PRODUCT INFORMATION

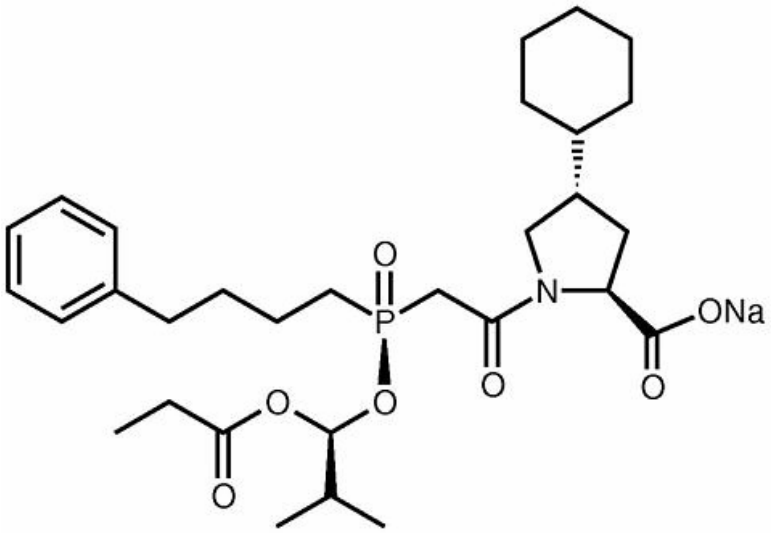
FOSINOPRIL / HCT WINTHROP 10MG/12.5MG AND 20MG/12.5MG TABLETS

NAME OF THE MEDICINE

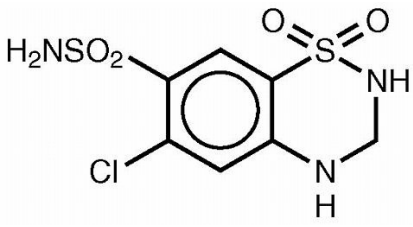
Fosinopril sodium / hydrochlorothiazide

Fosinopril sodium: Chemical name: sodium trans-l-proline, 4-cyclohexyl- 1-[[[2-methyl -1-(1-oxopropoxy) propoxy](4-phenylbutyl) phosphinyl] acetyl].
Molecular formula: $C_{30}H_{45}NNaO_7P$. MW: 585.65. CAS: 88889-14-9.

Hydrochlorothiazide: Chemical name: 6-chloro-3,4-dihydro- 2H-1,2,4-benzothiadiazine-7 -sulfonamide 1,1-dioxide.
Molecular formula: $C_7H_8ClN_3O_4S_2$. MW: 297.72. CAS: 58-93-5.



fosinopril sodium



hydrochlorothiazide

DESCRIPTION

Fosinopril sodium is the sodium salt of fosinopril, the ester prodrug of a long acting angiotensin converting enzyme (ACE) inhibitor, fosinopril diacid.
Fosinopril is a subclass of ACE inhibitors. It contains a phosphinate group which makes it different from other marketed ACE inhibitors. Fosinopril sodium is a white to off white crystalline powder. It is soluble in water (100 mg/mL), methanol and ethanol, and slightly soluble in hexane.

Hydrochlorothiazide is the 3,4-dihydro derivative of chlorothiazide. It is a white or practically white, crystalline powder which is very slightly soluble in water; soluble in acetone; sparingly soluble in ethanol (96%) but it dissolves in dilute solutions of alkali hydroxides.

Inactive ingredients: lactose anhydrous, carnauba wax, red iron oxide, crospovidone, pregelatinised starch, lactose monohydrate, zinc stearate.

PHARMACOLOGY

Pharmacodynamics

Fosinopril sodium. In humans and animals, fosinopril sodium following absorption is hydrolysed to the pharmacologically active fosinopril diacid, a specific competitive inhibitor of angiotensin converting enzyme (ACE).

ACE, a peptidyldipeptidase, catalyses the conversion of the decapeptide angiotensin I to the octapeptide angiotensin II. Angiotensin II is a potent vasoconstrictor and it also stimulates aldosterone secretion by the adrenal cortex, thereby contributing to sodium and fluid retention. The effects of fosinopril in hypertension appear to result primarily from inhibition of angiotensin II formation and decreased aldosterone secretion. Inhibition of ACE activity leads to decreased levels of angiotensin II, thereby resulting in diminished vasoconstriction, aldosterone secretion, peripheral vascular resistance, and sodium and fluid retention. Decreased levels of angiotensin II and the accompanying lack of negative feedback on renal secretion results in increases in plasma renin activity. Decreased level of aldosterone results in small increases of serum potassium.

Inhibition of ACE also interferes with the degradation of bradykinin a potent vasodepressor peptide, which may contribute to the therapeutic effect.

While the mechanism through which fosinopril lowers blood pressure is believed to be primarily suppression of the renin/ angiotensin/ aldosterone system, fosinopril has an antihypertensive effect even in patients with low renin hypertension. Although fosinopril was antihypertensive in all races studied, black hypertensive patients (usually a low renin hypertensive population) had a smaller average response to ACE inhibitor monotherapy than non-black patients.

Hydrochlorothiazide. The mechanism of antihypertensive effect of hydrochlorothiazide is unknown. Thiazide diuretics affect the renal tubular mechanisms of electrolyte reabsorption, increasing excretion of sodium and chloride

in approximately equivalent amounts. Natriuresis causes a secondary loss of potassium and bicarbonate. Hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion and decreases potassium. Concurrent administration of fosinopril attenuates the potassium loss associated with hydrochlorothiazide.

With hydrochlorothiazide, the onset of diuresis occurs in two hours, and peak effect at about four hours, and the action persists for approximately six to twelve hours.

Pharmacokinetics

In single dose studies in healthy volunteers concomitant administration of fosinopril and hydrochlorothiazide had little or no effect on the pharmacokinetics of either drug. Kinetic parameters for each constituent derived following either monotherapy or combination therapy are as follows:

Fosinopril sodium
Absorption. The extent of absorption for fosinopril is 30 to 40% and is essentially unaffected by food although the rate of absorption may be slowed.

The time to peak plasma concentrations of fosinopril diacid is approximately three hours and is independent of the dose of fosinopril administered. After single and multiple oral doses C_{max} and area under the curve (AUC) are directly proportional to the administered dose of fosinopril.

Distribution. Fosinopril diacid is highly protein bound (greater than or equal to 95%) but has negligible binding to cellular components of blood. It has a relatively small volume of distribution.

Studies in animals indicate that fosinopril and fosinopril diacid do not cross the blood-brain barrier but fosinopril diacid does cross the placenta of pregnant animals.

Metabolism. In healthy subjects and renally impaired patients, hydrolysis of fosinopril to the active fosinopril diacid is rapid and complete. This transformation probably occurs in the gastrointestinal mucosa and liver. After an oral dose of radiolabelled fosinopril, 75% of radioactivity in plasma was present as active fosinopril diacid, 20 to 30% as glucuronide conjugate and 1 to 5% as a para-hydroxy metabolite. The para-hydroxy metabolite is as potent an inhibitor of ACE as fosinopril diacid; the glucuronide conjugate is devoid of ACE inhibitory activity.

The conversion of fosinopril to fosinopril diacid may be slowed in patients with hepatic dysfunction although the extent of this conversion is unchanged.

Excretion. After intravenous administration, fosinopril diacid is eliminated approximately equally by the liver and kidneys. In healthy subjects, mean body clearance of intravenous fosinopril diacid was 26 to 39 mL/minute. In hypertensive patients with normal renal and hepatic function who received repeated doses of fosinopril, the effective $t_{1/2}$ for the accumulation of fosinopril diacid averaged 11.5 hours.

Fosinopril is not well dialysed with the clearance of fosinopril diacid by haemodialysis and peritoneal dialysis averaging 2 and 7% of urea clearance respectively.

Hydrochlorothiazide
Absorption. The extent of absorption for hydrochlorothiazide is 50 to 80%. Peak plasma concentrations of hydrochlorothiazide are reached approximately two hours after oral administration.

Distribution. Its apparent volume of distribution is 0.83 to 1.141 L/kg and its plasma protein binding is 68%. Hydrochlorothiazide does not cross the blood-brain barrier but does cross the placenta freely producing foetal plasma levels similar to those found in the maternal circulation.

Metabolism and excretion. Hydrochlorothiazide is not metabolised and is eliminated rapidly by the kidney.

The mean plasma half-life ranged from four hours in young subjects to eleven hours in the elderly.

Renal impairment. The pharmacokinetics of fosinopril diacid and hydrochlorothiazide were examined following administration of one fosinopril/hydrochlorothiazide 20/12.5 tablet once daily for five days, in subjects with renal impairment (mean creatinine clearance 56 mL/minute; range 27 to 76 mL/minute) and a group with normal renal function. Renal impairment led to increased serum concentrations of fosinopril diacid and hydrochlorothiazide with repeated administration. On day 5, the ratio of AUC geometric mean in the renal impaired group/ geometric mean in the normal group was 1.43 for fosinopril diacid and 2.24 for hydrochlorothiazide. Increased fosinopril diacid concentrations were reflected by greater ACE inhibition. It is not clear that steady-state would have been reached for fosinopril diacid in the renally impaired patients by day 5, so fosinopril diacid levels in such patients during chronic administration may be higher than in this study.

These findings are of no significance for patients who have been stabilised on coadminstered fosinopril and hydrochlorothiazide before switching to fosinopril/hydrochlorothiazide, as dose titration will have already taken place.

Hepatic insufficiency (alcoholic or biliary cirrhosis). No information is available from studies involving concurrent administration of fosinopril and hydrochlorothiazide. In studies using fosinopril alone, the extent of hydrolysis of fosinopril is not appreciably reduced, although the rate of hydrolysis may be slowed. The apparent total body clearance of fosinopril diacid is approximately one-half that in patients with normal hepatic function.

Elderly. In elderly male subjects (66 to 75 years old) with clinically normal renal and hepatic function, the mean peak concentration and systemic exposure of fosinopril diacid were respectively 21% (single dose) and 44% (multiple dose) and 19% (single dose) and 23% (multiple dose) greater than those observed in the young subjects (21

to 30 years old). For hydrochlorothiazide, the mean peak serum/ plasma concentration was increased by 27% (single dose) and 39% (multiple dose) for the elderly group compared to the young subjects. The area under the plasma concentration time curve (AUC) for hydrochlorothiazide was increased by 91% in the elderly group following multiple dosing.

CLINICAL TRIALS

Both agents reduce blood pressure by different but complementary mechanisms and are used in combination for the treatment of hypertension. Clinical studies have shown that blood pressure reduction achieved with the combination of fosinopril and hydrochlorothiazide was approximately additive. Peak blood pressure reductions were achieved six to eight hours after dosing and the hypertensive effect persisted for 24 hours. Symptomatic postural hypotension was infrequent but can occur in patients who are salt and/or volume depleted. Once daily doses of fosinopril and hydrochlorothiazide lowered 24 hour trough, seated systolic/ diastolic blood pressure by 10 to 17 mmHg/6 to 7 mmHg (10 mg/12.5 mg dose) and 11 to 13 mmHg/7 to 8 mmHg (20 mg/12.5 mg dose) when compared to placebo in the intention to treat population. These trough effects were 60 to 90% of the corresponding peak response. The effectiveness of the fosinopril/ hydrochlorothiazide combination was not influenced by age, sex or race. Abrupt withdrawal of the combination did not result in rebound hypertension.

INDICATIONS

Mild to moderate hypertension. Treatment should not be initiated with these combinations.

CONTRAINDICATIONS

Patients who are hypersensitive to fosinopril sodium or hydrochlorothiazide, other ACE inhibitors or other sulfonamide derived drugs (e.g. thiazides) or any of the inactive components of the tablets.

Patients with a history of hereditary and/or idiopathic angioedema or angioedema associated with previous treatment with an angiotensin converting enzyme inhibitor.

Pregnancy (see Precautions, Use in pregnancy).

Patients who are anuric.

PRECAUTIONS

Anaphylactoid and possibly related reactions

Head and neck angioedema. Severe life threatening angioedema has been reported rarely with angiotensin converting enzyme (ACE) inhibitors. The overall incidence is approximately 0.1 to 0.2%. There seems to be no sex difference in the incidence of angioedema or in the predisposition to angioedema in patients with heart failure or hypertension. In the majority of reported cases, the symptoms occurred during the first week of therapy. However, the onset of angioedema may be delayed for weeks or months. Patients may have multiple episodes of angioedema with long symptom free intervals. The aetiology is thought to be non-immunogenic and may be related to accentuated bradykinin activity. Angioedema may occur with or without urticaria but usually the angioedema involves nonpitting oedema of the skin and oedema of the subcutaneous tissues and mucous membranes.

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors. In such cases, the product should be discontinued promptly and appropriate monitoring instituted to ensure complete resolution of symptoms. In instances when swelling has been confined to the face and lips, the angioedema has generally resolved either without treatment or with antihistamines. Angioedema associated with laryngeal oedema is potentially life threatening. Where involvement of the tongue, glottis or larynx is likely to cause airway obstruction appropriate therapy, including adrenaline and oxygen administration, should be carried out promptly or the patient hospitalised. Patients who respond to medical treatment should be observed carefully for a possible re-emergence of symptoms of angioedema.

There are reports where changing the patient over to another ACE inhibitor was followed by recurrence of oedema and others where it was not. Because of the potential severity of this rare event another ACE inhibitor should not be used in patients with a history of angioedema to a drug of this class (see Contraindications).

Intestinal angioedema. Intestinal angioedema has been reported rarely in patients treated with angiotensin converting enzyme (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 CT scans 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.

Anaphylactoid reactions during desensitisation. Two patients undergoing desensitising treatment with hymenoptera venom while receiving another ACE inhibitor, enalapril, sustained life threatening anaphylactoid reactions. In the same patients, these reactions were avoided when the ACE inhibitor was temporarily withheld, but they reappeared upon inadvertent rechallenge. Therefore, caution should be used in patients treated with ACE inhibitors undergoing such desensitisation procedures.

Anaphylactoid reactions during high-flux dialysis/ lipoprotein apheresis membrane exposure. Patients haemodialysed using high-flux polyacrylonitrile ('AN69') membranes are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors.

Anaphylactoid reactions have also been reported in patients undergoing low density lipoprotein apheresis with dextran sulfate absorption. These combinations should therefore be avoided, either by use of a different class of medication or alternative membranes (e.g. cuprophane or polysulfone PSF for haemodialysis).

Neutropenia/ agranulocytosis. Agranulocytosis and bone marrow depression (including leucopenia/ neutropenia) have been reported with ACE inhibitors. These have mostly occurred in patients with pre-existing impaired renal function, collagen vascular disease, immunodepressant therapy or a combination of these complicating factors. Most episodes of leucopenia and neutropenia have been single, transient occurrences without any associated clinical symptoms. In addition, data to establish a causal relationship are currently lacking.

It is recommended that periodic monitoring of white blood cell counts should be considered in patients with collagen vascular disease, renal disease (serum creatinine greater than or equal to 180 micrommol/L) and those on multiple drug therapy with agents known to be nephrotoxic or myelosuppressive.

Thiazide diuretics have been also reported rarely to cause agranulocytosis and bone marrow depression.

Hypotension. Fosinopril/hydrochlorothiazide can cause symptomatic hypotension and should be used cautiously in patients receiving concomitant therapy with other antihypertensive agents. Symptomatic hypotension is most likely to occur in patients who are volume and/or salt depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with fosinopril/hydrochlorothiazide. A transient hypotensive response is not a contraindication to further doses which may be given without difficulty after replacement of salt and/or volume.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria, azotaemia and rarely with acute renal failure and death. In such patients fosinopril/hydrochlorothiazide therapy should be initiated under close medical supervision. Patients should be followed closely for the first two weeks of the treatment and whenever the dose is increased. The antihypertensive effect of thiazide diuretics may be increased in the post-sympathectomy patient.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, treated with intravenous infusion of physiological saline. Fosinopril/hydrochlorothiazide treatment usually can be continued following restoration of blood pressure and volume.

Hepatic failure. Rarely, ACE inhibitors have been associated with the syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients who develop jaundice or marked elevations of hepatic enzymes should discontinue receiving fosinopril/hydrochlorothiazide and receive appropriate medical attention.

Electrolyte imbalance/ hyperkalaemia. Determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia and hypochloraemic alkalosis). Patients should be periodically observed for clinical signs or symptoms of fluid and electrolyte imbalance, such as dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, nausea or vomiting. Although hypokalaemia may develop when thiazide diuretics are used, especially with brisk diuresis or in the presence of severe cirrhosis, concurrent therapy with fosinopril reduces diuretic induced hypokalaemia. The net effect of fosinopril/hydrochlorothiazide may be to elevate, reduce or leave serum potassium unchanged. Chloride deficit is generally mild and usually does not require treatment. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid gland with hypercalcaemia and hypophosphataemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption and peptic ulceration have not been seen. Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Metabolic disorders. Hyperuricaemia and gout may be precipitated by thiazides. Insulin requirements in diabetic patients may be altered and latent diabetes mellitus may become apparent during thiazide administration. Increases in cholesterol and triglyceride levels may be associated with thiazide therapy.

Cough. A persistent dry (non-productive) irritating cough has been reported with all ACE inhibitors in use. The frequency of reports has been increasing since cough was first recognised as a side effect of ACE inhibition. In various studies, the incidence of cough varies between 2 to > 9% depending upon the drug, dosage and duration of use. The cough is often worse when lying down or at night. The cough is more common in women (who account for two-thirds of the reported cases). Patients who cough may have increased bronchial reactivity compared to those who do not cough. The observed higher frequency of this complication in non-smokers may be due to higher level of tolerance to cough by smokers.

The mechanism of this adverse reaction is not clear but most likely to be secondary to the effects of converting enzyme inhibitor on kinins (bradykinin and/or prostaglandin) resulting in stimulation of pulmonary cough reflex. Once a patient has developed intolerable cough, an attempt may be made to switch the patient to another ACE inhibitor. The reaction may recur on rechallenge with another ACE inhibitor but this is not invariably the case. A change in antihypertensive regimen may be required in severe cases.

Systemic lupus erythematosus. Thiazide diuretics have been reported to cause exacerbation of systemic lupus erythematosus.

Surgery/ anaesthesia. In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, ACE inhibitors may block angiotensin II formation secondary to compensatory renin release and may thus augment the hypotensive response. If hypotension occurs, and is considered to be due to this mechanism, it can be corrected by volume expansion.

Dermatological reactions. Dermatological reactions characterised by maculopapular pruritic rashes and sometimes photosensitivity has been reported with another ACE inhibitor. Rare and sometimes severe skin reactions (e.g. lichenoid eruptions, psoriasis, pemphigus like rash, rosacea, Stevens-Johnson syndrome etc.) have been reported. A causal relationship is difficult to assess.

Patients who developed a cutaneous adverse event with one ACE inhibitor may be free of reaction when switched to another drug of the same class, but there are also reports of cross-reactivity.

Taste disturbances (dysgeusia). Taste disturbances were reported to be high (up to 12.5%) with high doses of another ACE inhibitor. The actual incidence of taste disturbance is probably low (< 0.5%) but data in this respect are scarce and difficult to interpret.

Taste disturbances with ACE inhibitors are described as suppression of taste or a metallic sensation in the mouth. The dysgeusia occurs usually in the first weeks of treatment and usually disappears within one to three months of treatment.

Impaired renal function. Fosinopril/hydrochlorothiazide is contraindicated in patients who are anuric.

Fosinopril/hydrochlorothiazide is not recommended in patients with severe renal disease (creatinine clearance less than 30 mL/minute). The cumulative effects of hydrochlorothiazide and hydrochlorothiazide associated precipitation of azotaemia may occur in some patients with impaired renal function.

As a consequence of inhibiting the renin/ angiotensin/ aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin/ angiotensin/ aldosterone system, treatment with ACE inhibitors may be associated with oliguria and/or progressive azotaemia but rarely with acute renal failure and/or death. In patients with congestive heart failure and pre-existing renal failure, fosinopril, like other ACE inhibitors should be used with caution. Although available data suggest minimal accumulation during ten days therapy with fosinopril 10 mg daily, dosage reduction of fosinopril in this patient group may be necessary and hence treatment with fosinopril/hydrochlorothiazide may be inappropriate. Renal function should be closely monitored.

In hypertensive patients with renal artery stenosis in one or both kidneys, increases in blood urea nitrogen and serum creatinine may occur during treatment with an ACE inhibitor. These increases are usually reversible upon discontinuation of therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients may develop increases in blood urea nitrogen and serum creatinine, usually minor and transient, when fosinopril was given concurrently with a diuretic. This effect is most likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of fosinopril/hydrochlorothiazide may be required.

Evaluation of the hypertensive patient should always include assessment of renal function (see Dosage and Administration). If a deterioration in renal function has occurred after treatment with one ACE inhibitor then it is likely to be precipitated by another and in these patients another class of antihypertensive agent should be preferred.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics. The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination, and periodically thereafter. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Impaired hepatic function. Fosinopril/hydrochlorothiazide should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Carcinogenesis, mutagenesis, impairment of fertility. At least one other ACE inhibitor has caused an increase in the incidence of oxyphilic renal tubular cells and oncocytomas in rats. The potential to cause this effect with other ACE inhibitors in humans is unknown. Moreover, the progression of oxyphilic cells to oncocytomas is rare in humans and when it does occur, it is considered to be benign.

In two year studies involving both mice and rats at doses up to 400 mg/kg daily, there was no evidence of a carcinogenic effect.

Neither fosinopril sodium nor the active fosinopril diacid 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 cytogenic 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.

There were no adverse reproductive effects in male and female rats treated with 15 to 60 mg/kg daily. There was no effect on pairing time prior to mating in rats until a daily dose of 240 mg/kg, a toxic dose, was given; at this dose, a slight increase in pairing time was observed.

Use in pregnancy (Category D)

(Category D: Drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.)

As with all ACE inhibitors, Fosinopril Winthrop should not be taken during pregnancy. Pregnancy should be excluded before starting treatment with Fosinopril Winthrop and avoided during treatment.

If a patient intends to become pregnant, treatment with ACE inhibitors must be discontinued and replaced by another form of treatment.

If a patient becomes pregnant while on ACE inhibitors, she must immediately inform her doctor to discuss a change in medication and further management.

Postmarketing experience with ACE inhibitors suggest that exposure *in utero*, particularly during the second and third trimesters, may be associated with hypotension and decreased renal perfusion in the foetus. ACE inhibitors have also been associated with foetal death *in utero*.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of neonatal hypotension, renal failure, skull hypoplasia and death. Oligohydramnios has also been reported, presumably resulting from decreased foetal renal function; oligohydramnios has been associated with foetal limb contractures, craniofacial malformations, hypoplastic lung development and intrauterine growth retardation. Prematurity and patent ductus arteriosus have been reported, although it is not clear whether these occurrences were due to ACE inhibitor exposure or to the mother's underlying disease.

A historical cohort study in over 29,000 infants born to non-diabetic mothers has shown 2.7 times higher risk for congenital malformations in infants exposed to any ACE inhibitor during 1st trimester compared to no exposure. The risk ratios for cardiovascular and central nervous system malformations were 3.7 times (95% confidence interval 1.89 to 7.3) and 4.4 times (95% confidence interval 1.37 to 14.02) respectively, compared to no exposure.

Use in lactation. Both fosinopril and hydrochlorothiazide are detectable in breast milk. Because of the potential for serious adverse reactions in breastfed infants from fosinopril/hydrochlorothiazide, a decision should be made whether to discontinue

breastfeeding or to discontinue fosinopril/hydrochlorothiazide, taking into account the importance of fosinopril/hydrochlorothiazide to the treatment of the mother.

Use in children. Safety and effectiveness in children have not been established.

Use in the elderly (> 65 years.) Among patients who received fosinopril/ hydrochlorothiazide in clinical studies, 20% were 65 to 75 years old. Overall differences in effectiveness or safety were not observed between these patients and younger patients, however greater sensitivity of some older individuals cannot be ruled out.

Interactions with other medicines

Alcohol, barbiturates or narcotics. Potentiation of thiazide diuretic induced orthostatic hypotension may occur.

Antacids. Antacids (aluminium hydroxide, magnesium hydroxide, simethicone) may impair absorption of fosinopril/hydrochlorothiazide. If concomitant administration of these agents is indicated dosing should be separated by two hours.

Antidiabetic drugs (oral agents and insulin). Thiazides may elevate blood glucose levels; thus dosage adjustments of antidiabetic agents may be necessary.

Antigout medication. Dosage adjustments of antigout medication may be necessary since hydrochlorothiazide may raise the level of blood uric acid. Increase in the dosage of probenecid or sulphinpyrazone may be necessary.

Calcium salts. Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.

Cholestyramine resin and colestipol hydrochloride. May delay or decrease absorption of hydrochlorothiazide. Fosinopril/hydrochlorothiazide should be taken at least one hour before or four to six hours after these medications.

Lithium. Increased serum lithium levels and risk of lithium toxicity have been reported in patients receiving ACE inhibitors and/or diuretic agents concomitantly with lithium. Fosinopril/hydrochlorothiazide and lithium should be coadministered with caution and frequent monitoring of serum lithium levels is recommended.

Inhibitors of endogenous prostaglandin synthesis. In some patients, these agents can reduce the effects of diuretics. Indomethacin has been reported to reduce the antihypertensive effect of other ACE inhibitors, especially in cases of low renin hypertension. Other nonsteroidal anti-inflammatory agents (e.g. aspirin) may have a similar effect.

In studies with concomitant administration of aspirin and fosinopril, the AUC for unbound fosinopril diacid was not altered, however the AUC for total (bound and

unbound) fosinopril diacid and 48 hour cumulatory urinary excretion were reduced by 42%.

Other diuretics and antihypertensive medications. Potassium sparing diuretics (e.g. amiloride, spironolactone, triamterene) or potassium supplements can increase the risk of hyperkalaemia. If concomitant use of fosinopril/hydrochlorothiazide and such agents is indicated, they should be given with caution, and the patients serum potassium monitored frequently.

Potassium supplements and salt substitutes. These supplements and salt substitutes should be used with caution and serum potassium should be monitored frequently.

Drugs used during surgery. The effects of nondepolarising muscle relaxants, preanaesthetics and anaesthetics used during surgery (e.g. tubocurarine chloride and gallamine triethiodide) may be potentiated by hydrochlorothiazide and dosage adjustments may be required. Fluid and electrolyte imbalances should be monitored and corrected prior to surgery. Caution should be used in patients taking fosinopril/hydrochlorothiazide and pressor agents (e.g. noradrenaline) who undergo surgery. Preanaesthetic and anaesthetic agents should be given in reduced dosage and if possible hydrochlorothiazide therapy discontinued one week prior to surgery.

Other agents. The bioavailability of fosinopril diacid is not altered by coadministration with cimetidine, digoxin, metoclopramide, nifedipine, propranolol, propantheline or warfarin.

Laboratory tests

Fosinopril may cause a false low measurement of serum digoxin levels with assays utilising the charcoal absorption method. Other kits which utilise the antibody coated tube method may be used instead. Therapy with fosinopril sodium should be interrupted for a few days before carrying out tests of parathyroid function.

Serum electrolytes. Hyperkalaemia, hyponatraemia (see also Precautions and Interactions with other medicines - Diuretics).

Renal function tests. Elevations, usually transient and minor, of blood urea nitrogen (BUN) and 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 pretreatment value) between the fosinopril and placebo treatment groups.

In placebo controlled trials in hypertension, a urinary albumin greater than or equal to 2+ or greater than or equal to 2 times the pretreatment value was seen in 2.8% of fosinopril treated and none of the placebo treated group. Increases in urinary albumin usually developed in patients with pre-existing proteinuria or diabetes and caused no clinical adverse effect.

Haematology. In controlled trials, a mean haemoglobin decrease of 0.13 g/dL was observed in fosinopril treated patients. In individual patients, decreases in haemoglobin or haematocrit were usually transient, small and not associated with symptoms. No patient was discontinued from therapy due to the development of anaemia.

Other. Leucopenia and eosinophilia have been reported; neutropenia (see Precautions).

Liver function tests. Elevations of transaminases, alkaline phosphatase and serum bilirubin have been reported. Fosinopril therapy was discontinued because of serum transaminase elevations in 0.7% of patients in hypertension studies. In the majority of cases, the abnormalities were either present at baseline or were associated with other aetiological factors. In those cases which were possibly related to fosinopril therapy, the elevations were generally mild and transient and resolved after discontinuation of therapy.

ADVERSE EFFECTS

Clinical trial data. Adverse events in patients receiving fosinopril/ hydrochlorothiazide were generally mild and transient and similar to those seen with the individual components taken separately. The incidence and type of adverse events in the elderly (greater than or equal to 65 years) were similar to those seen in younger. Table 1 displays the adverse events reported among subjects in active and placebo controlled clinical trials of combination fosinopril/ hydrochlorothiazide. It includes only those adverse events reported with an incidence of 1.0% or greater in subjects receiving fosinopril/hydrochlorothiazide 10mg/12.5mg or fosinopril/ hydrochlorothiazide 20mg/12.5mg.

Table 1

Adverse events reported in ≥ 1% of subjects

Body system Primary term	**fosinopril HCT 10/12.5mg n = 324 n (%)**	**fosinopril HCT 20/12.5mg n = 436 n (%)**	**fosinopril 10mg n = 124 n (%)**	**fosinopril 20mg n = 177 n (%)**	**Placebo n = 540 n (%)**
Endocrine/metabolic					
Sexual dysfunction	0	5 (1.1)	0	1 (0.6)	3 (0.6)
Gastrointestinal					
Dyspepsia/heartburn	6 (1.9)	1 (0.2)	0	3 (1.7)	5 (0.9)
Gastroenteritis	5 (1.5)	0	0	3 (1.7)	2 (0.4)
Nausea/vomiting	6 (1.9)	8 (1.8)	2 (1.6)	3 (1.7)	8 (1.5)
Pain, epigastric	2 (0.6)	5 (1.1)	0	2 (1.1)	1 (0.2)
General					
Fatigue	6 (1.9)	10 (2.3)	4 (3.2)	2 (1.1)	10 (1.9)
Influenza	4 (1.2)	5 (1.1)	1 (0.8)	2 (1.1)	10 (1.9)
Viral infection	0	6 (1.4)	2 (1.6)	2 (1.1)	4 (0.7)
Weakness	0	12 (2.8)**	1 (0.8)	2 (1.1)	1 (0.2)

Musculoskeletal					
Musculoskeletal pain	7 (2.2)	11 (2.5)	2 (1.6)	10 (5.6)	16 (3.0)
Nervous system					
Dizziness	2 (0.6)	13 (3.0)	5 (4.0)	4 (2.3)	12 (2.2)
Headache	12 (3.7)*	23 (5.3)*	9 (7.3)	14 (7.9)	63 (11.7)
Vertigo	1 (0.3)	5 (1.1)	0	0	7 (1.3)
Renal/genitourinary					
UTI	3 (0.9)	5 (1.1)	1 (0.8)	0	8 (1.5)
Respiratory					
Cough	13 (4.0)**	25 (5.7)**	4 (3.2)	8 (4.5)	6 (1.1)
Pharyngitis	8 (2.5)	2 (0.5)	1 (0.8)	6 (3.4)	7 (1.3)
Rhinitis	4 (1.2)	2 (0.5)	1 (0.8)	4 (2.3)	5 (0.9)
Sinus abnormality	1 (0.3)	6 (1.4)	0	1 (0.6)	15 (2.8)
Tracheobronchitis	4 (1.2)	1 (0.3)	1 (0.8)	1 (0.6)	4 (0.7)
URI	13 (4.0)	21 (4.8)	5 (4.0)	13 (7.3)	29 (5.4)

* indicates a significantly lower incidence compared to the placebo group at $p \leq 0.05$
** indicates a significantly greater incidence compared to the placebo group at $p \leq 0.05$

In placebo controlled clinical trials, the usual duration of therapy was two months. Discontinuations due to any clinical or laboratory adverse event were 3.5 and 4.3% in fosinopril/ hydrochlorothiazide treated and placebo treated patients, respectively. If the total clinical trial population is considered, withdrawals due to adverse events or laboratory abnormalities occurred in 2.6% of fosinopril/ hydrochlorothiazide treated patients, 2.7% of fosinopril treated patients, 2.7% of hydrochlorothiazide treated patients and 3.5% of placebo treated patients.

The following adverse drug reactions, possibly or more strongly associated causally with the use of fosinopril/ hydrochlorothiazide, were also reported during clinical trials.

The asterisk indicates adverse reactions that occurred in one patient only. The listing does not include events already presented in Table 1.

Cardiovascular. Uncommon. Oedema lower extremity*, cardiac rhythm disturbance*, subjective rhythm disturbance, ventricular rhythm disturbance*, flushing, orthostatic hypotension, hypertension, non-angina cardiac chest pain*, oedema and syncope.

Dermatological. Uncommon. Acne*, dermatitis*, ecchymosis*, extremity erythema*, bacterial skin infection* pruritus, rash and skin discomfort.

Endocrine/ metabolic. Uncommon. Breast disorder*, hot flushes, libido change, menstrual disorder* and polydipsia*.

Gastrointestinal. Uncommon. Abnormal stool*, constipation*, decreased appetite*, diarrhoea, abdominal distension*, dry mouth*, eructation*, gastrointestinal polyp excision*, gastritis*, increased appetite*, oral lesion*, intestinal obstruction* and abdominal pain.

General. Uncommon. Chest pain, chills*, cold sensation*, fever*, halitosis*, hyperhydrosis, malaise and weight loss*.

Hepatic/ biliary. Uncommon. Hepatitis*.

Immunological. Uncommon. Allergy* and angioedema*.

Musculoskeletal. Uncommon. Limitation of movement*, muscle cramp, musculoskeletal trauma*, musculoskeletal chest pain*, extremity swelling*, tendinitis* and extremity weakness.

Nervous system. Uncommon. Depression, neuropathy entrapment, memory impairment*, numbness*, somnolence, emotional lability/ disturbance, insomnia and paraesthesia.

Renal/ genitourinary. Uncommon. Abnormality urination, prostate disorder* and vaginal bleeding*.

Respiratory. Uncommon. Congestion*, subjective disorder of upper airway*, dyspnoea*, epistaxis*, sneezing*.

Special senses. Uncommon. Bad taste of medication*, ear abnormality*, ear infection* and hearing abnormality.

Laboratory test abnormalities. Serum electrolytes, uric acid, glucose, magnesium, cholesterol, triglycerides and calcium (see Precautions). Neutropenia, decreased haematocrit and haemoglobin, eosinophilia, elevated creatinine or blood urea nitrogen (BUN).

Other adverse events reported when fosinopril or hydrochlorothiazide are taken separately.

Cardiovascular. Sudden death, cardiac/ respiratory arrest, shock, hypertensive crisis, peripheral vascular disease/ claudication, angina/ myocardial infarct, cerebrovascular accident, hypotension, conduction disorder and palpitations.

Dermatological. Urticaria, photosensitivity.

Endocrine/ metabolic. Diabetes mellitus, gout.

Foetal/ Neonatal Morbidity and Mortality. The use of ACE inhibitors during pregnancy has been associated with foetal 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 foetal renal function; oligohydramnios in this setting has been associated with foetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported. More recently, prematurity, patent ductus arteriosus and other structural cardiac malformations, as well as neurologic malformations, have been reported following exposure limited to the first trimester of pregnancy. (See Precautions - Use in pregnancy)

Gastrointestinal. Bleeding, pancreatitis, tongue swelling, dysphagia, anorexia, weight change, pyrosis, sialoadenitis and flatulence.

General. Pain, xanthopsia.

Hepatic/ biliary. Jaundice (cholestatic) and/or liver enzyme abnormalities.

Haematological. Aplastic anaemia, megaloblastic anaemia, agranulocytosis, leucopenia, thrombocytopenia, purpura, haemolytic anaemia, lymphadenopathy.

Immunological. Necrotising angiitis, Stevens-Johnson syndrome, respiratory distress (including pneumonitis and pulmonary oedema), fever, anaphylaxis and toxic epidermal necrolysis (see also Dermatological).

Musculoskeletal. Arthralgia, arthritis and myalgia.

Nervous/ psychiatric. Lightheadedness, memory disturbance, drowsiness, confusion, behaviour change, mood change, tremor, sleep disturbance, cerebral infarction, transient ischaemic attack and restlessness, somnolence, insomnia, nervousness, dream abnormality, hallucinations.

Respiratory. Bronchospasm, pneumonia, pulmonary congestion, laryngitis/ hoarseness, sinusitis and pleuritis. A symptom complex of cough, bronchospasm, eosinophilia has been observed in two patients treated with fosinopril.

Renal/ genitourinary. Impotence, acute renal failure, renal insufficiency, interstitial nephritis, renal stones, abnormal urinary sediment.

Special senses. Taste disturbances, eye disturbances - other, transient blurred vision, vision disturbances, ear pain and tinnitus.

DOSAGE AND ADMINISTRATION

Adults including the elderly. The usual dose is one fosinopril/hydrochlorothiazide 10mg/12.5mg or one fosinopril/hydrochlorothiazide 20mg/12.5mg tablet once daily.

Children (< 18 years). The safety and efficacy of fosinopril/hydrochlorothiazide has not been established.

Hepatic impairment. The usual dose of fosinopril/hydrochlorothiazide is recommended in patients with mild to moderate hepatic impairment (see Precautions).

Renal impairment. The usual dose of fosinopril/hydrochlorothiazide is recommended for patients with mild to moderate renal impairment (creatinine clearance > 30 mL/minute, serum creatinine approximately less than or equal to 265 micromol/L). Fosinopril/hydrochlorothiazide is not recommended for patients with severe renal dysfunction (creatinine clearance < 30 mL/minute) since loop diuretics are preferred to thiazides in these patients (see Precautions).

OVERDOSAGE

No specific information is available on the treatment of overdose with fosinopril/hydrochlorothiazide; treatment should be symptomatic and supportive. Therapy with fosinopril/hydrochlorothiazide should be discontinued and the patient closely monitored. Suggested measures include administration of activated charcoal and correction of dehydration, electrolyte imbalance and hypotension by established procedures. Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Fosinopril is poorly removed from the body by haemodialysis or peritoneal dialysis. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Tablets, 10mg/12.5mg: Light pink, biconvex round tablet, embossed “E” above “341” on one side and plain on the other side. Available in bottles of 30 tablets.

Tablets, 20/12.5mg: Dark pink, biconvex round tablet, embossed “E” above “342” on one side and scored on the other side. Available in bottles of 30 tablets.

Store below 25ºC. Protect from moisture.

NAME AND ADDRESS OF THE SPONSOR

Fosinopril / HCT Winthrop is supplied in Australia by:
sanofi-aventis australia pty ltd
12-24 Talavera Road, Macquarie Park, NSW 2113
Freecall No: 1800 818 806

Fosinopril / HCT Winthrop is supplied in New Zealand by:
sanofi-aventis new zealand limited
Auckland, New Zealand
Freecall No: 0800 283 684

POISON SCHEDULE OF THE MEDICINE

Schedule 4 - Prescription Only Medicine

Date of TGA approval: 20/09/2007
Date of most recent amendment: 11/01/2008