PRODUCT MONOGRAPH

PrTEVA-FOSINOPRIL

(Fosinopril sodium)

10 mg and 20 mg Tablets

Angiotensin Converting Enzyme Inhibitor

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
M1B 2K9
www.tevacanada.com

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THERAPEUTIC CLASSIFICATION

Angiotensin Converting Enzyme Inhibitor

ACTION AND CLINICAL PHARMACOLOGY

TEVA-FOSINOPRIL (fosinopril sodium) is an angiotensin converting enzyme (ACE) inhibitor which is used in the treatment of mild to moderate essential hypertension and in the management of symptomatic congestive heart failure.

Following oral administration, TEVA-FOSINOPRIL, an ester prodrug, is rapidly hydrolyzed to fosinoprilat, its principal active metabolite.

ACE is a peptidyl dipeptidase that 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. Decreased levels of angiotensin II and the accompanying lack of negative feedback on renal renin secretion results in increases in plasma renin activity.

ACE is identical to kininase II. Thus, fosinopril may interfere with the degradation of bradykinin, a potent peptide vasodilator. However, it is not known whether this contributes to the therapeutic effects of TEVA-FOSINOPRIL.

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

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

PHARMACOKINETICS AND METABOLISM

Following oral administration, fosinopril (the prodrug) is absorbed slowly. The absolute absorption of fosinopril averaged 36% of an oral dose. The primary site of absorption is the proximal small intestine (duodenum/jejunum). While the rate of absorption may be slowed by the presence of food in the gastrointestinal tract, the extent of absorption of fosinopril is essentially unaffected. The bioavailability of fosinoprilat is reduced by about 20%.

Hydrolysis of fosinopril to the active fosinoprilat is rapid and complete. This biotransformation probably occurs in the gastrointestinal mucosa and liver.

After an oral dose of radiolabelled fosinopril to healthy subjects, 75% of radioactivity in plasma was present as active fosinoprilat, 20-30% as a glucuronide conjugate of fosinoprilat, and 1-5% as a p-hydroxy metabolise of fosinoprilat. In urine, 75% of the drug excreted was fosinoprilat, the remainder consisted primarily of the glucuronide conjugate of fosinoprilat. In rats, the para-hydroxy metabolise of fosinoprilat is as potent an inhibitor of ACE as fosinoprilat; the glucuronide conjugate of fosinoprilat is devoid of ACE inhibitor activity.

After single and repeated doses, areas under serum concentration-time curves (AUCs) and peak concentrations (C_{maxs}) were directly proportional to the dose of fosinopril. The time to reach peak concentrations (T_{max}) was independent of dose and achieved in approximately three hours.

In hypertensive patients with normal renal and hepatic function, who received repeated doses of fosinopril, the effective half-life for accumulation of fosinoprilat averaged 11.5 hours, while in patients with heart failure, the effective half-life was 14 hours. Fosinoprilat is highly protein-bound (≥ 95%), has a relatively small volume of distribution, and negligible binding to cellular components in blood.

After intravenous administration, elimination of fosinoprilat was shared equally by the liver and kidney. After an oral dose of radiolabelled fosinopril, approximately half of the absorbed dose was excreted in urine and the remainder was excreted in the feces. In normal subjects, the mean body clearance of intravenous fosinoprilat was between 26 and 39 mL/min.

In patients with renal insufficiency, fosinoprilat pharmacokinetic parameters (including absorption, bioavailability, protein binding, and biotransformation/ metabolism) were not appreciably altered by reduced renal function. The total body clearance of fosinoprilat in patients with impaired renal function (creatinine clearance < 80 mL/min/1.73m^2) was approximately 50% slower than in patients with normal renal function. Since hepatobiliary elimination partially compensates for diminished renal elimination, the body clearance of fosinoprilat does not appreciably differ with any degree of renal insufficiency including end-stage renal failure (creatinine clearance values < 10 mL/min/1.73 m^2). A modest increase in plasma AUC levels (less than two times that in normals) was observed in patients with various degrees of renal insufficiency, including end stage renal failure (see Dosage and Administration).

Clearance of fosinoprilat by hemodialysis and peritoneal dialysis averages 2% and 7%, respectively, of urea clearances.

In patients with hepatic insufficiency (alcoholic or biliary cirrhosis), the extent of absorption was not affected. In a single and multiple dose pharmacokinetic studies, the mean AUC for fosinoprilat were markedly increased (50-100%) as compared to those of patients with normal liver functions. The extent of hydrolysis of fosinopril was not appreciably reduced although the rate may be slowed. Patients with hepatic insufficiency could develop elevated plasma levels of unchanged fosinopril.

In elderly (male) subjects (65-74 years old) with clinically normal renal and hepatic function, there were no significant differences in the pharmacokinetic parameters of fosinoprilat as compared to those in younger subjects (20-35 years old).

Fosinoprilat was found to cross the placenta of pregnant animals.

Studies in animals indicate that fosinopril and fosinoprilat do not cross the blood-brain barrier.

PHARMACODYNAMICS

Administration of fosinopril sodium to patients with mild to moderate essential hypertension has reduced both supine and standing blood pressures with minimal effect on heart rate. Following administration of a single dose, the onset of an antihypertensive effect is seen within one hour with peak blood pressure reduction usually achieved by 3 to 6 hours after dosing. Achievement of maximum blood pressure lowering effect may require several weeks of therapy in some patients. At the recommended doses, antihypertensive effects are maintained throughout the 24-hour dosing interval in most patients. The effectiveness of fosinopril sodium appears to be similar in the elderly (over 65 years of age) and younger adult patients given the same daily dosages.

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

Abrupt withdrawal of fosinopril sodium has not resulted in rapid increase in blood pressure.

In hemodynamic study involving patients with mild to moderate hypertension, after three months of therapy, responses (changes in blood pressure, heart rate, cardiac index and peripheral vascular resistance) to various stimuli (e.g., isometric exercise, 45 degree head-up tilt, and mental challenge) were unchanged compared to baseline, suggesting that fosinopril sodium does not affect the activity of the sympathetic nervous system. Reduction in systemic blood pressure appears to have been mediated by a decrease in peripheral vascular resistance without reflex cardiac effects. Similarly, renal, splanchnic, cerebral, and skeletal muscle blood flow were unchanged compared to baseline, as was glomerular filtration rate.

Administration of fosinopril sodium to patients with congestive heart failure reduces afterload and preload of the heart, resulting in an increase in cardiac output, without reflex tachycardia. At

the recommended doses, the hemodynamic effects are maintained throughout the 24-hour dosing interval in most patients.

Administration of fosinopril sodium to hypertensive patients with proteinuria and microalbuminuria has resulted in significant reductions of urinary albumin excretion.

A comparative, two-way, single-dose, bioavailability study was performed under fasting conditions on TEVA-FOSINOPRIL (fosinopril sodium) 20 mg tablets and Monopril® 20 mg tablets by Bristol-Myers Squibb Canada Inc. The pharmacokinetic data calculated for the two fosinopril sodium formulations are tabulated below.

Single-Dose Pharmacokinetic Parameters for fosinoprilat (Fasting Conditions).

Geometric Mean Arithmetic Mean (CV %)			
	TEVA-FOSINOPRIL 1 x 20 mg	**Monopril®* 1 x 20 mg**	**Ratio of Geometric Means (%)**
AUC_T (ng.h/mL)	1784.2 1897.6 (34.4%)	1885.5 1989.4 (31.6%)	95
AUC_I (ng.h/mL)	1827.5 1942.7 (34.1%)	1926.6 2032.1 (31.5%)	95
C_{max} (ng/mL)	232.20 246.35 (33.5%)	245.20 256.20 (28.3%)	95
T_{max} ** (h)	3.521 (15.9%)	3.729 (17.7%)	-
$T_{½}$ ** (h)	15.21 (29.3%)	15.55 (23.50%)	-

* Monopril® Tablets, manufactured by Bristol-Myers Squibb Canada Inc., and purchased in Canada.
** The T_{max} and $T_{½}$ parameters are expressed as the arithmetic means (CV %).

INDICATIONS AND CLINICAL USE

TEVA-FOSINOPRIL (fosinopril sodium) is indicated in the treatment of mild to moderate essential hypertension. It may be used alone or in association with thiazide diuretics.

In using TEVA-FOSINOPRIL consideration should be given to the risk of angioedema (see WARNINGS).

TEVA-FOSINOPRIL should normally be used in those patients in whom treatment with a diuretic or a beta-blocker was found ineffective or has been associated with unacceptable adverse effects.

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

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

The safety and efficacy of concurrent use of TEVA-FOSINOPRIL with antihypertensive agents other than thiazide diuretics have not been established.

TEVA-FOSINOPRIL is indicated in the management of symptomatic congestive heart failure as adjunctive treatment with diuretics, and where appropriate digoxin. Treatment with TEVA-FOSINOPRIL should be initiated under medical supervision.

CONTRAINDICATIONS

TEVA-FOSINOPRIL (fosinopril sodium) is contraindicated in patients who are hypersensitive to this product 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, ACE inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected TEVA-FOSINOPRIL should be discontinued as soon as possible (see WARNINGS; Use in Pregnancy, and Information for Patients).

Head and Neck Angioedema

Angioedema has been reported in patients treated with ACE inhibitors, including fosinopril sodium. Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, TEVA-FOSINOPRIL 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 inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see CONTRAINDICATIONS).

Intestinal Angioedema
Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Hypotension
Symptomatic hypotension has occurred after administration of fosinopril sodium, usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with TEVA-FOSINOPRIL.

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 oliguria and/or progressive azotemia, and rarely, with acute renal failure and/or death. In patients with ischemic heart or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident (see ADVERSE REACTIONS). Because of the potential fall in blood pressure in these patients, therapy with TEVA-FOSINOPRIL should be started under close medical supervision. Such patients should be followed closely for the first weeks of treatment and whenever the dose of TEVA-FOSINOPRIL or diuretic is increased. Consideration should be given to reducing the diuretic dose in patients with normal or low blood pressure who have been treated vigorously with diuretics or who are hyponatremic.

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 is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion. However, lower doses of TEVA-FOSINOPRIL and/or reduced concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis
Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Current experience with fosinopril sodium shows the incidence to be rare and a causal relationship to the administration of TEVA-FOSINOPRIL has not been established. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and/or renal disease.

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

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; oligohydramnios in this setting has been 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.

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. Clearance of fosinoprilat by hemodialysis and peritoneal dialysis averages 2% and 7%, respectively of urea clearance.

Animal data: In pregnant rabbits, maternal toxicity was evident at doses ranging from 2.5 to 40 mg/kg/day (approximately 3 to 50 times the maximum human dose). Fosinopril was embryocidal in rabbits at 10 and 40 mg/kg/day (approximately 12 and 50 times the maximum human dose). These effects were probably due to marked decreases in blood pressure caused by ACE inhibition in this species. There were no teratogenic effects in rabbits at any dose level tested.

In pregnant rats, there was evidence of maternal toxicity at all dose levels tested, i.e. 25 to 400 mg/kg/day (about 30 to 500 times the maximum human dose). Slight reductions in placental weights and degree of skeletal ossification were observed at all dose levels, and fetal body weights were reduced in the high-dose group. Three similar orofacial malformations and one fetus with *situs inversus* occurred in fosinopril-treated animals. The association of these anomalies with treatment is uncertain.

Nursing Women
The presence of concentrations of ACE inhibitor have been reported in human milk. Use of ACE nhibitors 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 susceptible patients, concomitant diuretic use may further increase risk.

Use of TEVA-FOSINOPRIL (fosinopril) should include appropriate assessment of renal function.

Surgery/Anesthesia
ACE inhibitors may augment the hypotensive effects of anesthetics and analgesics. In patients undergoing surgery or during anesthesia with agents that produce hypotension, fosinopril will block the angiotensin II formation that could otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Hyperkalemia and Potassium-Sparing Diuretics
In clinical trials, elevated serum potassium (greater than 5.5 mEq/L) was observed in approximately 2.6% of hypertensive patients receiving fosinopril sodium. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in less than 0.1% of hypertensive patients. 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 (e.g., heparin) (see PRECAUTIONS - DRUG INTERACTIONS, ADVERSE REACTIONS).

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.

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.

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 including fosinopril sodium, in patients with or without pre-existing liver abnormalities (see ADVERSE REACTIONS). Fosinopril sodium

therapy was discontinued because of serum transaminase elevations in 0.7% of patients. In most cases the changes were reversed on discontinuation of the drug.

Should the patients receiving TEVA-FOSINOPRIL 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 investigation be carried out. Discontinuation of TEVA-FOSINOPRIL should be considered when appropriate.

TEVA-FOSINOPRIL should be used with particular 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.

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

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

Pediatric Use
The safety and effectiveness of TEVA-FOSINOPRIL in children have not been established, therefore, its use in this age group is not recommended.

Use in Elderly
Although clinical experience has not identified differences in response between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

Concomitant Diuretic Therapy: Patients concomitantly taking ACE inhibitors and diuretics, and 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 TEVA-FOSINOPRIL can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with TEVA-FOSINOPRIL. If it is not possible to discontinue the diuretic, the starting dose of TEVA-FOSINOPRIL can be reduced, and the patient should be closely observed for several hours following an initial dose and until blood pressure has stabilized. (see WARNINGS, and DOSAGE and ADMINISTRATION).

Decreases in serum sodium and increases in serum creatinine occurred more frequently in patients on concomitant diuretics than in those treated with TEVA-FOSINOPRIL alone. (See ADVERSE REACTIONS; Laboratory Test Abnormalities).

Agents Increasing Serum Potassium: Since TEVA-FOSINOPRIL decreases aldosterone production, elevation of serum potassium may occur. Potassium sparing diuretics such as spironolactone, triamterene or arniloride, 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.

Agents Causing Renin Release: The antihypertensive effect of TEVA-FOSINOPRIL is augmented by antihypertensive agents that cause renin release (e.g. diuretics).

With Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

With Inhibitors of Endogenous Prostaglandin Synthesis: It has been reported that indomethacin may reduce the antihypertensive effect of other ACE inhibitors, especially in cases of low renin hypertension. Other nonsteroidal anti-inflammatory agents (eg, aspirin) and selective COX-2 inhibitors may have a similar effect. In patients who are elderly, volume depleted (including those on diuretic therapy), or with compromised renal function, coadministration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, including fosinopril, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving fosinopril and NSAID therapy.

With Antacids: In a clinical pharmacology study, coadministration of an antacid (aluminum hydroxide, magnesium hydroxide, and simethicone) with fosinopril reduced serum levels and urinary excretion of fosinoprilat as compared with fosinopril administered alone, suggesting that antacids may impair absorption of fosinopril. Therefore if concomitant administration of these agents is indicated, dosing should be separated by two hours.

With Aspirin: In a study with concomitant administration of aspirin (acetylsalicylic acid) and fosinopril sodium the bioavailability of unbound fosinoprilat was not altered. Since it is believed that it is free fosinoprilat that inhibits ACE, the reduced bioavailability (30 to 40%) of bound fosinoprilat would not be expected to have a significant effect on the antihypertensive effects of fosinopril.

With Digoxin: In a study with concomitant administration of digoxin and fosinopril sodium, the bioavailability of fosinoprilat was not altered. The bioavailability of digoxin (i.e. AUC and C_{max}) appeared to be reduced slightly in the presence of fosinopril sodium. This reduction, of less than 20%, is considered to have little or no clinical relevance.

With Furosemide: In a steady-state pharmacokinetic study, coadministration of furosemide with fosinopril sodium increased the AUC of fosinoprilat by 26% and C_{max} by 25%. Furosemide levels were decreased.

With Warfarin: In a pharmacokinetic interaction study with warfarin, bioavailability parameters, the degree of protein binding and the anticoagulant effect (measured by prothrombin time) of warfarin were not significantly changed. The bioavailability of fosinoprilat was not altered by coadministration of fosinopril with warfarin.

Other: In separate single or multiple dose pharmacokinetic interaction studies with chlorthalidone, nifedipine, propranolol, hydrochlorothiazide, cimetidine, metoclopramide, and propantheline, the bioavailability of fosinoprilat was not altered by coadministration of fosinopril with any one of these drugs.

DRUG / LABORATORY TEST INTERACTION

Fosinopril sodium may cause a false low measurement of serum digoxin levels with the Digi-Tab® RIA kit for digoxin. Other kits such as the Coat-A-Count® RIA kit may be used.

INFORMATION FOR PATIENTS

Pregnancy: Since the use of TEVA-FOSINOPRIL during pregnancy can cause injury and even death of the developing fetus, patients should be advised to stop taking the medication and to report promptly to their physician if they become pregnant.

Breast-feeding: Patients should be advised that **TEVA-FOSINOPRIL** may pass into breast milk and that they should not breast-feed while taking **TEVA-FOSINOPRIL**.

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of TEVA-FOSINOPRIL. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, tongue, difficulty in swallowing or breathing); they should immediately stop taking TEVA-FOSINOPRIL and consult with their physician (see WARNINGS).

Hypotension: Patients should be cautioned to report light-headedness, especially during the first few days of TEVA-FOSINOPRIL therapy. If actual syncope occurs, the patients should be told to discontinue the drug and consult with their physician.

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 their physician.

Neutropenia: Patients should be advised to report promptly any signs or symptoms of infection (e.g., pharyngitis, fever) since these may be an early indicator of neutropenia (see WARNINGS and ADVERSE REACTIONS).

Impaired Liver Function: 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.

Hyperkalemia: Patients should be advised not to use potassium supplements or salt substitutes containing potassium without consulting their physician (see PRECAUTIONS and ADVERSE REACTIONS).

ADVERSE REACTIONS

Fosinopril sodium has been evaluated for safety in 1548 hypertensive patients. Of these, 1479 participated in controlled clinical trials, including 1048 who were treated with fosinopril sodium monotherapy. In heart failure trials, 516 patients were treated with fosinopril sodium, including 361 who participated in placebo-controlled trials. Fosinopril sodium has been evaluated for long-term safety in approximately 519 patients treated for one year or more.

Severe adverse reactions occurring in hypertensive patients treated with fosinopril sodium were: angioedema (1 case) and orthostatic hypotension (2.7%). Myocardial infarction (2 cases) and cerebrovascular accident (4 cases) occurred, possibly secondary to excessive hypotension in high risk patients (see WARNINGS). In 516 heart failure patients, the severe adverse reaction occurring with the highest frequency was angina pectoris (1.6%).

In placebo-controlled hypertensive trials, the most frequent adverse experiences were: nausea/vomiting, diarrhea, fatigue, musculoskeletal pain, headache, dizziness and cough. Discontinuation of therapy due to adverse events was required in 4.1% of the 688 patients. Cough was the cause for discontinuation of therapy in 0.4% of these patients.

In placebo-controlled heart failure trials, the most frequent adverse reactions were: dizziness, cough, headache and fatigue. Significant hypotension after the first dose of fosinopril sodium occurred in 2.4% of patients, while 0.8% discontinued due to first dose hypotension (see WARNINGS - Hypotension). Discontinuation of therapy due to adverse events was required in 7.8% of the 361 patients. Cough was the cause for discontinuation of therapy in 0.8% of these patients.

Adverse reactions occurring in 1% or more of the 1048 hypertensive and 361 congestive heart failure patients in controlled clinical trials who were treated with fosinopril sodium monotherapy are listed in Table 1.

TABLE 1

BODY SYSTEM / REACTION	HYPERTENSION[A] N = 1048 %	HEART FAILURE[B] N = 361 %
Cardiovascular		
Hypotension	-	4.4
Orthostatic Hypotension	1.4	1.9
Palpitation	-	1.4
Angina Pectoris	-	1.1
Edema	-	1.1
Dermatologic		
Rash	1.0	1.4
Endocrine/Metabolic		
Sexual Dysfunction	1.7	-
Gastrointestinal		
Nausea/Vomiting	1.4	2.2
Diarrhea	1.4	2.2
Pyrosis	1.0	-
Dry Mouth	1.0	-
Abdominal Pain	-	1.4
General		
Fatigue	2.8	4.7
Chest Pain (non-Cardiac)	-	2.2
Weakness	-	1.4
Musculoskeletal/Connective Tissue		
Musculoskeletal Pain	-	3.3
Muscle Cramp	-	1.4
Nervous System		
Headache	4.6	3.6
Dizziness	3.8	11.9
Insomnia	-	1.1
Respiratory		
Cough	4.0	9.7
Dyspnea	-	4.4
Upper Respiratory Infection	-	2.2

[A] Placebo and active controlled trials
[B] Placebo controlled trials

Clinical adverse reactions occurring in less than 1.0% of the 1479 hypertensive patients and 516 heart failure patients treated with fosinopril sodium in controlled clinical trials are listed below by body system:

Cardiovascular: Angina/myocardial infarction, cerebrovascular accidents, palpitations, syncope, edema, tachycardia, flushing, cardiac chest pain, hypertension, rhythm disturbances, heart failure, peripheral vascular disease of arteries, cardiac tamponade, coronary artery disease, hypertensive crisis, sudden death, cardiorespiratory arrest, shock, atrial rhythm disturbance, non-anginal chest pain, edema lower extremity, conduction disorder and bradycardia.

Dermatologic: Pruritus, dermatitis, skin induration, skin dryness, urticaria, skin eschar, photosensitivity, pruritic rash and nail abnormality. Pemphigus and Stevens-Johnson syndrome

have been reported with other ACE inhibitors and may occur rarely with fosinopril sodium as well.

Endocrine / Metabolic: Gout, libido change, breast disorder and menstrual disorder.

Gastrointestinal: Upper abdominal pain, abdominal distention, appetite change, constipation, flatulence, dysphagia, pancreatitis, hepatitis, tongue lesion and hepatomegaly.

General: Pain, excess sweating, change in weight, volume depletion, influenza, fever, hyperhidrosis and sensation of cold.

Hematologic: Lymphadenopathy, leucopenia, neutropenia (see WARNINGS), eosinophilia and hemolytic anemia.

Immunology / Sensitivity disorders: Angioedema.

Musculoskeletal / Connective tissue: Arthralgia, muscle ache, swelling extremity and weakness extremity.

Nervous System: Sleep disturbance, stress, paresthesia, mood change, equilibrium disturbance, drowsiness, tremor, cerebrovascular accident, mental activity disorder, memory disturbance, cranial nerve disorder, confusion, vertigo, cerebral infarction, transient ischemic attack, depression, numbness and behaviour change.

Renal / Genitourinary: Renal insufficiency, change in urinary frequency, abnormal urination and kidney pain.

Respiratory: Sinus abnormality, pharyngitis, rhinitis, epistaxis, hoarseness, laryngitis, breathing abnormality, asthma, bronchospasm, sinusitis, abnormal vocalization, tracheobronchitis and pleuritic chest pain. A symptom-complex of cough, bronchospasm and eosinophilia has been observed in two hypertensive patients treated with fosinopril.

Special senses: Eye irritation, vision disturbance, tinnitus, taste disturbance, ear pain, abnormal visual field and abnormal intraocular pressure.

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.

LABORATORY TEST FINDINGS

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia (see PRECAUTIONS: Drug Interactions, with Diuretics).

BUN/Serum creatinine: Elevations, usually transient and minor, of BUN or serum creatinine have been observed. In placebo-controlled clinical trials, there were no significant differences in the number of patients experiencing increases in serum creatinine (outside the normal range or 1.33 times the pre-treatment value) between the fosinopril and placebo treatment groups.

Urinary Albumin: In placebo controlled trials, a urinary albumin (two consecutive dip-stick values greater than 3+ or ≥ 2 times the pre-treatment value) unassociated with a rise in serum creatinine was seen in 0.4 percent of fosinopril sodium-treatment patients without pre-existing renal disease. Increases in urinary albumin usually developed in patients with pre-existing proteinuria or diabetes mellitus. In the majority of these patients, values returned to baseline despite continuation of therapy.

Hematology: In controlled trials, a mean hemoglobin decrease of 0.1 g/dL was observed in fosinopril treated patients. In individual patients decreases in hemoglobin or hematocrit were usually transient, small, and not associated with symptoms. No patient was discontinued from therapy due to the development of anemia.

Liver Function Tests: Elevations of transaminases, LDH, alkaline phosphatase and serum bilirubin have been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

No data are available regarding overdosage of TEVA-FOSINOPRIL (fosinopril sodium) in humans. The most likely clinical manifestation would be symptoms attributable to severe hypotension, which should be normally treated by intravenous volume expansion with 0.9% sodium chloride. Hemodialysis and peritoneal dialysis have little effect on the elimination of fosinoprilat.

DOSAGE AND ADMINISTRATION

Dosage of TEVA-FOSINOPRIL (fosinopril sodium) must be individualized.

Hypertension

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 TEVA-FOSINOPRIL may need to be adjusted.

Monotherapy

The recommended initial dose of TEVA-FOSINOPRIL is 10 mg once daily. Dosage should be adjusted according to blood pressure response, generally, at intervals of at least two weeks. The usual maintenance dose is 20 mg daily administered in a single daily dose. No additional blood pressure lowering effects were achieved with doses greater than 40 mg daily. A dose of 40 mg daily should not be exceeded.

In most patients, the antihypertensive effect of TEVA-FOSINOPRIL is maintained with a once daily dosage regimen. 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 TEVA-FOSINOPRIL alone, a diuretic may be added. After the addition of a diuretic, it may be possible to reduce the dose of TEVA-FOSINOPRIL.

Concomitant Diuretic Therapy: Symptomatic hypotension occasionally may occur following the initial dose of TEVA-FOSINOPRIL 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 TEVA-FOSINOPRIL to reduce the likelihood of hypotension (see WARNINGS). If the diuretic cannot be discontinued, an initial dose of 10 mg TEVA-FOSINOPRIL should be used with careful medical supervision for several hours and until blood pressure has stabilized. The dosage of TEVA-FOSINOPRIL should subsequently be titrated to the optimal response.

Heart Failure

TEVA-FOSINOPRIL is generally used in conjunction with a diuretic, with or without digoxin. Blood pressure and renal function should be monitored, both before and during treatment with TEVA-FOSINOPRIL, because severe hypotension, and more rarely renal failure, have been reported (see WARNINGS - Hypotension, PRECAUTIONS - Renal Impairment).

Initiation of therapy requires consideration of recent diuretic therapy, and the possibility of severe salt/volume depletion. If possible, the dose of diuretic should be reduced before beginning treatment to reduce the likelihood of hypotension (see PRECAUTIONS - Drug Interaction).

In patients with heart failure, the recommended initial dose of TEVA-FOSINOPRIL is 10 mg once daily, initiated under close medical supervision. If the initial dose of TEVA-FOSINOPRIL is well tolerated, the dose should be titrated over one to three weeks to 20 - 40 mg once daily. The occurrence of hypotension after the initial dose may not preclude careful dose titration with TEVA-FOSINOPRIL following effective management of hypotension.

In patients with severe congestive heart failure with or without renal insufficiency, therapy with TEVA-FOSINOPRIL should be initiated with caution (see WARNINGS - Hypotension). A lower starting dose should be considered.

Renal Impairment

In hypertensive patients with renal impairment and normal liver function no dosage adjustment is necessary. The recommended initial dose of TEVA-FOSINOPRIL is 10 mg once daily. Depending on the response, the dose should then be titrated to achieve the optimal response (see ACTION AND CLINICAL PHARMACOLOGY, and PRECAUTIONS). In such patients with heart failure, therapy should be initiated with caution.

Hepatic Impairment

In hypertensive patients with hepatic impairment and normal renal function no dosage adjustment is necessary. The recommended initial dose of TEVA-FOSINOPRIL is 10 mg once daily. Depending on the response, the dose should then be titrated to achieve the optimal response (see ACTION AND CLINICAL PHARMACOLOGY and PRECAUTIONS). In such patients with heart failure, therapy should be initiated with caution.

PHARMACEUTICAL INFORMATION

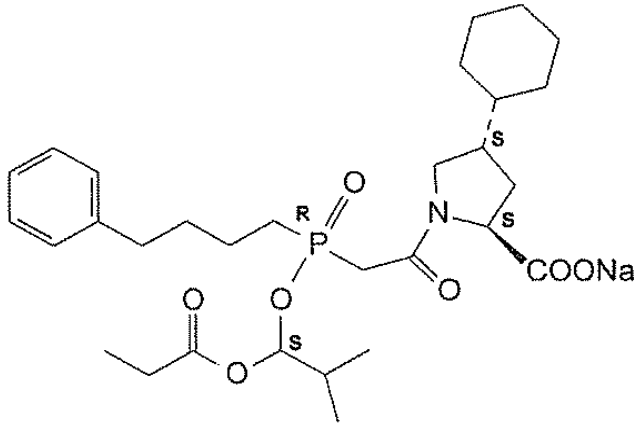
Drug Substance

Proper Name: Fosinopril sodium

Chemical Name: [1[S*(R*), 2α, 4β[-4-Cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)phosphinyl]acetyl]-L-proline sodium salt

Molecular Formula: $C_{30}H_{45}NNaO_7P$

Structural Formula:



Molecular Weight: 585.65

Description: Fosinopril sodium is a white to off-white crystalline powder with a pH of 5.80 (for an aqueous solution with a concentration of 0.2 mg/mL). It is soluble in water (freely soluble at pH 7, slightly soluble at pH 6 and very slightly soluble at pH ≥5, and chloroform, slightly soluble in hexane, freely soluble in methanol and sparingly soluble in alcohol.

pKa: 3.8 ± 0.6

Melting point: 195°C

Composition: In addition to the active ingredient, fosinopril sodium, each tablet contains anhydrous lactose, microcrystalline cellulose, crospovidone, povidone, sodium lauryl sulphate and glyceryl behenate.

STABILITY AND STORAGE RECOMMENDATIONS

Store bottles between 15° - 30°C. Keep bottle tightly closed. Protect from high humidity.

AVAILABILITY

TEVA-FOSINOPRIL 10 mg tablets are white to off-white, flat end diamond shaped, scored on one side, compressed tablets, engraved with **N** on one side and **1* 0** on the other.

TEVA-FOSINOPRIL 20 mg tablets are white to off-white, oval shaped, compressed tablets engraved with **N** on one side and **20** on the other.

TEVA-FOSINOPRIL 10 mg and 20 mg tablets are available in bottles of 100 tablets.

PHARMACOLOGY

Fosinopril sodium undergoes metabolic hydrolysis yielding the active ACE inhibitor, fosinoprilat. The potency of fosinoprilat was assessed in-vitro in the rabbit lung, guinea pig ileum, rat brain and rat kidney.

Fosinopril administered orally to conscious normotensive rats (10, 30, or 100 mg/kg), dogs (0.87, 2.7 or 30 mg/kg) and monkeys (0.6, 2.1 or 4.3 mg/kg) caused inhibition of Angiotensin I (Al) pressor response similar in magnitude to that caused by captopril, but with a longer duration of effect. Glycerol-induced renal impairment had no effect on the ability of fosinopril, administered orally at 0.81 mg/kg, to inhibit the AI pressor response in the rat. Fosinopril, administered orally to dogs at a dose of 30 mg/kg/day for 5 consecutive days, produced a similar magnitude and duration of Al pressor response inhibition on the first and fifth day.

Oral administration of fosinopril in spontaneously hypertensive rats (SHR), at doses of 10 or 30 mg/kg/day for 2 consecutive days, lowered blood pressure on each day without affecting heart rate. Hydrochlorothiazide (10 mg/kg) augmented the antihypertensive effect of fosinopril (10 mg/kg). Fosinopril administered orally to SHR at a dose of 30 mg/kg twice daily for 14 days caused a lowering of systolic blood pressure. Fosinopril produced a moderate blood pressure lowering in normotensive rats that was not dose related. Fosinopril, administered at a dose of 30 mg/kg/day for two days, did not lower blood pressure in mineralocorticoid-hypertensive rats.

Fosinopril was essentially completely hydrolyzed to fosinoprilat by the time it reached the general circulation in all species studied. The % absorption of an orally administered dose was lowest in rats (9.7 - 13.6%), whereas in dogs (21.7 - 29.6%) and monkeys (18.3 - 27.6%), it was similar to that in humans (31.5%).

After oral administration of ^{14}C-fosinopril and IV administration of ^{14}C-fosinoprilat, binding of radioactivity to plasma proteins was very extensive (88.7 to 99.7%) in all species studied.

Twenty-four hours after oral administration of a single 25 mg/kg dose of ^{14}C-fosinopril to male rats, tissue distribution of fosinoprilat was determined. The highest concentrations of fosinoprilat were found in the large intestine followed by the small intestine, plasma, liver, lungs and kidneys.

TOXICOLOGY

Acute Toxicity of fosinopril

Species	Sex (N)	Route	LD 50 (mg/kg)
Mouse	M 60 F 60	Oral	2720 2340
Mouse	M 235 F 75	Oral	2460 -3670
Mouse	M 60	I.V.	114
Mouse	M 60	I.P.	39
Rat	M 60 F 60	Oral	2850 2460
Rat	M 25 F 25	Oral	3200
Rat	M 50 F 50	I.P.	51.5 69
Dog	M 6 F 6	Oral	> 800 > 800

Signs of toxicity in mice and rats included decreased activity, diarrhea, soft or loose stools, transient weight loss, ataxia, salivation, slow respiration, convulsions, terminal collapse, gasping, cyanotic tails, loss of hind leg strength and prostration.

Signs of toxicity in dogs included loose feces and/or vomiting at doses of 200 mg/kg or more.

Acute Toxicity of fosinoprilat

Species	Sex (N)	Route	LD 50 (mg/kg)
Mouse	M 40	Oral	7100
Mouse	M 70	I.V.	425
Mouse	M 70 F 70	I.V.	605 580
Mouse	M 55	I.V.	415
Mouse	M 70	I.P.	550
Rat	M 50 F 50	I.V.	380 470
Rat	M 40	I.V.	375

Signs of toxicity in mice and rats included ataxia, convulsions, collapse, terminal collapse, decreased activity, transient weight loss, slower respiration rate, gasping, bloody exudates from

nares, nasal hemorrhage, hematuria, and local tissue irritation/cyanosis/ or necrosis at tail injection sites.

Subacute Toxicity

Species/Strain	Sex	N/Dose	Fosinopril Dose (mg/kg/day	Route	Duration	Effects
Mouse CD-1[a]	M F	6 6	0, 2, 10 or 50	I.V	2 weeks	50 mg/kg: Slightly decreased hematocrit and slightly decreased hemoglobin (F).
Rat CD	M F	6 6	0, 30, 100, 300 or 900 twice daily	Oral	2 weeks	All groups: Excessive salivation; lower absolute and relative heart weight. 200 mg/kg: Respiratory distress. One (M) died (likely incidental). 600 and 1800 mg/kg: Soft or loose feces, respiratory distress, stomach and intestines distended with gas, staining of oral and anogenital regions with yellowish brown fluid, congestion and/or hemorrhage in a few organs, especially lungs. 600 mg/kg: Moderate decrease in body weight gain (M). One (M) and two (F) died. 1800 mg/kg: Body-weight loss. Three (M) and one (F) died; remaining rats killed on day 3 or 4.
Rat CD	M F	10 10	0, 12.5, 50 or 200 twice daily	Oral	3 months	All groups: Salivation, lower absolute and relative heart weight. 25 and l00 mg/kg: Two (M) died in each group (possibly dosing accidents). 100 and 400 mg/kg: Occasional rales and salivation, moderately decreased body weight gain (M), renal juxtaglomerular cell hyperplasia. 400 mg/kg: Slightly increased BUN, SGPT, SOOT, urine bilirubin and potassium (M), slight decrease in RBC's (F), serum cholesterol and calcium (M), total protein and sodium. Moderately increased bone marrow myeloid/erythroid ratio. Two (M) and two (F) died (1 death was possibly a dosing accident).

[a] Study conducted with fosinoprilat (active metabolite)

Subacute Toxicity (cont'd)

Species/Strain	Sex	N/Dose	Fosinopril Dose (mg/kg/day	Route	Duration	Effects
Dog[a] (Beagle)	M F	2 2	0, 1, 5 or 25	I.V	2 weeks	5 and 25 mg/kg:Occasional soft feces, minimal to mild renal juxtaglomerular cell hyperplasia, minimal to mild, multifocal bile-ductule proliferation and mild inflammation in the liver. 25 mg/kg: Moderate discomfort during injection, thrombosis of cephalic veins, vasculitis and nerve degeneration in 1dog at injection site, small to moderate amounts of hemosiderin in liver. Moderate to marked increases in SGPT and alkaline phosphatase, slightly increased urine output, slightly decreased urine specific gravity.
Monkey (Cynomolgus)	M F	2 2	0, 25, 75 or 225 twice daily	Oral	2 weeks	50 and 150 mg/kg: Marked decrease in arterial blood pressure 150 mg/kg: Slightly decreased body weight, renal juxtaglomerular-cell hyperplasia; slightly increased BUN, decreased RBC's and bone-marrow erythroid cells. 450 mg/kg: Vomiting, inappetence, moderate body-weight loss, renal distal tubule dilation, juxtaglomerular-cell hyperplasia, myocardial degeneration and necrosis, myocardial or endocardial hemorrhage; aspiration pneumonia and congestion, hemorrhage or erosion of stomach. Markedly increased BUN and creatinine, moderately increased serum glucose and magnesium and moderate decreased serum sodium. Two (F) died; both (M) killed in poor condition.
Monkey (Cynomolgus)	M F	3 3	0, 6, 25 or 100 twice daily	Oral	3 months	200 mg/kg: Decreased body weight and food consumption; loose feces, occasional vomiting and/or salivation, lethargy; moderate decrease in arterial blood pressure, mild to severe multifocal dilation of renal cortical tubules, moderate multifocal necrosis of renal tubular epithelium, mild to moderate renal juxtaglomerular-cell hyperplasia. In one moribund female (sacrificed), marked increase in BUN and creatinine, slight to moderate increase in serum glucose, bilirubin and magnesium, slight tomoderate decrease in serum albumin, sodium and calcium, decrease of erythroid cells and reticulocyte counts. In others, slight decrease in erythrocytes, slight increase in BUN and slight decrease in serum sodium and magnesium. One (F) died. 50 mg/kg: One (M) and one (F) killed in poor condition (likely dosing accidents).

a Study conducted with fosinoprilat (SQ 27,519)

Chronic Toxicity

Species/Strain	Sex	N/Dose	Fosinopril Dose (mg/kg/day	Route	Duration	Effects
Rat CD	M F	40 40	0, 25, 100 or 400	Oral (diet)	1 year (10M, 10F/group sacrificed at 6 months and at 15 weeks post-dose)	100 and 400 mg/kg: Slight to moderate decrease in body weight gain, slight to moderate decreases in heart and liver weights. Slightly decreased serum proteins and calcium. 400 mg/kg: Slight to moderate increase in SGOT, very slight decrease in erythrocyte parameters at week 13, slight increase in BUN and SGPT (transient); slight decrease in serum cholesterol; slight to moderate decrease in urinary protein excretion and slight, transient increase in urine pH. After post-dose period: Increased heart weights and decreased liver weights (M). Some high dose rats had ocular changes in retina (no histopathologic changes).
Dog (Beagle)	M F	6 6	0, 12, 50 or 200	Oral	1 year (3M, 3F/group evaluated at 3 month post-dose)	12, 50 and 200 mg/kg: Slight moderate decrease in arterial blood pressure. 50 mg/kg: Slight decrease in serum proteins. 200 mg/kg: One moribund dog killed day 10: showed signs of depression and marked weight loss prior to sacrifice and mild renal tubular dilation. Also marked increase of BUN and serum creatinine, moderate increase in serum glucose, SGPT, magnesium. Slight decrease in serum sodium and potassium. Other dogs - soft, loose feces, minimal hyperplasia of juxtaglomelular cells. Slight decrease in erythrocytic parameters (M). Slight decrease in serum proteins and urine specific gravity; slight increase in BUN and creatinine.

Reproduction and Teratoloy

Species/Strain	No. of Animals and Sex	Fosinopril Doses and Frequency	Route	Results
Rat CD	28 M, 28 (20-26 pregnant) F per group	0, 15, 60 or 240 mg/kg dosed as follows: M - for 10 weeks prior to mating and during 2-week mating period; F - for 2 weeks prior to mating and until day 13 of gestation (one-half of each group) or until day 22 of lactation (remaining half).	Oral	15, 60 and 240 mg/kg: Slight to moderate decrease in body-weight gain (M). 15 mg/kg: One (F) died (likely dosing accident). 60 mg/kg: Two (M) and one (F) died. 240 mg/kg: Moderately decreased food consumption (M): slight increase in pairing time; and a slight decrease in olfactory sense in F_1 males. Thirteen (M) and eight (F) died (four deaths likely dosing accidents).
Rat CD	24-28 (20-27 pregnant) F per group	0, 12.5, 62.5 or 200 mg/kg twice daily from day 7 through 16 of gestation	Oral	25, 125 and 400 mg/kg daily: Slight to moderate decreases in maternal body-weight gain and food consumption; and slightly decreased placental weight and degree of skeletal ossification[a]. 125 mg/kg daily: One death; orofacial malformations[e] in IF; and situs inversus in IF. 400 mg/kg daily: Five deaths; reduced fetal body weight and orofacial malformationse in IM and IF.
Rabbit New Zealand White[C]	18 (14-17 pregnant) F per treated groups; 18 (18 pregnant) and 24 (20 pregnant) F per control groups	0, 0 (saline[b]), 0.5, 2.5, 10, 40, or 40 (saline[b]) mg/kg on days 7 through 19 of gestation	Oral	2.5 mg/kg: One death. 10 mg/kg: Five deaths; embryo-fetotoxicity[d]. 40 mg/kg: Twelve deaths; embryo-fetotoxicity. 40 mg/kg (with saline): 4 deaths; embryo-fetotoxicity (less than that observed at 40 mg/kg without saline).
Rat CD	25 (23-25 pregnant) F per group	0, 10, 40 or 160 mg/kg daily from day 14 of gestation through day 21 of lactation	Oral	10 and 40 mg/kg: Two deaths each (likely dosing accidents). 160 mg/kg: Two deaths and two sacrifices[f]. Slightly to moderately decreased body-weight gain and food consumption in dams; and slightly lower body weight in neonates at weaning.

a Primarily bones in the skull and the sacral vertebrae.
b These groups received a saline solution in place of drinking water.
c One control fetus and five drug-treated fetuses had a major malformation. Three of the five malformations in the treated groups were meningoceles; the control fetus also had a meningocele. There was no dose-response trend and no significant difference in the incidence of malformations between control and drug-treated fetuses.
d Embryonal or fetal deaths. NOTE: Protein casts in the kidneys of most does that died suggested renal injury.
e Microstomia and micrognathia. Similar malformations were observed historically among control rats.
f All pups cast by these dams were dead or died shortly after parturition.

Carcinogenicity and Mutagenicity Studies

In two-year studies involving both mice and rats at doses up to 400 mg/kg daily (500 times the maximum human dose), there was no evidence of a carcinogenic effect.

Neither fosinopril sodium nor the active fosinoprilat was mutagenic in: the Ames microbial mutagen test, the mouse lymphoma forward mutation assay, or a mitotic gene conversion assay. Fosinopril was also not genotoxic in a mouse micronucleus test *in vivo* and a mouse bone marrow cytogenetic assay *in vivo*.

In the Chinese hamster ovary cell cytogenetic assay, fosinopril increased the frequency of chromosomal aberrations when tested without metabolic activation at a concentration that was toxic to the cells. However, there was no increase in chromosomal aberrations at lower drug concentrations without metabolic activation or at any concentration with metabolic activation.

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