PRODUCT MONOGRAPH

[Pr] ALTACE® PLUS FELODIPINE

(Felodipine Extended Release + Ramipril)

Film-coated Tablets: 2.5 + 2.5 mg, and 5 + 5 mg

Antihypertensive Agent

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THERAPEUTIC CLASSIFICATION

Antihypertensive Agent

ACTION AND CLINICAL PHARMACOLOGY

Altace Plus Felodipine (felodipine ER/ramipril) is a formulation containing extended-release felodipine, a dihydropyridine calcium channel blocker, along with immediate-release ramipril, an angiotensin converting enzyme (ACE) inhibitor.

Ramipril:
Ramipril is an ACE inhibitor. Following oral administration, ramipril is rapidly hydrolyzed to ramiprilat, its principal active metabolite. ACE catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE activity leads to decreased levels of angiotensin II thereby resulting in decreased vasoconstriction and decreased aldosterone secretion. The latter decrease may result in a small increase in serum potassium (see PRECAUTIONS). Decreased levels of angiotensin II and the accompanying lack of negative feedback on renal renin secretion result in increases in plasma renin activity.

ACE is identical to kininase II. Thus, ramipril may also block the degradation of the vasodepressor peptide bradykinin, which may contribute to its therapeutic effect.

Felodipine:
The therapeutic effect of the dihydropyridine class of calcium channel blockers 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 indicate 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 Pharmacodynamics).

Pharmacokinetics

Ramipril:

Following oral administration, ramipril is rapidly absorbed with peak plasma concentrations occurring within 1 hour. The extent of absorption of ramipril is 50-60% and is not significantly altered by the presence of food in the gastrointestinal tract, although the rate of absorption is reduced.

Following absorption, ramipril is rapidly hydrolyzed in the liver to its active metabolite, ramiprilat, reaching peak plasma concentrations 2-4 hours after drug intake. The serum protein binding of ramipril is about 73% and that of ramiprilat is 56%.

Ramipril is almost completely metabolized to the active metabolite ramiprilat, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat, all of which are inactive. After oral administration of ramipril, about 60% of the parent drug and its metabolites are excreted in the urine, and about 40% are found in the feces. Drug recovered in the feces may represent both biliary excretion of metabolites and/or unabsorbed drug. Less than 2% of the administered dose is recovered in urine as unchanged ramipril.

Following a single administration of up to 5 mg of ramipril, plasma concentrations of ramipril and ramiprilat increase in a manner that is greater than proportional to dose; after a single administration of 5 mg to 20 mg of ramipril the plasma concentrations for both are dose-proportional. The non-linear pharmacokinetics observed at the lower doses of ramipril can be explained by the saturable binding of ramiprilat to ACE. At steady-state, the 24-hour AUC for ramiprilat is dose-proportional over the recommended dose range. The absolute bioavailabilities of ramipril and ramiprilat were 28% and 44% respectively when 5mg of oral ramipril was compared to 5mg given intravenously.

Plasma concentrations of ramiprilat decline in a triphasic manner. The initial rapid decline, which represents distribution of the drug, has a half life of 2-4 hours. Because of its potent binding to ACE and slow dissociation from the enzyme, ramiprilat shows two elimination phases. The apparent elimination phase has a half-life of 9-18 hours, and the terminal elimination phase has a prolonged half-life of > 50 hours. After multiple daily doses of ramipril 5-10 mg, the half-life of ramiprilat concentrations was 13-17 hours, but was considerably prolonged at 2.5 mg (27-36 hours).

After once-daily dosing, steady state plasma concentrations of ramiprilat are reached by the fourth dose. Steady-state concentrations of ramiprilat are higher than those seen after the first dose of ramipril especially at low doses (2.5 mg).

The urinary excretion of ramipril, ramiprilat, and their metabolites is reduced in patients with impaired renal function. In patients with creatinine clearance < 40ml/min/1.73m^2, increases in

C_{max} and AUC of ramipril and ramiprilat compared to normal subjects were observed following multiple dosing with 5 mg ramipril (see DOSAGE AND ADMINISTRATION).

In patients with impaired liver function, plasma ramipril levels increased about 3-fold, although peak concentrations of ramiprilat in these patients were not different from those seen in patients with normal hepatic function.

A single dose pharmacokinetics study conducted in a limited number of elderly patients indicated that peak ramiprilat levels and the AUC for ramiprilat are higher in older patients (see PRECAUTIONS).

Felodipine:
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 felodipine 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 felodipine 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 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_{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_{max} of felodipine increased about threefold as compared to administration with water. When 10 mg felodipine extended release tablets were administered 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 felodipine administration, a significant pharmacokinetic interaction was observed (see PRECAUTIONS - Interaction with Grapefruit Juice).

Plasma concentrations of felodipine, after a single oral 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.

Ramipril + Felodipine:
With Altace Plus Felodipine, the pharmacokinetics of ramipril, ramiprilat and felodipine are essentially unaltered compared to the individual components.

Pharmacodynamics
Ramipril:
Administration of ramipril to patients with mild to moderate essential hypertension results in a reduction of both supine and standing blood pressure usually with little or no orthostatic change or change in heart rate. Symptomatic postural hypotension is infrequent, although this may occur in patients who are salt-and/or volume depleted (see WARNINGS).

In single-dose studies, doses of 5-20 mg of ramipril lowered blood pressure within 1-2 hours, with peak reductions achieved 3-6 hours after dosing. At recommended doses given once daily, antihypertensive effects have persisted over 24 hours.

The effectiveness of ramipril appears to be similar in the elderly (over 65 years of age) and younger adult patients given the same daily doses.

In studies comparing the same daily dose of ramipril given as a single morning dose or as a twice daily dose, blood pressure reductions at the time of morning trough blood levels were greater with the divided regimen.

While the mechanism through which ramipril lowers blood pressure appears to result primarily from suppression of the renin-angiotensin-aldosterone system, ramipril has an antihypertensive effect even in patients with low-renin hypertension.

The antihypertensive effect of ACE inhibitors is generally lower in black patients than in non-blacks.

The antihypertensive effect of ramipril and thiazide diuretics used concurrently is greater than that seen with either agent used alone.

Abrupt withdrawal of ramipril has not resulted in a rapid increase in blood pressure.

Felodipine:
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 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 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.

Ramipril + Felodipine:

Double-blind clinical studies have shown that the effects of concurrent use of felodipine ER and ramipril are additive with respect to lowering systolic and diastolic blood pressure in mild to moderate hypertensives.

INDICATIONS AND CLINICAL USES

Altace Plus Felodipine (felodipine ER/ramipril) is indicated for the treatment of mild to moderate essential hypertension in patients for whom combination therapy is appropriate.

Altace Plus Felodipine is not indicated for initial therapy. Patients in whom felodipine ER and ramipril are initiated simultaneously can develop symptomatic hypotension (see WARNINGS – Hypotension).

Patients should be titrated with individual drugs. If the fixed combination represents the dosage determined by this titration, the use of Altace Plus Felodipine may be more convenient in the management of patients. If during maintenance therapy dosage adjustment is necessary, it is advisable to use individual drugs.

They can be tried as initial agents in those patients in whom diuretics and/or beta blockers are contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

In using ramipril, consideration should be given to the risk of angioedema (see WARNINGS).

The safety and efficacy of ramipril in renovascular hypertension has not been established and therefore its use in this condition is not recommended.

CONTRAINDICATIONS

Altace Plus Felodipine (felodipine ER/ramipril) is contraindicated in:

- patients with known hypersensitivity to felodipine or other dihydropyridines, ramipril or any other ACE inhibitors, or any of the excipients of the formulation;
- patients with a history of angioedema;
- patients with haemodynamically relevant bilateral renal artery stenosis, or unilateral renal artery stenosis in the single kidney**.**
- patients with hypotensive states.
- women of childbearing potential, in pregnancy, and during lactation. Fetal malformations and adverse effects have been reported in animals

Concomitant use of ACE inhibitors and extracorporeal treatment leading to contact of blood with negatively charged surfaces must be avoided (see PRECAUTIONS, Anaphylactoid reactions during membrane exposure).

Teratogenic Effects
Studies in pregnant rabbits administered doses of 0.46, 1.2, 2.3 and 4.6 mg/kg/day felodipine (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 abnormalities 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 groups treated with felodipine 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 felodipine 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

Serious Warnings and Precautions

When used in pregnancy, angiotensin converting enzyme (ACE) inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected, Altace Plus Felodipine should be discontinued as soon as possible.

Angioedema
Angioedema-Head and Neck
Angioedema has been reported in patients with ACE inhibitors, including ramipril. Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the face, tongue or glottis occurs, Altace Plus Felodipine (felodipine ER/ramipril) should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, although antihistamines may be useful in relieving symptoms. Where there is involvement of tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy (including, but not

limited to 0.3 to 0.5 ml of subcutaneous epinephrine solution 1:1000) should be administered promptly (see ADVERSE REACTIONS).

Angioedema – Intestinal
Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases facial angioedema also occurred. The intestinal angioedema symptoms resolved after stopping the ACE inhibitor.

The incidence of angioedema during ACE inhibitor therapy has been reported to be higher in black than in non-black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see CONTRAINDICATIONS).

Angioedema, including laryngeal edema, may occur especially following the first dose of Altace Plus Felodipine.

Congestive Heart Failure
The safety and efficacy of the felodipine component in Altace Plus Felodipine has not been established in patients with heart failure. Caution should, therefore, be exercised when using Altace Plus 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 with felodipine have not demonstrated negative inotropic effects.

Hypotension, Myocardial Ischemia
Altace Plus 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 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.

Symptomatic hypotension occurs usually after the first or second dose or when the dose is increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, vomiting, in other situations in which a significant activation of the renin-angiotensin system is to be anticipated such as in patients with severe, and particularly with malignant hypertension, in patients with haemodynamically relevant left-ventricular outflow impediment (e.g., stenosis of the aortic valve) or in patients with haemodynamically relevant renal artery stenosis.

In patients with ischemic heart disease or cerebrovascular disease, an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident (see ADVERSE REACTIONS). Because of the potential fall in blood pressure in these patients, therapy with

Altace Plus Felodipine should be started under close medical supervision. Such patients should be followed closely for the first weeks of treatment and whenever the dose of Altace Plus Felodipine is increased. In patients with severe congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension and has been associated with oligouria, and/or progressive azotemia, and rarely, with acute renal failure and/or death.

Generally, it is recommended that dehydration, hypovolaemia or salt depletion be corrected before initiating treatment (in patients with heart failure, however, such corrective action must be carefully weighed against the risk of volume overload). When these conditions have become clinically relevant, treatment with Altace Plus Felodipine must only be started or continued if appropriate steps are taken concurrently to prevent an excessive fall in blood pressure and deterioration of renal function.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of 0.9% sodium chloride. A transient hypotensive response may not be a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion in hypertensive patients. However, lower doses of Altace Plus Felodipine and/or reduced concomitant diuretic therapy should be considered.

Beta-Blocker Withdrawal
Altace Plus 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
Altace Plus Felodipine should be used with caution in the presence of fixed 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.

Neutropenia/agranulocytosis
Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Rare cases of agranulocytosis, neutropenia or leukopenia have been reported in which a causal relationship to ramipril cannot be excluded. Current experience with the drug shows the incidence to be rare. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and/or renal disease (see PRECAUTIONS – Monitoring and Laboratory Tests).

Pregnant Women
See CONTRAINDICATIONS

ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, Altace Plus Felodipine should be discontinued as soon as possible.

Pregnancy must be excluded before starting treatment. Pregnancy must be avoided in cases where treatment with Altace Plus Felodipine is required. If the patient intends to become pregnant, treatment with Altace Plus Felodipine must be discontinued.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function, associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development.

Prematurity, and patent ductus arteriosus and other structural cardiac malformations, as well as neurologic malformations, have also been reported following exposure in the first trimester of pregnancy.

Infants with a history of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for impaired renal function; however, limited experience with those procedures has not been associated with significant clinical benefit.

It is not known if ramipril or ramiprilat can be removed from the body by hemodialysis.

Animal Data: No teratogenic effects of ramipril were seen in studies of pregnant rats, rabbits, and cynomolgus monkeys. The doses used were: 10, 100, or 1000 mg/kg in rats (2500 times maximum human dose), 0.4, 1.0, or 2.5 mg/kg in rabbits (6.25 times maximum human dose), and 5, 50, 500 mg/kg in cynomolgus monkeys (1250 times maximum human dose). In rats, the highest dose caused reduced food intake in the dams, with consequent reduced birth weights of the pups and weight development during lactation period. In rabbits, maternal effects were mortalities (high and middle dose) and reduced body weight. In monkeys, maternal effects were mortalities (high and middle dose), vomiting, and reduced weight gain.

Nursing Women

The presence of concentrations of ACE inhibitor have been reported in human milk. The use of Altace Plus Felodipine is contraindicated during breast-feeding.

PRECAUTIONS

Due to the additive actions of an ACE inhibitor with a calcium-channel blocker, concomitant therapy of felodipine and ramipril may result in hypotension. In controlled studies, hypotension was observed in 0.1% of uncomplicated hypertensive patients. Dizziness occurred more frequently than placebo (see ADVERSE EVENTS).

Renal Impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk; therefore, discontinuation of diuretic therapy may be required.

Use of Altace Plus Felodipine (felodipine ER/ramipril) should include appropriate assessment of renal function.

Altace Plus Felodipine should be used with caution in patients with renal insufficiency as they may require reduced or less frequent doses (see DOSAGE AND ADMINISTRATION). Close monitoring of renal function during therapy should be performed as deemed appropriate in patients with renal insufficiency.

Anaphylactoid reactions during membrane exposure

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (i.e. polyacrylonitrile [PAN]) and treated concomitantly with an ACE inhibitor. Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agents.

Anaphylactoid reactions during LDL apheresis

Rarely, patients receiving ACE inhibitors during low density lipoprotein apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding the ACE inhibitor therapy prior to each apheresis.

Anaphylactoid reactions during desensitisation

There have been isolated reports of patients experiencing sustained life-threatening anaphylactoid reactions while receiving ACE inhibitors during desensitization treatment with hymenoptera (bees, wasps) venom. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld for at least 24 hours, but they have reappeared upon inadvertent rechallenge.

Hyperkalemia and Potassium-Sparing Diuretics
Elevated serum potassium (greater than 5.7 mEq/l) was observed in approximately 1% of hypertensive patients in clinical trials with ramipril. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was not a cause of discontinuation of therapy in any hypertensive patient. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia or other drugs associated with increases in serum potassium (see PRECAUTIONS - Drug Interactions).

Surgery/Anesthesia
In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ramipril blocks angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume repletion.

Aortic Stenosis
There is concern on theoretical grounds, that patients with aortic stenosis might be a particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Patients with Impaired Liver Function
Hepatitis (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy with ACE inhibitors in patients with or without pre-existing liver abnormalities. In most cases the changes were reversed on discontinuation of the drug.

Elevations of liver enzymes and/or serum bilirubin have been reported with Altace Plus Felodipine (see ADVERSE REACTIONS). Should the patient receiving Altace Plus Felodipine experience any unexplained symptoms particularly during the first weeks or months of treatment, it is recommended that a full set of liver function tests and any other necessary investigations be carried out. Discontinuation of Altace Plus Felodipine should be considered when appropriate.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. In patients with impaired liver function, response to the treatment with ramipril may be either increased or reduced. In addition, in patients in whom severe liver cirrhosis with oedema and/or ascites is present, the renin-angiotensin system may be significantly activated. Ramipril should be used with particular caution in patients with pre-existing liver abnormalities.

Altace Plus Felodipine should be used with caution in patients with pre-existing liver abnormalities. In such patients baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effects should apply.

Rarely, ACE inhibitors, including ramipril, have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

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

Pediatric Use
The safety and effectiveness of Altace Plus Felodipine in children have not been established; therefore use in this age group is not recommended.

Patient Alertness
Some undesirable effects (e.g. some symptoms of a reduction in blood pressure such as lightheadedness, dizziness, syncope) may be accompanied by an impairment of the ability to concentrate and react. This may constitute a risk in situations where these abilities are of special importance, e.g., when driving a car or operating machinery (see ADVERSE REACTIONS).

Use in Elderly
Although clinical experience with Altace Plus Felodipine has not identified differences in response between the elderly (> 65 years) and younger patients, greater sensitivity of some older individuals cannot be ruled out. Patients over 65 years of age may have elevated plasma concentrations of felodipine and, therefore, may require lower doses of Altace Plus 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 felodipine daily should not be exceeded (see DOSAGE AND ADMINISTRATION- Felodipine, Use in the elderly).

Cough
A dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose of ramipril, has been reported. Such possibility should be considered as part of the differential diagnosis of cough.

Gingival Hyperplasia
Felodipine can induce gingival enlargement in patients with pronounced gingivitis and periodontitis. However, such changes may be reversed by measures of good oral hygiene and mechanical debridement of the teeth.

Peripheral Edema
Mild to moderate peripheral edema was the most common adverse event in the clinical trials investigating felodipine effects. 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 felodipine daily to about 30 percent in those over 60 years taking 20 mg felodipine 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.

Monitoring and Laboratory Tests

Hematological monitoring
Periodic monitoring of white blood cell counts should be considered to permit detection of a possible leukopenia. More frequent monitoring is advised in the initial phase of treatment and in patients with impaired renal function, those with concomitant collagen disease (e.g. lupus erythematosus or scleroderma) or those treated with other drugs that can cause changes in the blood picture (see Drug Interactions – Allopurinol, Immunosuppressants, Corticosteroids, Procainamide, Cytostatics and other substances that may change the blood picture).

Renal function monitoring
Use of ramipril should include appropriate assessment of renal function, particularly in the initial weeks treatment with an ACE inhibitor. Close monitoring of renal function during therapy should be performed as deemed appropriate in patients with renal insufficiency.
Particularly careful monitoring is required in patients with:

- heart failure
- renovascular disease, including patients with haemodynamically relevant unilateral renal artery stenosis. In the latter patient group, even a small increase in serum creatinine may be indicative of unilateral loss of renal function.
- impairment of renal function
- kidney transplant

Electrolyte monitoring
It is recommended that serum potassium be monitored regularly. More frequent monitoring of serum potassium is necessary in patients with impaired renal function.

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 and during treatment with Altace Plus Felodipine 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 P450 system, mainly via the CYP 3A4 isoenzyme. Coadministration 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, 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 P450 system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, warfarin. An increase in the plasma levels of

felodipine may be expected.

Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, rifampin. A decrease in the plasma levels of felodipine may be expected.

Drugs known to be biotransformed via P450 include: benzodiazepines, flecainide, imipramine, propafenone, terfenadine, theophylline.

Concomitant Diuretic Therapy: Due principally to the ramipril component, patients concomitantly taking Altace Plus Felodipine and diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy. The possibility of hypotensive effects after the first dose of ramipril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ramipril. If it is not possible to discontinue the diuretic, the starting dose of ramipril should be reduced and the patient should be closely observed for several hours following the initial dose and until blood pressure has stabilized (see WARNINGS and DOSAGE AND ADMINISTRATION). Regular monitoring of serum sodium is recommended in patients undergoing concurrent diuretic therapy.

Other substances with antihypertensive potential (e.g. nitrates): Potentiation of the antihypertensive effect is to be anticipated.

Vasopressor sympathomimetics: These may reduce the antihypertensive effect of Altace Plus Felodipine. Particularly close blood pressure monitoring is recommended.

Agents Increasing Serum Potassium: Since ramipril decreases aldosterone production, elevation of serum potassium may occur. Potassium sparing diuretics such as spironolactone, triamterene or amiloride, or potassium supplements should be given only for documented hypokalemia and with caution and frequent monitoring of serum potassium, since they may lead to a significant increase in serum potassium. Salt substitutes which contain potassium should also be used with caution (see also Nonsteroidal Anti-inflamatory Agents and acetylsalicylic acid).

Agents Causing Renin Release: The antihypertensive effect of ramipril is augmented by antihypertensive agents that cause renin release (i.e. diuretics).

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be further increased.

Antacids: In one open-label, randomized, cross-over single dose study in 24 male subjects, it was determined that the bioavailability of ramipril and the pharmacokinetic profile of ramiprilat were not affected by concomitant administration of the antacid, magnesium and aluminum hydroxides.

Warfarin: The co-administration of ramipril with warfarin did not alter the anticoagulant effects.

Acenocoumarol: In a multi-dose, double-blind, placebo-controlled, pharmacodynamic interaction study with 14 patients with mild hypertension administered both ramipril and therapeutic doses of acenocoumarol, blood pressure, thrombotest time and coagulation factors were not significantly changed.

Heparin: rise in serum potassium concentration possible.

Nonsteroidal Anti-inflammatory Agents and acetylsalicylic acid: The antihypertensive effects of ACE inhibitors may be reduced with concomitant administration of nonsteroidal anti-inflammatory agents (e.g. indomethacin). Concomitant treatment of ACE inhibitors and nonsteroidal anti-inflammatory drugs may lead to an increased risk of worsening of renal function and an increase in serum potassium (see also Agents Increasing Serum Potassium).

Cimetidine: In healthy volunteers, pharmacokinetic studies showed an approximately 50 percent increase in the area under the felodipine 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 felodipine, and therefore Altace Plus Felodipine, be used when given concomitantly with cimetidine.

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

Phenytoin, Carbamazepine and Phenobarbitol: In a pharmacokinetic 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: increased vasodilatation. Alcohol may enhance the hemodynamic effects of Altace Plus Felodipine.

Salt: Increased dietary salt intake may attenuate the antihypertensive effect of Altace Plus 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.

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

Digoxin: When concomitantly administered 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. In one open-label study in 12 subjects, administered multiple doses of both ramipril and digoxin, no changes were found in serum levels of ramipril, ramiprilat, and digoxin.

Antidiabetic agents (e.g. insulin, metfomin, sulfonylurea derivates): ACE inhibitors may reduce insulin resistance. In isolated cases, such reduction may lead to hypoglycaemic reactions in patients concomitantly treated with antidiabetics. Particularly close blood glucose monitoring is, therefore, recommended in the initial phase of co-administration.

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood picture: increased likelihood of haematological reactions.

ADVERSE REACTIONS

The combination of ramipril and felodipine ER in a 1:1 ratio has been evaluated in 763 hypertensive patients in short-term double-blind trials and 278 patients during long term studies for 1 year. The most frequent clinical adverse experiences were headache (8.4%), increased cough (5.9%), vasodilatation (3.0%), bronchitis (2.9%) and dizziness (2.6%).

Adverse events that occurred have been previously reported for felodipine or ramipril as monotherapy for the treatment of hypertension. In clinical trials with the combination of felodipine and ramipril, peripheral edema and vasodilatation occurred at a lower incidence than with felodipine monotherapy (Table 1). The most common adverse events occurring in ≥ 1% of patients on combination therapy are shown in the following table:

Table 1. Incidence (%) of adverse events on monotherapy vs combination therapy

Body system Adverse event	Felodipine[1] Monotherapy n=486	Ramipril[2] Monotherapy n=585	All FR[3] Combinations n=1042
Nervous system			
Headache	8.2	6.3	8.4
Dizziness	2.3	3.2	2.6
Vertigo	1.2	0.5	1.9
Respiratory system			
Cough increased	3.3	6.7	5.9
Bronchitis	0.6	0.3	2.9
Upper respiratory infection	2.5	1.4	1.2
Cardiovascular system			

Vasodilatation	5.8	2.4	3.0
Palpitation	1.0	0.7	1.4
Body as a whole			
Back pain	1.6	1.0	2.4
Infection	2.7	3.1	2.3
Asthenia	1.2	2.7	2.3
Flu syndrome	1.2	1.4	1.9
Accidental injury	0.4	0.9	1.1
Abdominal pain	0.6	0.9	1.0
Metabolic and Nutritional			
Peripheral edema	5.6	1.0	2.4
Digestive system			
Nausea	1.9	1.7	2.0
Diarrhea	0.4	1.0	1.2

FR = felodipine ER + ramipril combination therapy
1 This column includes patients receiving felodipine ER 2.5 mg (n=213), 5 mg (n=233) or 10 mg (n=40).
2 This column includes patients receiving ramipril 2.5 mg (n=255), 5 mg (n=289) or 10 mg (n=41).
3 This column includes only felodipine ER + ramipril combinations administered in a 1:1 dosage ratio.

During clinical trials serious adverse event occurred on study medication in 30 of 2198 patients (1.4%). The following serious adverse events were observed in 13 of 680 (1.9%) patients treated with the 2.5/2.5 mg dosage strength: myocardial infarction (2 patients), gastroenteritis, influenza, epistaxis, colon carcinoma, cerebrovascular accident (2 patients), hemiplegia, retinal disorder, hydronephrosis, abdominal pain (2 patients), carcinoma, blurred vision, dizziness, heaviness in extremities, minor stroke, surgery (2 patients), accidental injury (2 patients), arthralgia, sinus bradycardia, joint disorder, angina pectoris, shock, sweating, and vomiting. The following serious adverse events were observed in 5 of 429 (2.0%) patients treated with the 5.0/5.0 mg dosage strength: colon carcinoma, gastroenteritis, pulmonary embolism, abdominal pain (2 patients), and malignant cerebral tumor.

Of the 680 patients treated with the 2.5/2.5 mg dosage strength, 27 patients (4.0%) discontinued due to adverse events. Of the 429 patients treated with the 5.0/5.0 mg dosage strength, 15 patients (3.5%) discontinued due to adverse events.

Treatment-emergent clinical adverse events that occurred with an incidence of <1% but in at least two patients in double-blind and long term safety trials (1 year) are listed below by body system:

Body as a Whole: fever, pain, pain in extremity, surgery, carcinoma, face edema, neck pain.

Cardiovascular System: arrhythmia, extrasystoles, tachycardia, T inverted, angina pectoris, ECG abnormal, myocardial infarction, chest pain, migraine, postural hypotension, peripheral vascular disorder, cerebrovascular accident.

Digestive System: periodontal abscess, colitis, constipation, anorexia, dyspepsia, eructation, flatulence, gastroenteritis, gastrointestinal disorder, gastrointestinal pain, vomiting, liver fatty deposit, sore throat, enteritis, gastritis.

Endocrine System: diabetes mellitus.

Metabolic and Nutritional Disorders: gout, edema.

Musculo-skeletal System: arthralgia, arthritis, arthrosis, joint disorder, muscle cramps, myalgia.

Nervous System: dry mouth, hot flashes, sweating increased, sleep disorders, abnormal dreams, anxiety, depression, insomnia, nervousness, somnolence, hypesthesia, libido decreased, paresthesia.

Respiratory System: bronchospasm, dyspnea, respiratory disorder, sputum increased, laryngitis, pneumonia, pharyngitis, rhinitis, epistaxis, sinusitis.

Skin and Appendages: rash, eczema, urticaria, pruritis, skin disorder,

Special Senses: tinnitus, otitis media, conjunctivitis, eye disorder, abnormal vision, blurred vision.

Urogenital System: dysuria, increased urinary frequency, cystitis, urinary tract infection, polyuria, pyelonephritis.

Laboratory findings:
Hemoglobin and hematocrit: Trend analyses of long-term therapy indicated decreases in hemoglobin. Reductions in hemoglobin and hematocrit have been reported with the use of ACE inhibitors but are rarely of clinical importance.

Hyperkalemia: (see PRECAUTIONS)

Others: It is known that ACE inhibitors can cause elevations of liver enzymes and/or bilirubin in isolated cases. This has also been observed with Altace Plus Felodipine.

In addition to those reported above, other adverse experiences have been previously reported with the individual components felodipine and ramipril.

Felodipine -component Adverse Reaction:
The following adverse events may occur in connection with felodipine treatment:

Body as a whole: peripheral edema, asthenia, chest pain, facial edema, flu-like illness, fever.

Cardiovascular: palpitations, warm sensation/flushing, tachycardia, premature beats, postural hypertension, bradycardia.

Gastrointestinal: nausea, dyspepsia, constipation, abdominal pain, diarrhea, vomiting, dry mouth, flatulence, acid regurgitation, cholestatic hepatitis, gingival hyperplasia, gingivitis, salivary gland enlargement.

Metabolic: ALT (SGPT) increased.

Musculoskeletal: arthralgia, muscle cramps, myalgia.

Nervous/Psychiatric: headache, dizziness, paraesthesia, insomnia, depression, anxiety disorders, irritability, nervousness, somnolescence, decrease in libido, tremor, confusion.

Respiratory: upper respiratory infection, cough, dyspnea, epistaxis.

Dermatologic: rash, 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%) were myocardial infarction, hypotension, syncope, angina pectoris, arrhythmia, and anemia.

Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty. Furthermore, isolated cases of extrasystoles, arthralgia, myalgia, parasthesiae, hypersensitivity reactions (such as urticaria), elevations of liver enzymes, confusion and insomnia have been reported, but it has not been possible to establish a definite connection with felodipine.

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 these changes were considered to be of clinical significance.

Ramipril-component Adverse Reactions

The following adverse events may occur in connection with ramipril treatment:

Body as a whole: peripheral edema, asthenia, rash, anaphylactoid reactions, angioneurotic edema.

Cardiovascular: symptomatic hypotension, postural hypotension, flushing, syncope, angina pectoris, arrhythmia, chest pain, palpitations, myocardial infarction, tachycardia, vascular stenosis, cerebrovascular disorders (including ischaemic stroke)**,** disturbed orthostatic regulation, exacerbation of perfusion disturbances due to vascular stenoses.

Respiratory: increased cough, nasal congestion, sinusitis, bronchitis, bronchospasm (including aggravated asthma).

CNS: anxiety, amnesia, confusion, convulsions, depression, dizziness, fatigue, impaired hearing, hearing loss, insomnia, nervousness, neuralgia, neuropathy, paresthesia, polyneuritis, sleep disturbances, somnolence, tinnitus, tremor, vertigo, vision disturbances (including blurred vision), burning sensation (mainly to skin of face and extremities), smell disturbances, impaired psychomotor skills (impaired reactions), attention disturbances , disorders of balance, lightheadness , restlessness, precipitation or intensification of Raynaud's phenomenon.

Dermatologic: apparent hypersensitivity reactions (with manifestations of urticaria, pruritus, or rash, with or without fever), photosensitivity, purpura, erythema multiforms, pemphigus, Stevens-Johnson syndrome. Angioedema with fatal outcome (may be/become life-threatening, rarely severe courses can cause fatal obstruction).

In addition, the following cutaneous or mucosal reactions may occur: maculopapular rash, maculo-papular exanthema, psoriasiform exanthema, erythroderma/exfoliative dermatitis, exacerbation of psoriasis, lichenoid exanthema, pemphigoid exanthema and enanthema, reversible alopecia, and toxic epidermal necrolysis or onycholysis.

Gastrointestinal: hepatic failure, cholestatic jaundice, hepatitis (cases of fatal outcome have been very exceptionally reported), abdominal pain (sometimes with enzyme changes suggesting pancreatitis), upper abdominal pain, pancreatitis (cases of fatal outcome have been very exceptionally), increased levels of pancreatic enzymes, decreased appetite, anorexia, constipation, diarrhea, dry mouth, glossitis, aphtous stomatitis, gastritis, intestinal angioedema, digestive disturbances, dyspepsia, dysphagia, gastroenteritis, nausea, increased salivation, taste disturbance, vomiting, abdominal discomfort. In isolated cases liver damage (including acute liver failure) may occur.

Rarely, ACE inhibitors, including ramipril, have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death.

Renal: impaired renal function, oliguria, and acute renal failure. Increases in blood urea nitrogen (BUN) and serum creatinine. Rarely, a deterioration of pre-existing proteinuria may develop (though ACE inhibitors usually reduce proteinuria) or an increase in urinary output (in connection with an improvement in cardiac performance).

Haematologic: agranulocytosis, leucopenia, eosinophilia, thrombocytopenia, pancytopaenia, bone marrow depression and hemolytic anemia.

Other: arthralgia, arthritis, dyspnea, edema, epistaxis, impotence, transient erectile impotence, increased sweating, malaise, myalgia, weight gain, conjunctivitis, muscle cramps, reduced libido, loss of taste, depressed mood, gynaecomastia.

A symptom complex has been reported which may include fever, vasculitis, myalgia, arthralgia/arthritis, a positive ANA (antinuclear antibody), elevated ESR, eosinophilia and leucocytosis. Rash, photosensitivity or other dermatologic manifestations may also occur.

Clinical laboratory test findings: increased creatinine; increases in blood urea nitrogen (BUN); decreases in red blood cell count, hemoglobin or hematocrit; hyponatraemia; elevations of liver enzymes, serum bilirubin, uric acid, blood glucose; proteinuria and significant increases in serum potassium.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

To date there have been no reports of overdosage with Altace Plus Felodipine (felodipine/ramipril) in humans. Given the absence of practical experience with overdosage, the following is a synopsis of experiences gained with the individual components.

Ramipril:

Symptoms:

Limited data are available regarding overdosage of ramipril in humans. Two cases of overdosage have been reported.

Overdosage may cause excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, and renal failure.

Management:

In the case of an overdosage with ramipril, the most likely clinical manifestation would be symptoms attributable to severe hypotension, which would normally be treated by intravenous volume expansion with normal saline. It is not known if ramipril or ramiprilat can be removed from the body by hemodialysis.

Primary detoxification by, for example, gastric lavage, administration of adsorbents, sodium sulfate; (if possible during the first 30 minutes). In the event of hypotension administration of α1-adrenergic agonists (e.g. norepinephrine, dopamine) or angiotensin II (angiotensinamide), which is usually available only in scattered research laboratories, must be considered in addition to volume and salt substitution.

No experience is available concerning the efficacy of forced diuresis, alteration in urine pH, haemofiltration, or dialysis in speeding up the elimination of ramipril or ramiprilat. If dialysis or haemofiltration is nevertheless considered, see also “PRECAUTIONS, Anaphylactoid reactions during membrane exposure” section.

Felodipine:

Symptoms:

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

Management:

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

Dosage must be individualized. A fixed combination is not recommended for initial therapy. The dose of Altace Plus Felodipine (felodipine/ramipril) should be determined by titration to the individual components. Altace Plus Felodipine tablets must not be divided, crushed or chewed. The tablets should not be administered with a meal rich in carbohydrates or fat (see ACTION AND CLINICAL PHARMACOLOGY- Pharmacokinetics).

Once the patient has been successfully titrated with the individual components as described below, Altace Plus Felodipine may be substituted if the titrated dose and dosing schedule can be achieved by the fixed combination (see INDICATIONS AND CLINICAL USE and WARNINGS, Hypotension).

Altace Plus Felodipine is available in doses of 2.5/2.5 mg and 5.0/5.0 mg (felodipine ER/ramipril).

Felodipine: For felodipine monotherapy, the usual recommended initial dose is 5 mg once daily. 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 dose 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 not usually required in patients with renal impairment.

Use in the Elderly: Patients over 65 years 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).

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 - Patients with Impaired Liver Function).

Ramipril: Dosage of ramipril must be individualized. Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation and salt restriction. The dosage of other antihypertensive agents being used with ramipril may need to be adjusted.

Monotherapy: The recommended initial dosage of ramipril in patients not on diuretics is 2.5mg once daily. Dosage should be adjusted according to blood pressure response, generally, at intervals of at least two weeks. The usual dose range is 2.5 to 10mg once daily. A daily dose of 20mg should not be exceeded.

In some patients treated once daily, the antihypertensive effect may diminish towards the end of the dosing interval. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either twice daily administration with the same total daily dose, or an increase in dose should be considered. If blood pressure is not controlled with ramipril alone, a diuretic may be added. After the addition of a diuretic, it may be possible to reduce the dose of ramipril.

Concomitant Diuretic Therapy: Symptomatic hypotension occasionally may occur following the initial dose of ramipril and is more likely in patients who are currently being treated with a diuretic. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with ramipril to reduce the likelihood of hypotension (see WARNINGS). If the diuretic cannot be discontinued, an initial dose of 1.25 mg ramipril should be used with careful medical supervision for several hours and until blood pressure has stabilized. The dosage of ramipril should subsequently be titrated (as described above) to the optimal response.

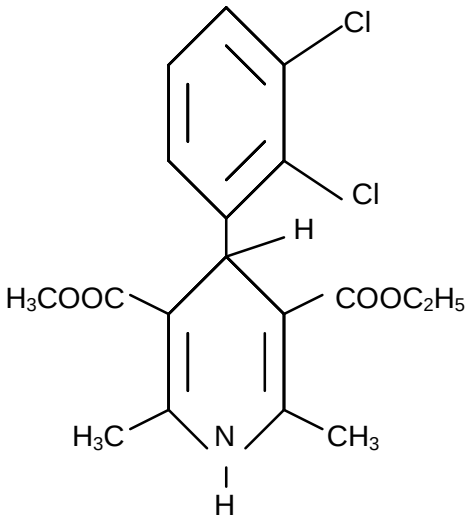
Use in renal impairment: For patients with a creatinine clearance below 40ml/min/1.73m^2 (serum creatinine above 2.5 mg/dL), the recommended initial dose is 1.25 mg ramipril once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 5mg. In patients with severe renal impairment (creatinine clearance below 10ml/min/1.73m^2) the maximum total daily dose of 2.5 mg should not be exceeded.

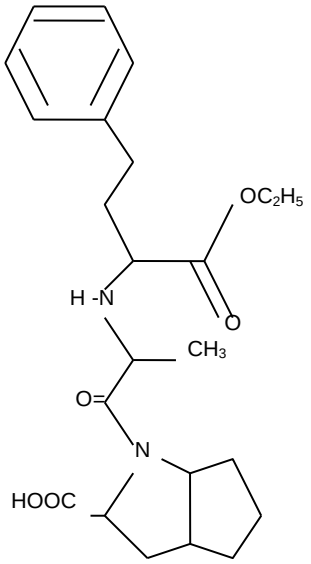
PHARMACEUTICAL INFORMATION

Drug Substances

Proper Name: extended-release felodipine + ramipril

Structural Formula:





Molecular Formula:

felodipine: $C_{18}H_{19}Cl_2NO_4$ ramipril: $C_{23}H_{32}N_2O_5$

Molecular Weight:

felodipine: 384.26 ramipril: 416.52

Chemical Name:

felodipine: 3,5-pyridinecarboxylic acid, 4-(2,3-dichorophenyl)-1,4-dihydro 2,6-dimethyl-, ethyl methyl ester

ramipril: 2-[N-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-(1S,3S,5S)-2-azabicyclo[3.3.0]octane-3-carboxylic acid

Description: Felodipine is a slightly yellowish, crystalline powder with a melting point of 142°C to 145°C. It is not hygroscopic. It is soluble in acetone, dichloromethane, ethanol, heptane, methanol, 2-propanolol, n-octanol, and practically insoluble in water.

Ramipril is a white to off-white crystalline powder with a melting point of 105^{o} C ^{to} 112^{o} C. Slightly soluble in water, and freely soluble in ethanol

and methanol.

Composition

ALTACE Plus Felodipine 2.5 mg + 2.5 mg tablets contain extended-release felodipine 2.5 mg and ramipril 2.5 mg. Non-medicinal ingredients are: hydroxypropylcellulose, hydroxypropylmethylcellulose, iron oxide, lactose anhydrous, maize starch, microcrystalline cellulose, paraffin, polyethylene glycol, polyoxyl 40 hydrogenated castor oil, propyl gallate, sodium aluminium silicate, sodium stearyl fumarate, titanium dioxide.

ALTACE Plus Felodipine 5 mg + 5 mg tablets contain extended-release felodipine 5 mg and ramipril 5 mg. Non-medicinal ingredients are: hydroxypropylcellulose, hydroxypropylmethylcellulose, iron oxide, lactose anhydrous, maize starch, microcrystalline cellulose, paraffin, polyethylene glycol, polyoxyl 40 hydrogenated castor oil, propyl gallate, sodium aluminium silicate, sodium stearyl fumarate, titanium dioxide.

Stability and Storage Recommendations
Store ALTACE Plus Felodipine tablets between 15 ^{o} C to 30^{o} C and protect from moisture.

AVAILABILITY OF DOSAGE FORMS

ALTACE Plus Felodipine is supplied as circular, biconvex, film-coated, two-layered tablets with felodipine in an extended-release gel matrix formulation in one layer and rapidly dissolving ramipril in the other layer.

Altace Plus Felodipine 2.5 mg + 2.5 mg tablet: Film-coated, apricot, circular, two-layered, biconvex tablet engraved on one side and 2.5 mg on the other and containing 2.5 mg extended release felodipine and 2.5 mg ramipril.

Altace Plus Felodipine 5 mg + 5 mg tablet: Film-coated, reddish-brown, circular, two-layered, biconvex tablet engraved on one side and 5 mg on the other and containing 5 mg extended release felodipine and 5 mg ramipril.

Each tablet strength is available in blister packages of 30 tablets and in polyethylene bottles of 100, 300, or 500 tablets.

INFORMATION FOR THE CONSUMER

Your doctor has prescribed a new medication to help control your blood pressure. Altace Plus Felodipine is a combination of two different medications (felodipine and ramipril). Felodipine belongs to the group of drugs called "calcium channel blockers" or "calcium antagonists". Ramipril belongs to the group of drugs called “Angiotensin Converting Enzyme inhibitors” or ACE inhibitors.

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 Altace Plus Felodipine.**

What is hypertension?

Hypertension is the medical term for high blood pressure. When blood flows through the blood vessels it pushes against their walls, almost like water pushing against the sides of a hose. Blood pressure is like that "push". When blood pressure is high (like the water pressure in a hose when the nozzle is partially shut), damage can occur to the heart and blood vessels.

Although you may not feel any symptoms for years, hypertension can lead to stroke, heart attack, kidney disease and other serious conditions.

What causes hypertension?

In most cases, the exact cause of hypertension is not known. But we do know that several factors increase the risk of developing the disease.

Family history: Hypertension, like some other diseases, can run in families. If your parents have high blood pressure, your chances of developing it are greater.

Age: The risk of developing hypertension increases with age.

Race: In North America, there is a higher incidence of hypertension among blacks than among whites.

Diabetes: Diabetics are at higher risk of developing hypertension than non-diabetics.

Weight: The risk of high blood pressure is higher in people who are overweight.

Drinking: Heavy alcohol consumption increases risk of hypertension, as well as stroke and kidney disease.

Sedentary lifestyle: A physically inactive lifestyle can contribute to hypertension.

Smoking: While not a direct cause of hypertension, smoking a cigarette will temporarily increase blood pressure. Smoking also increases the risk of heart disease in people with high blood pressure.

Keeping your blood pressure controlled

Your doctor has prescribed Altace Plus Felodipine, a medication that helps to control blood pressure. Altace Plus Felodipine opens blood vessels to reduce blood pressure, like the way opening a hose reduces water pressure. It is not, however, a cure.

But it takes more than just medication to reduce blood pressure. Discuss the risk factors, and how they apply to your lifestyle, with your doctor. You may have to modify some of your daily habits to keep your blood pressure down.

When to take your medication

You can take your medication with a meal, or if you prefer, on an empty stomach. It is important to take it at the same time every day as prescribed by your doctor. Grapefruit juice increases the amount of felodipine in your body and should be avoided.

Swallow Altace Plus Felodipine whole with a glass of water. Do not crush, break or suck on the tablets.

Try to take Altace Plus Felodipine with something you do regularly each day; for example, upon waking or at breakfast. This will help you remember each dose.

Altace Plus 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.

Remember, hypertension is a long-term disease without symptoms. Just because you feel fine does not mean you can stop taking your medication. If you stop, serious complications of the disease may occur. Therefore, you should continue to take it regularly, as prescribed by your doctor.

Missed a dose?

If you forget to take your Altace Plus Felodipine tablet, you can still take it within 12 hours after the normal time. If it has been *more* than 12 hours, simply wait until it is time for your next dose.

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

Managing your lifestyle

The "lifestyle" part of your treatment is as important as your medication. By working as a team with your doctor, you can help reduce the risk of hypertension complications to maintain the style of life you are accustomed to.

Together, you and your physician can determine how each of the following applies to you:

Diet: Generally, avoid fatty foods and food that is high in salt or cholesterol.

Exercise: Exercise regularly. It will help to keep your weight down, make you feel more energetic and is a good way to deal with stress. If you are not exercising regularly, be sure to discuss a fitness plan with your doctor.

Smoking: Avoid it completely.

Alcohol: Avoid alcoholic beverages until you have discussed their use with your doctor. Alcohol consumption may alter your blood pressure and/or increase the possibility of dizziness or fainting.

Side effects

Along with its intended action, any medication, including Altace Plus Felodipine, may cause side effects. With Altace Plus Felodipine these include headache, coughing, flushing or a feeling of warmth, swelling of the ankles, dizziness, back pain, or nausea. With your first dose of Altace Plus Felodipine your blood pressure may drop too low and you may experience dizziness, fatigue or light-headedness. Some of these side effects may disappear once your system becomes used to the medication. If they persist, discuss this with your doctor. Your medication might have to be reduced or changed.

If you are suffering from excessive sweating, vomiting or diarrhea, you may loose too much water and experience potential problems of low blood pressure. See your doctor.

A rare, but potentially more serious, side effect is called angioedema - characterized by swollen mouth, lips, tongue, eyes, throat or difficulty in swallowing or breathing. **If you notice swelling or feel pain in these areas, inform your doctor immediately. You should also inform your doctor if you have an unexplained fever, rash or itching.**

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 Altace Plus Felodipine with your doctor or pharmacist. Do not stop taking Altace Plus Felodipine on your own.

Serious Warnings and Precautions

Altace Plus Felodipine should not be used during pregnancy. If you discover that you are pregnant while taking Altace Plus Felodipine, stop the medication and please contact your physician as soon as possible

Keep your doctor informed

Before taking Altace Plus Felodipine, it is important that you inform your doctor of the following:

- Are you currently taking any other medications, whether on prescription or otherwise? This is especially important if you are taking diuretics (water pills) or any other medication to reduce blood pressure which may add to the blood pressure lowering effect of Altace Plus Felodipine. You should not be taking salt substitutes, potassium supplements or potassium containing medicine without the advice of your doctor.

- Do you suffer from any conditions other than hypertension? The presence of other medical problems may affect the use of Altace Plus Felodipine. Make sure you tell your doctor if you have any other medical problems, especially if you have diabetes, liver disease, kidney disease, heart or blood vessel disease.

- If you are being treated for other conditions by other doctors, keep them all informed of which medications you are taking. Some drugs may have negative effect on other drugs. If you have to undergo any dental or other surgery, inform the dentist or physician in charge that you are taking this medicine.

- **You are pregnant, breast-feeding or thinking of becoming pregnant.** Taking Altace Plus Felodipine during pregnancy can cause injury and even death to your baby. This medicine should not be used during pregnancy. If you become pregnant while taking Altace Plus Felodipine, stop the medication and report to your doctor as soon as possible. It is possible that Altace Plus Felodipine passes into breast milk. You should not breast-feed while taking Altace Plus Felodipine.

- Are you possibly allergic to Altace Plus Felodipine (felodipine and/or ramipril) including any of its non-medicinal ingredients (hydroxypropylcellulose, hydroxypropylmethylcellulose, lactose, maize starch, microcrystalline cellulose, polyethylene glycol, castor oil, propyl gallate, sodium aluminium silicate, sodium stearyl fumarate, iron oxide, titanium dioxide, paraffin)?

- After you have started taking Altace Plus Felodipine, it is important that you tell your doctor at once about any unexplained symptom you might experience. Examples of this are unexplained fever, rash, itching, any sign of infection, viral-like symptoms, flu-like symptoms, coughing, sore throat, abdominal pain, loss of appetite, sad mood, or jaundice.

Some Precautions You Should Take

Keep Altace Plus Felodipine 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 will no longer need should be carefully discarded. Small quantities may be disposed of in the toilet, or you may wish to seek advice from your pharmacist.

Check with your doctor if you want to drink alcohol (including wine with your meals) while you are taking Altace Plus Felodipine. Drinking alcohol while on Altace Plus 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 Altace Plus 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 Altace Plus Felodipine on your own**.

How to Store Altace Plus Felodipine

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

Remember

Use this drug as directed by your doctor.
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 Altace Plus Felodipine.

PHARMACOLOGY

RAMIPRIL

Study	Species	No./ group	Route	Dose	Results
MECHANISM OF ACTION					
Inhibition of Angiotensin I-induced pressor response after oral ramipril	rat dog	6 3	oral oral	0.1, 0.3 1.0 mg/kg	A dose-dependant inhibition was observed, lasting more than 6 hours
Effect of pre-treatment with ramipril on BP changes induced by iv angiotensin I, angiotensin II, and sympathomimetics	rat	5 or 6	oral	1.0 mg/kg	Effects of angiotensin I and indirect-acting sympathomimetics are inhibited, while the effects of angiotensin II and direct-acting sympathomimetics are unaffected by ramipril
Effect of ramipril on Na-depleted (furosemide treated) dogs	dog	6	oral	10 mg/kg	Ramipril-induced increase in plasma renin activity is enhanced by furosemide; ramipril has no influence on heart rate
In vitro inhibition of ACE by ramipril	rabbit lung		in vitro		IC_{50} = 26±8 nmol/L
Effect of ramipril and captopril on renal blood flow, renal vasculature resistance and blood pressure	rat	5	IA	0.1 mg/kg	Ramipril caused a greater increase in renal blood flow and decrease in renal vasculature resistance than a 10-fold higher dose of captopril; this without the decrease in systemic BP observed with captopril
EFFECTS ON BLOOD PRESSURE					
Spontaneously hypertensive rats	rat	5	oral	1 mg/kg (acute) 0.01, 0.1, 1, 10 mg/kg/day (five weeks)	Significant decreases in BP (all doses) which persisted for: 2 weeks (chronic) or 72 hours (acute)
Kidney perinephretic hypertension (no increase in plasma renin activity)	dog	5	oral	10 mg/kg (acute) 1 mg/kg/day (5 days)	Significant decrease of systemic blood pressure
2 kidney, 1 clip hypertension	rat	8	oral	1, 10 mg/kg (acute)	Blood pressure was normalized
Release of an occluded renal pedicle	rat	6	oral	0.1 mg/kg (acute)	Hypertension was completely prevented

FELODIPINE

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 - 5μmol/kg. When felodipine was mixed in with the diet of SHR (3 studies, duration of 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 vasodilatation, 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 baroflex 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 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.

RAMIPRIL + FELODIPINE

Study	Species	No./ group	Route	Dose mg/kg (R= ramipril; F= felodipine)	Results
MECHANISM OF ACTION					
Influence of felodipine on the saldiuretic effect of ramipril	dog	4-5M	oral	R+F 10+0.5 R+F 10+5	Diuretic and natriuretic effects of ramipril neutralized in combination with felodipine 5 mg/kg
Effects on urinary excretion, renal clearances, and plasma renin activity in dogs	dog	4-6M	oral	R+F 10+0.5 R+F 10+5	Felodipine did not change the urinary excretion of urine, Na^+, K^+ and the glomerular filtration rate, renal plasma flow, osmolar clearance and plasma renin activity following pre-treatment with ramipril.
EFFECTS ON BLOOD PRESSURE					
Acute effects on BP and HR responses in spontaneously hypertensive rats	rat	6-20M	oral	F+R 3+1 F+R 10+1	Coadministration of ramipril had no acute synergistic influence on effects produced by felodipine
Chronic effects on BP, HR and serum solutes in spon-taneously hypertensive rats	rat	15M	oral	F+R 1+1 F+R 3+1	Coadministration of ramipril produced synergistic effects on blood pressure without additional adverse effects.

Pharmacokinetics
RAMIPRIL

Study Parameter (after oral ramipril)	Results		
	Rat (2 mg/kg)	**Dog (2 mg/kg)**	**Human (10 mg)**
GI absorption of ^{14}C-ramipril	56%	43%	56%
Maximal blood levels of radioactivity	0.5 hrs	0.5-1 hrs	0.3 hrs
Plasma t1/2 of radioactivity	0.6 hrs	1.0 and 3.8 hrs (biphasic)	0.5 and 2.9 hrs (biphasic)
Distribution of radioactivity	High concentration in liver, kidney, and lungs. Total fetus: 0.05% Breast milk: 0.25%	-	-
Serum protein binding (concentration range of 0.01-10 µg/ml)	ramipril: - ramiprilat: 41%	ramipril : 72% ramiprilat: 47%	ramipril: 73% ramiprilat: 56%
Metabolism	Metabolized to ramiprilat	metabolized to ramiprilat and inactive diketopiperazines	
Excretion of radioactivity	urine: 26% feces: 71% $t_{1/2}$ (both): 1.6-4.8 and 23-42 hrs	urine: 15% $t_{1/2}$: 9.3 hrs feces: 79% $t_{1/2}$: 8 hrs	urine: 56% $t_{1/2}$: 7.2 and 127 hrs feces: 40% $t_{1/2}$: 11 and 110 hrs

FELODIPINE

Felodipine is rapidly and completely absorbed after oral administration in rats and dogs. First-pass elimination reduces oral bioavailability 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 iv doses. In the terminal phase, distribution volumes are 10 to 20 L/kg. The binding to plasma proteins is > 99.5% in the 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 iv 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

Species	Sex	Route	LD_{50} (mg/kg)
		Ramipril	
Mouse	Male	oral	10,933
Mouse	Female	oral	10,048
Rat	Male	oral	> 10,000
Rat	Female	oral	> 10,000
Dog	Male	oral	> 1,000
Mouse	Male	intravenous	1,194
Mouse	Female	intravenous	1,158
Rat	Male	intravenous	688
Rat	Female	intravenous	609
		Felodipine	
Mouse	Male	oral	240
Mouse	Female	oral	264
Rat	Male	oral	2390
Rat	Female	oral	2250
Mouse	Male	intravenous	8.6
Mouse	Female	intravenous	10.4
Rat	Male	intravenous	6.8
Rat	Female	intravenous	6.4
		Ramipril + Felodipine	
Mouse	male/female	oral	≅ 500
Rat	male/female	oral	1,987*
Rat	male/female	oral	>2,000

* administered in a ratio of 1:2 (ramipril/felodipine)

The LD_{50} of the combination (ramipril + felodipine) is reduced proportionately to the reduction in the content of felodipine, demonstrating that the toxicity of the combination is largely determined by felodipine. With the combination, deaths occurred within 24 hrs in mice and up to 7 days in rats. Clinical signs of toxicity were reduced motility and increased respiration. Bristling fur, reddish-brown discoloration about the mouth and nose and increased salivation was observed in rats receiving the 1:1 ramipril/felodipine combination. No compound-related gross morphological changes were observed at the end of the follow-up period for these animals. Rats receiving a 1:2 ratio of the combination also exhibited reddish, encrusted or narrowed palpebral fissures and red areas in the mucous of the small intestine or cecum indicating greater toxicity of this ratio.

Repeated-dose Toxicity

Ramipril

Species	Duration	No. of animals/ group	Route	Dose mg/kg/day	Effects
Mouse	28 days 90 days	2M, 2F 3M, 3F	oral	1000	Reduced erythrocytes, hemoglobin, hematocrit, increased reticulocytes. Hyperplasia of juxtaglomerular apparatus.
Rat	30 days	10-15M, 10-15F	oral	2.5, 80, 2500	At all doses: decrease in body weight, reduced liver weight and increased kidney weight. At 80 & 2500 mg/kg/d: reduced heart weight. At 2500 mg/kg/d: reduced erythrocytes, hematocrit and bilirubin, increased BUN.
Rat	3 months	10-15M, 10-15F	oral	2.5, 80, 500	All doses: reduced chloride and GOT, increased phosphorus and BUN. At 80 mg/kg/d: reduced heart, liver, prostate weight, increased kidney weight. Atrophic segments of renal tubules. Increased serum creatinine. At 500 mg/kg/d: reduced body and heart weight, increased kidney and adrenal weight. Reduced erythrocytes, hemoglobin, hematocrit; increased bilirubin. Increased number of atrophic renal tubular segments. Moderate gastric mucosa necroses.
Rat	3 months	10M, 10F	oral	500, 1/3 Ringer solution for drinking	Increased number of tubular atrophies.
Rat	6 months	10-20M, 10-20F	oral	0.1, 0.25, 3.2, 40, 500	At all doses: serum bilirubin increased, reduced heart weight. At 40 and 500 mg/kg/d: increased kidney weight. Reduced erythrocytes, hemoglobin, hematocrit; increased BUN. Distal tubular atrophies; fibromuscular pad formations in gastric mucosa/muscularis not proliferative in nature.
Rat	6 months	20M, 20F	oral	3.2, 40, 500, 1/3 Ringer solution for drinking	All doses: fibromuscular or solitary pad formation in gastric fundus mucosa/muscularis.
Rat	18 months	20-25M, 20-25F	oral	0.25, 3.2, 40, 500	At 3.2 to 500 mg/kg/d: fibromuscular pads in gastric fundus mucosa, focal atrophies in renal cortex, partly with cysts. At 40 and 500 mg/kg/d: anemia, increased BUN and serum creatinine, urinary epithelial cells. Reduced heart weight and increased kidney and adrenal weight.
Dog	30 days	2M, 2F	oral	3.2, 32	No pathological findings
Dog	3 months	3-4M, 3-4F	oral	3.2, 32, 320	At 320 mg/kg/d: anemia, increased BUN and serum creatinine, impaired erythropoiesis. Juxtaglomerular hyperplasia.
Dog	6 months	6M, 6F	oral	3.2, 32, 320	At 32 mg/kg/d: anemia, juxtaglomerular hyperplasia. At 320 mg/kg/d: reduced body weight. Increased BUN and serum creatinine. Distal tubular atrophies with round cell infiltrations. Anemia, juxtaglomerular hyperplasia.
Dog	12 months	6M, 6F	oral	2.5, 25, 250	At all doses: reduced body weight. At 25 and 250 mg/kg/d: anemia and leukopenia, impaired erythropoiesis, increased hemosiderin deposition in liver and spleen, juxtaglomerular hyperplasia. At 250 mg/kg/day: increased BUN and serum creatinine.
Monkey	6 months	4-5M, 4-5F	oral	0.5, 16, 500	At 16 and 500 mg/kg/d: increased BUN, juxtaglomerular hyperplasia, reduced body weight. At 500 mg/kg/d: diarrhea, anemia, increased serum creatinine, some urinary casts, leukocytes and epithelial cells.
Monkey	6 months	5M, 5F	oral	2, 8	No pathological findings.

Felodipine:

Species	Duration	No. of Animals/ Group	Route	Dose mg/kg/day	Deaths/Group		Effects
					M	F	
Rat	1 month	6M, 6F	oral	0 2 5.8 19.2 57.6 192	 1	 6	At the 57.6 mg/kg/day dose: hyperemia manifested in redness of mucous membranes, nose and ears. Decrease in mean food intake and body weight in females in 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.
Rat	5 weeks	10M, 10F	oral	0 2 10 50 180	 5	 9	The 50 mg/kg/day 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 180 mg/kg/day 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.
Rat	6 months	25M, 25F	oral	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 the 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 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 attributable to felodipine.
Rat	2 weeks	10M, 10F	i.v.	0 0.04 0.12 0.38			Dose levels 0.12 and 0.38 mg/kg/day produced peripheral vasodilation, apparent hyperthermia 1-3 hours after dosing. Higher liver weight gain in males. Males given 0.38 mg/kg/day dose showed inferior body weight gain during first 4 days of treatment.
Dog	1 month	2M, 2F	oral	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 increases of heart and kidney weights.
Dog	12 months 2 x day	5M, 5F	oral	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.

Repeated-dose toxicity - Felodipine (cont.)

Species	Duration	No. of Animals/ Group	Route	Dose mg/kg/day	Deaths/Group		Effects
					M	F	
Dog	6 months 2 x day	3M, 3F	oral	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 3.8 mg/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.

Ramipril + Felodipine

Duration	Species	No. of Animals/ Group	Route	Dose mg/kg/ day	Effects
3 months	Rat	15M, 15F	oral	2, 20, 200	2 - 200 mg/kg/d: elevated kidney to body weight ratios (M) 20 and 200 mg/kg/d: decreased erythrocytes (M); increased urea (M); elevated kidney to body weight ratio (F), increased adrenal weights (M) 200 mg/kg/d: decreased food consumption and body weight; sunken flanks, bristling coat, stilted gait, narrowed palpebral fissures, red nose encrustation, hypothermia, increased salivation; decreased erythrocytes, hemoglobin (M), hematocrit (M), increased urea, creatinine (F), inorganic phosphorus (F), glucose (F); decreased pituitary weight (F)
90 days	Monkey	4M, 4F	oral	0.5, 4.0, 32	All doses: non-significant decrease in thymus weight4.0 and 32 mg/kg/d: decreased food and water consumption, decreased erythrocytes 32 mg/kg/d: decreased hemoglobin, hematocrit; increased serum glucose, potassium, urea, creatinine; decreased calcium; glucose and ketone bodies in one animal; hyperplasia of the renal juxtaglomerular apparatus

Carcinogenicity

RAMIPRIL

There was no evidence of a carcinogenic effect when ramipril was administered for 104 weeks to NMRI mice at doses up to 1000 mg/kg/day and to Wistar rats at doses up to 500 mg/kg/day.

FELODIPINE

The carcinogenic effect of felodipine has been studied in mice (50M, 50F/group) at doses of 40, 120 and 360 µmol/kg over 99 weeks and rats (50M, 50F/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 animals terminally sacrificed from other groups.

Incidence of Hepatocellular Neoplasms in Mice

Group	Sex	No. of Animals[1]/Group[2]	Dose (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

Few neoplasms (10; 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 of 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, 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 luteneizing 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 the 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.

Mutagenicity

Ramipril was not mutagenic in the Ames microbial mutagen test, the HGPRT test in V79 cells, the micronucleus test in mice and the UDS test in human A549 cells. Felodipine has not shown any mutagenic activity.

Reproduction and Teratology

RAMIPRIL

Species and Strain	No. of Animals/ Group	Dose mg/kg/day	Duration	Results
Rat (Wistar)	32M/32F	5, 50, 500	M: 60 days before mating F: 14 days before mating to end of lactation	At 50 and 500 mg/kg/d: parental renal pelvis enlargement, offspring light brown discoloration of kidney tissue and dilatation of renal pelvis. At 500 mg/kg/d: parents yellow-white colouring and induration of renal marrow. Fertility normal.
Rat (Wistar)	20F	10, 100, 1000	Days 7-17 of gestation	At 1000 mg/kg/d: reduced food consumption in mothers, reduced body weight gains of young. One young circular non-ossified area in supraoccipital bone, one young distortion of right scapula. No teratogenic effects.
Rat (Wistar)	20-30F	0.32, 1.25, 5, 10, 100, 1000	Day 17 of gestation to Day 21 of lactation	At 100 and 1000 mg/kg/d: decreased gestation body weight in young, enlarged to Day 21 renal pelvis up to hydronephrosis with light brown colouring of renal cortex and marrow.
Rat (Sprague-Dawley)	20F	100	Day 17 of gestation to Day 21 of lactation	Young: enlarged renal pelvis and light brown coloration of kidney tissue.
Rabbit (Himalayan)	15F	0.4, 1, 2.5	Days 6-18 of gestation	At 0.4 mg/kg/d: one abortion, one fetus with diaphragm hernia. At 1 mg/kg/d: one abortion, one premature delivery, two animals died, no animals gained weight. One dead fetus with possible hydrocephalus. At 2.5 mg/kg/d: two animals died, no animals gained weight, one fetus with diaphragm hernia, one with first cervical aplasia and aplasia of one thorax vertebra and one rib pair.
Monkey (Cynomolgus)	4-13F	5, 50, 500	Days 20-25 of gestation	All doses: no signs of teratogenesis. At 5 mg/kg/d: two abortions, seven diarrhea, two vomiting, ten weight loss. At 50 mg/kg/d: one animal died, three abortions, seven diarrhea, two vomiting, ten weight loss. At 500 mg/kg/d: three animals died, one abortion, four weight loss, four vomiting, four diarrhea

Reproduction and Teratology cont.

FELODIPINE

Species and Strain	No. of Animals/ Group	Dose/Route (mg/kg/day)	Duration	Results
Rat (Sprague-Dawley)	15M/30F	0, 3.8, 9.6, 26.9 oral	M: Approx. 11 weeks[1] F: Approx 10 weeks[1] (Seg.I)	Parents (Dams): Dose dependent prolongation of parturition and hard labour in the animals receiving 9.6 or 26.9 mg/kg. Litters: Dose dependently increased frequencies of late fetal deaths and early postnatal deaths in animals receiving 9.6 or 26.9 mg/kg.
Rat (Sprague-Dawley)	20F	0, 3.8, 9.6, 26.9 oral	Days 6-15 of gestation (Seg.II)	Dams: 26.9 mg/kg/d: slightly lower food consumption during the dosing period and slightly reduced body weight gain in dams towards the end of the dosing period. Litters: No signs of embryotoxic, teratogenic or fetotoxic effects related to treatment could be detected in the litters.
Rat (Sprague-Dawley)	20F	0, 1.2, 3.8, 11.5 oral	From Day 15 of gestation to Day 20 post partum (Seg. III)	Dams: 11.5 mg/kg/d: slight prolongation of the gestation period, prolonged parturition and hard labour in dams. Increased frequency of stillborn fetuses and early postnatal deaths.
Rabbit (New Zealand White)	5F	0, 3.8, 9.6, 19.2 oral	Days 6-19 of gestation (Seg. II, pilot study)	Dams: One control and two high dose animals were found dead during the study. Dose-dependent decrease in body weight changes and food consumption values. Litters: in a dose-dependent manner, 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 mean fetal lengths were less than control in all treated groups. These effects had an insignificant dose relation.
Rabbit (New Zealand White)	15F	0, 1.2, 2.3, 4.6 oral	Days 6-19 of gestation (Seg.II)	Dams: 1.2 mg/kg/d: 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. 2.3 mg/kg/d: depression, thickening of mammary tissue. Incidence of premature deliveries slightly higher than control and weight losses during Days 20-29 higher than control; these effects were also observed in the animals receiving 4.6 mg/kg. 4.6 mg/kg: depression, body weight loss, thickening of mammary tissue, premature deliveries as above. Litters: dose-related skeletal anomalies were observed in the extremities of fetuses in all treated groups. 1.2 mg/kg/d: small distal phalanges in the 4th digits of hind feet. 2.3 mg/kg/d: 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. 4.6 mg/kg/d: 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 mating (max. 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

Reproduction and Teratology cont. - **FELODIPINE**

Species and Strain	No. of Animals/ Group	Dose/Route (mg/kg/day)	Duration	Results
Rabbit (New Zealand White)	15F	0, 2.3, 4.6 oral	Days 6-18 of gestation (Seg.II)	Dams (2.3 mg/kg): reduced food intake during first few days of dosing; this was also seen in the animals receiving 4.6 mg/kg (dose related). Suppression of body weight gain during the first few days of dosing, also seen in the animals receiving 4.6 mg/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 Litters (2.3 mg/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, 2.3 and 4.6 mg/kg. Dams (4.6 mg/kg): reduced food intake and suppression of body weight gain as described above; weight 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 non-specific signs after initiation of dosing, particularly in animals receiving 4.6 mg/kg. - A higher incidence of non-accidental deaths and abortions after this initiation of dosing. Litters 4.6 mg/kg: digital anomalies as observed at 2.3 mg/kg. Increased preimplantation loss and sight increase in early post-implantation. Reduced litter size and litter weight.
Rabbit (New Zealand White)	21 F 21 F 20 F 20F	0 4.6 4.6 4.6 oral	Days 6-28 Days 6-12 Days 13-18 Days 6-28 of gestation (Seg. II)	Dams (Days 6-12): in all treatment groups treatment was associated with an initial decline in general condition indicated by reduced food intake, low fecal 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 weight 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. Litters (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 weight lower in all treatment groups, the decrease was minimal for animals dosed Days 6-12. Lower values for litter weight in all treatment groups. Increased incidence of fetuses with an extra rib associated with initiation of treatment on Day 6. Dams (Days 13-18): initial decline in general condition as described above. No significant effect on mammary glands with regard to palpable thickening or increased weight Litters (Days 13-18): lower corpora lutea count contribution to a reduced litter size. Decreased mean fetal weight, and lower values for litter weight. 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). Dams (Days 6-28): see Days 6-12. Also, increased mammary weight gain. Litters Days 6-28: reduced litter size, decreased mean fetal and litter weight. Increased incidence of fetuses with an extra rib and anomalies of the claws occurred.

Reproduction and Teratology cont. - FELODIPINE

Species and Strain	No. of Animals/ Group	Dose/Route mg/kg/day	Duration	Results
Rabbit (New Zealand White)	10 F 10 F 20 F 19 F	0 0 4.6 4.6 oral	Days 6-18 of gestation (Seg. II)	Dams: reduced body weight gain from start of dosing, compensated on Day 14 and reduced food consumption during the dosing period in treated animals. Increased weights due to hyperplasia of mammary glands, in excess of normal gestational one, in treated animals killed on Day 29. In animals killed on Day 35, no differences were observed with respect to weight or histomorphological appearance of the mammary glands. Litters: 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	4.6 4.6 oral	Day 13 Days 13-18 of gestation	The clinical signs observed and the effects on body weight gain, food consumption and mammary glands were essentially the same as those seen in earlier performed studies in the rabbit.
Rabbit (New Zealand White)	8 F (not pregnant)	0 0.46 4.6 oral	13 days (Days 0-12)	Reduced food consumption, decreased body weight during the dosing period in animals receiving 4.6 mg/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.
Rabbit (New Zealand White)	9 F 15 F 11 F	0 0.46 4.6[2] oral	Days 6-18 of gestation (Seg. II)	Dams (0.46 mg/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. Litters (0.46 mg/kg (Day 29 of Gestation)): fetal loss was slightly increased compared to the control group. Dams (4.6 mg/kg signs of maternal toxicity): body weight gain and food consumption were decreased during the first part of the dosing period. Mammary Glands: treatment induced enlarged mammary glands. The mammary gland weights 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 histological architecture, however, did not differ from that of the control animals. Litters (0.46 and 4.6 mg/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 4.6 mg/kg only. In addition, 6 pups at 4.6 mg/kg showed an extra center of ossification between the middle and distal phalanx of the pollex.

[2] The dose level of 4.6 mg/kg had been used on 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.

Reproduction and Teratology cont. - **FELODIPINE**

Species and Strain	No. of animals/ group	Dose/Route mg/kg/day	Duration	Results
Rabbit (New Zealand White)	28 F[3] 32 F[3]	0 4.6 oral	Days 6-18 of gestation (Seg.II)	Dams: 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 weight, 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 gestation hyperplasia. Changes in mammary glands were still present, although less marked in the dose group on Day 32 post parturition. The mean weights 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. Litters: 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.

[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.

Reproduction and Teratology cont. - **FELODIPINE**

Species and Strain	No. of Animals/ Group	Dose mg/kg/day	Duration	Results
Rabbit (New Zealand White)	3F[4] 3F 3F 3F 3F 3F 3F 3F	4.6 4.6 4.6 4.6 4.6 4.6 4.6 4.6 oral	13 14 15 16 15 16 17 18	Dams: *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 weight 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. Litters: *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)	4F 4F 4F 3F 4F 6F	- 4.6[5] 4.6 4.6 4.6 4.6 oral	single, Day 16 of gestation	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 ([3]200 nmol/L) and 24 hours ([3] 100 nmol/L). Concentrations in Fetal Tissue: Mean concentrations were 4-6 times lower than those observed 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. Concentrations in Amniotic Fluid: These were about 2 to 4 times lower than those in fetal tissue. Histological Examination of 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. Eight hours after dose: Marked edema of limb plates and occasional 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 mesenchymal and ectoderm. 24 hours after dose: As at 12 hours after dose. Also occasional small necroses in the apex of the 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 4.6 mg/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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