PRODUCT MONOGRAPH

PrSANDOZ FELODIPINE

(felodipine)

Extended Release Tablets
5 mg and 10 mg

Manufacturer’s Standard

Antihypertensive Agent

Sandoz Canada Inc.
145 Jules-Léger
Boucherville, Quebec
J4B 7K8

Control Number: 182441

Date of Revision: March 4, 2015
THERAPEUTIC CLASSIFICATION

Antihypertensive Agent

ACTION AND CLINICAL PHARMACOLOGY

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 $914 \pm 355$ mL/min in hypertensive patients, $606 \pm 245$ mL/min in elderly hypertensive patients and $1337 \pm 413$ mL/min in young healthy volunteers. Its mean terminal half-life was $24.5 \pm 7.0$ hours in hypertensive patients, $27.5 \pm 8.4$ hours in elderly hypertensive patients and $14.1 \pm 5.6$ 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 ($t_{\text{max}}$), and a reduced maximum plasma concentration ($C_{\text{max}}$). The mean $t_{\text{max}}$ ranges from 2.5 to 5 hours. The area under the plasma concentration versus time curve and $C_{\text{max}}$ are linearly related to the dose in the 10 to 40 mg range. Following administration of felodipine to hypertensive patients, mean $C_{\text{max}}$ 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 $C_{\text{max}}$ and AUC after repeated dosing is approximately threefold and indicates a need for individualized dosing.

The bioavailability of felodipine is not influenced by the presence of food in the gastrointestinal tract. However, the peak plasma concentration of felodipine ($C_{\text{max}}$) is significantly increased by 1.5 to 2 fold when felodipine 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 $C_{\text{max}}$ may cause a clinically significant fall in blood pressure. Therefore felodipine should not be administered with meals rich in carbohydrate or fat. However, the absorption characteristics of felodipine are not affected when felodipine 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).

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 $C_{\text{max}}$ of felodipine increased about threefold as compared to administration with water. When felodipine extended release tablets were administered as felodipine 10 mg with 250 mL grapefruit juice felodipine AUC and $C_{\text{max}}$ values doubled as compared to those observed with water. When grapefruit juice was taken for up to 24 hours prior to felodipine 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 felodipine 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% 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 felodipine 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**

Sandoz Felodipine (felodipine) is indicated in the treatment of mild to moderate essential hypertension. Sandoz Felodipine 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.

Sandoz Felodipine 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 felodipine 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 felodipine with other antihypertensive agents has not been established.
CONTRAINDICATIONS

Felodipine is contraindicated in:

1. Patients with a known hypersensitivity to felodipine or any other components of Sandoz Felodipine.

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/m² 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 felodipine in patients with heart failure has not been established. Caution should, therefore, be exercised when using felodipine 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
Felodipine 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 ischaemia. 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**
Felodipine 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**
Felodipine should be used with caution in the presence of left ventricular outflow obstruction.

**Dermatologic Lesion**
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.

**Concomitant Use With Strong Inhibitors of CYP3A4**
Use of felodipine with drugs that result in strong inhibition of CYP3A4, such as ketoconazole,
clarithromycin, ritonavir, may lead to increased plasma levels of felodipine and associated
serious adverse events (see DRUG INTERACTIONS). Such concomitant use should be avoided.

An observational study demonstrated an increased risk of hospitalisation with acute kidney
injury when felodipine was used concomitantly with clarithromycin in elderly patients
(> 65 years of age) compared to when it was used concomitantly with azithromycin, odds ratio
[felodipine: 2.97 (95% C.I. 1.09-8.06)].

**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 felodipine (see ACTION AND CLINICAL
PHARMACOLOGY - Pharmacokinetics). These patients should have their blood pressure
monitored closely during initial administration and after dosage adjustment of felodipine. 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 felodipine (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics). These patients should have their blood pressure monitored closely during initial administration and after dosage adjustment of felodipine. A dosage of 10 mg daily should not be exceeded (see DOSAGE AND ADMINISTRATION - Use in Patients with Impaired Liver Function).

**Gingival Hyperplasia**
Felodipine can induce gingival enlargement in patients with pronounced gingivitis and periodontitis. However, such changes may be avoided or reversed by measures of good oral hygiene and mechanical debridement of the teeth. In very rare instances, felodipine has also caused gingivitis.

**Pregnancy and Lactation**
See CONTRAINDICATIONS.

**Use in Children**
Felodipine 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 felodipine, the potential for a significant increase in pharmacodynamic effects exists (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics). Therefore, the consumption of grapefruit juice prior to or during treatment with felodipine should be avoided.

**Lactose**
Sandoz Felodipine contains lactose and should not be given to patients with hereditary galactose intolerance or glucose-galactose malabsorption.

**DRUG INTERACTIONS**

**Overview**
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. Co-administration 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.

**Cytochrome P-450 Enzyme Substrates**
Drugs known to be substrates of the cytochrome P-450 system include: benzodiazepines, flecainide, imipramine, propafenone, terfenadine, theophylline (see Table 1).

**Cytochrome P-450 Enzyme Inhibitors**
Drugs known to be inhibitors of the cytochrome P-450 system include: azole antifungals (ketoconazole and itraconazole), cimetidine, cyclosporine, erythromycin, quinidine, warfarin. Enzyme inhibitors of the cytochrome P450 3A4 system have been shown to cause an increase in felodipine plasma concentrations (see Table 1).

**CYP 3A4 Enzyme Inducers**
Enzyme inducers of the cytochrome P450 3A4 system have been shown to cause a decrease in plasma concentrations of felodipine, e.g. *Hypericum perforatum* (Saint John’s Wort) (see Drug-Herb Interactions).

Drugs known to be inducers of the cytochrome P-450 3A4 isoenzyme include: phenobarbital, phenytoin, rifampin (see Table 1).

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

**Drug-Drug Interactions**
The drugs listed in Table 1 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

**Table 1 Established or Potential Drug-Drug Interactions**

<table>
<thead>
<tr>
<th>Proper Name</th>
<th>Effect</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Alcohol induces vasodilation.</td>
<td>Alcohol can enhance the hemodynamic effects of felodipine</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>A pharmacokinetic study of felodipine in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of felodipine. The AUC and C\text{\textsubscript{max}} of metoprolol, however, were increased approximately 31 and 36 percent, respectively.</td>
<td>In controlled clinical trials, however, beta-blockers including metoprolol were concurrently administered with felodipine and were well tolerated.</td>
</tr>
<tr>
<td>Digoxin</td>
<td>When given concomitantly with felodipine as conventional tablets the peak plasma concentration (C\text{\textsubscript{max}}) of digoxin was significantly increased.</td>
<td>With the extended release formulation of felodipine there was no significant change in C\text{\textsubscript{max}} or AUC of digoxin.</td>
</tr>
<tr>
<td>Proper Name</td>
<td>Effect</td>
<td>Clinical Comment</td>
</tr>
<tr>
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</tr>
<tr>
<td>Tacrolimus</td>
<td>Felodipine may increase the concentration of tacrolimus.</td>
<td>When used together, the tacrolimus serum concentration should be monitored and the tacrolimus dose may need to be adjusted.</td>
</tr>
</tbody>
</table>

**Cytochrome P-450 Enzyme Substrates**

<table>
<thead>
<tr>
<th>Proper Name</th>
<th>Effect</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines, Flecainide, Imipramine, Propafenone, Terfenadine, Theophylline</td>
<td>Enzyme substrates of the cytochrome P450 3A4, when co-administered with felodipine, may act like P450 3A4 inhibitors and cause an increase in felodipine plasma concentrations.</td>
<td>Dose adjustment and monitoring may be required.</td>
</tr>
</tbody>
</table>

**Cytochrome P-450 Enzyme Inhibitors**

<table>
<thead>
<tr>
<th>Proper Name</th>
<th>Effect</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>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&lt;sub&gt;max&lt;/sub&gt; of felodipine when given concomitantly with cimetidine.</td>
<td>It is anticipated that a clinically significant interaction may occur. Therefore, it is recommended that low doses of felodipine be used when given concomitantly with cimetidine.</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>In elderly patients (&gt; 65 years of age), concomitant use of felodipine with clarithromycin was associated with increased risk of hospitalization with acute kidney injury.</td>
<td>Avoid concomitant use.</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Concomitant treatment with erythromycin has been shown to cause an increase in felodipine plasma levels. Co-administration of felodipine extended-release tablets with erythromycin resulted in approximately 2.5-fold increase in the AUC and C&lt;sub&gt;max&lt;/sub&gt;, and about 2-fold prolongation in the half-life of felodipine.</td>
<td>It is expected that a clinically significant interaction may occur. Therefore, low doses of felodipine are recommended to be used when given concomitantly with erythromycin.</td>
</tr>
<tr>
<td>Itraconazole, Ketoconazole</td>
<td>Co-administration of another extended release formulation of felodipine with itraconazole resulted in approximately 8-fold increase in the AUC, more than 6-fold increase in the C&lt;sub&gt;max&lt;/sub&gt;, and 2-fold prolongation in the half-life of felodipine.</td>
<td>Caution should be used when CYP 3A4 inhibitors are co-administered with felodipine and a conservative approach to dosing felodipine should be taken.</td>
</tr>
</tbody>
</table>

**CYP 3A4 Enzyme Inducers**

<table>
<thead>
<tr>
<th>Proper Name</th>
<th>Effect</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin, Carbamazepine and Phenobarbital</td>
<td>In a pharmacokinetic study maximum plasma concentrations of felodipine were considerably lower in epileptic patients on long term anticonvulsant therapy (phenytoin, carbamazepine,</td>
<td>Since a clinically significant interaction may be anticipated, alternative antihypertensive therapy should be considered in these patients.</td>
</tr>
</tbody>
</table>
Proper Name | Effect | Clinical Comment
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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.

**Drug-Food Interactions**

**Grapefruit juice**
Co-administration of felodipine with grapefruit juice resulted in more than 2-fold increase in the AUC and C\text{max}, but no prolongation in the half-life of felodipine (see ACTIONS AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

**Food**
The bioavailability of felodipine is influenced by the presence of food. When administered with either a high fat or carbohydrate diet, C\text{max} is significantly increased by approximately 1.5 to 2.0 fold; AUC is unchanged. This may cause a clinically significant fall in blood pressure. Therefore, felodipine should not be administered with meals rich in carbohydrate or fat (see ACTIONS AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

**Drug-Herb Interactions**

*Hypericum perforatum*
St-John's Wort is an inducer of CYP 3A4 and has been shown to cause a decrease in plasma concentrations of felodipine. Therefore, dosage of felodipine may have to be increased.

**ADVERSE REACTIONS**

In 861 patients with essential hypertension treated once daily with 2.5 to 10 mg 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 2 below. These events are reported from controlled clinical trials with patients who were randomized to either a fixed dose of felodipine 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 felodipine 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 2  Percent of Patients With Adverse Events In Controlled Trials of Felodipine (N=861)* as Monotherapy without Regard to Causality (Incidence of Discontinuations Shown in Parentheses)

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

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

Adverse events that occurred in 0.5 up to 1.5 percent of patients who received felodipine in all controlled clinical trials at the recommended dosage range of 2.5 to 10 mg once a day or during post-marketing experience are listed below. These events are listed in order of decreasing severity within each category regardless of relationship to felodipine 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:** Pruritus, 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.

**OVERDOSAGE**

For management of a suspected drug overdose, contact your regional Poison Control Centre.

**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 α1-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**
Sandoz Felodipine 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\(^1\) 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.

**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 Children**
Sandoz Felodipine is not recommended in children (see PRECAUTIONS - Use in Children).

**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).

**Use in Patients with Renal Impairment**
Modification of the recommended dosage is usually not required in patients with renal impairment.

\(^1\) Sandoz Felodipine is NOT available as 2.5 mg extended release tablets.
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: felodipine

Chemical Name: Ethyl methyl (RS ) - 4 - ( 2 , 3 -dichlorophenyl ) - 1 , 4 -dihydro - 2 , 6 -dimethylpyridine-3,5-dicarboxylate

Structural Formula:

![Structural Formula](image)

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

Molecular Weight: 384.26

Description: Felodipine is a white or light yellow, crystalline powder. It is practically insoluble in water, freely soluble in acetone, in ethanol; in methanol and in methylene chloride.
STORAGE AND STABILITY

Store Sandoz Felodipine at 15-30°C. Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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

Sandoz Felodipine 5 mg: Pale red to grey-red, round biconvex film-coated tablet, embossed “F5” on one side.

Sandoz Felodipine 10 mg: Pale red to grey-red, round biconvex film-coated tablet, embossed “F10” on one side.

Tablet Core: Felodipine, Hydroxypropyl-methylcellulose, Lactose monohydrate, Magnesium stearate, Microcrystalline cellulose and Sodium Lauryl Sulphate

Coating Layer: Ferric oxide (red), Ferric oxide (yellow), Hydroxypropyl-methylcellulose, Lactose monohydrate, Polyethylene glycol and Titanium dioxide

Each tablet strength is available in blisters of 30 and bottles of 100.

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

Comparative bioavailability Studies

A randomized, 3-way crossover, bioequivalence study was performed using Sandoz Felodipine, Plendil® and Renedil® 10 mg extended release tablets as a single 10 mg dose in healthy adult males under fasting, fed, and steady-state conditions. The tables below show that Sandoz Felodipine is bioequivalent to the Canadian Reference Product, Plendil®, and to another modified release formulation that is currently marketed in Canada, Renedil®:

Fasting Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sandoz Felodipine (A)</th>
<th>&quot;Plendil®&quot; (B)</th>
<th>&quot;Renedil®&quot; (C)</th>
<th>A vs. B % Ratio of Geometric Means (90% Confidence Interval)</th>
<th>A vs. C % Ratio of Geometric Means (90% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{AUC}_T) (pg(\text{h}/\text{mL}))</td>
<td>32468.18 (42.09)</td>
<td>35672.80 (37.30)</td>
<td>34656.34 (45.17)</td>
<td>91.02 (84.68-97.83)</td>
<td>93.69 (87.16-100.70)</td>
</tr>
<tr>
<td>(\text{AUC}_\text{∞}) (pg(\text{h}/\text{mL}))</td>
<td>34184.44 (42.56)</td>
<td>37239.45 (38.36)</td>
<td>36504.92 (46.26)</td>
<td>91.80 (85.38-98.69)</td>
<td>93.64 (87.10-100.68)</td>
</tr>
<tr>
<td>(\text{C}_{\text{max}}) (pg/mL)</td>
<td>2040 (52.16)</td>
<td>2450 (53.57)</td>
<td>2420 (51.64)</td>
<td>83.27 (74.04-93.66)</td>
<td>84 (74.68-94.48)</td>
</tr>
<tr>
<td>(T_{\text{max}}) (h)</td>
<td>4.50 (1.00-12.0)</td>
<td>4.50 (2.00-16.1)</td>
<td>4.50 (2.50-12.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(T_{\frac{1}{2}}) (h)</td>
<td>16.08 (34.55)</td>
<td>16.37 (27.77)</td>
<td>16.94 (30.45)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(\text{\textsuperscript{a}}\) Expressed as the median (range) only
\(\text{\textsuperscript{b}}\) Expressed as the arithmetic mean (CV\%) only
Plendil® is manufactured by AstraZeneca Canada Inc. and was purchased in Canada
Renedil® is manufactured by Aventis Pharma Inc. and was purchased in Canada
Fed Study

Felodipine
(1 x 10 mg extended-release tablet)
From measured data uncorrected for potency

Geometric Mean Arithmetic Mean (CV %)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sandoz Felodipine (A)</th>
<th>Plendil® (B)</th>
<th>Renidil® (C)</th>
<th>A vs. B % Ratio of Geometric Means (90% Confidence Interval)</th>
<th>A vs. C % Ratio of Geometric Means (90% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;T&lt;/sub&gt; (pg•h/mL)</td>
<td>38590.76 (42.27)</td>
<td>39355.26 (33.65)</td>
<td>38769.07 (34.08)</td>
<td>98.06 (91.07-105.58)</td>
<td>99.54 (92.44-107.18)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;∞&lt;/sub&gt; (pg•h/mL)</td>
<td>39840.50 (43.30)</td>
<td>40748.79 (34.00)</td>
<td>40298.54 (34.85)</td>
<td>97.77 (90.78-105.30)</td>
<td>98.86 (91.79-106.48)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (pg/mL)</td>
<td>6420 (42.47)</td>
<td>6795.77 (37.92)</td>
<td>7105.74 (31.14)</td>
<td>94.48 (84.70-105.38)</td>
<td>90.35 (81.01-100.78)</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; § (h)</td>
<td>4.50 (2.00-24.0)</td>
<td>4.50 (2.00-8.03)</td>
<td>4.50 (2.50-8.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; ε (h)</td>
<td>18.86 (22.08)</td>
<td>20.02 (20.56)</td>
<td>21.22 (21.50)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

§ Expressed as the median (range) only
ε Expressed as the arithmetic mean (CV%) only

Plendil® is manufactured by AstraZeneca Canada Inc. and was purchased in Canada
Renidil® is manufactured by Aventis Pharma Inc. and was purchased in Canada
Steady-state Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sandoz Felodipine*</th>
<th>Plendil®†</th>
<th>Renedil®††</th>
<th>% Ratio of Geometric Means (A/B)</th>
<th>% Ratio of Geometric Means (A/C)</th>
<th>90% Confidence Interval (A/B)</th>
<th>90% Confidence Interval (A/C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;tau&lt;/sub&gt; (pg*h/mL)</td>
<td>35776.2 (48.8)</td>
<td>40099.2 (49.7)</td>
<td>39976.0 (45.9)</td>
<td>89.2</td>
<td>89.5</td>
<td>82.5-96.5</td>
<td>82.8-96.8</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (pg/mL)</td>
<td>2396.6 (41.3)</td>
<td>2928.5 (45.2)</td>
<td>2967.4 (37.7)</td>
<td>81.8</td>
<td>80.8</td>
<td>73.2-91.4</td>
<td>72.2-90.3</td>
</tr>
<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt; (pg/mL)</td>
<td>832.9 (57.0)</td>
<td>832.9 (63.1)</td>
<td>816.0 (63.3)</td>
<td>100.5</td>
<td>102.1</td>
<td>88.5-114.2</td>
<td>89.8-116.0</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;§ (h)</td>
<td>5.00 (61.3)</td>
<td>5.27 (53.0)</td>
<td>5.38 (46.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Sandoz Felodipine 10 mg, Sandoz Canada  
†Plendil® 10 mg felodipine extended-release tablets, AstraZeneca Canada Inc.  
††Renedil® 10 mg felodipine extended-release tablets, Aventis Pharma Inc.  
§ Expressed as the arithmetic mean (CV%) only
DETAILED 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 mcmol/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 mcmol/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 mcml/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. Firstpass elimination reduces oral bioavailability to 20 to 30% for a dose of 5 mcml/kg. This is comparable with the 15% availability in man. Saturation of the first-pass elimination at high felodipine doses to the rat, 150 mcml/kg, results in almost 100% bioavailability.

Felodipine exhibits multiexponentially declining plasma concentration-time curves after IV 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 (14C) 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 mcmol/kg IV and 5 mcmol/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

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 mcmol/kg felodipine given orally, and after repeated doses of 10 mcmol/kg felodipine b.i.d. given orally for 7 days followed by 20 mcmol/kg felodipine b.i.d. given orally for 3 days. After single administration of felodipine 80 mcmol/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 mcmol/kg b.i.d. dose level. Two dogs died at the dose level 20 mcmol/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 than 80 mcmol/kg. With repeated daily doses it has been shown that 20 mcmol/kg (7.7 mg/kg) twice daily with four hour intervals, may be lethal to dogs.

Table 3

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>ROUTE</th>
<th>SEX</th>
<th>NO. OF ANIMALS</th>
<th>DOSE LEVELS mg/kg</th>
<th>LD50 VALUES mg/kg</th>
<th>LD50 VALUES µmol/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice</td>
<td>PO</td>
<td>Male</td>
<td>10</td>
<td>100-700</td>
<td>240 (185-279)</td>
<td>630 (480-730)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>10</td>
<td>150-750</td>
<td>264 (189-330)</td>
<td>690 (490-860)</td>
</tr>
<tr>
<td>Mice</td>
<td>IV</td>
<td>Male</td>
<td>10</td>
<td>6-12</td>
<td>8.6 (8.0-9.5)</td>
<td>22 (21-25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>10</td>
<td>5-12.5</td>
<td>10.4 (9.2-11.8)</td>
<td>27 (24-31)</td>
</tr>
<tr>
<td>Rats</td>
<td>PO</td>
<td>Male</td>
<td>6</td>
<td>1000-4500</td>
<td>2390 (1710-2840)</td>
<td>6230 (4450-7380)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>6</td>
<td>125-4500</td>
<td>2250 (1300-3850)</td>
<td>5900 (3400-10000)</td>
</tr>
<tr>
<td>Rats</td>
<td>IV</td>
<td>Male</td>
<td>6</td>
<td>5-10</td>
<td>6.8 (5.9-7.5)</td>
<td>18 (15-19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>6</td>
<td>3-8</td>
<td>6.4 (4.9-7.1)</td>
<td>17 (13-19)</td>
</tr>
</tbody>
</table>

In a single study, Beagle dogs (2 male, 2 female) were studied after single doses of 20, 40 and 80 mcmol/kg felodipine given orally, and after repeated doses of 10 mcmol/kg felodipine b.i.d. given orally for 7 days followed by 20 mcmol/kg felodipine b.i.d. given orally for 3 days. After single administration of felodipine 80 mcmol/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 mcmol/kg b.i.d. dose level. Two dogs died at the dose level 20 mcmol/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 than 80 mcmol/kg. With repeated daily doses it has been shown that 20 mcmol/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 IV administration in rats.

The studies performed are summarized in Table 4.
### Table 4

<table>
<thead>
<tr>
<th>Species</th>
<th>No. of Animals/Sex/Group</th>
<th>Route of Administration</th>
<th>Frequency of Dosing</th>
<th>Dose Groups (mcmol/kg)</th>
<th>Deaths/Group M</th>
<th>Toxic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats</td>
<td>6</td>
<td>PO</td>
<td>Once daily for one month.</td>
<td>0, 5, 15, 50, 150, 500</td>
<td>0, 2, 15, 19.2, 57.6, 192</td>
<td>At the 150 mcml/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.</td>
</tr>
<tr>
<td>Rats</td>
<td>10</td>
<td>PO</td>
<td>Once daily for 5 weeks.</td>
<td>0, 5, 26, 130, 470</td>
<td>0, 2, 10, 50, 180</td>
<td>The 130 mcml/kg group showed decreased food consumption (most notable on earlier treatment days), lowered levels of plasma neutral fat, increased in liver weight and decreases in submaxillary gland weight. Male weight gain was suppressed. The 470 mcml/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.</td>
</tr>
<tr>
<td>Rats</td>
<td>25</td>
<td>PO</td>
<td>Once daily for 6 months.</td>
<td>0, 5, 25, 125</td>
<td>0, 2, 9.6, 48.0</td>
<td>Distinct hyperemia of the ears, lasting several hours after treatment in all 3 active groups. In mid and high dose groups, males became 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.</td>
</tr>
</tbody>
</table>
Table 4 (continued)

<table>
<thead>
<tr>
<th>Species</th>
<th>No. of Animals/ Sex/Group</th>
<th>Route of Administration</th>
<th>Frequency Duration of Dosing</th>
<th>Dose Groups (µmol/kg)</th>
<th>Deaths/ Group (mg/kg)</th>
<th>Toxic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats</td>
<td>10</td>
<td>IV</td>
<td>Once daily for two weeks.</td>
<td>0 saline</td>
<td>M F</td>
<td>Dose levels 0.3 and 1.0 mc mol/kg produced peripheral vasodilation and apparent hyperthermia 1-3 hours after dosing. Higher liver weight gain in males. Males given 1 mc mol/kg dose showed inferior body weight gain during first 4 days of treatment.</td>
</tr>
<tr>
<td>Dogs</td>
<td>2</td>
<td>PO</td>
<td>Once daily for 1 month.</td>
<td>0 0</td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Dogs</td>
<td>5 grp 1</td>
<td>PO</td>
<td>Twice daily for 12 months in grps 1-4.</td>
<td>0 0</td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Dogs</td>
<td>5 grp 2</td>
<td>PO</td>
<td>Twice daily for 12 months in grps 1-4.</td>
<td>1.0 b.i.d. 0.38 b.i.d</td>
<td></td>
<td>Decrease in osmolality of the urine in mid dose females and both sexes of the high dose. 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.</td>
</tr>
<tr>
<td>Dogs</td>
<td>5 grp 3</td>
<td>PO</td>
<td>Twice daily for 12 months in grps 1-4.</td>
<td>3.0 b.i.d. 1.2 b.i.d</td>
<td></td>
<td>* The initial high dose was 10 mc mol/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.</td>
</tr>
<tr>
<td>Dogs</td>
<td>5 grp 4</td>
<td>PO</td>
<td>Twice daily for 12 months in grps 1-4.</td>
<td>6.0 b.i.d. 2.3 b.i.d</td>
<td>1* 1*</td>
<td></td>
</tr>
</tbody>
</table>
Reproduction Studies
Please refer to Table 6.

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 mcmol/kg over 99 weeks and rats (50 males and 50 females/group) at
doses of 20, 60 and 180 mcmol/kg over 112 weeks. In the mouse study, the high dose group
(360 mcmol/kg) showed an increased incidence of hepatocellular neoplasms (carcinomas and
adenomas) compared with the animals terminally sacrificed from the other groups (see Table 5).

Table 5  Incidence Of Hepatocellular Neoplasms In Mice

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex</th>
<th>No. of Animals¹/Group²</th>
<th>Dose Level mcmol/L</th>
<th>Total No. of Mice with Adenomas¹</th>
<th>Total No. of Mice with Carcinomas¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>93 (14)</td>
<td>0</td>
<td>3</td>
<td>18 (2)</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>41 (9)</td>
<td>40</td>
<td>3</td>
<td>8 (1)</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>42 (9)</td>
<td>120</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>39 (25)</td>
<td>360</td>
<td>0</td>
<td>11 (3)</td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>94 (36)</td>
<td>0</td>
<td>1 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>46 (14)</td>
<td>40</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>48 (25)</td>
<td>120</td>
<td>2</td>
<td>1 (1)</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>42 (28)</td>
<td>360</td>
<td>2 (1)</td>
<td>3</td>
</tr>
</tbody>
</table>

¹ Number of animals entering week 54 and continuing to termination of the study.
² Numbers in brackets are the number of mice that died between week 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".

Sandoz Felodipine
A repeat study in male mice with felodipine in doses of 40, 90 and 180 mcg/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 a 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 6  Fertility And Reproduction Studies

<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>No. of Animals /Group</th>
<th>Period of Administration</th>
<th>Route of Administration</th>
<th>mcmol/kg</th>
<th>mg/kg</th>
<th>Dams</th>
<th>Litters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats, Sprague Dawley</td>
<td>15 M</td>
<td>Appr. 11 weeks(^1)</td>
<td>PO</td>
<td>0</td>
<td>3.8</td>
<td>Parents</td>
<td>Dose dependently increased frequencies of late fetal deaths and early postnatal deaths in animals receiving 25 mcmol/kg or 70 mcmol/kg.</td>
</tr>
<tr>
<td></td>
<td>30 F</td>
<td>Appr. 10 weeks(^1) (Seg I)</td>
<td>PO</td>
<td>10</td>
<td>3.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rats, Sprague Dawley</td>
<td>20 F</td>
<td>Days 6-15 of gestation (Seg II)</td>
<td>PO</td>
<td>25</td>
<td>9.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70</td>
<td>26.9</td>
<td>70 mcmol/kg</td>
<td>Slightly lower food consumption during the dosing period and slightly reduced body weight gain towards the end of the dosing period.</td>
</tr>
<tr>
<td>Rats, Sprague Dawley</td>
<td>20 F</td>
<td>From day 15 of gestation to day 20 post part. (Seg III)</td>
<td>PO</td>
<td>0</td>
<td>3.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>11.5</td>
<td>30 mcmol/kg</td>
<td>Slight prolongation of the gestation period, prolonged parturition and hard labour.</td>
</tr>
<tr>
<td>Rabbit, New Zealand White</td>
<td>5 F</td>
<td>Days 6-19 of gestation (seg II, pilot study)</td>
<td>PO</td>
<td>0</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>3.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabbit, New Zealand White</td>
<td>15 F</td>
<td>Days 6-19 of gestation (Seg II)</td>
<td>PO</td>
<td>25</td>
<td>9.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50</td>
<td>19.2</td>
<td>30 mcmol/kg</td>
<td>Increased frequencies of stillborn fetuses and early postnatal deaths.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
\(^1\)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 6 (continued)

<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>No. of Animals /Group</th>
<th>Period of Administration</th>
<th>Route of Administration</th>
<th>Dams</th>
<th>Litters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit, New Zealand White</td>
<td>15 F</td>
<td>Days 6-18 of gestation (Seg II)</td>
<td>PO</td>
<td>6 mc mol/kg</td>
<td>6 mc mol/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>Reduced food intake during first few days of dosing; this was also seen in the animals receiving 12 mc mol/kg (dose related). Suppression of body wt gain during the first few days of dosing, also seen in the animals receiving 12 mc mol/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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td>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 mc mol/kg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td>Digital anomalies as observed above. Increased preimplantation loss and sight increase in early post-implantation Reduced litter size and litter weight.</td>
</tr>
</tbody>
</table>

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 mc mol/kg.
- A higher incidence of nonaccidental deaths and abortions after this initiation of dosing.
<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>No. of Animals/Group</th>
<th>Period of Administration</th>
<th>Route of Administration</th>
<th>mc mol/kg</th>
<th>mg/kg</th>
<th>Dams</th>
<th>Litters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit, New Zealand White</td>
<td>21 F</td>
<td>Days 6-28</td>
<td>PO</td>
<td>0</td>
<td></td>
<td>Days 6-12</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>21 F</td>
<td>Days 6-12</td>
<td></td>
<td>12</td>
<td>4.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 F</td>
<td>Days 13-18</td>
<td></td>
<td>12</td>
<td>4.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 F</td>
<td>Days 6-28 of gestation (Seg II)</td>
<td></td>
<td>12</td>
<td>4.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Days 13-18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Days 6-28</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Days 6-28</td>
</tr>
</tbody>
</table>
Table 6 (continued)

<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>No. of Animals /Group</th>
<th>Period of Administration</th>
<th>Route of Administration</th>
<th>mcmol/kg</th>
<th>mg/kg</th>
<th>Dams</th>
<th>Litters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit, New Zealand White</td>
<td>10 F</td>
<td>Days 6 - 18 of gestation (Seg II)</td>
<td>PO</td>
<td>0</td>
<td>0</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Rabbit, New Zealand White</td>
<td>10 F</td>
<td>Days 13-18 of gestation</td>
<td>PO</td>
<td>12</td>
<td>4.6</td>
<td>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.</td>
<td>N/A</td>
</tr>
<tr>
<td>Rabbit, New Zealand White</td>
<td>8 F</td>
<td>13 days (Days 0-12)</td>
<td>PO</td>
<td>1.2</td>
<td>0.46</td>
<td>Reduced food consumption and decreased body wt during the dosing period in animals receiving 12 mcmol/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.</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Sandoz Felodipine*
Table 6 (continued)

<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>No. of Animals / Group</th>
<th>Period of Administration</th>
<th>Route of Administration</th>
<th>Plasma Concentration</th>
<th>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.</th>
<th>Litters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit, New Zealand White</td>
<td>9 F</td>
<td>Days 6 - 18 of gestation (Seg II)</td>
<td>PO</td>
<td>1.2 mc mol/kg</td>
<td>0.46</td>
<td>12 mc mol/kg (Day 29 of Gestation) Fetal loss was slightly increased compared to the control group. 1.2 and 12 mc mol/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.</td>
</tr>
<tr>
<td>Rabbit, New Zealand White</td>
<td>15 F</td>
<td>Days 6 - 18 of gestation (Seg II)</td>
<td>PO</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rabbit, New Zealand White</td>
<td>11 F</td>
<td>Days 6 - 18 of gestation (Seg II)</td>
<td>PO</td>
<td>1.2 mc mol/kg</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>Rabbit, New Zealand White</td>
<td>28 F3</td>
<td>Days 6-18 of gestation (Seg II)</td>
<td>PO</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rabbit, New Zealand White</td>
<td>32 F3</td>
<td>Days 6-18 of gestation (Seg II)</td>
<td>PO</td>
<td>12</td>
<td>4.6</td>
<td></td>
</tr>
</tbody>
</table>

Table continued...
Table 6 (continued)

<table>
<thead>
<tr>
<th>Species and Strain</th>
<th>No. of Animals/Group</th>
<th>Period of Administration</th>
<th>Route of Administration</th>
<th>mc mol/kg</th>
<th>mg/kg</th>
<th>Dams</th>
<th>Litters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit, New Zealand White</td>
<td>1/I 3 F4</td>
<td>13</td>
<td>PO</td>
<td>12</td>
<td>4.6</td>
<td>Clinical Observations</td>
<td>Effects on Distal Phalanges</td>
</tr>
<tr>
<td></td>
<td>2/I 3 F</td>
<td>14</td>
<td>PO</td>
<td>12</td>
<td>4.6</td>
<td>One dam dosed on Day 16 aborted on Day 20 and was killed on Day 23 for humanitarian reasons.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/I 3 F</td>
<td>15</td>
<td>PO</td>
<td>12</td>
<td>4.6</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4/I 3 F</td>
<td>16</td>
<td>PO</td>
<td>12</td>
<td>4.6</td>
<td>Two dams dosed on Day 16 showed pale livers and distended caecum. Also two dams dosed on Day 17 showed pale livers.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/II 3 F</td>
<td>15</td>
<td>PO</td>
<td>12</td>
<td>4.6</td>
<td>Terminal Autopsy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2/II 3 F</td>
<td>16</td>
<td>PO</td>
<td>12</td>
<td>4.6</td>
<td>Two dams dosed on Day 16 showed pale livers and distended caecum. Also two dams dosed on Day 17 showed pale livers.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/II 3 F</td>
<td>17</td>
<td>PO</td>
<td>12</td>
<td>4.6</td>
<td>Two dams dosed on Day 16 showed pale livers and distended caecum. Also two dams dosed on Day 17 showed pale livers.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4/II 3 F</td>
<td>18</td>
<td>PO</td>
<td>12</td>
<td>4.6</td>
<td>Two dams dosed on Day 16 showed pale livers and distended caecum. Also two dams dosed on Day 17 showed pale livers.</td>
<td></td>
</tr>
</tbody>
</table>

Rabbit, New Zealand White | 1 4 F | single, Day 16 of gestation | PO | - | - | THIS STUDY DID NOT DIFFERENTIATE BETWEEN DAMS AND LITTERS |
| 2 4 F | | | 12 | 4.6 | Concentration of Felodipine in Maternal Plasma, Fetal Tissue and Amniotic Fluid |
| 3 4 F | | | 12 | 4.6 | 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). |
| 4 3 F | | | 12 | 4.6 | 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. |
| 5 4 F | | | 12 | 4.6 | Concentration in Amniotic Fluid: These were about 2 to 4 times lower than those in fetal tissue. |
| 6 6 F | | | 125 | 4.6 | 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 site 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 mc mol/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.
REFERENCES


AstraZeneca Canada Inc., Mississauga (ON), Canada, PLENDIL® Product Monograph (felodipine extended release tablets, 2.5 mg, 5 mg and 10 mg), Control No.: 177716; Date of Revision: January 15, 2015.

Sanofi-aventis Canada Inc., Laval (QC), Canada, RENEDIL® Product Monograph (felodipine extended release tablets, 2.5 mg, 5 mg and 10 mg), Control No.: 105393; Date of Revision: April 26, 2006
PART III: CONSUMER INFORMATION

Sandoz Felodipine
felodipine extended release tablets

This leaflet is part III of a three-part "Product Monograph" published when Sandoz Felodipine was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Sandoz Felodipine. Contact your doctor or pharmacist if you have any questions about the drug.

WARNINGS AND PRECAUTIONS

BEFORE you use Sandoz Felodipine talk to your doctor or pharmacist if:

- you are pregnant or plan to become pregnant.
- you are breast feeding.
- you have or have had heart failure.
- you ever had heart or blood vessel disease.
- you have very low blood pressure.
- you are older than 65 years of age.
- you are allergic to "non-medicinal" substances like food products, preservatives, or dyes, which may be present in Sandoz Felodipine tablets (See ‘WHAT THE NONMEDICINAL INGREDIENTS ARE”).
- you have ever had a bad, unusual or allergic reaction to "felodipine".

This medicine contains lactose. Tell your doctor if you have an intolerance to some sugars.

A few patients report mild tenderness or swelling of their gums while taking Sandoz Felodipine. This effect can be prevented or reversed 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.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist about any medicines you are taking or have recently taken, including prescription medications (the ones your doctor writes for you), and over-the-counter medications like cold or allergy medication, or natural health products (herbal medicines). If you visit more than one doctor make sure that each knows about all the medicines you are taking.

Certain medicines or alcohol or food may affect the way Sandoz Felodipine works.

Drug-Drug Interactions
Drugs that may interact with Sandoz Felodipine include:

- certain anti-ulcer drugs (cimetidine)
- antibiotics (erythromycin, clarithromycin)
- antimalarials (itraconazole, ketoconazole),
- sleeping pills (barbiturates)
- drugs used to prevent epilepsy (phenytoin, carbamazepine).
- tacrolimus. Treatment with Sandoz Felodipine may affect the level of tacrolimus (a medicine given to prevent the body from rejecting a transplanted organ, e.g. kidney or liver) in your blood.

Drug-Food Interactions
Food that may interact with Sandoz Felodipine includes:

- Grapefruit juice may also affect treatment with Sandoz Felodipine. Do not eat grapefruit or drink grapefruit juice while on Sandoz Felodipine.
- Alcohol

ABOUT THIS MEDICATION

What the medication is used for:
Sandoz Felodipine is used to treat hypertension (high blood pressure).

What it does:
Sandoz Felodipine contains the ingredient called felodipine. It belongs to the group of drugs called "calcium channel blockers" or "calcium antagonists".

Sandoz Felodipine relaxes your blood vessels, which lets your blood flow more easily and helps lower your blood pressure.

Sandoz Felodipine is formulated as extended release tablets which control the speed of the drug being delivered to the body and ensure even effects over the day.

When it should not be used:
Sandoz Felodipine should not be used if you:
- are allergic to felodipine or any of the nonmedicinal ingredients in Sandoz Felodipine tablets.
- have a known allergy to other dihydropyridines (calcium channel blockers).
- are pregnant. You should tell your doctor as soon as possible if you become pregnant while using Sandoz Felodipine.
- are breast feeding.
- are age 18 or younger.

What the medicinal ingredient is:
Felodipine

What the nonmedicinal ingredients are:
Tablet Core: hydroxypropyl-methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose and sodium lauryl sulphate

Coating Layer: ferric oxide (red), ferric oxide (yellow), hydroxypropyl-methylcellulose, lactose monohydrate, polyethylene glycol and titanium dioxide

What dosage forms it comes in:
Extended release tablets 5 mg and 10 mg felodipine
• Food rich in carbohydrate and fat

**Drug-Herb Interactions**
Herbs that may interact with Sandoz Felodipine include:
• St. John’s Wort

**PROPER USE OF THIS MEDICATION**

**Usual dose:**

**Adults**
Take Sandoz Felodipine 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.

Do not take any Sandoz Felodipine if it is not prescribed for you.

• Sandoz Felodipine 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 Sandoz Felodipine with something you do regularly each day; for example, upon waking or at breakfast. This will help you remember each dose.
• Swallow Sandoz Felodipine whole with a glass of water. Do not crush, chew, break or suck on the tablets.
• Sandoz Felodipine 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. Sandoz Felodipine 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).

Check with your doctor if you want to drink alcohol (including wine with your meals) while you are taking Sandoz Felodipine. Drinking alcohol while on Sandoz Felodipine 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 Sandoz Felodipine even when you feel well.** A constant amount of drug is needed in your body to control your blood pressure. **Do not stop taking Sandoz Felodipine on your own.**

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

**Missed Dose:**
If you miss a dose of Sandoz Felodipine 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 than 12 hours when you remember, do not take the missed dose. Just take the next dose on time.

**Never take a double dose of Sandoz Felodipine** 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 AND WHAT TO DO ABOUT THEM**
Along with its effects on controlling blood pressure, Sandoz Felodipine, like any medication, may include side effects. Some side effects may occur when Sandoz Felodipine 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 Sandoz Felodipine.

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;
• a racing heartbeat;
• flushing or a feeling of warmth;
• headache;
• dizziness;
• 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 Sandoz Felodipine with your doctor and pharmacist. **Do not stop taking Sandoz Felodipine on your own.**

Other side effects have been reported in a few cases. These include too low blood pressure (hypotension) as fainting or dizziness, tingling in the hands, arms, feet or legs, stomach upset, diarrhea, nausea, vomiting, abdominal pain, the need to urinate frequently, fever, 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.

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

<table>
<thead>
<tr>
<th>Symptom / effect</th>
<th>Talk with your doctor or pharmacist</th>
<th>Stop taking drug and seek immediate medical help</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Rash or itchiness</td>
<td>☑</td>
</tr>
</tbody>
</table>

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

If you take more than the recommended number of doses of Sandoz Felodipine, you may suffer from very low blood pressure and sometimes slow heart rate. Therefore, it is very important that you take the number of doses prescribed by your doctor. If you experience symptoms such as feeling faint, light-headedness or dizziness, contact your doctor or pharmacist immediately.
### SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

<table>
<thead>
<tr>
<th>Symptom / effect</th>
<th>Talk with your doctor or pharmacist</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Increased liver enzymes (symptoms like yellowing of the skin or eyes)</td>
<td>![OK]</td>
</tr>
<tr>
<td><strong>Isolated cases</strong></td>
<td>Allergic reactions (symptoms like swelling of the face, lips, tongue and/or throat; rash or other skin reactions; difficulty breathing)</td>
<td>![OK]</td>
</tr>
</tbody>
</table>

*If you think you have these side effects, it is important that you seek medical advice from your doctor immediately.*

*This is not a complete list of side effects. For any unexpected effects while taking Sandoz Felodipine, contact your doctor or pharmacist.*

### HOW TO STORE IT

Store Sandoz Felodipine at 15-30°C. Protect from light.

Do not keep Sandoz Felodipine in the bathroom.

**Keep Sandoz Felodipine out of sight and reach of children.**

Do not keep or use Sandoz Felodipine after the expiry date indicated on the package. Unused medicines which you know you will no longer need should be carefully discarded. You may wish to seek advice from your pharmacist.

### REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program Health Canada Postal Locator 0701E Ottawa, Ontario K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

**NOTE:** Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

### MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Sandoz Canada Inc., at:

1-800-361-3062

or by written request at:

145 Jules-Léger

Boucherville QC

J4B 7K8

Or by e-mail at:

medinfo@sandoz.com

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