STARIL®

Fosinopril Sodium
TABLETS

Use in Pregnancy:
When used in pregnancy, ACE inhibitors can cause injury and even death to the developing fetus.

COMPOSITION :
STARIL Tablets 10 mg: White, flat end, diamond tablets each containing fosinopril sodium 10 mg.
STARIL Tablets 20 mg: White, round biconvex tablets each containing fosinopril sodium 20 mg.
Other ingredients: Crospovidone, lactose, sodium stearyl fumarate, microcrystalline cellulose, povidone.
Pharmacological Action:
Fosinopril,{(4S)-4-Cyclohexyl-1-[(RS)-2-methyl-1-(propionyloxy)propoxy] (4 -phenylbutyl)
=phosphinoylacetyl} -L-proline; sodium salt, is the ester prodrug of an angiotensin converting enzyme (ACE) inhibitor, fosinoprilat. Angiotensin converting enzyme is a peptidyl dipeptidase enzyme that catalyses a number of peptide conversions. These include the conversion of decapeptide Angiotensin I to the octapeptide, Angiotensin II.
Fosinopril also inhibits kininase, the enzyme that degrades bradykinin. Reduction of blood pressure with low (0.1 mg/kg), medium (0.3 mg/kg) and high (0.6 mg/kg) target doses of once-daily fosinopril was evaluated in a randomized double-blind study of 252 children and adolescents aged 6 to 16 years of age with
hypertension or high-normal blood pressure. At the end of the four weeks of treatment, the mean reduction from baseline in trough systolic blood pressure was similar for children treated with low, medium and high dose fosinopril. No dosage response relationship was demonstrated between the three doses. The optimum dosage has not been determined in children of any age. An appropriate dose strength is not available for
children weighing less than 50kg.
PHARMACOKINETICS:
The absolute absorption of fosinopril averaged 36% of an oral dose, and was not affected by the presence of food. Rapid and complete hydrolysis to active fosinoprilat occurs in the gastrointestinal mucosa and liver.
The time to reach Cmax is independent of dose, achieved in approximately three hours and consistent with peak inhibition of the angiotensin I pressor response 3 to 6 hours following administration.
The effective T ½ for accumulation of fosinoprilat averaged 11.5 hours.In patients with heart failure; the effective T 1/2 was 14 hours. Fosinoprilat is highly protein bound (> 95%), has a relatively small volume of distribution and negligible binding to cellular components in blood. Unlike other ACE inhibitors, elimination of fosinopril is by both hepatic and renal routes allowing compensatory excretion by the alternative route in
patients with renal or hepatic insufficiency.
Limited pharmacokinetic data in children and adolescents were provided by a single-dose pharmacokinetic study in 19 hypertensive patients 6 to 16 years of age who received 0.3mg/kg of a solution of fosinopril.

Whether AUC and Cmax values of fosinoprilat (active form of fosinopril) in children from 6 to 16 years of age were comparable to those seen in adults receiving 20 mg of fosinopril as a solution, has to be demonstrated.
The terminal elimination half-life for fosinoprilat was 11-13 hours and similar at all stages studied.
INDICATIONS
Hypertension:
STARIL (FOSINPRIL SODIUM) is indicated in the treatment of hypertension where standard therapy is ineffective or inappropriate because of adverse effects. STARIL (FOSINPRIL SODIUM) may be used alone as initial therapy or in combination with other antihypertensive agents.
The antihypertensive effects of STARIL (FOSINPRIL SODIUM) and diuretics used concomitantly are approximately additive.
Heart Failure:
STARIL (FOSINPRIL SODIUM) is indicated for the treatment of heart failure in combination with a diuretic. In these patients, STARIL (FOSINPRIL SODIUM) improves symptoms and exercise tolerance, reduces severity of heart failure and decreases the frequency of hospitalisation for heart failure.
DOSAGE AND ADMINISTRATION
Recommended Dose and Dosage Schedule:
Hypertensive patients not being treated with diuretics:
The dose range is 10 to 40 mg per day administered in a single dose and without regard to meals. The normal starting dose for patients is 10 mg once a day. Dosage may need to be adjusted after approximately 4 weeks according to blood pressure response. No additional blood pressure lowering is achieved with doses greater than 40 mg daily. If blood pressure is not adequately controlled with STARIL (FOSINPRIL SODIUM) alone, a diuretic can be added.
Use with concomitant diuretic therapy:
The diuretic should preferably be discontinued for several days prior to beginning therapy with STARIL (FOSINPRIL SODIUM) to reduce the risk of an excessive hypotensive response. If blood pressure is inadequately controlled after an observation period of approximately 4 weeks, diuretic therapy may be resumed. Alternatively, If diuretic therapy cannot be discontinued, an initial dose of 10 mg of STARIL
(FOSINPRIL SODIUM) should be used with careful medical supervision for several hours, until blood pressure has stabilized. In diuretic treated hypertensive patients, mean cerebral blood flow is maintained between 4 and 24 hours after STARIL (FOSINPRIL SODIUM), despite significant reduction in blood pressure.
Heart Failure:
The recommended initial dose is 10mg once daily, initiated under close medical supervision. If the initial dose is well tolerated patients should then be titrated to a dose of up to 40mg once daily. The appearance of hypotension after the initial dose should not preclude careful dose titration of STARIL (FOSINPRIL SODIUM), following effective management of the hypotension. STARIL (FOSINPRIL SODIUM) should be used in conjunction with a diuretic.

Heart Failure - High Risk Patients:
It is recommended that treatment is initiated in hospital for patients with severe cardiac failure (NYHA IV) and those at particular risk of first dose hypotension, i.e. patients on multiple or high dose diuretics (e.g.> 80mg frusemide), patients with hypovolaemia, hyponatraemia (serum sodium < 130 meq/l), preexisting hypotension (systolic blood pressure <90 mmHg), patients with unstable cardiac failure and those on high-dose vasodilator therapy.
Use in the elderly (over 65 Years):
No dosage reduction is necessary in patients with clinically normal renal and hepatic functions as no significant differences in the pharmacokinetic parameters or antihypertensive effect of fosinoprilat have been found compared with younger subjects.
Use in impaired renal function:
It is advisable to initiate treatment at a dose of 10 mg. Depending on the response, the dose should then be titrated to achieve the desired therapeutic effect.
Absorption, bioavailability, protein binding, biotransformation and metabolism are not appreciably altered by reduced renal function. In patients with impaired renal function, the total body clearance of fosinoprilat is approximately 50% slower than that in patients with normal renal functions. However, since hepatobiliary elimination compensates at least partially for diminished renal elimination, the body clearance of fosinoprilat is not appreciably different over a wide range of renal insufficiency (creatinine clearances ranging from <10 to 80 ml/min/l.73m2, i.e. including end-stage renal failure).
Clearance of fosinoprilat by haemodialysis and peritoneal dialysis averages 2% and 7%, respectively, of urea clearances.
Use in hepatic insufficiency (alcoholic or biliary cirrhosis):
It is advisable to initiate treatment at a dose of 10 mg. Although the rate of hydrolysis may be slowed, the extent of hydrolysis is not appreciably reduced in patients with hepatic impairment. In this group of patients, there is evidence of reduced hepatic clearance of fosinoprilat with compensatory increase in renal excretion.
Children and adolescents
Use in this age group is not recommended.
There is limited clinical trial experience of the use of fosinopril in hypertensive children aged 6 years and above. The optimum dosage has not been determined in children of any age. An appropriate dose strength is not available for children weighing less than 50 kg.
CONTRAINDICATIONS:
A history of hypersensitivity to STARIL (FOSINPRIL SODIUM) or any of the tablets excipients .
Pregnancy: STARIL (FOSINPRIL SODIUM) is contraindicated in pregnancy. It has been shown to be lethal to rabbit foetuses at doses that were maternally toxic.
Oligohydramnios and neonatal hypotension and/or anuria have been reported following use of ACE inhibitors in the second and third trimester of pregnancy.
Nursing mothers: STARIL (FOSINPRIL SODIUM) should not be given to nursing mothers as fosinoprilat have been detected in human breast milk.

PRECAUTIONS:
Pretreatment assessment of renal function: Evaluation of the hypertensive patient should include assessment of renal function prior to initiation of therapy and during treatment where appropriate
WARNINGS:
Hypotension: as with all ACE inhibitors, a hypotensive response may be observed. If this occurs it is usually associated with the first dose and in most instances symptoms are relieved simply by the patient lying down. A transient hypotensive episode is not a contraindication to continuing therapy once the patient's blood pressure has been stabilized.
As with other ACE inhibitors, patients at risk of an excessive hypotensive response sometimes as assoicated with renal dysfunction, include those with: congestive heart failure, renovascular hypertension, renal dialysis, or volume and/or salt depletion of any aetiology. In patients with anyone of these risk factors, it may be prudent to discontinue or reduce the dose of diuretic therapy or take other measures to ensure adequate hydration prior to initiating fosinopril treatment. Treatment of these high risk patients
should be initiated under careful medical supervision and they should be followed closely, particularly if it becomes necessary to resume or increase the dose of diuretic or STARIL (FOSINPRIL SODIUM).
Impaired Renal Function: When treated With ACE inhibitors, patients with pre-existing congestive heart failure, renovascular hypertension (especially renal artery stenosis), and salt or volume depletion of any aetiology are at increased risk of developing findings indicative of renal dysfunction, including: increases in BUN and serum creatinine and potassium; proteinuria; changes in urine volume (including oliguria/anuria); and an abnormal urinalysis. Dosage reduction and/or discontinuation of diuretic and/or fosinopril may be required.
Anaphylactoid-like Reactions: Recent clinical observations have shown a high incidence of anaphylactoid-like reactions during haemodialysis with high-flux dialysis membranes(e.g AN69) in patients receiving ACE inhibitors. Therefore, this combination should be avoided. Similar reactions during LDL aphoresis with dextran sulphate absorption have been observed. Rare instances of anaphylactoid reactions during desensitisation treatment (hymenoptera venom) have been recorded with other ACE inhibitors .
Angioedema involving the extremities, face, lips, mucous membranes,tongue, glottis or larynx has been seen in patients treated with ACE inhibitors. If such symptoms occur during treatment with STARIL (FOSINPRIL SODIUM), therapy should be discontinued.
Intestinal angioedema has also been reported very rarely in patients treated with ACE inhibitors and should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.
Liver Function: Rare potentially fatal cases of cholestatic jaundice and hepatocellular injury have been reported with ACE inhibitors. Patients who develop jaundice or marked elevations of hepatic enzymes should discontinue ACE inhibitor treatment.
Hyperkalaemia: When treated with ACE inhibitors, patients at risk of developing hyperkalaemia include those with renal insufficiency, diabetes mellitus, and those using concomitant

potassium-sparing diuretics, potassium supplements and/or potassium containing salt substitutes.
Neutropenia: ACE inhibitors have been reported rarely to cause agranulocytosis and bone marrow depression; these occur more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Monitoring of white blood cell counts should be considered in such patients.
Surgery / Anaesthesia: ACE inhibitors may augment the hypotensive effects of anaesthetics and analgesics. If hypotension occurs in patients undergoing surgery / anaesthesia and concomitantly receiving ACE inhibitors; it can usually be corrected by intravenous administration,of fluid.
DRUG INTERACTIONS:
Diuretics:
As with all ACE inhibitors, an exaggerated hypotensive response may be expected when STARIL (FOSINPRIL SODIUM) is administered concomitantly with diuretics.
Since increases in serum potassium have been observed with ACE inhibitors, including fosinopril, the potassium wasting effect of most diuretics may be blunted by concomitant ACE inhibitor therapy.
Decreases in serum sodium and increases in serum creatinine occurred more frequently in patients receiving concomitant diuretics than in those treated with fosinopril alone.
Concomitant administration with potassium sparing diuretics may lead to hyperkalaemia.
Potassium supplements and potassium-sparing diuretics:
Fosinopril can attenuate potassium loss caused by a thiazide diuretic. Potassium-sparing diuretics or potassium supplements can increase the risk of hyperkalaemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution and the patient's serum potassium should be monitored frequently.
Antacids:
Coadministration of antacids with STARIL (FOSINPRIL SODIUM) has been shown to reduce serum levels and urinary excretion of fosinoprilat as compared with STARILFOSINPRIL SODIUM) administered alone, suggesting that antacids may impair absorption of fosinopril.
Administration of STARIL (FOSINPRIL SODIUM) and antacids should be separated by at least 2 hours.
Non Steroidal Anti-inflammatory Drugs:
Non steroidal anti-inflammatory drugs may interfere with the anti-hypertensive effect.
However, concomitant administration of a single dose of 325 mg aspirin did not result in a clinically significant reduction in anti-hypertensive effect.
Lithium:
Concomitant therapy with lithium may increase the serum lithium concentration.
Other Anti-Hypertensive Agents:
Combination with other anti-hypertensive agents such as beta blockers, methyldopa, calcium antagonists, and diuretics may increase the anti-hypertensive efficacy.

Other Drugs:
In pharmacokinetic studies with nifedipine, propranolol, cimetidine, metoclopramide and propantheline the bioavailability of fosinoprilat was not altered by coadministration of STARIL (FOSINPRIL SODIUM) with anyone of these drugs.
STARIL (FOSINPRIL SODIUM) has been used concomitantly with paracetamol, antihistamines, hypoglycaemic agents, insulin, lipid-lowering agents or oestrogen without evidence of clinically important adverse events.
Laboratory tests:
STARIL (FOSINPRIL SODIUM) may cause a false low measurement of serum digoxin levels with assays using the charcoal absorption method for digoxin. Other kits which use the antibody coated-tube method may be used.
PREGNANCY AND LACTATION:
See contraindication
SIDE EFFECTS:
In placebo controlled studies, there were no significant differences in clinical adverse experiences.
The most commonly reported side effects with STARIL (FOSINPRIL SODIUM) were dizziness, cough, upper respiratory symptoms, gastrointestinal disturbances, palpitations/chest pain, rash/pruritus, musculoskeletal pain/paraesthesia, fatigue and taste disturbance.
As with other ACE-inhibitors, hypotension, including orthostatic hypotension, has been reported in STARIL (FOSINPRIL SODIUM) heart failure trials Pancreatitis has been rarely reported in patients treated with ACE inhibitors; in some cases this has proved fatal.
The incidence and type of side effects did not differ between elderly and younger patients.
Laboratory test findings showed some modest, usually transient, decreases in haemoglobin and haematocrit values.and, infrequently, small increases in blood urea.
OVERDOSE:
Blood pressure should be monitored and if hypotension develops, volume expansion is the treatment of choice. Fosinoprilat cannot be removed from the body by dialysis.
STORAGE
Store below 25° C in a dry place.
PACKAGE
STARIL 10 mg tablets: Boxes of 30 tablets (10 mg fosinopril sodium).
Reg. N° Lebanon 97038/12
STARIL 20mg tablets: Boxes of 30 tablets (20 mg fosinopril sodium).
Reg. N° Lebanon 97037/12
Instruction to the patient:
KEEP OUT OF REACH OF CHILDREN

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Rev. 05/2013 905138-A.1