PRODUCT MONOGRAPH

MYLAN-CAPTOPRIL

(captopril, USP)

TABLETS, USP

12.5, 25, 50 and 100 mg

Angiotensin-Converting Enzyme Inhibitor

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THERAPEUTIC CLASSIFICATION

Angiotensin-Converting Enzyme Inhibitor

ACTIONS AND CLINICAL PHARMACOLOGY

MYLAN-CAPTOPRIL (captopril) is an angiotensin-converting enzyme inhibitor, which is used in the treatment of hypertension and heart failure.

The mechanism of action of captopril has not yet been fully elucidated. It appears to lower blood pressure and be an adjunct in the therapy of congestive heart failure primarily through suppression of the renin-angiotensin-aldosterone system; however, there is no consistent correlation between renin levels and response to the drug. Renin, an enzyme synthesized by the kidneys, is released into the circulation where it acts on a plasma globulin substrate to produce angiotensin I, a relatively inactive decapeptide. Angiotensin I is then converted by angiotensin-converting enzyme (ACE) to angiotensin II, a potent endogenous vasoconstrictor substance.

Angiotensin II also stimulates aldosterone secretion from the adrenal cortex, thereby contributing to sodium and fluid retention.

Captopril prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE, a peptidyldipeptide carboxy hydrolase.

ACE is identical to "bradykininase" and captopril may also interfere with the degradation of the vasopressor peptide, bradykinin. However, the effectiveness of captopril in therapeutic doses appears to be unrelated to potentiation of the actions of bradykinin. Increased concentrations of bradykinin or prostaglandin E_2 may also have a role in the therapeutic effect of captopril, especially in low-renin hypertension.

Inhibition of ACE results in decreased plasma angiotensin II and increased plasma renin activity (PRA), the latter resulting from loss of negative feedback on renin release caused by reduction in angiotensin II. The reduction of angiotensin II leads to decreased aldosterone secretion, and, as a result, small increases in serum potassium may occur along with sodium and fluid loss.

The antihypertensive effects persist for a longer period of time than does demonstrable inhibition of circulating ACE. It is not known whether the ACE present in vascular endothelium is inhibited longer than the ACE in circulating blood.

Administration of captopril results in a reduction of peripheral arterial resistance in hypertensive patients with either no change, or an increase, in cardiac output. There is an increase in renal

blood flow following administration of captopril and glomerular filtration rate is usually unchanged. In instances of rapid reduction of long-standing or severely elevated blood pressure, the glomerular filtration rate may decrease transiently.

Peak reductions of blood pressure usually occur within 60 to 90 minutes after oral administration of a single dose of captopril. The duration of effect appears to be dose-related. The reduction in blood pressure may be progressive, so to achieve maximal therapeutic effects, several weeks of therapy may be required. The blood pressure lowering effects of captopril and thiazide-type diuretics appear to be additive. In contrast, captopril and beta-blockers have a less than additive effect.

Blood pressure is lowered to about the same extent in both standing and supine positions. Orthostatic effects and tachycardia are infrequent but may occur in volume-depleted patients. Abrupt withdrawal of captopril has not been associated with a rapid increase in blood pressure.

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

In patients with heart failure, captopril significantly decreased systemic vascular resistance (afterload), reduced pulmonary capillary wedge pressure (preload) and pulmonary vascular resistance, increased cardiac output (stroke index), and increased exercise tolerance time (ETT). Clinical improvement has been observed in some patients where acute hemodynamic effects were minimal.

Captopril has been studied in patients with diabetic nephropathy, most of whom had hypertension, with type I insulin-dependent diabetes mellitus, retinopathy and proteinuria $ 500 mg/day, in a multicenter, double blind, placebo-controlled trial. In this study, captopril has shown to decrease the rate of progression of renal insufficiency and to reduce associated clinical sequelae for the combined end-point of end- stage renal disease (dialysis or renal transplantation) or death (from all causes). The effect on reduction of all-cause mortality alone was not statistically significant. No dosage adjustment was made according to creatinine clearance. Patients who had already progressed to severe renal failure were not included in the clinical trial.

Studies in rats and cats indicate that captopril does not cross the blood-brain barrier to any significant extent.

Pharmacokinetics

Following oral administration of therapeutic doses of captopril, rapid absorption occurs with peak blood levels at about 1 hour. The presence of food in the gastrointestinal tract reduces absorption by about 30 to 40 percent. Based on C-14 labelling, average minimal absorption is approximately 70 to 75 percent. In a 24-hour period, over 95 percent of the absorbed dose is eliminated in the urine; 40 to 50 percent is unchanged drug although it appears this percentage may be smaller in patients with congestive heart failure; most of the remainder is the disulfide dimer of captopril and captopril-cysteine disulfide.

Approximately 25 to 30 percent of the circulating drug is bound to plasma proteins. The apparent elimination half-life for total radioactivity in blood is about 4 hours. The half-life of unchanged captopril is approximately 2 hours.

In patients with normal renal function, absorption and disposition of a labelled dose are not altered after 7 days of captopril administration. In patients with renal impairment, however, retention of captopril occurs (see **DOSAGE AND ADMINISTRATION**).

A comparative, two-way bioavailability study was conducted to compare MYLAN-CAPTOPRIL (captopril) 50 mg tablets against a Canadian Reference Brand Product of captopril 50 mg tablets. The pharmacokinetic data calculated for the MYLAN-CAPTOPRIL and Reference Product tablet formulations is tabulated below:

Parameter	**Geometric Mean Arithmetic Mean (C.V.)**		
	Test	**Reference**	**Ratio of Means %**
AUC_t (ng.h/mL)	487.9 503.5 (23.6)	483.0 496.7 (23.9)	101.0
AUC_i (ng.h/mL)	512.9 526.6 (22.8)	512.9 524.8 (24.2)	100.1
C_{max} (ng/mL)	379.9 397.8 (30.4)	370.9 385.5 (29.0)	102.4
T_{max}* (h)	0.8333 (0.3351)	0.8021 (0.2082)	
$T_{½}$* (h)	0.7778 (0.3722)	0.9035 (0.5468)	

* For T_{max} and $T_{½}$ arithmetic (standard deviation) are presented.

INDICATIONS AND CLINICAL USE

MYLAN-CAPTOPRIL (captopril) is indicated for the treatment of essential or renovascular hypertension. It is usually administered in association with other drugs, particularly thiazide diuretics. The blood pressure lowering effects of captopril and thiazides are approximately additive.

In using captopril, consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS).

a) In patients with normal renal function:

Captopril should normally be used in those patients in whom treatment with diuretics or beta-blockers was found ineffective or has been associated with unacceptable adverse effects.

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

b) In patients with impaired renal function:

In these patients, particularly those with collagen vascular disease, captopril should be reserved for hypertensives who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations (see WARNINGS).

CONGESTIVE HEART FAILURE

Captopril is indicated in the treatment of congestive heart failure as concomitant therapy with a diuretic in patients who have not responded adequately to digitalis and diuretics or in whom the administration of digitalis is contraindicated or has been associated with unacceptable side effects. Captopril therapy must be initiated under close medical supervision.

MYOCARDIAL INFARCTION

Captopril is indicated to improve survival, delay the onset of symptomatic heart failure and reduce hospitalizations for heart failure following myocardial infarction in clinically stable patients with left ventricular dysfunction manifested as an ejection fraction of # 40%.

DIABETIC NEPHROPATHY

Captopril is indicated for the treatment of diabetic nephropathy (proteinuria $ 500 mg/day) in patients with type I insulin-dependent diabetes mellitus and retinopathy.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected, captopril should be discontinued as soon as possible (see WARNINGS, Pregnancy and Information for the Patient).

CONTRAINDICATIONS

MYLAN-CAPTOPRIL is contraindicated in patients with a history of hypersensitivity to the drug and in patients with a history of angioedema related to previous treatment with an Angiotensin-Converting Enzyme inhibitor.

WARNINGS

Serious Warning

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

Angioedema

Angioedema has been reported in patients treated with ACE inhibitors, including captopril. Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, captopril 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 the 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**).

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 inhibitory therapy may be at increased risk of angioedema while receiving an ACE inhibitor.

Proteinuria

Total urinary proteins greater than 1 g/day were seen in less than 1 percent of patients receiving captopril. These have been predominantly in those who had prior renal disease, or in those receiving relatively high doses (in excess of 150 mg/day), or both. In patients without prior evidence of renal disease, the incidence of proteinuria was 0.5 percent. In those patients without prior evidence of renal disease receiving 150 mg or less per day, the incidence was 0.2 percent. Parameters of renal function, such as BUN and serum creatinine, were seldom altered in the patients with proteinuria. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued, but some patients had persistent proteinuria. Nephrotic syndrome occurred in about one-fifth of the proteinuric patients.

Membranous glomerulopathy was found in biopsies taken from proteinuric patients. A causal relationship to captopril has not been established since pretreatment biopsies were not taken and membranous glomerulopathy has been shown to occur in hypertensive patients not receiving captopril.

Since most cases of proteinuria occurred by the eighth month of therapy, patients with prior renal disease or those receiving captopril at doses greater than 150 mg/day should have urinary protein estimations (dipstick on first morning urine, or quantitative 24-hour urine) prior to therapy, at approximately monthly intervals for the first nine months of treatment, and periodically thereafter. When proteinuria is persistent, 24-hour quantitative determinations provide greater

precision. For patients who develop proteinuria exceeding 1 g/day, or proteinuria that is increasing, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis

Neutropenia (<1000/mm^3) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis.

The risk of neutropenia is dependent on the clinical status of the patient:
In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen disease), neutropenia has been seen in 1 patient out of over 8,600 exposed.

In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk of neutropenia in clinical trials was about 1 per 500, a frequency over 15 times that for uncomplicated hypertension. Daily doses of captopril were relatively high in these patients, particularly in view of their diminished renal function. In patients with renal failure, use of allopurinol concomitantly with captopril has been associated with neutropenia.

In patients with collagen vascular disease (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7 percent of patients in clinical trials.

While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. About half of the reported cases had serum creatinine >1.6 mg/dL and more than 75 percent were in patients also receiving procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

The neutropenia has been detected within 3 months after captopril was started. Bone marrow examinations in patients with neutropenia consistently showed myeloid hypoplasia, frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen.

In general, neutrophils returned to normal in about two weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13 percent of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.

If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically.

In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution.

All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, white cell counts should be performed without delay.

Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count $<1000/mm^3$) the physician should withdraw captopril and closely follow the patient's course.
Since captopril decreases aldosterone production, elevation of serum potassium may occur rarely, especially in patients with renal failure (see PRECAUTIONS -Drug Interactions).

Hypotension

Excessive hypotension was seen in hypertensive patients but is a possible consequence of captopril use in severely salt-/volume-depleted persons such as those treated vigorously with diuretics, for example patients with severe congestive heart failure (see PRECAUTIONS - Drug Interactions).

In heart failure, where the blood pressure was either normal or low, decreases in mean blood pressure greater than 20 percent were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and produces either no symptoms or brief mild light-headedness, although in rare instances, it has been associated with arrhythmia or conduction defects. Hypotension was the reason for discontinuation of drug in 3.6 percent of patients with heart failure.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS THERAPY SHOULD BE STARTED UNDER CLOSE MEDICAL SUPERVISION. A low starting dose may minimize the hypotensive effect (see DOSAGE AND ADMINISTRATION). Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of MYLAN-CAPTOPRIL, or diuretic, is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident. Hypotension in itself is not a reason to discontinue MYLAN-CAPTOPRIL. If associated symptoms are troublesome or persist, they are usually relieved by a reduction in the dose of either MYLAN-CAPTOPRIL or diuretic.

Pregnant women

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

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. Captopril may be removed from the general circulation by hemodialysis.

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, 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.

Animal Data: Captopril was embryocidal in rabbits when given in doses 2 to 70 times (on a mg/kg basis) the maximum recommended human dose, and low incidences of craniofacial malformations were seen. These effects in rabbits were most probably due to the particularly marked decrease in blood pressure caused by the drug in this species. Captopril was also embryocidal in sheep when given in doses similar to those given in humans. Captopril given to pregnant rats at 400 times the recommended human dose continuously during gestation and lactation caused a reduction in neonatal survival.

No teratogenic effects have been observed after large doses of captopril were administered to hamsters and rats.

Nursing women

The presence of concentrations of ACE inhibitor have been reported in human milk. Use of ACE inhibitors is not recommended during breast-feeding.

PRECAUTIONS

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 susceptable patients, concomitant diuretic use may further increase risk.

Use of MYLAN-CAPTOPRIL (captopril) should include appropriate assessment of renal function.

Hyperkalemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. When treated with ACE inhibitors, patients at risk for the development of

hyperkalemia include those with: renal insufficiency; diabetes mellitus; and those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or other drugs associated with increases in serum potassium (e.g., heparin). The incidence of hyperkalemia related or possibly related to therapy in the diabetic patients studied with nephropathy and proteinuria was 3.6% and was a reason for discontinuation of the drug in 1% of the patients. Hyperkalemia was defined as persistent elevation of serum potassium to 6.0 mg/dL or more in the absence of a remediable cause, such as other drugs, volume depletion, exogenous potassium supplements, etc.

Impaired Liver Function

Elevations of liver enzymes and/or serum bilirubin, cases of cholestatic jaundice, and of hepatocellular injury with or without secondary cholestasis, have occurred during therapy with captopril in patients without pre-existing liver abnormalities. In most cases the changes were reversible on discontinuation of the drug. Should the patient receiving MYLAN-CAPTOPRIL experience any unexplained symptoms (see Information for the Patient), particularly during first weeks or months of treatment, it is recommended that a full set of liver enzyme tests and other necessary investigations be carried out. Discontinuation of MYLAN-CAPTOPRIL should be considered when appropriate.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. MYLAN-CAPTOPRIL should be used with particular caution in patients with pre-existent liver abnormalities. Such patients should have their baseline liver function tests obtained before

administration of the drug. Close monitoring of response and metabolic effects should apply to these patients.

Cough

Cough has been reported with the use of captopril. Characteristically, ACE-inhibitor induced cough is non productive, persistent and resolves after discontinuation of the dose. Captopril induced cough should be considered as part of the differential diagnosis of cough.

Valvular Stenosis

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

Surgery/Anesthesia

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, captopril will block angiotensin II formation secondary to compensatory renin release. This may lead to hypotension, which can be corrected by volume expansion.

Anaphylactoid reactions during membrane exposure

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g., 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 desensitization

There have been isolated reports of patients experiencing sustained life threatening anaphylactoid reactions while receiving ACE inhibitors during desensitizing 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.

Nursing Mothers

Following oral administration, concentrations of unchanged captopril in human milk are approximately 1 percent of those in maternal blood. The effect of low levels of captopril on the nursing infant has not been determined. Caution should be exercised when captopril is administered to a nursing woman, and, in general, nursing should be interrupted.

Use in Children

Safety and effectiveness in children have not been established although there is limited experience with the use of captopril in children from 2 months to 15 years of age with secondary hypertension and varying degrees of renal insufficiency. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

Information for the Patient

Patients should be told that taking MYLAN-CAPTORPRIL during pregnancy can cause injury and even death to the developing fetus. Patients should be advised to stop taking the medication and to contact their physician as soon as possible if they become pregnant while taking MYLAN-CAPTORPRIL.

Patients should be advised that MYLAN-CAPTORPRIL may pass into breast milk and that they should not breast-feed while taking MYLAN-CAPTORPRIL.

Patients should be told to report promptly any indication of infection (e.g., sore throat, fever), which may be a sign of neutropenia, or of progressive edema, which might be related to proteinuria and nephrotic syndrome.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Patients should be advised to return to the physician if he/she experiences any symptoms possibly related to liver dysfunction. This would include viral like symptoms in the first weeks to months of therapy (such as fever, malaise, muscle pain, rash or adenopathy which are possible

indicators of hypersensitivity reactions), or if abdominal pain, nausea or vomiting, loss of appetite, jaundice, itching or any other unexplained symptoms occur during therapy.

Patients should be warned against interruption or discontinuation of antihypertensive medications without the physician's advice.

Patients treated for severe congestive heart failure should be cautioned to increase their physical activity slowly.

Since the use of captopril during pregnancy can cause injury and even death of the developing fetus, patients should be advised to report promptly to their physician if they become pregnant.

Drug Interactions

Diuretic Therapy:

Patients on diuretics and especially those in whom diuretic therapy was recently instituted, as well as those on severe dietary salt restriction or dialysis, may occasionally experience a precipitous reduction of blood pressure usually within the first hour after receiving the initial dose of captopril (see **WARNINGS**).

When feasible the hypotensive effects may be minimized by either discontinuing the diuretic or increasing the salt intake approximately one week prior to initiation of treatment with MYLAN-CAPTOPRIL. Alternatively, provide medical supervision for at least 1 hour after the initial dose. If hypotension occurs, the patient should be placed in a supine position and, if necessary,

receive an intravenous infusion of normal saline. This transient hypotensive response is not a contraindication to further doses, which can be given without difficulty once the blood pressure, has increased after volume expansion.

Agents Having Vasodilator Activity:

Data on the effect of concomitant use of other vasodilators in patients receiving captopril for heart failure are not available; therefore, nitroglycerin or other nitrates (as used for management of angina) or other drugs having vasodilator activity should, if possible, be discontinued before starting captopril. If resumed during MYLAN-CAPTOPRIL therapy, such agents should be administered cautiously, and perhaps at lower dosage.

Agents Causing Renin Release:

Captopril's effect will be augmented by antihypertensive agents that cause renin release. For example, diuretics (e.g., thiazides) may activate the renin-angiotensin-aldosterone system.

Agents Affecting Sympathetic Activity:

The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Therefore, agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) should be used with caution. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive.

In heart failure, special caution is necessary since sympathetic stimulation is a vital component supporting circulatory function and inhibition with beta-blockade always carries a potential hazard of further depressing myocardial contractility.

Agents Increasing Serum Potassium:

Since captopril 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 then with caution, since they may lead to a significant increase of serum potassium. Salt substitutes which contain potassium should also be used with caution.

Inhibitors of Endogenous Prostaglandin Synthesis:

It has been reported that indomethacin may reduce the antihypertensive effect of captopril, especially in cases of low renin hypertension. Other nonsteroidal anti-inflammatory agents (e.g., aspirin) may also have this effect.

The blood pressure lowering effects of captopril and beta-blockers are less than additive.

In patients with renal failure, the use of allopurinol concomitantly with captopril has been associated with neutropenia.

In patients with heart failure, the use of procainamide concomitantly with captopril has been associated with neutropenia.

Drug/Laboratory Test Interaction:

Captopril may cause false-positive reactions for urinary acetone and for dipstick tests for urinary ketones.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In the event of overdosage, correction of hypotension would be of primary concern. Volume expansion with an intravenous infusion of normal saline is the treatment of choice for restoration of blood pressure.

Captopril may be removed from the general circulation by hemodialysis.

ADVERSE REACTIONS

Hypertension and Congestive Heart Failure

Reported incidences are based on clinical trials involving approximately 7,000 patients treated with captopril.

Renal: Approximately 1 of every 100 patients developed proteinuria (see **WARNINGS**).

Each of the following has been reported in approximately 1 to 2 of 1000 patients and are of uncertain relationship to drug use: renal insufficiency, renal failure, polyuria, oliguria and urinary frequency.

Hematologic: Neutropenia/agranulocytosis has occurred (see **WARNINGS**). Cases of anemia, thrombocytopenia and pancytopenia have been reported.

Dermatologic: A rash occurred in 8.5 percent of patients with normal renal function and 13 percent of patients with evidence of prior renal functional impairment. It was dose-related, having occurred in 7 percent of patients at doses of 150 mg or less per day. The rash is usually maculopapular, but rarely urticarial, and generally occurs during the first four weeks of therapy. The rash is usually mild and disappears within a few days of dosage reduction, short-term treatment with an antihistaminic agent, and/or discontinuing therapy; remission may occur even if captopril is continued. Pruritus, without rash, occurs in about 2 percent of patients. Between 7 and 10 percent of patients with skin rash have shown an eosinophilia and/or positive ANA titers. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported.

Allergic: Angioedema of the face, mucous membranes of the mouth, or of the extremities has been observed in approximately 1 of 1000 patients and is reversible on discontinuance of captopril therapy. Serum sickness and bronchospasm have been reported. One case of laryngeal edema has been reported.

Cardiovascular: Hypotension may occur; see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy.

Tachycardia, chest pain, and palpitations have each been observed in approximately 1 of 100 patients.

Angina pectoris, myocardial infarction, Raynaud's syndrome and congestive heart failure have each occurred in 2 to 3 of 1000 patients.

Flushing or pallor has been reported in 2 to 5 of 1000 patients.

Alterations in Taste: Two percent of patients receiving 150 mg or less per day of captopril developed a diminution or loss of taste perception. At doses in excess of 150 mg/day, 7 percent of patients experienced this effect. Taste impairment is reversible and usually self-limited (2 to 3 months) even with continued drug administration. Weight loss may be associated with the loss of taste.

The following have been reported in about 0.5 to 2 percent of patients:

Gastrointestinal: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers and peptic ulcer.

Central Nervous System: dizziness, headache, malaise, fatigue, insomnia and paresthesia.

Others: dry mouth, dyspnea, cough, alopecia, impotence, loss of libido, disturbed vision, and itching and/or dry eyes.

Other clinical adverse effects reported since the drug was marketed are listed below by body system. In many cases, an incidence or causal relationship cannot be accurately determined.

General	:	asthenia, gynecomastia
Cardiovascular	:	cardiac arrest, cerebrovascular accident, syncope
Dermatologic	:	bullous pemphigus, Stevens-Johnson syndrome
Gastrointestinal	:	pancreatitis, glossitis
Hematologic	:	anemia, including aplastic and hemolytic
Hepatobiliary	:	hepatitis, including rare cases of necrosis, cholestasis (see **PRECAUTIONS**)
Metabolic	:	symptomatic hyponatremia
Musculoskeletal	:	myalgia, myasthenia
Nervous/Psychiatric	:	ataxia, confusion, depression, nervousness, somnolence
Respiratory	:	bronchospasm, eosinophilic pneumonitis, rhinitis
Special Senses	:	blurred vision

As with other ACE inhibitors, a syndrome has been reported which includes: fever, myalgia, arthralgia, rash or other dermatologic manifestations, eosinophilia and an elevated ESR. Findings have usually resolved with discontinuation of treatment.

Altered Laboratory Findings

Elevations of liver enzymes and/or serum bilirubin have occurred (see PRECAUTIONS). Rare cases of cholestatic jaundice, and of hepatocellular injury with or without secondary cholestasis, have been reported in association with captopril administration.

Elevation of BUN and serum creatinine may occur, especially in patients who are volume-depleted or who have renovascular hypertension. In instances of rapid reduction of long-standing or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN.

Small increases in the serum potassium concentration frequently occur, especially in patients with renal impairment (see **PRECAUTIONS**).

Diabetic Nephropathy

In 400 patients treated with captopril, the overall adverse reactions profile appeared to be similar to the above. However, the following adverse reactions have occurred more frequently in women than in men: dizziness (31% vs 20%), cough (23% vs 17%) and pharyngitis (20% vs 14%). In 395 patients treated with placebo, the incidences were: dizziness (22%), cough (15%) and pharyngitis (11%) in women and men combined.

The incidence of hypotension or orthostatic hypotension was 5.3% and was a reason for discontinuation of the drug in 1.8% of the patients.

The incidence of hyperkalemia related or possibly related to therapy in the diabetic patients studied with nephropathy and proteinuria was 3.6% and was a reason of discontinuation of the drug in 1% of the patients. Hyperkalemia was defined as persistent elevation of serum potassium to 6.0 mg/dL or more in the absence of a remediable cause, such as other drugs, volume depletion, exogenous potassium supplements, etc.

In patients with serum creatinine $ 1.5 mg/dL, the incidence of a marked abnormality in hemoglobin (a drop > 3 gram/dL) was 6% in patients treated with captopril versus 0% in those on placebo.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In the event of overdosage, correction of hypotension would be of primary concern. Volume expansion with an intravenous infusion of normal saline is the treatment of choice for restoration of blood pressure.

Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION

MYLAN-CAPTOPRIL (captopril) tablets should be taken one hour before meals. DOSAGE MUST BE INDIVIDUALIZED.

Adults: Hypertension:

Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation, salt restriction, and other clinical circumstances. If possible,

discontinue the patient's previous antihypertensive drug regimen for one week before starting MYLAN-CAPTOPRIL. If this is impossible, especially in severe hypertension, the diuretic should be continued.

The initial dose of MYLAN-CAPTOPRIL is 25 mg b.i.d. or t.i.d. If a satisfactory reduction of blood pressure has not been achieved after one or two weeks, the dose may be increased to 50 mg b.i.d. or t.i.d. The dose of captopril in hypertension usually does not exceed 150 mg daily. Therefore, if the blood pressure has not been satisfactorily controlled after one to two weeks at this dose (and the patient is not already receiving a diuretic), a modest dose of thiazide-type diuretic (e.g., hydrochlorothiazide 25 mg daily) should be added. The diuretic dose may be increased at one- to two-week intervals until its highest usual antihypertensive dose is reached.

If MYLAN-CAPTOPRIL is being started in a patient already receiving a diuretic, MYLAN-CAPTOPRIL therapy should be initiated under close medical supervision (see WARNINGS AND PRECAUTIONS [Drug Interactions] regarding hypotension), with dosage and titration of captopril as noted above.

In severe hypertension, if further blood pressure reduction is required, the dose of MYLAN-CAPTOPRIL may be increased to 100 mg b.i.d. or t.i.d. and then, if necessary, to 150 mg b.i.d. or t.i.d., while continuing the diuretic. The usual dose range is 25 to 150 mg b.i.d. or t.i.d. A maximum daily dose of 450 mg given in three equally divided doses should not be exceeded.

For patients with accelerated or malignant hypertension, when temporary discontinuation of current antihypertensive therapy is not practical or desirable, or when prompt titration to more normotensive blood pressure levels is indicated, the diuretic should be continued but other concurrent antihypertensive medication stopped and MYLAN-CAPTOPRIL dosage promptly initiated at 25 mg 3 times a day, under close medical supervision. When necessitated by the patient's clinical condition, the daily dose of MYLAN-CAPTOPRIL may be increased every 24 hours under continuous medical supervision until a satisfactory blood pressure response is obtained or the maximum dose of MYLAN-CAPTOPRIL is reached. In this regimen, addition of a more potent diuretic, e.g., furosemide, may also be indicated.

Beta-blockers may also be used in conjunction with captopril therapy (see **PRECAUTIONS** - Drug Interactions), but the effects of the two drugs are less than additive.

Heart Failure:

Initiation of therapy requires consideration of recent diuretic therapy and the possibility of severe salt/volume depletion. In patients with either normal or low blood pressure, who have been vigorously treated with diuretics and who may be hyponatremic and/or hypovolemic, a starting dose of 6.25 or 12.5 mg t.i.d. may minimize the magnitude or duration of the hypotensive effect (see WARNINGS, [Hypotension]). For these patients, titration to the usual daily dosage can then occur within the next several days.

For most patients the usual initial daily dosage is 25 mg t.i.d. After a dose of 50 mg t.i.d. is reached, further increases in dosage should be delayed, where possible, for at least 2 weeks to determine if a satisfactory response occurs. Most patients studied have had a satisfactory clinical improvement at 50 or 100 mg t.i.d. A maximum daily dose of 450 mg of MYLAN-CAPTOPRIL should not be exceeded.

MYLAN-CAPTOPRIL is to be used in conjunction with a diuretic and digitalis. MYLAN-CAPTOPRIL therapy must be initiated under very close medical supervision.

Left Ventricular Dysfunction after Myocardial Infarction

The recommended dose for long-term use in patients following a myocardial infarction is a target maintenance dose of 50 mg t.i.d.

Therapy may be initiated as early as three days following a myocardial infarction. After a single dose of 6.25 mg, MYLAN-CAPTOPRIL therapy should be initiated at 12.5 mg t.i.d. MYLAN-CAPTOPRIL should then be increased to 25 mg t.i.d. during the next several days and to a target dose of 50 mg t.i.d. over the next several weeks as tolerated (see CLINICAL PHARMACOLOGY).

MYLAN-CAPTOPRIL may be used in patients treated with other post-myocardial infarction therapies, e.g. thrombolytics, aspirin, beta blockers.

Diabetic Nephropathy

The recommended daily dose of captopril for long-term use to treat diabetic nephropathy is 25 mg t.i.d.

If further blood pressure reduction is required, other antihypertensive agents such as diuretics, beta adrenoceptor blockers, centrally acting agents or vasodilators may be used in conjunction with MYLAN-CAPTOPRIL.

Dosage Adjustment in Renal Impairment

Because captopril is excreted primarily by the kidneys, excretion rates are reduced in patients with impaired renal function. These patients will take longer to reach steady-state levels of captopril and will reach higher steady state levels for a given daily dose than patients with normal renal function. Therefore, these patients may respond to smaller or less frequent doses.

Captopril is removed by hemodialysis.

Renal Impairment Due to Diabetic Nephropathy (with or without hypertension)

Captopril at doses of 25 mg t.i.d. was well tolerated in patients with diabetic nephropathy and mild to moderate renal impairment (see PRECAUTIONS - Hyperkalemia). Accordingly, no dose adjustment based on creatinine clearance is recommended for these patients.

Captopril has not been studied in patients with diabetic nephropathy and severe renal impairment (creatinine clearance # 30 mL/min/1.73m2). These patients can be expected to have a higher steady-state concentrations for a given daily dose than those with normal renal function or mild-

moderate renal impairment, and therefore may respond to smaller or less frequent doses. Doses may be adjusted based on clinical observation.

Renal Impairment Not Due to Diabetic Nephropathy

For patients with significant renal impairment not due to diabetic nephropathy, initial daily dosage of MYLAN-CAPTOPRIL should be reduced, and smaller increments utilized for titration, which should be quite slow (one to two week intervals). After the desired therapeutic effect has been achieved, the dose should be slowly back-titrated to determine the minimal effective dose. When concomitant diuretic therapy is required, a loop diuretic (e.g., furosemide), rather than a thiazide diuretic, is preferred in these patients with impaired renal function. (See **PRECAUTIONS**, Anaphylactoid reactions during membrane exposure)

The following table which is based on theoretical considerations may be useful as a guide to minimize drug accumulation.

Creatinine Clearance ($mL/min/1.73m^2$)	Dosage Interval (Hours)
> 75	8
75-35	12-24
34-20	24-48
19-8	48-72
7-5	72-108 (3 to 4.5 days)

Captopril is removed by hemodialysis.

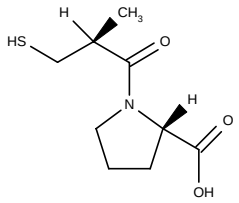
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name : captopril, USP

Chemical Name : 1[(2S)-3-mercapto-2-methylpropionyl]-L-proline

Structural Formula :



Molecular Formula : $C_9H_{15}NO_3S$

Molecular Weight : 217.2

Description : White to off-white crystalline powder with a slight acid-sulfhydryl odour; soluble in water, methanol and ethanol, and sparingly soluble in chloroform and ethyl acetate.

Composition

MYLAN-CAPTOPRIL tablets contain 12.5, 25, 50 or 100 mg of captopril, USP.

Stability and Storage Recommendations

Store at room temperature (15 to 30°C). Protect from moisture. Keep bottles tightly closed.

AVAILABILITY OF DOSAGE FORMS

MYLAN-CAPTOPRIL (captopril) is available as tablets containing:

12.5 mg of captopril: Each white, capsule-shaped tablet with partial bisect and "G" on one side and partial bisect and "C 12.5" on the other, contains: captopril 12.5 mg. Bottles of 100.

25 mg of captopril: Each white, square, biconvex tablet with "C 25" on one side and quadrasected on the other, contains: captopril 25 mg. Bottles of 100.

50 mg of captopril: Each white, oval, biconvex tablet with "C 50" on one side and with a partial bisect and "G" on the other, contains: captopril 50 mg. Bottles of 100.

100 mg of captopril: Each white, oval, biconvex tablet with "C 100" on one side and with a partial bisect and "G" on the other, contains: captopril 100 mg. Bottles of 100.

PHARMACOLOGY

Captopril, administered orally, decreased mean blood pressure in intact spontaneously hypertensive rats, renal hypertensive rats and renal hypertensive dogs. Captopril did not lower blood pressure in spontaneously and renal hypertensive rats that were bilaterally nephrectomized.

In anesthetized intact dogs, intravenously administered captopril caused a decrease in blood pressure, coronary and peripheral vascular resistance, renal vascular resistance and an increase in renal blood flow.

Renal blood flow was found to increase following administration of single oral doses of 5 to 25 mg of captopril to normotensive sodium-depleted or sodium-loaded subjects and to sodium-depleted hypertensive patients. The greatest increase occurred in the hypertensive patients (average 45%, range 0-73%) while the least increase occurred in the sodium-loaded normotensive patients (average 9%, range 8-54%).

In a renal function study in monkeys with hyperplasia of the renal juxtaglomerular apparatus induced by chronic captopril therapy, the various indices of renal function were not compromised in comparison with control animals, despite the lower systemic blood pressure and the presence of the hyperplasia.

Single 100 mg doses of captopril-^{14}C were administered to 15 patients with various degrees of renal impairment (creatinine clearances ranging from 0 to 56 mL/minute). The blood half-life for the radioactivity was found to be inversely related to endogenous creatinine clearance with a linear relationship between creatinine clearance and the overall elimination rate constant for total radioactivity.

In tissue-distribution studies in rats, the highest concentrations of orally-administered captopril were found in the kidney, liver, blood and lung.

An increase in cerebral blood flow after captopril administration has been found in spontaneously hypertensive rats.

In human studies, single oral doses of 2.5 to 20 mg of captopril produced 90 to 100% inhibition of pressor responses induced by intravenous administration of angiotensin I. Blockade was noted within 15 minutes. Captopril had no significant effect on the pressor response to angiotensin II.

In clinical studies, during long-term therapy, approximately 80 to 85% of patients with chronic congestive heart failure exhibited sustained improvement in their functional status and progressive improvement in their ability to perform treadmill exercise.

TOXICOLOGY

Acute Toxicity:

Species	Sex	Route of Administration	LD_{50}(mg/kg)
Mouse	M	oral	5650-7900
	F	oral	6000-7300
Mouse	M	i.v.	970-1130
	F	i.v.	810-1290
Mouse	M	i.p.	270-415
	F	i.p.	340-490
Rat	M	oral	6000
	F	oral	5500
Rat	M	i.p.	410
	F	i.p.	380

Signs of toxicity in mice were respiratory depression, ataxia, convulsions, loss of grip strength, transient weight loss, edema of tail, collapse, and irritation at the site of intravenous injection. Signs of toxicity in rats were diarrhea, transient weight loss, cyanosis, ataxia and convulsions. Most deaths occurred within 1 day.

Resumé: Pertinent Findings in Animals

Chronic oral toxicity studies were conducted in rats (2 years), dogs (47 weeks; 1 year), mice (2 years), and monkeys (1 year). Significant drug-related toxicity included effects on hematopoiesis, renal toxicity, erosion/ulceration of the stomach, and variation of retinal blood vessels.

Reductions in hemoglobin and/or hematocrit values were seen in mice, rats, and monkeys at doses of 500 to 1500 mg/kg/day. Anemia, leukopenia, thrombocytopenia, and bone marrow depression occurred in dogs at doses of 80 to 300 mg/kg/day. The reductions in hemoglobin and hematocrit values in rats and mice were only significant at 1 year and returned to normal with continued dosing by the end of the study. Marked anemia was seen at all dose levels (80 to 300 mg/kg/day) in dogs, whereas moderate to marked leukopenia was noted only at 150 to 300 mg/kg and thrombocytopenia at 300 mg/kg. The anemia could be reversed upon discontinuation of dosing. Bone marrow suppression occurred to a varying degree, being associated only with dogs that died or were sacrificed in a moribund condition in the 1-year study. However, in the 47-week study at a dose of 300 mg/kg/day, bone marrow suppression was found to be reversible upon continued drug administration.

Captopril caused hyperplasia of the juxtaglomerular apparatus of the kidneys at doses 70 to 2000 mg/kg in rats and mice, at 200 to 600 mg/kg in monkeys and at 200 mg/kg/day in dogs.

Gastric erosions/ulcerations were increased in incidence at 200 and 2000 mg/kg doses in male rats and at 300 and 650 mg/kg doses in dogs and monkeys, respectively. Rabbits developed gastric and intestinal ulcers when given oral doses of approximately 300 mg/kg for only 5 to 7 days.

In the two-year rat study, irreversible and progressive variations in the calibre of retinal vessels (focal sacculations and constrictions) occurred at all dose levels (70 to 2000 mg/kg/day) in a

dose-related fashion. The effect was first observed in the 88th week of dosing, with a progressively increased incidence thereafter, even after cessation of dosing.

Subacute Toxicity

Species	Strain	Sex	# of Animals per Group	# of Groups	Dose (mg/kg/day)	Route	Duration of Study	Toxic Effects
Rat	Charles-River	M F	6 6	5 5	0, 50, 150, 450, or 30-3000 (progressively increasing doses)	Oral	1 month	High Dose: slight growth retardation (F only); slightly decreased erythrocytic parameters; slight leukocytosis. 3 Highest Doses: slight to moderate increase in BUN; dose-related slight to moderate growth retardation (M only). All Doses: slightly increased water intake.
Dog	Beagle	M F	2 2	4 4	0, 25, 75, 225	Oral	1 month	High & Mid Doses: decreased erythrocytic parameters; increased urine calcium. All doses: increased urine magnesium (significant only in mid-dose group).
Dog	Beagle	M F	2,3 2,3	2 2	0, 200-600 (i.e. wk 1 = 200 wk 2-4 = 400 wk 5 = 600	Oral	5 weeks	200 mg/kg: decreased food consumption and body weight (F only); slight increase in BUN. 400 mg/kg: 1 death and 3 sacrifices due to GI distress and kidney dysfunction. 600 mg/kg: (2 remaining dogs); occasional emesis and loose feces; slight to moderate increased BUN, creatinine, total protein, potassium, calcium and cholesterol.
Monkey	Rhesus	M F	1 2	4 4	0, 25, 75, 225	Oral	1 month	No toxic effects.
Monkey	Rhesus	M F	2 2	4 4	0, 50, 150, 450	Oral	3 month	High Dose: loose feces, decreased weight gain and erythrocytic parameters; increased BUN, sodium, and retention of BSP. High & Mid Doses: dose-related mild to moderate hyperplasia of juxtaglomerular apparatus.

Chronic Toxicity and Carcinogenicity

Species	Strain	Sex	# of Animals per Group	# of Groups	Dose (mg/kg/day)	Route	Duration of Study	Toxic Effects
Mouse	Charles-River	M F	65 65	4 4	0, 50, 150, 450-1350	Oral	2 years	High Dose: slight retardation of body-weight gain (M only); slight increase of serum alkaline phosphatase (F only). All Doses: slight decrease in erythrocytic parameters & slight increase in BUN; slightly lower heart weight and hyperplasia of renal juxtaglomerular apparatus. No evidence of carcinogenicity was observed.
Rat	Charles-River	M F	65 65	4 4	0, 50, 150, 450-1350	Oral	2 years	High Dose: slight increase in SGPT; slight increase in BUN (F only). All doses: slight to moderate retardation of body weight gain; very slight decrease in erythrocytic parameters (dose-related) and serum total protein; slight dose-related increase in BUN (M only); lower mean heart weights; dose-related changes in retinal vessels, thickening of renal afferent arterial walls due to hyperplasia of juxtaglomerular and arterial smooth muscle cells. No evidence of carcinogenicity was observed.

Chronic Toxicity

Species	Strain	Sex	# of Animals per Group	# of Groups	Dose (mg/kg/day)	Route	Duration of Study	Toxic Effects
Dog	Beagle	M F	4 4	4 4	0, 50, 100, 200	Oral	1 year	High Dose: 1 sacrificed with renal dysfunction - marked tubular dilation and mild hyperplasia of juxtaglomerular apparatus; slight increase in BUN. High & Mid Doses: emesis. All Doses: bone marrow suppression involving myeloid and/or erythroid series - 5 dogs sacrificed or died; anemia.
Dog	Beagle	M F	4 4	1 1	200	Oral	47 weeks	Effects reported in previous study corroborated.
Monkey	Rhesus	M/F	13,7 7,9	4	0, 50, 150, 450	Oral	1 year	High Dose: loose feces, slight increases in serum potassium. High & Mid Doses: slight decrease in erythrocytic parameters and serum sodium; slight to moderate increases in BUN; hyperplasia of juxtaglomerular apparatus.

Reproduction and Teratology

Species & Strain	Sex	# of Animals per Group	# of Groups	Dose (mg/kg/day)	Route	Treatment Period	Toxic Signs
Rat (Charles-River)	M F	12 36	5 5	0, 50, 300, 1800, 1800	Oral	10 weeks prior to mating. 2 weeks prior to mating. Dosing continued in half of females until Day 13 of gestation. Remaining females dosed through gestation and 21 days of lactation.	No effects on fertility and reproduction; no embryotoxic, fetotoxic, or teratogenic effect.
Rat (Charles-River)	F	19-22	4	0, 50, 450, 4000	Oral	Days 7-16 of gestation.	Mean food consumption and body weight gain significantly reduced in 4000 mg/kg/day group. 6 deaths of mothers due to gastric ulceration (5 from high-dose group). No embryotoxic, fetotoxic or teratologic effects.
Hamster (Golden Syrian)	F	24, 24, 24, 26, 8, 6	6	0, 50, 450, 1000, 2000, 4000	Oral	Days 7-13 of gestation.	Death due to gastric ulcers in 12 of 14 dams of 2000 and 4000 mg/kg. 88% incidence of embryonic death in 2 remaining dams at 2000 mg/kg. No embryotoxic, fetotoxic or teratologic effects at doses of 1000 mg/kg.
Rabbit (New Zealand)	F	15-20	6	0, 0, 15, 50, 150, 450	Oral	Days 7-19 of gestation.	Gastric ulcers (6-19% incidence) in all dosed does; dose-related incidence of fetal death in all treated groups - thought due to hypotension (dose-related) in does rather than direct fetotoxic effect; hydrocephalus (2%) and microphthalmia (2.7%) in fetuses of 3 lower dose groups.
Rat (Charles-River)	F	16-23	3	0, 50, 400, 3000	Oral	Day 15 of gestation through Day 21 of lactation	Reduced postnatal growth and viability of offspring of 1 dose group.

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