PRODUCT MONOGRAPH

Pr JAMP-FOSINOPRIL

Fosinopril Sodium Tablets USP

10 mg and 20 mg

Angiotensin Converting Enzyme Inhibitor

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets, 10 mg and 20 mg	none *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

JAMP-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 JAMP-FOSINOPRIL consideration should be given to the risk of angioedema (see WARNINGS AND PRECUATIONS-General-*Angioedema*).

JAMP-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.

JAMP-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 JAMP-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 JAMP-FOSINOPRIL with antihypertensive agents other than thiazide diuretics have not been established.

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

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- Patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

General

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, JAMP-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).

Cardiovascular

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 JAMP-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 – Less Common Clinical Trial Adverse Drug Reaction (< 1%) - Cardiovascular). Because of the potential fall in blood pressure in these patients, therapy with JAMP-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 JAMP-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 JAMP-FOSINOPRIL and/or reduced concomitant diuretic therapy should be considered.

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.

Hematologic

Neutropenia/Agranulocytosis

Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Current experience with JAMP-FOSINOPRIL shows the incidence to be rare and a causal relationship to the administration of JAMP-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.

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 DRUG INTERACTIONS, ADVERSE REACTIONS).

Hepatic/Biliary/Pancreatic

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 JAMP-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 JAMP-FOSINOPRIL should be considered when appropriate.

JAMP-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.

Immune

Anaphylactoid reaction 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 reaction 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.

Peri-Operative Considerations

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 11 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.

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 JAMP-FOSINOPRIL should include appropriate assessment of renal function

Respiratory

Cough

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

Special Populations

Pregnant Women
ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, JAMP-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, 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 susbtituting 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 inhibitors is not recommended during breast-feeding.

Pediatrics: The safety and effectiveness of JAMP-FOSINOPRIL in children have not been established, therefore, its use in this age group is not recommended.

Geriatrics (> 65 years of age): 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.

Monitoring and Laboratory Tests

Fosinopril 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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 AND PRECAUTIONS – Cardiovascular - *Hypotension*). 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 AND PRECAUTIONS - Cardiovascular - *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.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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 - Adverse Drug Reactions

	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

Table 1 - Adverse Drug Reactions		
	HYPERTENSION[A] n= 1048 (%)	**HEART FAILURE[B] n= 361 (%)**
Edema	-	1.1
Dermatologic		
Rash	1.0	1.4
Endocrine/Metabolic		
Sexual Dysfunction	1.7	-
Gastointestinal		
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

Table 1 - Adverse Drug Reactions		
	HYPERTENSION[A] n= 1048 (%)	**HEART FAILURE[B] n= 361 (%)**
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

Less Common Clinical Trial Adverse Drug Reactions (<1%)
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 AND

PRECAUTIONS-Hematologic- *Neutropenia/Agranulocytosis*), 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.

Laboratory Test Findings

Abnormal Hematologic and Clinical Chemistry Findings
Serum Electrolytes: Hyperkalemia (see WARNINGS AND PRECAUTIONS – Hematologic – *Hyperkalemia and Potassium-sparing Diuretics*), hyponatremia (see DRUG INTERACTION-Drug-Drug Interaction-Concomitant Diuretic Therapy).

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 $\geq$ 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.

Post-Market Adverse Drug Reactions

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.

DRUG INTERACTIONS

Drug-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 JAMP-FOSINOPRIL (fosinopril sodium) can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with JAMP-FOSINOPRIL. If it is not possible to discontinue the diuretic, the starting dose of JAMP-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 PRECAUTIONS- Cardiovascular - *Hypotension*, 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 fosinopril sodium alone. (See ADVERSE REACTIONS- Laboratory Test Findings – BUN/Serum Creatinine).

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

Agents Causing Renin Release: The antihypertensive effect of fosinopril sodium 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 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 Cmax) 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 Cmax 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-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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 JAMP-FOSINOPRIL may need to be adjusted.

Monotherapy
The recommended initial dose of JAMP-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 JAMP-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 JAMP-FOSINOPRIL alone, a diuretic may be added. After the addition of a diuretic, it may be possible to reduce the dose of JAMP-FOSINOPRIL.

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

Heart Failure

JAMP-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 JAMP-FOSINOPRIL, because severe hypotension, and more rarely renal failure, have been reported (see WARNINGS AND PRECAUTIONS – Cardiovascular –*Hypotension,* - 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 DRUG INTERACTIONS - Drug-Drug

Interaction-Concomitant Diuretic Therapy).

In patients with heart failure, the recommended initial dose of JAMP-FOSINOPRIL is 10 mg once daily, initiated under close medical supervision. If the initial dose of JAMP-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 JAMP-FOSINOPRIL following effective management of hypotension.

In patients with severe congestive heart failure with or without renal insufficiency, therapy with JAMP-FOSINOPRIL should be initiated with caution (see WARNINGS AND PRECAUTIONS - Cardiovascular –*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 JAMP-FOSINOPRIL (fosinopril sodium) 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 – Special Populations and Conditions - Renal Insufficiency, WARNINGS AND PRECAUTIONS – Renal Impairment). 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 JAMP-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 – Special Populations and Conditions - Hepatic Insufficiency). In such patients with heart failure, therapy should be initiated with caution.

Recommended Dose and Dosage Adjustment
Dosage of JAMP-FOSINOPRIL must be individualized.

OVERDOSAGE

No data are available regarding overdosage of JAMP-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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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, 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 fosinopril.

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

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.

Pharmacokinetics

Absorption: 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%.

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

Distribution: 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 phydroxy metabolite 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 metabolite of fosinoprilat is as potent an inhibitor of ACE as fosinoprilat; the glucuronide conjugate of fosinoprilat is devoid of ACE inhibitor activity.

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.

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

Excretion: 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 ($\geq$ 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.

Special Populations and Conditions

Geriatrics: 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).

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

Hepatic Insufficiency: 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.

Renal Insufficiency: In patients with renal insufficiency, 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 mUmin/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 mUmin/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.

Genetic Polymorphism: No data is available.

STORAGE AND STABILITY

Store at room temperature (15 -30°C). Keep container tightly closed. Protect from high humidity.

DOSAGE FORMS, COMPOSITION AND PACKAGING

JAMP-FOSINOPRIL (fosinopril sodium) 10 mg tablets are white to off-white, capsule shaped tablets debossed with 'JF' and a scoreline on one side and '10' and scoreline on the other side.

JAMP-FOSINOPRIL 20 mg tablets are white to off-white, capsules shaped tablets debossed with 'JF' on one side and '20' on the other side.

In addition to the active ingredient, fosinopril sodium, each tablet contains anhydrous lactose, colloidal silicon dioxide, crospovidone, microcrystalline cellulose, povidone, and talc.

JAMP-FOSINOPRIL, in tablets of 10 mg and 20 mg, are available in bottles of 90 and 100 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

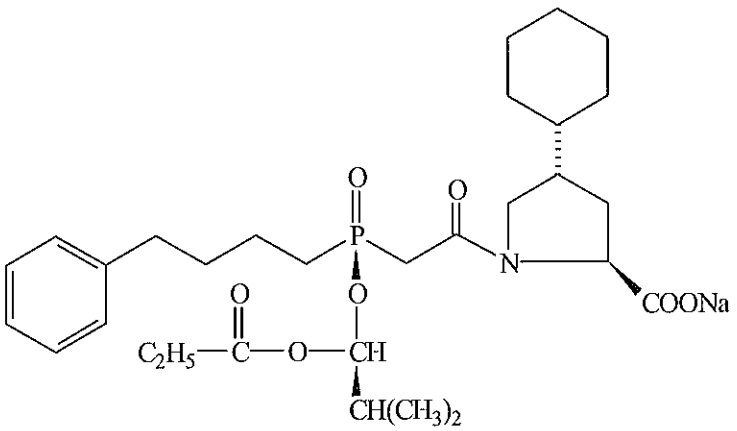
Drug Substance

Proper name: fosinopril sodium USP

Chemical name: (1) L-proline,4-cyclohexyl-l-[[[2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl) phosphinyl]acetyl] -, sodium salt, [1[S* (R*), 2α, 4β] –
(2) : (4S) -4-cyclohexyl-1-[[(R) – [(S)-1-hydroxy-2-methylpropoxy] (4-phenylbutyl)] phosphinyl] acetyl-L-proline propionate (ester), sodium salt

Molecular formula (molecular mass): $C_{30}H_{45}NNaO_7P$ (585.65)

Structural formula:



Physicochemical properties: Fosinopril sodium is a white to off-white crystalline powder with a melting point of 195°C and a pH of 7.08 in aqueous solution. Fosinopril sodium is practically insoluble in aqueous pH 1.2 and 4.5 and freely soluble in aqueous pH 6.8. It is freely soluble in methanol and soluble in chloroform. It has an optical rotation ($[\alpha]^{25}_D$) of -5.7°.

CLINICAL TRIALS

One comparative bioavailability study was performed under fasting conditions using 27 healthy adult male and female volunteers. A summary of the pharmacokinetic parameters is given in the table below;

Fosinoprilat 1 x 20 mg Fosinopril Sodium tablet From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means**	90% Confidence Interval**
AUC_T (ng x hr/mL)	2765.00 2933.242 (35.3%)	2759.94 2981.220 (41.8%)	100	91.9 – 109
AUC_I (ng x hr/mL)	2831.39 2993.770 (34.3%)	2826.93 3042.716 (40.9%)	100	92.3 – 109
C_{max} (ng/mL)	463.31 495.519 (37.5%)	477.20 507.152 (37.5%)	97.1	88.5 – 106
T_{max} [ε] (hrs)	3.557 (18.9%)	3.290 (23.0%)		
$T_{½}$ [ε] (hrs)	6.214 (32.4%)	6.818 (35.3%)		

* JAMP-FOSINOPRIL 20 mg Tablet

† MONOPRIL™ 20 mg Tablet (BMS Canada, Inc.) were purchased in Canada

** Calculation based on least squares estimate

ε expressed as the arithmetic mean (CV%) only.

DETAILED 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 (AI) 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 AI 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	Oral	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 100 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, SGOT, 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) ([a] study conducted with fosinoprilat (SQ 27,519))	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 1 dog 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 to moderate 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).

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 (10 M, 10 F/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, 3 F/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 Teratology

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 1F; and situs inversus in IF. 400 mg/kg daily: Five deaths; reduced fetal body weight and orofacial malformations[e] in 1M 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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PART III: CONSUMER INFORMATION

[Pr]JAMP-FOSINOPRIL
Fosinopril Sodium Tablets USP
10 mg and 20 mg

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

ABOUT THIS MEDICATION

What the medication is used for:
JAMP-FOSINOPRIL is used in the treatment of mild to moderate essential hypertension and in the management of symptomatic congestive heart failure.

What it does:
Fosinopril is in a class of medications called angiotensin converting enzyme (ACE) inhibitor. Its main action is to lower blood pressure by preventing the effects of angiotensin II (a chemical that narrows the blood vessels). By blocking angiotensin II effects, the blood vessels relax, letting the blood flow more smoothly, thereby lowering the blood pressure.

When it should not be used:
Do not use JAMP-FOSINOPRIL if:

- you are allergic to fosinopril or any other component in the product or the container (see *What the important non-medicinal ingredient are*),
- you are allergic to any other medication in the same class called angiotensin-converting enzyme (ACE) inhibitors such as enalapril, captopril, lisinopril, quinapril, ramipril etc.
- you have a history of angioedema (angioneurotic edema), a condition that causes swelling of the face, extremities, eyes, lips, tongue, difficulty in breathing after taking an angiotensin-converting enzyme (ACE).
- you have been diagnosed with hereditary angioedema or idiopatic angioedema (angioedema of unknown cause).

What the medicinal ingredient is:
fosinopril sodium

What the important nonmedicinal ingredients are:
anhydrous lactose, colloidal silicon dioxide, crospovidone, microcrystalline cellulose, povidone, and talc.

What dosage forms it comes in:
tablets, 10 mg and 20 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
JAMP-FOSINOPRIL should not be used during pregnancy. Stop the medication and contact your physician as soon as possible, if you discover that you are pregnant while taking JAMP-FOSINOPRIL.

BEFORE you use JAMP-FOSINOPRIL talk to your physician or pharmacist if:

- You are pregnant. Taking JAMP-FOSINOPRIL during pregnancy can cause injury and even death to your baby.
- You are breast-feeding. It is possible that JAMP-FOSINOPRIL passes into the breast milk. You should not breast-feed while taking JAMP-FOSINOPRIL.
- You suffer from low blood pressure.
- You have any of these conditions:
  - heart or blood vessel disease
  - liver disease
  - kidney disease
- You are vomiting.
- You have diarrhea
- You are going to have any surgery.
- You want to use any potassium supplements or salt substitutes containing potassium.
- You find that you are excessively sweating and feel dehydrated.
- You have any allergies to this drug or its ingredients or components of the container.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with JAMP-FOSINOPRIL include: other medicines used to reduce blood pressure, acetyl salicylic acid (Aspirin®); diuretics (water pills) ; lithium; potassium supplements; salt substitutes that contain potassium; medicines that contains potassium; antacids; and certain medications that tend to increase pressure, such as non-prescription preparations for appetite control, asthma, colds, coughs, hay fever and sinus problems.

PROPER USE OF THIS MEDICATION

Usual dose:
Based on your condition, your doctor will decide the usual dose of JAMP-FOSINOPRIL you need to take.

The dosage of JAMP-FOSINOPRIL must be individualized.

Overdose:
It is important to follow the instructions from your doctor or pharmacist. If you or someone have taken more than the recommended dose at once contact your doctor or nearest hospital emergency department immediately.

Missed Dose:
If a dose of this medication is missed, it should be taken as soon as possible. This will help to keep a constant amount of medication in the blood. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

Symptom / effect		Talk with your physician or pharmacist		Stop taking drug and call your physician or pharmacist
		Only if severe	In all cases	
Common	Fatigue	T		
	Dizziness/ Lightheadedness	T		
	Hypotension		T	
	Headache	T		
	Rash/itching		T	
	Nausea/Vomiting/ Diarrhea	T		
	Cough			
	Chest pain		T	
	Dyspnea		T	
			T	
Uncommon	Allergic reactions/ Angioedema			T
	Flu-like symptoms (such as fever, malaise, muscle pain)		T	
	Liver impairment such as jaundice, dark/brown urine		T	
	Abdominal pain	T		
	Loss of appetite	T		
	Fainting			

If you notice any of the following, you may need medical attention.

- Symptoms of angioedema such as: sudden difficulty in breathing or swallowing, swelling of face, eyes, lips, tongue and/or throat, hands or feet. The black patients are at increased risk of these types of reactions to ACE inhibitors.
- Dizziness, light headedness or fainting following exercise, and/or when it is hot and you have lost a lot of water by sweating.

- Flu-like symptoms such as fever, malaise, muscle pain, rash, itching, abdominal pain, nausea, vomiting, diarrhea, jaundice, loss of appetite.
- The initial dose may cause a greater fall in blood pressure than will occur following continued treatment. You may notice this as faintness or dizziness and it may help to lie down. If concerned, please consult your physician or pharmacist.
- Dry cough
- Unusual tiredness and/or weakness
- Headache

Contact your physician or pharmacist if you notice any of the above or have other side effects. Seek medical attention, if the condition persists or worsens.

This is not a complete list of side effects. For any unexpected effects while taking JAMP-FOSINOPRIL contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15 -30°C). Keep container tightly closed. Protect from high humidity.

Keep out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.jamppharma.com or by contacting the sponsor, JAMP Pharma Corporation at: 1.866.399.9091

This leaflet was prepared by JAMP Pharma Corporation.

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