

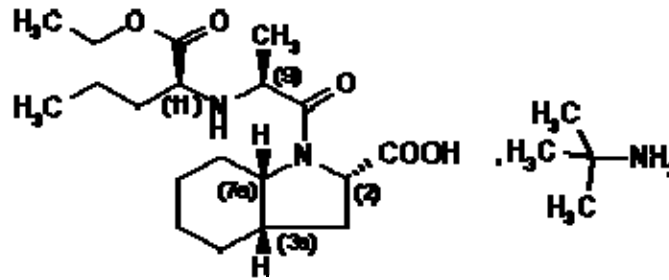
APO-PERINDOPRIL TABLETS

NAME OF THE MEDICINE

Perindopril erbumine.

Chemical Name: tert-butylammonium(2S,3aS,7aS)-1-N-[(S)-1-ethoxycarbonylbutyl]-L-alanyl)perhydroindole -2-carboxylate

Structural Formula:



Molecular Formula: $C_{19}H_{32}N_2O_5 \cdot C_4H_{11}N$

CAS Registry Number: 107133-36-8

DESCRIPTION

Perindopril is a dipeptide monoacid monoester with a perhydroindole group and no sulfhydryl radical. Perindopril erbumine is a white powder, readily soluble in purified water, 95% ethanol and chloroform. Perindopril has five asymmetric centres. The drug is synthesised stereoselectively so that it is a single enantiomer (all S stereochemistry).

Perindopril erbumine is an angiotensin converting enzyme inhibitor.

PHARMACOLOGY

Mechanism of Action

Perindopril (prodrug), following hydrolysis to perindoprilat, inhibits angiotensin converting enzyme (ACE) both in vitro and in vivo. It is thought that ACE inhibitors reduce blood pressure by inhibiting the enzyme which catalyses the conversion of angiotensin I to angiotensin II. Decreased plasma angiotensin II leads to increased plasma renin activity and a decrease in aldosterone. In addition to its effects on circulating ACE, perindopril binds to and inhibits tissue converting enzyme, predominantly in the kidney and vascular wall. The contribution of this mechanism to the overall antihypertensive effect of perindopril is unknown. Animal studies have demonstrated reversal of vascular hypertrophy and an improvement in the ratio of elastin to collagen in the vessel wall. Studies in humans have demonstrated an improvement in the viscoelastic properties of large vessels and in compliance. Studies in animals and humans suggest that specific and competitive suppression of the renin angiotensin aldosterone system is the main mechanism by which blood pressure is reduced. However, antihypertensive activity has also been observed in patients with low renin activity. Perindopril may also inhibit the degradation of the potent vasodepressor peptide bradykinin and this action may contribute to its antihypertensive action. Perindopril appears to reduce peripheral resistance and may influence arterial compliance.

Pharmacodynamics

Studies carried out in animal models of hypertension have shown that perindopril is a specific competitive angiotensin I converting enzyme inhibitor. The administration of perindopril to patients with essential hypertension results in a reduction in supine and standing blood pressure without any significant effect on heart rate. Abrupt withdrawal of perindopril has not been associated with a rebound rise in blood pressure. Single dose studies have demonstrated that peak inhibition of ACE

activity and peak reduction in blood pressure occurs four to six hours after administration. The duration of these effects are dose related and, at the recommended dose range, both effects have been shown to be maintained over a 24 hour period.

In haemodynamic studies carried out in animal models of hypertension, blood pressure reduction after perindopril administration was accompanied by a reduction in peripheral arterial resistance and improved arterial wall compliance. In studies carried out in patients with essential hypertension the reduction in blood pressure was accompanied by a reduction in peripheral resistance with no change or a small increase in renal blood flow, and no change in glomerular filtration rate. An increase in the compliance of large arteries was also observed. When perindopril is administered together with a thiazide type diuretic, the antihypertensive activity of perindopril may be potentiated in some patients and this effect is evident after four weeks of treatment. Perindopril, like other ACE inhibitors, may compensate for thiazide induced hypokalaemia.

In one study of 48 patients when low dose perindopril (2.0 mg) was compared with correspondingly low doses of enalapril (2.5 mg) or captopril (6.25 mg) in patients with congestive heart failure, significantly different blood pressure responses were noted. Blood pressure fell significantly with captopril and enalapril following the first dose. However, while perindopril inhibited plasma ACE comparably with enalapril, the blood pressure changes were insignificant and similar to placebo for up to ten hours of regular observation. Data regarding the possibility of a late hypotensive response are not available for perindopril.

Pharmacokinetics

Following oral administration, perindopril is rapidly absorbed with a bioavailability of 24%. Elimination is rapid, occurring predominantly via the urine. Plasma half-life is approximately one hour. Bioavailability of the active metabolite perindoprilat is approximately 27%. Peak plasma concentrations of perindoprilat occur three to four hours after oral administration of perindopril and protein binding of perindoprilat is 20%, principally to ACE. Perindoprilat binds to plasma and tissue ACE and free perindoprilat is eliminated through the urine. The terminal half-life of the unbound fraction is approximately 17 hours. The terminal half-life, which corresponds to the disassociation of perindoprilat from ACE, is approximately 25 to 30 hours.

When perindopril is administered chronically, steady state of perindoprilat concentration is reached within four days, and perindoprilat does not accumulate. Food intake may reduce hepatic biotransformation to perindoprilat.

The elimination of perindoprilat is reduced in elderly patients and in patients with cardiac and renal failure (see **DOSAGE AND ADMINISTRATION**). Apart from perindoprilat, the administration of perindopril leads to the formation of five other metabolites, all of which are inactive and exist in very low quantities. One of these is the glucuronoconjugate of perindoprilat which is formed by a hepatic first-pass effect. This effect does not appear to have any influence on the kinetics of perindoprilat.

CLINICAL TRIALS

Patients with Stable Coronary Artery Disease

The effects of perindopril were compared to placebo in patients with stable coronary artery disease with no clinical signs of heart failure. The EUROPA (EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease) study was a multicentre, international, randomised, double blind, placebo-controlled clinical trial lasting 4 years. 12218 patients aged over 18 were randomised: 6110 patients to high dose perindopril 8 mg and 6108 patients to placebo.

The primary endpoint was the composite of cardiovascular mortality, non-fatal myocardial infarction, and/or cardiac arrest with successful resuscitation.

The trial population had evidence of coronary artery disease documented by previous myocardial infarction at least 3 months before screening, coronary revascularisation at least 6 months before screening, angiographic evidence of stenosis (at least 70% narrowing of one or more major coronary arteries), or positive stress test in men with a history of chest pain.

Study medication was added to conventional therapy, including medication used for the management of hyperlipidaemia, hypertension and diabetes mellitus. Patients randomised to perindopril were initiated on

perindopril 2 mg or perindopril 4 mg for 2 weeks, and then titrated up to perindopril 8 mg during the 2 following weeks. Perindopril 8 mg was then maintained for the whole duration of the study. If this dose was not well tolerated, it could be reduced to perindopril 4mg once daily.

Most of the patients also received platelet inhibitors, lipid-lowering agents and beta-blockers. At the end of the study, the proportions of patients on these concomitant medications were 91%, 69% and 63% respectively.

The results of the EUROPA study, specifically the primary endpoint and its components (cardiovascular mortality, non-fatal myocardial infarction or resuscitated cardiac arrest) for the intention-to-treat (ITT) population are presented in the following table.

EUROPA Study Results (ITT population) ^{Note 1}

	Perindopril (n=6110)	Placebo (n=6108)	Absolute Risk Reduction [95% CI]	NMT ^{Note 2} over 4.2 yr trial period (per year)	Relative Risk Reduction [95% CI]	p (log-rank)
Cardiovascular events (<i>Primary composite endpoint</i>)	488 (8.0%)	603 (9.9%)	1.9% [0.87; 2.90]	54 (227)	20% [9; 29]	0.0003
Primary Endpoint Component :						
– Cardiovascular mortality	215 (3.5%)	249 (4.1%)	non- significant	-	14% [-3; 28]	0.107
– Non-fatal MI ^{Note 3}	295 (4.8%)	378 (6.2%)	1.4% [0.55; 2.17]	74 (311)	22% [10; 33]	0.001
– Cardiac arrest with successful resuscitation	6 (0.1%)	11 (0.2%)	non- significant	-	46% [-47; 80]	0.223
Secondary Endpoints :						
Total mortality	375 (6.1%)	420 (6.9%)	non- significant	-	11% [-2; 23]	0.101
Non-fatal and fatal MI	320 (5.2%)	418 (6.8%)	1.6% [0.76; 2.44]	63 (265)	23.9% [12, 34]	<0.001

Notes:

1. The EUROPA study was designed to have adequate statistical power to detect a treatment effect on the composite primary endpoint, and not for the individual components.
2. NNT = Number of patients needed to be treated to prevent one event.
3. MI = Myocardial Infarction.

The reduction in the primary composite endpoint was mainly due to a reduction in the number of non-fatal myocardial infarctions. There was no significant reduction in the rate of cardiovascular mortality or total mortality in patients taking perindopril compared to those taking placebo.

After a mean follow-up of 4.2 years, treatment with perindopril erbumine 8 mg once daily resulted in a significant relative risk reduction of 20% (95%CI: 9-29) in the primary combined endpoint: 488 patients (8.0%) reported events in the perindopril group compared to 603 patients (9.9%) in the placebo group (p = 0.0003). Improvements in the primary composite endpoint achieved statistical significance after 3 years of continuous treatment on perindopril.

INDICATIONS

- Treatment of hypertension.
- Treatment of heart failure.

In such patients it is recommended that perindopril be given with a diuretic and/or digoxin under close medical supervision. (The safety and efficacy of perindopril have not been demonstrated for New York Heart Association category IV patients).

- Patients with established coronary artery disease (see **CLINICAL TRIALS**), who are stable on concomitant therapy and have no heart failure, to reduce the risk of nonfatal myocardial infarction or cardiac arrest.

CONTRAINDICATIONS

- History of previous hypersensitivity to perindopril or to any component of the formulation.
- Breastfeeding mothers.
- Bilateral or unilateral renal artery stenosis.
- Patients with a history of hereditary and/or idiopathic angioedema, or angioedema associated with previous treatment with an angiotensin converting enzyme (ACE) inhibitor (see **PRECAUTIONS**).
- During pregnancy (see **PRECAUTIONS**, Use in Pregnancy).
- Patients haemodialysed using high flux polyacrylonitrile (AN69) membranes who are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. This combination should therefore be avoided, either by use of alternative antihypertensive drugs or alternative membranes (e.g. cuprophane or polysulphone (PSF)) for haemodialysis.

PRECAUTIONS

Angioedema

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor.

Life threatening angioedema has been reported with most of the ACE inhibitors. The overall incidence with some ACE inhibitors is approximately 0.1 to 0.2%. The aetiology is thought to be non-immunogenic and may be related to accentuated bradykinin activity. Usually the angioedema is non-pitting oedema of the skin, mucous membrane and subcutaneous tissue.

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors and has been reported on rare occasions with perindopril. In such cases, perindopril should be promptly discontinued and the patient carefully observed until the swelling disappears.

Where such cases have been described with other ACE inhibitors and swelling has been confined to the face and lips, the condition has generally resolved without treatment although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal oedema may be fatal or near fatal. In most cases symptoms occurred during the first week of treatment and the incidence appears to be similar in both sexes or those with heart failure or hypertension.

Where there is involvement of the tongue, glottis or larynx likely to cause airway obstruction, appropriate therapy (e.g. adrenaline and oxygen) should be given promptly. Treatment of progressive angioedema should be aggressive and, failing a rapid response to medical therapy, mechanical methods to secure an airway should be undertaken before massive oedema complicates oral or nasal intubation.

Patients who respond to medical treatment should be observed carefully for a possible rebound phenomenon.

The onset of angioedema associated with the 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.

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

There are reports when changing a patient to another ACE inhibitor was followed by a recurrence of angioedema 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**).

Rarely, patients receiving ACE inhibitors during low density lipoprotein (LDL) apheresis with dextran sulphate have experienced life threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Hypotension

Hypotension has been reported in patients commencing treatment with ACE inhibitors. Excessive hypotension is rarely seen in uncomplicated hypertension but is a potential consequence of perindopril use in severely salt/volume depleted patients with impaired renal function, those treated vigorously with diuretics, after severe diarrhoea or patients on dialysis (see **PRECAUTIONS, Interactions with other medicines** and **ADVERSE EFFECTS**).

Administration of perindopril 2 mg to patients with mild to moderate heart failure was not associated with any significant reduction in blood pressure.

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed. This may be associated with syncope, neurological deficits, 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 at low doses under very close supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dosage is increased, or diuretic therapy is commenced or increased.

Patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident should be closely followed for the first two weeks of treatment and whenever the dose of perindopril and/or diuretic is increased. In all high risk patients it is advisable to initiate treatment with perindopril 2 mg.

If hypotension occurs, the patient should be placed in a supine position and if necessary infused with normal saline. A transient hypotensive response is not a contraindication to further doses, which can usually be given without difficulty when blood pressure has increased following volume expansion.

Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice 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.

Cough

A persistent dry (non-productive) irritating cough has been reported with most of the ACE inhibitors. The frequency of reports has been increasing since cough was first recognised as a side effect of ACE inhibitor therapy. In various studies, the incidence of cough varies between 2 and 15% depending upon

the drug, dosage and duration of use.

The cough is often worse when lying down or at night and has been reported more frequently in women (who account for two-thirds of reported cases). Patients who cough may have increased bronchial reactivity compared with those who do not. The observed higher frequency of this side effect in non-smokers may be due to a higher level of tolerance or smokers to cough.

The cough is most likely due to stimulation of the pulmonary cough reflex by kinins (bradykinin) and/or prostaglandins which accumulate because of ACE inhibition. Once a patient has developed intolerable cough, an attempt may be made to switch the patient to another ACE inhibitor; the reaction may recur but this is not invariably the case. A change to another class of drugs may be required in severe cases.

Proteinuria

Perindopril treatment has occasionally been associated with mild or transient proteinuria (< 1 g per 24 hours). However in the majority of patients with pre-existing proteinuria treated with perindopril, proteinuria disappeared or remained stable. ACE inhibitors have a real potential to delay the progression of nephropathy in diabetic as well as hypertensive patients.

Neutropenia / Agranulocytosis / Thrombocytopenia / Anaemia

Neutropenia / agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors.

In patients with normal renal function and no other complicating factors, neutropenia occurs rarely.

Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Hyperkalaemia

Since ACE inhibitors reduce angiotensin II formation resulting in decreased production of aldosterone, an increase in serum potassium may be observed. However, hyperkalaemia (> 5.5 mmol/L) is more likely in patients with some degree of renal impairment or those treated with potassium sparing diuretics or with potassium supplements and/or consuming potassium containing salt substitutes. In some patients, hyponatraemia may coexist with hyperkalaemia. Diabetics and elderly patients may be at increased risk. It is recommended that serum electrolytes (including sodium, potassium and urea) should be measured from time to time when ACE inhibitors are given, especially when diuretics are also prescribed.

Dermatological Reactions

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

Patients who develop a cutaneous reaction with one ACE inhibitor might not when switched to another drug of the same class, but there are reports of cross reactivity.

Taste Disturbances (Dysgeusia)

Taste disturbances were reported to be common (prevalence up to 12.5%) with high doses of one 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 may disappear in most cases within one to three months of treatment.

Agents Causing Renin Release

The effect of perindopril may be enhanced by concomitant administration of antihypertensive agents which cause renin release.

Surgery and Anaesthesia

In patients undergoing major surgery or who require anaesthesia, hypotension due to anaesthetic agents may be greater receiving ACE inhibitors because of interference with compensatory mechanisms associated with the renin angiotensin system. If perioperative hypotension occurs, volume expansion would be required.

Valvular Stenosis

There has been some concern on theoretical grounds that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators, including ACE inhibitors. Vasodilators may tend to drop diastolic pressure, and hence coronary perfusion pressure, without producing the concomitant reduction in myocardial oxygen demand than normally accompanies vasodilatation. The true clinical importance of this concern is uncertain.

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, and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases are usually reversible upon discontinuation of ACE inhibitor treatment. ACE inhibitors should be avoided in patients with known or suspected renal artery stenosis. When an ACE inhibitor is given to a patient with stenosis of the renal artery supplying a solitary kidney or bilateral renal artery stenosis, acute renal insufficiency may occur. ACE inhibition may also cause a decrease in renal function in patients with stenosis of the artery supplying a transplanted kidney. It is believed that renal artery stenosis reduces the pressure in the afferent glomerular arteriole, and transglomerular hydrostatic pressure is then maintained by angiotensin II induced constriction of the efferent arteriole. When an ACE inhibitor is given, the efferent arteriole relaxes, glomerular filtration pressure falls, and renal failure may result. The thrombotic occlusion of a stenosed renal artery can be precipitated by ACE inhibitors.

Some hypertensive patients with no apparent pre-existing renovascular disease have developed increases in blood urea nitrogen and serum creatinine, which are usually minor and transient. This is more likely to occur in patients with pre-existing renal impairment or those on diuretics. Dosage reduction of the ACE inhibitor and/or discontinuation of the diuretic 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, it is likely to be precipitated by another, and in these patients usage of another class of antihypertensive agent would be preferable. Patients with unilateral renal artery disease present a special problem as deterioration of function may not be apparent from measurement of blood urea and serum creatinine.

Some ACE inhibitors have been associated with the occurrence of proteinuria (up to 0.7%) and/or decline in renal function in patients with one or more of the following characteristics: old age, pre-existing renal disease, concomitant treatment with potassium sparing diuretics or high doses of other diuretics, limited cardiac reserve or treatment with a non-steroidal anti-inflammatory drug (NSAID).

Perindopril is dialyzable with a clearance of 70 mL/minute.

Impaired Hepatic Function

Biotransformation of perindopril to perindoprilat occurs mainly in the liver. Studies in patients with impaired hepatic function have shown that kinetic parameters of perindopril were not modified by hepatic failure. With the exception of bioavailability, which was increased, kinetic parameters of perindoprilat (including T_{max}) were also unchanged. The increase in bioavailability could be due to inhibition of the formation of perindopril metabolites other than perindoprilat (see PHARMACOLOGY, Mechanisms of Action and Pharmacokinetics). The administration of perindopril leads to the formation of a glucuronoconjugate derivative of perindoprilat by a hepatic first-pass effect. The kinetic parameters of perindoprilat glucuronide are not modified by hepatic failure. The small changes on the kinetics of perindoprilat do not justify the need to change the usual dosage in most patients with hepatic failure.

Use in Pregnancy (Category D)

As with all ACE inhibitors, Apo- Perindopril should not be taken during pregnancy. Pregnancy should be excluded before starting treatment with Apo- Perindopril and avoided during the treatment.

If the 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.

Perindopril or its metabolites have been shown to cross the placenta and distribute to the foetus in pregnant animals.

There are no adequate and well controlled studies of ACE inhibitors in pregnant women, but foetotoxicity is well documented in animal models. Data, however, show that ACE inhibitors cross the human placenta. Post-marketing experience with all ACE inhibitors suggests 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*.

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.

When ACE inhibitors have been used during the 2nd and 3rd trimesters of pregnancy, there have been reports of foetal hypotension, renal failure, skull hypoplasia and death.

Oligohydramnios has been reported, presumably resulting from decreased foetal renal function; oligohydramnios has been associated with foetal limb contractures, craniofacial deformities, hypoplastic lung development and intrauterine growth retardation. Prematurity and patent ductus arteriosus have been reported, however it is not clear whether these events were due to ACE inhibitor exposure or to the mother's underlying disease.

Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia. If such complications arise, appropriate medical treatment should be initiated to support blood pressure and renal perfusion.

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. Accompanying texts should be consulted for further details.

Use in Lactation

Animal studies have shown that perindopril and its metabolites are excreted in milk during lactation, but there are no human data. It is therefore recommended that perindopril should not be given to lactating women as the possible effect on the newborn is unknown.

Use in Children

Use of perindopril in children is not recommended as data establishing safety and effectiveness in children are not available.

Use in the Elderly

Renal insufficiency is commonly observed in elderly people. Care should therefore be taken when prescribing perindopril to elderly hypertensive patients. The initial dose of perindopril in the elderly should always be 2 mg daily and patients should be monitored closely during the initial stages of treatment (see **DOSAGE AND ADMINISTRATION**).

In a study of 91 elderly patients with a mean age of 71.9 years, a 6% increase in serum potassium occurred in the first month of treatment and subsequently remained stable. There was no change in the group in blood urea, creatinine or creatinine clearance.

Particular care should be taken in elderly patients with congestive heart failure who have renal and/or hepatic insufficiency.

Carcinogenicity

At least one ACE inhibitor has caused an increase in the incidence of oxyphilic renal tubular cells and oncocytomas in rats. The potential of 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 to be benign.

Interactions with Other Medicines

Diuretics

When a diuretic is added to the therapy of a patient receiving an ACE inhibitor, the antihypertensive effect is usually additive. Patients receiving diuretics, especially those in whom diuretic therapy was recently instituted or in those with intravascular volume depletion, may sometimes experience an excessive reduction of blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects may be minimised by discontinuing the diuretic and ensuring adequate hydration and salt intake prior to commencing ACE inhibitor therapy. If it is not possible to discontinue the diuretic, the starting dose of the ACE inhibitor should be reduced and the patient closely observed for several hours following the initial dose of the ACE inhibitor and until the blood pressure has stabilised.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors. Use of perindopril with lithium is not recommended, but if the combination is necessary, careful monitoring of serum lithium levels should be performed.

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

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 perindopril.

Agents Affecting Serum Potassium

ACE inhibitors can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. The concomitant therapy of an ACE inhibitor with a potassium containing diuretic (e.g. spironolactone, triamterene or amiloride), potassium supplement or potassium sparing salt substitute can increase the risk of hyperkalaemia, therefore if co-administration is indicated they should be used with caution and the patient's serum potassium should be monitored frequently.

Antidiabetic Agents (e.g. Insulin, Hypoglycaemic Sulphonylureas)

Reported with captopril and enalapril.

The use of ACE inhibitors may increase the hypoglycaemic effect in diabetics receiving treatment with insulin or with hypoglycaemic sulphonylureas. The onset of hypoglycaemic episodes is very rare (improvement in glucose tolerance with a resulting reduction in insulin requirements).

Non-Steroidal Anti-Inflammatory Drugs

Drugs with prostaglandin synthetase inhibitor properties (e.g. indomethacin) may diminish the antihypertensive efficacy of concomitantly administered ACE inhibitors. However, clinical studies have not demonstrated any interaction between perindopril and indomethacin or other NSAIDs.

Tetracycline and Other Drugs that Interact with Magnesium

The simultaneous administration of tetracycline with an ACE inhibitor may significantly reduce the absorption of tetracycline, possibly due to the magnesium content in the ACE inhibitor tablets. This interaction should be considered if coprescribing an ACE inhibitor and tetracycline or other drugs that interact with magnesium.

Agents Affecting Sympathetic Activity

As the sympathetic nervous system plays an important part in physiological blood pressure regulation, caution should be exercised with concomitant administration of a drug with sympathetic activity and perindopril.

Effects on ability to drive or operate machinery

When driving or operating machines it should be taken into account that occasionally dizziness or weariness related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication.

Effect on laboratory tests

Increases in blood urea and plasma creatinine, hyperkalaemia reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension. Elevation of liver enzymes and serum bilirubin have been reported rarely (See **ADVERSE EFFECTS**).

ADVERSE EFFECTS

Adverse events that have been observed during treatment with perindopril are listed below ranked under the following frequency: Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10000, <1/1000); very rare (<1/10000 and including isolated reports).

Psychiatric and Nervous System Disorders

Common: headache, dizziness, vertigo, paraesthesia
 Uncommon: mood or sleep disturbances (insomnia, dream abnormality)
 Very rare: depression, confusion, hallucinations

Ear / Labyrinth and Eye Disorders

Common: tinnitus, vision disturbance

Cardiovascular Disorders

Common: hypotension and effects related to hypotension, palpitations, flushing, impaired peripheral circulation
 Very rare: arrhythmia, angina pectoris, myocardial infarction and stroke - possibly secondary to excessive hypotension in high risk patients, vasculitis

Respiratory, Thoracic and Mediastinal Disorders

Common: cough, dyspnoea, epistaxis, discomfort on exertion
 Uncommon: bronchospasm
 Very rare: eosinophilic pneumonia, rhinitis

Gastrointestinal Disorders

Common: nausea, vomiting, abdominal pain, dysgeusia, diarrhoea, dyspepsia, constipation
 Uncommon: dry mouth
 Very rare: pancreatitis

Hepatobiliary Disorders

Very rare: hepatitis, either cytolytic or cholestatic

Skin and Subcutaneous Tissue Disorders

Common: rash, pruritus
 Uncommon: urticaria, angio-oedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx
 Very rare: erythema multiforme

Musculoskeletal, Connective Tissue and Bone Disorders

Common: muscle cramps

Renal and Urinary Disorders

Uncommon: renal insufficiency

Very rare: acute renal failure

Reproductive System and Breast Disorders

Uncommon: impotence

General Disorders

Common: asthenia

Uncommon: sweating, atypical chest pain

Blood and the Lymphatic System Disorders

Very rare: decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/neutropenia, agranulocytosis or pancytopenia. An unexplained change in prothrombin ratio was reported in one patient. Haemolytic anaemia has been reported in patients with congenital G-6PDH deficiency.

Withdrawals

In total, 56 of 1,275 patients studied (4.4%) stopped treatment because of adverse reactions. In a specific study of 632 patients in which 36 patients (5.7%) withdrew because of adverse events. A plausible or probable relationship with perindopril treatment was considered to exist in 19 cases (3%).

Laboratory Changes

A small reduction in haemoglobin and haematocrit has been reported. (This has been noted with other ACE inhibitors). Rare cases of hyperkalaemia have been noted.

Slight increases in urea and in plasma creatinine levels, reversible when treatment is stopped, have been noted. These increases are more frequent in cases of renal artery stenosis, arterial hypertension treated with diuretics, renal insufficiency, renovascular hypertension and severe heart failure. Elevation of liver enzymes and serum bilirubin have been reported rarely.

DOSAGE AND ADMINISTRATION

Food intake may reduce hepatic biotransformation of perindopril to perindoprilat. While this effect had not been shown to be clinically significant, it is recommended that perindopril should be taken before meals.

Renal Impairment

In patients with renal failure, treatment should begin with 2 mg daily. Dosage should be adjusted as indicated below according to creatinine clearance. Creatinine and potassium levels should be closely monitored.

CREATININE CLEARANCE (mL/min)	DOSAGE
Between 30 and 60	One 2 mg tablet daily
Between 15 and 30	One 2 mg tablet every 2 days
Below 15	One 2 mg tablet on day of dialysis [Perindopril is dialysable (70 mL/min)].

Hypertension

The usual starting dose of perindopril is 4 mg once daily, taken in the morning. Optimum control of blood pressure is achieved by increasing the dose, titrating it against the blood pressure to a maximum of 8 mg once daily.

A starting dose of perindopril 2 mg/day is recommended in the following patients who may be at risk of ACE inhibitor induced hypotension.

- **Combination with a Diuretic**

The administration of perindopril to patients under current diuretic therapy may induce hypotension and sometimes, but more rarely, acute renal failure, at the beginning of the treatment. It is recommended to monitor plasma creatinine during the first month of treatment.

- **Elderly Hypertensives**

Elderly hypertensive patients should start treatment with 2 mg daily, with titration to 4 mg if necessary. It is recommended that renal function be assessed before starting treatment.

- **Other Patients Who May Be at Risk of ACE Inhibitor Induced Hypotension**

Patients with renovascular hypertension, salt and/or volume depletion, or cardiac decompensation may have a strongly activated renin angiotensin aldosterone system. These patients may experience an excessive drop in blood pressure following the first dose of an ACE inhibitor.

Congestive Heart Failure

Note: Treatment of congestive heart failure with perindopril should be initiated under close medical supervision.

2 mg is the usual starting dose, which should be given with a diuretic and/or digitalis. This is increased to 4 mg daily for maintenance.

Patients with severe hepatic or renal impairment and/or severe salt/volume depletion are particularly sensitive to ACE inhibitors. Doses in these patients should be carefully titrated, as no pharmacokinetic and dose titration studies have been conducted.

Reduction of Risk of Cardiovascular Events

In patients with stable coronary artery disease, Perindopril should be introduced at a dose of one 4 mg tablet once daily for two weeks, and then increased to one 8 mg tablet once daily, depending on tolerance and renal function.

Elderly patients should receive one 2 mg tablet once daily for one week, then one 4 mg tablet once daily the next week, before increasing the dose up to one 8 mg tablet once daily depending on tolerance and renal function (see above table under **DOSAGE AND ADMINISTRATION, Renal Impairment**).

OVERDOSAGE

Limited data are available for overdosage in humans.

Symptoms

Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough.

Treatment

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. Perindopril may be removed from the general circulation by haemodialysis (see **PRECAUTIONS**). Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

Contact the Poison Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Apo-Perindopril 2 mg Tablets

White, round, biconvex tablets, engraved “APO” on one side and “PE2” on the reverse.

Blister packs of 30.

AUST R number 151911.

Apo-Perindopril 4 mg Tablets

White, capsule shaped, biconvex tablets, engraved “PE” bisect “4” on one side, and “APO” on the reverse.

Blister packs of 30.

AUST R number 151912.

Apo-Perindopril 8 mg Tablets

White, capsule shaped, biconvex tablets, engraved “PE” bisect “8” on one side, and “APO” on the reverse.

Blister packs of 30.

AUST R number 151913.

Apo-Perindopril Tablets are intended for oral administration. Each tablet contains perindopril 2, 4 or 8 mg.

In addition, the inactive ingredients in each tablet include lactose anhydrous and magnesium stearate.

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

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine.

NAME AND ADDRESS OF THE SPONSOR

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