

APO-PERINDOPRIL

This product may not be interchangeable with similar products on the New Zealand market.

1. APO-PERINDOPRIL (2mg, 4mg and 8mg tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Perindopril erbumine 2mg, 4mg and 8mg

Excipient(s) of known effect

APO-PERINDOPRIL contain Lactose.

APO-PERINDOPRIL are gluten free.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

APO-PERINDOPRIL 2mg tablets are white, round, biconvex tablets identified by an engraved "APO" on one side and "PE2" on the reverse.

APO-PERINDOPRIL 4mg tablets are white, capsule-shaped, biconvex tablets identified by an engraved "APO" on one side and "PE" bisect "4" on the reverse.

APO-PERINDOPRIL 8mg tablets are white, capsule-shaped, biconvex tablets identified by an engraved "APO" on one side and "PE" bisect "8" on the reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

APO-PERINDOPRIL is indicated for:

- the treatment of hypertension;
- the treatment of heart failure. In such patients it is recommended that APO-PERINDOPRIL be given with a diuretic and/or digoxin under close medical supervision. (The safety and efficacy of APO-PERINDOPRIL has not been demonstrated for New York Heart Association Category IV patients);
- Reduction of risk of cardiovascular events (cardiovascular mortality, myocardial infarction or cardiac arrest) in patients with established coronary artery disease who are stable on concomitant therapy.

4.2 Dose and method of administration

Food intake may reduce hepatic biotransformation of perindopril to perindoprilat. However, whilst this effect has not been shown to be clinically significant, it is recommended that APO-PERINDOPRIL should be taken before meals.



APO-PERINDOPRIL

Renal Impairment

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

| <u>Creatinine Clearance (mL/min)</u> | <u>Dosage</u> |
|--------------------------------------|------------------|
| Between 30 and 60 | 2mg daily |
| Between 15 and 30 | 2mg every 2 days |

Below 15 2mg on day of dialysis [Perindopril is dialyzable (70mL/min)]. Hypertension

The usual starting dose of APO-PERINDOPRIL is 2mg once daily, taken in the morning. Optimum control of blood pressure is achieved by increasing the dose, titrating it against the blood pressure. Dosage should be adjusted according to each patients needs and may be increased from 2mg to 4mg then to a maximum of 8mg once daily.

A starting dose of 2mg per day of APO-PERINDOPRIL is recommended in the following patients who may be at risk of ACE inhibitor-induced hypotension:

Combination with a Diuretic

The administration of APO-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 2mg daily, and the dosage increased to 4mg 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 ren in-angiotensin-aldosterone system. These patients may experience an excessive drop in blood pressure following the first dose of an ACE inhibitor.

Congestive Heart Failure

Treatment of congestive heart failure with APO-PERINDOPRIL should be initiated under close medical supervision.

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

APO-PERINDOPRIL

Reduction of risk of cardiovascular events

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

Elderly patients should receive 2mg once daily for one week, then 4mg once daily the next week, before increasing the dose up to 8mg once daily depending on tolerance and renal function (see above table under *4.2 Dose and Method of Administration - Renal impairment*).

4.3 Contraindications

APO-PERINDOPRIL is contraindicated:

- in patients with a history of previous hypersensitivity to the active ingredient perindopril or any of the excipient ingredients present in APO-PERINDOPRIL;
- during pregnancy and for lactating women;
- in patients with bilateral or unilateral renal artery stenosis;
- in patients with a history of hereditary and/or idiopathic angio-oedema or angio-oedema associated with previous ACE-inhibitor treatment; and
- in 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 (eg. cuprophane or polysulphone PSF).

4.4 Special warnings and precautions for use

Hyperkalaemia

Since ACE inhibitors reduce angiotensin II formation resulting in decreased production of aldosterone, an increase in serum potassium may be observed. However, hyperkalaemia (>5.5mmol/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 co-exist 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.

Angioedema

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

Angio-oedema 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.

APO-PERINDOPRIL

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. Angio-oedema 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 angio-oedema 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 angio-oedema associated with use of ACE inhibitors may be delayed for weeks or months.

Patients may have multiple episodes of angio-oedema with long symptom-free intervals. Angio-oedema may occur with or without urticaria.

There are reports when changing a patient to another ACE inhibitor was followed by recurrence of angio-oedema and others where it was not. Because of the potential severity of this rare event, another ACE inhibitor should not be used in patients with a history of angio-oedema, to a drug of this class (see *4.3 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 APO-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 *4.4 Special Warnings and Precautions for use* and *4.8 Undesirable effects*). Administration of APO-PERINDOPRIL 2mg to patients with mild-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 impairment, excessive hypotension has been observed. This may be associated with

APO-PERINDOPRIL

syncope, neurological deficits, oliguria and/or progressive increase in blood nitrogen, 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 APO-PERINDOPRIL and/or diuretic is increased. In all high-risk patients it is advisable to initiate treatment with APO-PERINDOPRIL 2mg.

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.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on RAAS activity, treatment with ACE inhibitors may be associated with oliguria and/or progressive increase in blood nitrogen, 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 in 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 *4.2 Dose and Method of Administration*). If deterioration in renal function has occurred after treatment with one ACE inhibitor, then it is likely to be precipitated by another and in these patients usage of another class of antihypertensive agent would be preferable. Patients with unilateral renal artery disease present a special problem as

APO-PERINDOPRIL

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.

Perindopril is dialysable with a clearance 70mL/min.

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.

Impaired Hepatic Function

Biotransformation of perindopril to perindoprilat mainly occurs 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 5.2 Pharmacokinetics Properties). The administration of perindopril leads to the formation of a glucuroconjugate derivative of perindoprilat by a hepatic first-pass effect. The kinetic parameters of perindoprilat glucuronide are not modified by hepatic failure. The small changes in the kinetics of perindoprilat do not justify the need to change the usual dosage in most patients with hepatic failure.

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 class-effect of ACE inhibitor therapy with the incidence of cough varying between 2-15% 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 2/3 of the 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 of 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.

APO-PERINDOPRIL

Proteinuria

Perindopril treatment has occasionally been associated with mild or transient proteinuria (<1 gram/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. APO-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 APO-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.

Dermatological Reactions

Dermatological reactions characterised by maculo-papular pruritic rashes and sometimes photosensitivity has 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 are scarce and difficult to interpret.

Taste disturbances with ACE inhibitors have been described as suppression of taste or a metallic sensation in the mouth. Any dysgeusia usually occurs in the first weeks of treatment and may disappear in most cases within 1-3 months.

Agents Causing Renin Release

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

Dual blockade of the renin-angiotensin-aldosterone system

As a consequence of inhibiting the renin-angiotensin-aldosterone system, hypotension, syncope, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (e.g.

APO-PERINDOPRIL

by adding an angiotensin II receptor antagonist to an ACE-inhibitor) is therefore not recommended in patients with already controlled blood pressure and should be limited to individually defined cases with close monitoring of renal function.

Surgery and Anaesthesia

In patients undergoing major surgery or who require anaesthesia, hypotension due to anaesthetic agents may be greater in patients 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 that normally accompanies vasodilatation. The true clinical importance of this concern is uncertain.

Elderly Patients

Renal insufficiency is commonly observed in elderly people. Care should therefore be taken when prescribing APO-PERINDOPRIL to elderly patients. The initial dose of APO-PERINDOPRIL in the elderly should always be 2mg daily and patients should be monitored closely during the initial stages of treatment (See 4.2 *Dose and Method of 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.

Paediatric Use

Use of APO-PERINDOPRIL in children is not recommended as no data establishing safety or effectiveness in children are available.

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 the ACE inhibitor class to cause this effect in man is unknown. Moreover, the progression of oxyphilic cells to oncocytomas is rare in humans and when this occurs, it is considered as benign.

4.5 Interactions with other medicines and other forms of interactions

Lithium

Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. These drugs should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

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 ensuring adequate hydration and salt intake prior to commencing ACE inhibitor therapy. 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.

Combination use of ACE inhibitors, 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.

Agents affecting serum potassium

The ACE inhibitor class can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. The concomitant use of an ACE inhibitor with a potassium-sparing diuretic (e.g. spironolactone, triamterene, or amiloride), potassium supplement, or potassium-containing 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 monitored frequently.

Antidiabetic agents (eg. 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

APO-PERINDOPRIL

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 or indomethacin or other non-steroidal anti-inflammatory drugs.

Vildagliptin, Sirolimus and Everolimus

Patients taking concomitant DPP-IV inhibitor (e.g. vildagliptin) or mTOR inhibitor (e.g. everolimus, sirolimus) therapy may be at increased risk for angioedema. Caution should be used when starting a DPP-IV inhibitor or mTOR inhibitor in a patient already taking an ACE inhibitor.

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 co-prescribing 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 APO-PERINDOPRIL.

Effects on laboratory tests

A small reduction in haemoglobin and haematocrit has been reported. (This has been noted with other ACE inhibitors). An unexplained change in prothrombin ratio was reported in one patient. Rare cases of hyperkalaemia have been noted.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 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.'

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. The ACE-inhibitor class has also been associated with foetal death *in utero*.

A historical cohort study in over 29,000 infants born to non-diabetic mothers has shown



APO-PERINDOPRIL

2.7 times higher risk for congenital malformations in infants exposed to ACE inhibitors during the 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.

APO-PERINDOPRIL

When ACE inhibitors have been used during the second and third 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 intra-uterine 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.

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 APO-PERINDOPRIL should not be given to lactating women as the possible effect on the newborn is unknown.

4.7 Effects on ability to drive and use machines

The antihypertensive effect in individual cases may be symptomatic. Treatment with any blood pressure lowering agent may, therefore, affect the ability to drive, cross the road safely or operate machinery, especially at the start of treatment or when changing over from other preparations, or during concomitant use of alcohol.

4.8 Undesirable effects

The most frequent adverse reactions noted in clinical studies were as follows (incidence 2% - 5.3%):

- Respiratory, thoracic and mediastinal disorders: Cough (3.1%). ACE-inhibitor-induced cough is generally a nocturnal, dry, irritating laryngeal cough occurring at the beginning of treatment. Using these criteria perindopril -induced cough was reported in 18 cases (1.4%). Treatment was discontinued in 6 cases.
- Gastrointestinal disorders Dizziness (4.2%) and nausea or epigastric pain (2.4%) leading to withdrawal in 0.5% of patients.
- General disorders and administration site conditions: Headache (5.3%) usually at the beginning of treatment and resulting in withdrawal of treatment in 7 of 1275 patients (0.5%), Asthenia (4.9%) leading to withdrawal in 0.4% of cases.

Other adverse reactions reported with an incidence of between 0.5% and 2% were as follows:

- Metabolism and nutrition disorders: oedema
- Nervous system disorders: insomnia, drowsiness, mood disturbance, paraesthesia

APO-PERINDOPRIL

- Eye disorders: visual disturbances
- Cardiac disorders: palpitations, flushing, impaired peripheral circulation
- Respiratory, thoracic and mediastinal disorders: dyspnoea, discomfort on exertion, epistaxis
- Gastrointestinal disorders: nausea, dry mouth, dyspepsia, diarrhoea, vomiting.
- Skin and subcutaneous tissue disorders: rash, pruritus, sweating
- Musculoskeletal and connective tissue disorders: muscle cramps
- Reproductive system and breast disorders: sexual dysfunction
- General disorders and administration site conditions: atypical chest pain, abdominal pain, faintness on standing, impaired taste, tinnitus

Withdrawals

In total, 56 of 1275 patients (4.4%) studied 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%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Limited data are available for overdosage in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. 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 *4.4 Special Warnings and Precautions for use*). Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

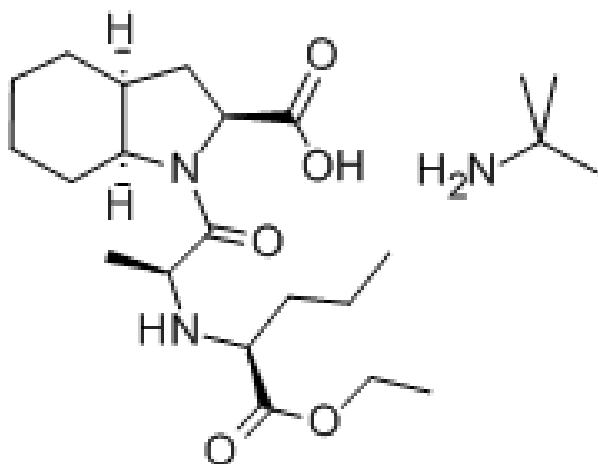
Advice on overdose management can be obtained from the national Poisons Information Centre by telephoning 0800 764 766.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics Properties

Pharmacotherapeutic group: Cardiovascular system, Agents acting on the renin-angiotensin system, ACE Inhibitors, plain
ATC code: C09AA04

Chemical Structure:



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 man 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.

5.2 Pharmacokinetics Properties

Following oral administration, perindopril is rapidly absorbed and is 61-85% bioavailable. Elimination is rapid, occurring predominantly via the urine. Plasma half-life is approximately 1 hour. Biotransformation of perindopril to the active metabolite perindoprilat is approximately 20%. Peak plasma concentrations of perindoprilat occur 3 to 4 hours after oral administration of perindopril and protein binding of perindoprilat is

APO-PERINDOPRIL

below 30%. Perindoprilat binds to plasma and tissue ACE, and free perindoprilat is eliminated through the urine. The elimination half-life of the free fraction is between 3 and 5 hours. The terminal half-life, which corresponds to the dissociation of perindoprilat from ACE, is approximately 25 to 30 hours. When perindopril is administered chronically, steady-state perindoprilat concentration is reached within 4 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 4.2 *Dose and Method of Administration*). Apart from perindoprilat, the administration of perindopril leads to the formation of 5 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.

5.3 Preclinical safety data

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 4-6 hours after administration. The durations 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 in which low-dose perindopril (2mg) was compared with correspondingly low doses of enalapril (2.5mg) or captopril (6.25mg) 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, whilst perindopril inhibited plasma ACE comparably with enalapril, the blood pressure changes were insignificant and similar to placebo for up to 10 hours of regular observation. Data regarding possibility of a late hypotensive response are not available for perindopril.

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

APO-PERINDOPRIL

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 perindopril 8mg and 6108 patients to placebo.

The main evaluation criterion 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 were initiated at 2 or 4 mg doses of perindopril for 2 weeks, then titrated up to 8mg during the 2 following weeks. The 8mg dose was maintained afterwards for the duration of the study. If this dose was not well tolerated, it could be reduced to 4mg once daily or matching placebo.

Most of the patients received platelet inhibitors, lipid lowering agents and beta-blockers during the study. 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 MI or cardiac arrest) for the intention-to-treat population (ITT) are presented in Table 1.

Table 1 - EUROPA study results (primary composite endpoint and components) (ITT)

| | Perindopri I (N=6110) | Placebo (N=6108) | RRR (95% CI) | ARR (95% CI) | P (log-rank) |
|--|--------------------------------------|-----------------------------|-------------------------|--------------------------|-------------------------|
| Cardiovascular events (<i>Primary composite endpoint</i>) | 488 (8.0%) | 603 (9.9%) | 20% [9; 29] | 1.9% [0.87; 2.90] | 0.0003 |
| <i>Primary endpoint component:</i> | | | | | |
| – Cardiovascular mortality | 215 (3.5%) | 249 (4.1%) | 14% [-3; 28] | 0.6% [-0.12; 1.24] | 0.107 |
| – Non-fatal MI ^{Note 3} | 295 (4.8%) | 378 (6.2%) | 22% [10; 33] | 1.4% [0.55;2.17] | 0.001 |
| – Cardiac arrest with successful resuscitation | 6 (0.1%) | 11 (0.2%) | 46% [-47; 80] | 0.1% [-0.05; 0.21] | 0.223 |

Notes:

- *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*

APO-PERINDOPRIL

- RRR= Relative Risk Reduction
- ARR= Absolute Risk Reduction

After a mean follow-up of 4.2 years, the treatment with perindopril 8mg once daily resulted in a significant relative risk reduction of 20% [95% CI: 9.4; 28.6] in the primary combined endpoint: 488 (8.0%) patients reported events in the perindopril group compared to 603 (9.9%) patients in the placebo group ($p = 0.0003$). The benefit was particularly marked with regard to the non-fatal myocardial infarction component of the composite endpoint.

The risk reduction was consistent irrespective of whether patients were hypertensive or not, diabetic or not, and irrespective of age, gender or history of myocardial infarction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

APO-PERINDOPRIL tablets contain the following excipients:

- Lactose anhydrous
- Magnesium Stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

48 months from the date of manufacture

6.4 Special precautions for storage

Store at or below 25°C, protect from heat, light and moisture

6.5 Nature and contents of container

APO-PERINDOPRIL Tablets are packed in blisters of 30 tablets and 90 tablets.

Not all pack sizes and strengths may be available.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine



APO-PERINDOPRIL

SPONSOR

Apotex NZ Ltd
Private Bag 102-995
North Shore Mail Centre
Auckland
Telephone: (09) 444 2073
Fax: (09) 444 2951

8. DATE OF FIRST APPROVAL

22 November 2012

9. Date of Preparation

21 January 2021

Summary Table of Changes

| Section changed | Summary of new information |
|------------------------|--|
| 4.5 | Interactions mostly related to Cilazapril – information regarding Vildagliptin, Sirolimus and Everolimus added |