allowed to litter normally and to rear their pups up to Day 32 post parturition, when all pups and dams were killed.

Table 5. (continued)

Species and Strain	No. of Animals/Group	Period of Administration	Route of Administration				
				µmol/kg	mg/kg	Dams	Litters
Rabbit, New Zealand White	1/I 3 F[4] 2/I 3 F 3/I 3 F 4/I 3 F 1/II 3 F 2/II 3 F 3/II 3 F 4/II 3 F	13 14 15 16 15 16 17 18	p.o.	12 12 12 12 12 12 12 12	4.6 4.6 4.6 4.6 4.6 4.6 4.6 4.6	Clinical Observations One dam dosed on Day 16 aborted on Day 20 and was killed on Day 23 for humanitarian reasons. One dam dosed on Day 17 was found dead on Day 29 of pregnancy. Two dams dosed on Days 15 and 18, respectively, aborted and one dam dosed on Day 15 gave premature birth. Retardation in body wt gain, reduced food consumption and reduced water intake were observed after the dosing day. The effects were most pronounced and lasted for the longest period of time in dams treated on Day 16 or 17 of gestation. Terminal Autopsy Two dams dosed on Day 16 showed pale livers and distended caecum. Also two dams dosed on Day 17 showed pale livers.	Effects on Distal Phalanges No abnormalities of the fetal phalanges were observed after treatment of the dam on Day 13 or 18, while all fetuses showed reduced degree of ossification of one or more of the distal phalanges if treatment had occurred on Day 14, 15, 16 or 17 of gestation. The most pronounced effects were observed on Day 16, when all examined fetuses showed either reduced or very reduced size of one more of the distal phalanges. The hypoplasia of the phalanges induced on Day 16 was in general, in contrast to other days of treatment, visible at external examination before alizarin staining of the skeletons.
Rabbit, New Zealand White	1 4 F 2 4 F 3 4 F 4 3 F 5 4 F 6 6 F	single, Day 16 of gestation	p.o.	- 12 12 12 12 12[5]	- 4.6 4.6 4.6 4.6 4.6	THIS STUDY DID NOT DIFFERENTIATE BETWEEN DAMS AND LITTERS Concentration of Felodipine in Maternal Plasma, Fetal Tissue and Amniotic Fluid **Plasma Concentrations:** The highest felodipine concentrations (~ 350 nmol/L) were recorded at 4 hours after treatment; concentrations were still high at 12 hours (≥ 200 nmol/L) and 24 hours (≥ 100 nmol/L). **Concentrations in Fetal Tissue:** Mean concentrations in fetal tissue were 4-6 times lower than those seen in maternal plasma. The levels were virtually constant between 4 and 12 hours after treatment (~ 50 nmol/kg) and at 24 hours they were around 20 nmol/kg. **Concentration in Amniotic Fluid:** These were about 2 to 4 times lower than those in fetal tissue. Histological Examination of the Limb Plates Fetuses from dams treated with felodipine: **2 and 4 Hours After Dose:** Marked expansion of limb plates due to extensive mesenchymal edema. Widening of the thin-walled embryonal vessels, and the border between the cartilaginous primordium of phalanges and surrounding, undifferentiated mesenchymal less well-defined. **8 Hours After Dose:** Marked edema of limb plates and occasionally ruptures of marginal blood vessels, with hemorrhage. **12 Hours After Dose:** Mesenchymal edema of limb plates somewhat less pronounced. In addition to hemorrhages, occasional digital blister caused by cleavage vesicles between the mesenchymal and ectoderm. **24 Hours After Dose:** As at 12 hours after dose. Also occasional small necroses in the apex of digits, most often at the side of the 3rd phalange.	

[4] The study was divided into two experiments, I and II, in which the dams were treated on different days of gestation.

[5] The dose level of 12 µmol/kg had been used as the highest dose in several previous segment II studies in the rabbit, and was known to cause maternal toxicity, enlargement of the mammary glands and minor skeletal effects in the offspring.

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