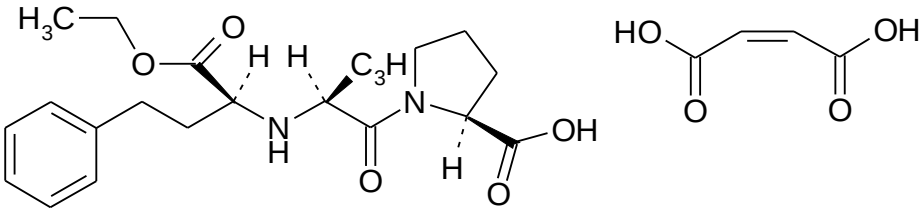
PRODUCT INFORMATION
ENALAPRIL/HCT SANDOZ® 20 mg/6 mg TABLETS

NAME OF THE MEDICINE

Enalapril/HCT Sandoz 20 mg/6 mg contains enalapril maleate 20 mg and hydrochlorothiazide 6 mg.

Enalapril maleate
Chemical name: (S)-1-[N-[1- (ethoxycarbonyl) -3-phenylpropyl]-L-alanyl] -L-proline, (Z)-2-butenedioate salt (1:1)

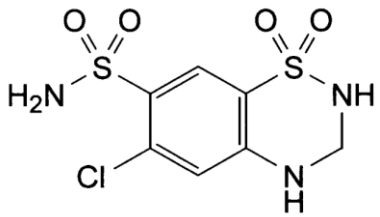
Empirical formula:



$C_{20}H_{28}N_2O_5.C_4H_4O_4$ MW: 492.53 CAS: 76095-16-4

Hydrochlorothiazide
Chemical name: 6-chloro- 3,4-dihydro- 2H-1,2,4-benzo-thiadiazine -7-sulfonamide 1,1-dioxide

Empirical formula:



$C_7H_8ClN_3O_4S_2$. MW: 297.74 CAS: 58-93-5

DESCRIPTION

Enalapril maleate
Enalapril maleate is the ethyl ester of the parent diacid, enalaprilat.

Enalapril maleate is a white to off white crystalline powder. It is sparingly soluble in water, soluble in ethanol and freely soluble in methanol and dimethyl formamide.

Hydrochlorothiazide
Hydrochlorothiazide is a white, or practically white, crystalline powder. It is slightly soluble in water, but freely soluble in sodium hydroxide solution.

Excipients: lactose monohydrate, magnesium stearate, maize starch, sodium bicarbonate, purified talc

PHARMACOLOGY

Pharmacodynamics
Enalapril/HCT (enalapril maleate and hydrochlorothiazide) is a combination of an angiotensin converting enzyme inhibitor (enalapril maleate) and a diuretic (hydrochlorothiazide).

Enalapril/HCT 20mg/6mg provides antihypertensive activity. Enalapril maleate and hydrochlorothiazide have been used singly and concomitantly for the treatment of hypertension. Although 6 mg of hydrochlorothiazide alone does not produce a clinically significant antihypertensive effect compared with placebo, when 6 mg of hydrochlorothiazide is combined with enalapril a clinically synergistic effect on blood pressure is achieved. The antihypertensive effect is maintained for at least 24 hours.

Enalapril maleate
Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyses the conversion of angiotensin I to the pressor substance angiotensin II. After absorption, enalapril is hydrolysed to enalaprilat, which inhibits ACE. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release) and decreased aldosterone secretion.

ACE is identical to kininase II. Thus enalapril may also block the degradation of bradykinin, a potent vasodepressor peptide. However, the role that this plays in the therapeutic effects of enalapril remains to be elucidated.

While the mechanism through which enalapril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, which plays a major role in the regulation of blood pressure, enalapril is antihypertensive even in patients with low renin hypertension.

Administration of enalapril maleate to patients with hypertension results in a reduction of both supine and standing blood pressure without a significant increase in heart rate.

Symptomatic postural hypotension is infrequent. In some patients the development of optimal blood pressure reduction may require several weeks of therapy. Abrupt withdrawal of enalapril maleate has not been associated with rapid increase in blood pressure.

Effective inhibition of ACE activity usually occurs two to four hours after oral administration of an individual dose of enalapril. Onset of antihypertensive activity was usually seen at one hour, with peak reduction of blood pressure achieved by four to six hours after administration. The duration of effect is dose related. However, at recommended doses, antihypertensive and haemodynamic effects have been shown to be maintained for at least 24 hours.

In haemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate. Following administration of enalapril maleate there was an increase in renal blood flow; glomerular filtration rate was unchanged. However, in patients with low pretreatment glomerular filtration rates, the rates were usually increased.

Hydrochlorothiazide
Hydrochlorothiazide is a diuretic and antihypertensive agent which increases plasma renin activity. The mechanism of the antihypertensive effect of thiazides is unknown. Hydrochlorothiazide usually does not affect normal blood pressure.

Enalapril maleate and hydrochlorothiazide
Although enalapril alone is antihypertensive even in patients with low renin hypertension, concomitant administration of hydrochlorothiazide in these patients leads to greater reduction of blood pressure. The mechanism for this synergy is unknown.

Pharmacokinetics

Enalapril maleate
Absorption
Oral enalapril maleate is rapidly absorbed, with peak serum concentrations of enalapril occurring within one hour. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril maleate is approximately 60%. The extent of absorption of enalapril is similar for the various doses in the recommended therapeutic range.

Distribution
Peak serum concentrations of enalaprilat occur three to four hours after an oral dose of enalapril maleate. Protein binding is approximately 50%. The serum concentration profile of enalaprilat exhibits a prolonged terminal phase, apparently associated with binding to ACE. In subjects with normal renal function, steady state serum concentrations of enalaprilat were achieved by the fourth day of administration of enalapril maleate. The plasma concentration time profile of enalaprilat was complex with several exponentials including a very prolonged terminal phase ($t_{1/2} > 30$ hours). The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril maleate is eleven hours.

Metabolism
Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin converting enzyme inhibitor. Except for conversion to enalaprilat, there is no evidence for significant metabolism of enalapril. The extent of hydrolysis of enalapril is similar for the various doses in the recommended therapeutic range.

Excretion
Excretion of enalapril is primarily renal. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril.

Hydrochlorothiazide
Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours.

Enalapril maleate/ hydrochlorothiazide
There are no bioavailability data on the Enalapril/HCT 20mg/6mg combination tablet. Concomitant multiple doses of enalapril maleate and hydrochlorothiazide have little or no effect on the bioavailability of these drugs. Various tablet combinations of enalapril and hydrochlorothiazide have been shown in studies to be bioequivalent to concomitant administration of the separate entities. However, in a study comparing the bioavailability of a 10 mg enalapril/25 mg hydrochlorothiazide combination tablet and the single entity tablets given concomitantly, both the AUC and C_{max} for enalaprilat were approximately 20% lower in the combination tablet than in the single enalapril tablet. This suggests that hydrochlorothiazide may have an effect on the pharmacokinetics of enalapril when they are given in a combination tablet. Enalapril/HCT 20mg/6mg may be assumed to be clinically bioequivalent to the separate entities.

There are no data on the possible pharmacokinetic interactions between enalapril and hydrochlorothiazide in the Enalapril/HCT 20mg/6mg combination tablet. There are no pharmacokinetic data on the use of Enalapril/HCT 20mg/6mg in patients with hepatic or renal failure.

The absorption of oral enalapril maleate was not influenced by the presence of food in the gastrointestinal tract when examined in studies of the single agent enalapril maleate tablet. No food interaction studies have been performed with the combination enalapril maleate/hydrochlorothiazide tablets.

INDICATIONS

Mild to moderate hypertension. Treatment should not be initiated with this fixed dose combination.

CONTRAINDICATIONS

Enalapril/HCT 20mg/6mg is contraindicated in

- Patients with anuria
- Patients who are hypersensitive to any component of this product and in patients with a history of angioneurotic oedema relating to previous treatment with an angiotensin converting enzyme inhibitor, and in patients with hereditary or idiopathic angioedema
- Patients who have shown hypersensitivity to other sulphonamide derived drugs
- Patients with renal artery stenosis
- Severe renal and hepatic impairment
- Use during pregnancy (see also PRECAUTIONS, USE IN PREGNANCY)
- Use during lactation (see also PRECAUTIONS, USE IN LACTATION).

Enalapril/HCT 20mg/6mg should not be administered with aliskiren in patients with diabetes (see INTERACTIONS WITH OTHER MEDICINES).

PRECAUTIONS

Enalapril maleate

Hypersensitivity/Angioneurotic Edema
Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril maleate. In such cases enalapril maleate should be promptly discontinued and the patient carefully observed until the swelling disappears. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient. Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery.

Where there is involvement of the tongue, glottis or larynx likely to cause airway obstruction appropriate therapy, which may include subcutaneous adrenaline solution 1:1000 (0.3 to 0.5 mL), and/or measures to ensure a patent airway, should be promptly administered. (See ADVERSE EFFECTS)

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks.

Patients receiving coadministration of ACE inhibitor and mTOR (mammalian target of rapamycin) inhibitor (e.g., temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment).

The onset of angioedema associated with use of ACE inhibitors may be delayed for weeks or months. Patients may have multiple episodes of angioedema with long symptom free intervals. Angioedema may occur with or without urticaria.

Hypotension
As with all antihypertensive therapy, excessive hypotension may occur in some patients. In patients with heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotaemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and if the dose of Enalapril/HCT 20mg/6mg is increased.

Similar considerations may apply to patients with ischaemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses. Following restoration of effective blood volume and pressure reinstitution of therapy at reduced dosage may be possible; or either of the components may be used appropriately alone.

Neutropenia/agranulocytosis
Another angiotensin converting enzyme inhibitor has been shown to cause agranulocytosis and bone marrow depression (including leucopenia/neutropenia). These reports generally involve patients who have pre-existing renal dysfunction and/or collagen vascular disease, some of whom have received concomitant immunosuppressant therapy. Most reports describe transient episodes for which a causal relationship to the ACE inhibitor could not be established. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. International marketing experience has revealed cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded.

It is recommended that periodic haematological monitoring be considered in patients with diseases known to affect bone marrow function (e.g. renal dysfunction, collagen vascular disease, etc.) and/or who are taking concomitant therapy known to be associated with bone marrow depression.

Aortic stenosis/hypertrophic cardiomyopathy
As with all vasodilators, ACE inhibitors should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

Surgery/anaesthesia
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, enalapril blocks angiotensin II formation, secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia (see also INTERACTIONS WITH OTHER MEDICINES, *Serum potassium*)
Risk factors for the development of hyperkalaemia include renal insufficiency, worsening of renal function, age (>70 years),diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements, or potassium containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g., heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole).

The use of potassium supplements, potassium sparing diuretics, or potassium containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal, arrhythmias.

If concomitant use of Enalapril/HCT 20mg/6mg and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

The combination of enalapril and a low-dose diuretic cannot exclude the possibility of hyperkalaemia to occur.

Anaphylactoid reactions during hymenoptera desensitisation
Rarely, patients receiving ACE inhibitors during desensitisation with hymenoptera venom have experienced life threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each desensitisation.

Cough
A persistent, non-productive, ticklish cough has been reported in some patients undergoing treatment with enalapril and other ACE inhibiting drugs. The cough is often worse when lying down. The cough is more common in women (who account for about two-thirds of reported cases). The patients who cough may have increased bronchial reactivity compared to those who do not cough. It may disappear in some patients with continued use, or diminish or disappear if the dose of the drug is reduced.

In those in whom cough persists, the drug should be discontinued. The cough usually returns on rechallenge. No residual effects have been reported.

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

Primary aldosteronism
Patients with primary aldosteronism will generally not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin system.

Hydrochlorothiazide

Fluid/electrolyte imbalance
Patients should be observed for clinical signs of fluid or electrolyte imbalance, e.g. volume depletion, hyponatraemia, hypochloraemic alkalosis, hypomagnesaemia or hypokalaemia which may occur during intercurrent diarrhoea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients.

Hepatic Disease
Thiazides 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.

Acute myopia and secondary angle-closure glaucoma
Hydrochlorothaizide, a sulphonamide, has been associated with an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss.
The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains

uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamides or penicillin allergy.

Postsympathectomy
The antihypertensive effects of thiazide diuretics may be increased in the postsympathectomy patient.

Systemic lupus erythematosus
Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.

Enalapril maleate and hydrochlorothiazide

Metabolic and endocrine effects
Experience with therapeutic doses of hydrochlorothiazide higher than that contained in Enalapril/HCT 20mg/6mg indicates that thiazide therapy may impair glucose tolerance, increase cholesterol and triglyceride levels and decrease serum sodium, magnesium and potassium levels. In clinical studies with 6mg of hydrochlorothiazide, however, no clinically significant effect on glucose, cholesterol, triglycerides, sodium, magnesium or potassium was reported.

Thiazide therapy has been associated with the development of hyperuricaemia and/or gout in certain patients. This hyperuricaemic effect appears to be dose related, and is not clinically significant at the 6mg dose contained in Enalapril/HCT 20mg/6mg. In addition, enalapril may increase urinary uric acid and thus attenuate the hyperuricaemic effect of hydrochlorothiazide.

Although no data exist for Enalapril/HCT 20mg/6mg, thiazide therapy may decrease urinary calcium excretion. Marked hypercalcaemia may be evidence of occult hyperparathyroidism. Thiazides should be discontinued before performing tests for parathyroid function.

Preclinical safety data
Enalapril/HCT 20mg/6mg has greater toxicity than that of the component agents. In particular, studies in rats, dogs and monkeys showed that the renal toxic effects of enalapril maleate are increased when the drug is given in combination with hydrochlorothiazide. The combination of enalapril maleate and hydrochlorothiazide produced gastrointestinal toxicity (haemorrhage, erosion and necrosis) in dogs, but similar effects have not been observed with enalapril, and these were considered to be secondary to uraemia as a result of renal toxicity in dogs given high doses of enalapril.

Impaired renal function
Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 mL/minute or below (i.e. moderate or severe renal insufficiency).

Enalapril/HCT 20mg/6mg should not be administered to patients with renal insufficiency (creatinine clearance < 80 mL/minute) until titration of enalapril has shown the need for the doses present in the combination tablet. (See DOSAGE AND ADMINISTRATION)
Azotaemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing azotaemia and oliguria occur during treatment of renal disease, the diuretic should be discontinued.

Some hypertensive patients with no apparent pre-existing renal disease have developed usually minor and transient increases in blood urea and serum creatinine when enalapril has been given concomitantly with a diuretic. If this occurs during therapy with Enalapril/HCT 20mg/6mg, the combination should be discontinued. Reinstitution of therapy at reduced dosage may be possible; or either of the components may be used appropriately alone.

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen with angiotensin converting enzyme (ACE) inhibitors.

There are no data on the use of Enalapril/HCT 20mg/6mg in patients with renal function impairment.

Evaluation of the hypertensive patient should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Haemodialysis patients
The use of Enalapril/HCT 20mg/6mg is not indicated in patients requiring dialysis for renal failure (see DOSAGE AND ADMINISTRATION). Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69®) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Impaired hepatic function
Thiazides 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

Enalapril maleate
There was no evidence of a carcinogenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day. Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively, and showed no evidence of carcinogenicity.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.

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

Hydrochlorothiazide
Two year feeding studies in mice and rats uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The studies, however, uncovered equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 and in the Chinese hamster ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO sister chromatid exchange (clastogenicity) and in the mouse lymphoma cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1,300 microgram/mL, and in the *Aspergillus nidulans* nondisjunction assay at an unspecified concentration.

Enalapril maleate and hydrochlorothiazide
Neither enalapril nor enalaprilat, nor enalapril in combination with hydrochlorothiazide, was mutagenic in the Ames microbial mutagen test with or without metabolic activation.

The combination of enalapril and hydrochlorothiazide was also negative in an *in vitro* alkaline elution assay in rat hepatocytes and in an *in vitro* chromosome aberration assay.

Effects on fertility
There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril. The effects of hydrochlorothiazide or the enalapril maleate/ hydrochlorothiazide combination on fertility and reproductive performance have not been evaluated.

Use in pregnancy. (Category D)
Australian Pregnancy Categorisation (Category D): Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Enalapril/HCT 20mg/6mg contains an ACE inhibitor and therefore should not be used during pregnancy.

Enalapril maleate
As with all ACE inhibitors, enalapril should not be taken during pregnancy. Pregnancy should be excluded before starting treatment with Enalapril/HCT 20mg/6mg and avoided during the 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.

There are no adequate and well controlled studies of enalapril in pregnant women. Data, however, show that enalapril crosses the human placenta. Post marketing experience with all

ACE inhibitors suggest that exposure *in utero* may be associated with hypotension and decreased renal perfusion in the foetus. ACE inhibitors have also been associated with foetal death *in utero*. There have been reports of foetal and neonatal damage, including hypotension, anuria, reversible or irreversible renal failure, hyperkalaemia, skull hypoplasia and death when ACE inhibitors have been used during the second and third trimesters of pregnancy.

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 first 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.

There is a potential risk of foetal hypotension, decreased birth weight and decreased renal perfusion or anuria in the foetus from *in utero* exposure to ACE inhibitors.

Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the foetus. 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, although it is not clear whether these were due to ACE inhibitor exposure. In addition, use of ACE inhibitors during the first trimester of pregnancy has been associated with a potentially increased risk of birth defects.

Any neonate exposed to enalapril *in utero* should be observed closely for adequate urine output, blood pressure and hyperkalaemia. If required, appropriate medical measures should be initiated including administration of fluids or dialysis to remove enalaprilat from the circulatory system.

The maternal and foetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and foetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day. Enalapril was not teratogenic in rabbits. There was no foetotoxicty or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril. Foetotoxicity expressed as a decrease in average foetal weight occurred in rats given 1,200 mg/kg/day of enalapril, but did not occur when these animals were supplemented with saline.

Hydrochlorothiazide
Thiazides, related diuretics and loop diuretics enter the foetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopenia has been reported with thiazides and related diuretics. Loop diuretics like frusemide and bumetanide are probably also associated with this risk. During the latter part of pregnancy products of this type should therefore only be given on sound indications, and then in the lowest effective dose.

The routine use of diuretics in otherwise healthy pregnant women with or without mild oedema is not indicated and exposes mother and foetus to unnecessary hazard. Diuretics do not prevent development of toxaemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxaemia.

Thiazides cross the placental barrier and appear in cord blood. Therefore, the use of hydrochlorothiazide when pregnancy is present or suspected requires that the benefits of the drug be weighed against possible hazards to the foetus. These hazards include foetal or neonatal

jaundice, thrombocytopenia and possibly other adverse reactions which occurred in the adult.

Enalapril maleate and hydrochlorothiazide
Reproductive toxicity studies in rats, mice and rabbits suggested that maternal toxicity and foetal toxicity (based on decreased foetal weight) may be increased when enalapril maleate and hydrochlorothiazide are given in combination than when each drug is given alone.

Use in lactation
Both enalapril and thiazides appear in human milk. If use of the drug is deemed essential, the patient should stop breastfeeding.

Paediatric use
Safety and effectiveness in children have not been established.

Use in the elderly
In clinical studies the efficacy and tolerability of enalapril maleate and hydrochlorothiazide, administered concomitantly, were similar in both elderly and younger hypertensive patients.

Effects on ability to drive and use machines
When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

Effects on laboratory tests
Laboratory test findings which have been reported with the use of enalapril alone include

Serum Electrolytes: Hyperkalaemia (see PRECAUTIONS), hyponatraemia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in some patients with essential hypertension treated with enalapril alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis (see PRECAUTIONS).

Haemoglobin and Haematocrit: Small decreases in haemoglobin and haematocrit occur frequently in hypertensive patients treated with enalapril but are rarely of clinical importance unless another cause of anaemia coexists.

Other (Causal Relationship Unknown): In marketing experience, rare cases of pancreatitis, neutropenia, thrombocytopenia, bone marrow depression, and agranulocytosis have been reported. A few cases of haemolysis have been reported in patients with G6PD deficiency.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

INTERACTIONS WITH OTHER MEDICINES

Other antihypertensive therapy
The antihypertensive effect of Enalapril/HCT 20mg/6mg is augmented by antihypertensive agents that cause renin release (e.g. diuretics).

The combination of enalapril maleate with beta-adrenergic blocking agents, methyldopa or calcium entry blockers has been shown to improve the efficacy of lowering the blood pressure.

Ganglionic blocking agents or adrenergic blocking agents, combined with enalapril, should only be administered under careful observation of the patient.

Serum potassium – (See also PRECAUTIONS, Hyperkalaemia)
Serum potassium usually remains within normal limits. The use of potassium supplements, potassium sparing agents or potassium containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium. If concomitant use of Enalapril/HCT 20mg/6mg and any of these agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

Lithium
Diuretic agents and ACE inhibitors reduce the renal clearance of lithium and add a high risk of lithium toxicity. Concomitant use is not recommended. Refer to the package inserts for lithium preparations before use of such preparations.

Non-steroidal anti-inflammatory drugs Including Selective Cyclooxygenase-2 Inhibitors
Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive drugs. Therefore, the antihypertensive effect of angiotensin II receptor antagonists or ACE inhibitors may be attenuated by NSAIDs including selective COX-2 inhibitors.

In some patients with compromised renal function (e.g. elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible.

These interactions should be considered in patients taking NSAIDs including selective COX-2 inhibitors concomitantly with diuretics and ACE inhibitors. Therefore, the combination should be administered with caution in patients with compromised renal function.

In some patients, the administration of a nonsteroidal anti-inflammatory agent including a selective cyclooxygenase-2 inhibitor can reduce the diuretic, natriuretic and antihypertensive effects of diuretics.

Combination use of angiotensin converting enzyme 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. The combination of drugs from these three classes should be used with caution, particularly in elderly patients or those with pre-existing renal impairment.

Dual Blockade of the Renin-Angiotensin-Aldosterone System
It has been reported in the literature that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, dual blockade of the renin-angiotensin aldosterone system is associated with a higher frequency of hypotension, syncope, hyperkalaemia, and changes in renal function (including acute renal failure) as compared to use of a single renin-angiotensin-aldosterone system agent. Dual blockade (e.g., by adding an ACE inhibitor to an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function. Closely monitor blood pressure, renal function, and electrolytes in patients on Enalapril/HCT 20mg/6mg and other agents that affect the RAAS. Do not coadminister aliskiren with Enalapril/HCT 20mg/6mg in patients with diabetes. Avoid use of aliskiren with Enalapril/HCT 20mg/6mgin patients with renal impairment (GFR < 60ml/min)

Nondepolarising muscle relaxants
Thiazides may increase the responsiveness to tubocurarine.

Gold
Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including enalapril.

Mammalian Target of Rapamycin (mTOR) Inhibitors
Patients taking concomitant mTOR inhibitor (e.g., temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema (see PRECAUTIONS).

Co-trimoxazole (trimethoprim/sulfamethoxazole)
Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (see PRECAUTIONS).

Increasing the QT Interval (e.g., quinidine, procainamide, amiodarone, sotalol)
Increased risk of *torsades de pointes*.

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

Antidiabetic drugs
For oral agents and insulin, dosage adjustment of the antidiabetic drug may be required as thiazides can increase blood glucose concentration.

Cholestyramine and colestipol resins
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43%, respectively.

Corticosteroids, ACTH (adrenocorticotrophic hormone)
Intensified electrolyte depletion, particularly hypokalaemia, may occur when corticosteroids or ACTH are used with thiazide diuretics.

Kaliuretic diuretics (e.g., furosemide), carbenoxolone, or laxative abuse
Hydrochlorothiazide may increase the loss of potassium and/or magnesium.

Pressor amines (e.g. adrenaline)
Possible decreased response to pressor amines may occur but not sufficiently to preclude their use.

ADVERSE EFFECTS

Enalapril/HCT 20mg/6mg is usually well tolerated. In clinical studies, side effects have usually been mild and transient and in most instances have not required interruption of therapy.

The most common side effects reported during clinical study with Enalapril/HCT 20mg/6mg were headache (1%) and cough (3%).
No clinically important changes in standard laboratory parameters were associated with administration of Enalapril/HCT 20mg/6mg.

The following undesirable effects have been reported for enalapril hydrochlorothiazide, enalapril alone or hydrochlorothiazide alone either during clinical studies or after the drug was marketed include:

Very common (> 1/10); common (> 1/100, < 1/10); uncommon (> 1/1,000, < 1/100); rare (> 1/10,000, < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders
Uncommon: anemia (including aplastic and hemolytic)
Rare: neutropenia, decreases in hemoglobin, decreases in hematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, leukopenia, pancytopenia, lymphadenopathy, autoimmune diseases

Endocrine disorders
Not known: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Metabolism and nutrition disorders
Common: hypokalemia, increase of cholesterol, increase of triglycerides, hyperuricemia
Uncommon: hypoglycemia, hypomagnesemia, gout*
Rare: increase in blood glucose
Very rare: hypercalcemia

Nervous system and psychiatric disorders
Common: headache, depression, syncope, taste alteration
Uncommon: confusion, somnolence, insomnia, nervousness, paraesthesia, vertigo, decreased libido*
Rare: dream abnormality, sleep disorders, paresis (due to hypokalemia), hallucinations.

Eye disorders
Very common: blurred vision

Ear and labyrinth disorders
Uncommon: tinnitus

Cardiac and vascular disorders
Very common: dizziness
Common: hypotension, orthostatic effects including hypotension, rhythm disturbances, angina pectoris, tachycardia
Uncommon: flushing, palpitations, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients
Rare: Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders
Very common: cough
Common: dyspnea, pharyngeal pain
Uncommon: rhinorrhea, sore throat and hoarseness, bronchospasm/asthma
Rare: respiratory distress (including pneumonitis and pulmonary edema), pulmonary infiltrates, rhinitis, allergic alveolitis/ eosinophillic pneumonia

Gastrointestinal disorders
Very common: nausea
Common: diarrhea, abdominal pain
Uncommon: ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, gastric irritations, dry mouth, flatulence*, peptic ulcer
Rare: stomatitis/aphthous ulcerations, glossitis, taste disturbances
Very rare: intestinal angioedema

Hepatobiliary disorders
Rare: hepatic failure, hepatic necrosis (maybe fatal), hepatitis - either hepatocellular or cholestatic jaundice, cholecystitis (in particular in patients with pre-existing cholelithiasis)

Skin and subcutaneous tissue disorders
Common: rash (exanthema)
angioneurotic edema of the face, extremities, lips, tongue, glottis and/or larynx
Uncommon: pruritus, urticaria, alopecia
Rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, purpura, hyperhidrosis, cutaneous lupus erythematosus, erythroderma, pemphigus, diaphoresis.

A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

Musculoskeletal, connective tissue and bone disorders
Common: muscle cramps†
Uncommon: arthralgia*

Renal and urinary disorders
Uncommon: renal dysfunction, renal failure, proteinuria

Rare: oliguria, interstitial nephritis

Reproductive system and breast disorders
uncommon: impotence
Rare: gynecomastia

General disorders and administration site conditions
Very common: asthenia
Common: chest pain, fatigue
Uncommon: malaise, fever

Investigations
Common: hyperkalemia, increases in serum creatinine
Uncommon: increases in blood urea, hyponatremia
Rare: elevations of liver enzymes, elevations of serum bilirubin

* These ADRs are only relevant for doses of hydrochlorothiazide 12.5 mg and 25 mg.
† The frequency of muscle cramps as common pertains to doses of hydrochlorothiazide 12.5 mg and 25 mg, whereas, the frequency of the event is uncommon as it pertains to 6 mg doses of hydrochlorothiazide.

Angioedema
Angioedema has been reported in patients receiving enalapril maleate. Angioedema associated with laryngeal oedema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with Enalapril/HCT 20mg/6mg should be discontinued and appropriate therapy instituted immediately. (See PRECAUTIONS). In very rare cases, intestinal angioedema has been reported with angiotensin converting enzyme inhibitors including enalapril.

Additional side effects seen post marketing are myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see PRECAUTIONS - Hypotension), angina pectoris and muscle cramps.

Potential adverse effects

Additional side effects which have been seen with other combinations of enalapril and hydrochlorothiazide or with hydrochlorothiazide alone and may be potential side effects with Enalapril/HCT 20mg/6mg are the following:

Other Combinations Of Enalapril And Hydrochlorothiazide

Tachycardia, flatulence, decreased libido, dry mouth, gout, arthralgia, hyperglycemia, hyperuricemia, hypokalemia, non-orthostatic hypotension.

Hydrochlorothiazide
Gastric irritation, cramping, diarrhoea, sialoadenitis, xanthopsia, leukopenia, agranulocytosis, aplastic anemia, hemolytic anemia, purpura, photosensitivity, fever, necrotizing angiitis (vasculitis), respiratory distress (including pneumonitis and pulmonary oedema), interstitial nephritis, anaphylactic reaction, hyperglycemia, glycosuria, hyperuricemia, electrolyte imbalance (including hypokalemia), restlessness, muscle spasm, weakness, transient blurred vision.

DOSAGE AND ADMINISTRATION

Enalapril/HCT 20mg/6mg is supplied as tablets for oral administration.
Treatment with Enalapril/HCT 20mg/6mg should only be commenced after titration of the enalapril component has been shown not to be effective in achieving the required lowering of blood pressure.

Hypertension
In hypertension, the usual dosage of Enalapril/HCT 20mg/6mg is one tablet, administered once daily.

Prior diuretic therapy
Symptomatic hypotension may occur following the initial dose of Enalapril/HCT 20mg/6mg; this is more likely in patients who are volume or salt depleted as a result of prior diuretic therapy. The diuretic therapy should be discontinued for two to three days prior to initiation of therapy with Enalapril/HCT 20mg/6mg. Patients receiving concomitant diuretic and ACE inhibitor therapy in doses greater than or equal to those contained in Enalapril/HCT 20mg/6mg may be transferred to Enalapril/HCT 20mg/6mg without discontinuation of the diuretic.

Dosage in renal insufficiency
Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 mL/minute or below (i.e. moderate or severe renal insufficiency).
In patients with creatinine clearance of > 30 and < 80 mL/minute, Enalapril/HCT 20mg/6mg should be used only after titration of the enalapril component.
The recommended initial dose of enalapril maleate, when used alone, in mild renal insufficiency is 5 mg.

OVERDOSAGE

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

No specific information is available on the treatment of overdosage with Enalapril/HCT 20mg/6mg. Treatment is symptomatic and supportive. Therapy with Enalapril/HCT 20mg/6mg should be discontinued and the patient observed closely. If possible, activated charcoal should be given within one hour of ingestion, with then correction of dehydration, electrolyte imbalance and hypotension by established procedures.

If ingestion is recent, take measures aimed at eliminating enalapril maleate (e.g., emesis, gastric lavage, administration of absorbents, and sodium sulphate).

Enalapril maleate
The most prominent features of overdosage reported to date are marked hypotension, beginning some six hours after ingestion of tablets, concomitant with blockade of the renin-angiotensin system and stupor. Symptoms associated with overdosage of ACE inhibitors may include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. Serum enalaprilat levels 100 and 200-fold higher than usually seen after therapeutic doses have been reported after ingestion of 300 and 440 mg of enalapril maleate, respectively.

The recommended treatment of overdosage is intravenous infusion of normal saline solution. Enalaprilat may be removed from the general circulation by haemodialysis. (See Precautions, Impaired renal function, Haemodialysis patients).
Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

Hydrochlorothiazide
The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalaemia may accentuate cardiac arrhythmias.

PRESENTATION AND STORAGE CONDITIONS

Enalapril/HCT Sandoz 20mg/6mg are white, oval, biconvex tablets with snap tab on one side, scored and marked "EN20" on the other side, packed in aluminium/aluminium blisters of 30 tablets.

Store below 25 °C. Protect from light and moisture.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park, NSW 2113
Australia
Tel: 1800 726 369

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 11/07/2007

DATE OF MOST RECENT AMENDMENT: 20/10/2017