AUSTRALIAN PRODUCT INFORMATION – REAPTAN® (PERINDOPRIL ARGININE / AMLODIPINE BESILATE) Tablets

1 NAME OF THE MEDICINE

Perindopril arginine / Amlodipine besilate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active components of REAPTAN are perindopril arginine and amlodipine besilate.

Each REAPTAN 5/5 tablet contains 5 mg of perindopril arginine and 5 mg of amlodipine (as besilate[‡])

Each REAPTAN 5/10 tablet contains 5 mg of perindopril arginine and 10 mg of amlodipine (as besilate[‡])

Each REAPTAN 10/5 tablet contains 10 mg of perindopril arginine and 5 mg of amlodipine (as besilate[‡])

Each REAPTAN 10/10 tablet contains 10 mg of perindopril arginine and 10 mg of amlodipine (as besilate[‡])

Excipient with known effect: contains sugars as lactose

For the full list of excipients, *see section 6.1 - List of excipients.*

3 PHARMACEUTICAL FORM

REAPTAN 5/5 is a white, rod-shaped tablet engraved with 5/5 on one face and the Servier company logo on the other face.

REAPTAN 5/10 is a white, square-shaped tablet engraved with 5/10 on one face and the Servier company logo on the other face.

REAPTAN 10/5 is a white, triangular-shaped tablet engraved with 10/5 on one face and the Servier company logo on the other face.

REAPTAN 10/10 is a white, round tablet engraved with 10/10 on one face and the Servier company logo on the other face.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

REAPTAN is indicated as substitution therapy for the treatment of hypertension and/or stable coronary heart disease in patients already controlled with separate doses of perindopril and amlodipine, given concurrently at the same dose level. Treatment should not be initiated with this combination.

4.2 DOSE AND METHOD OF ADMINISTRATION

REAPTAN (perindopril arginine/ amlodipine) is available in strengths of 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg as substitution therapy for patients already controlled with separate doses of

[‡] Amlodipine doses are given as active base

perindopril (5 or 10 mg) and amlodipine (5 or 10 mg), given concurrently at the dose level as indicated in the table below. Treatment should not be initiated with this combination.

Table 1. Dose conversion from perindopril and amlodipine to REAPTAN.

perindopril		amlodipine	REAPTAN
arginine	erbumine		
5 mg	4 mg	5 mg	REAPTAN 5/5
5 mg	4 mg	10 mg	REAPTAN 5/10
10 mg	8 mg	5 mg	REAPTAN 10/5
10 mg	8 mg	10 mg	REAPTAN 10/10

Food intake may reduce hepatic biotransformation of perindopril to perindoprilat. Recommended treatment is one tablet per day as a single dose, preferably to be taken in the morning and before a meal.

As perindopril and amlodipine may be used for different clinical indications, dose adjustments should be based on clinical judgment and the individual patient profile.

Adjustments can be made by decreasing or increasing the dose of either perindopril and/or amlodipine using separate perindopril and/or amlodipine products within the recommended dose range until clinical stability is re-established. Consult the Product Information of the individual perindopril and/or amlodipine products being used when adjusting the dose.

In the event that down-titration is required, adjustments using amlodipine 2.5 mg or a dose of perindopril equivalent to perindopril arginine 2.5 mg, as separate products should be considered until clinical stability is re-established.

Patients with impaired renal function and elderly patients

Elimination of perindoprilat is decreased in the elderly and in patients with renal failure. Therefore, the usual medical follow-up will include frequent monitoring of creatinine and potassium.

Where down-titration is required *to achieve clinical stability in patients with a CrCl < 60mL/min*, adjustments using amlodipine 2.5 mg or a dose of perindopril equivalent to perindopril arginine 2.5 mg, as separate products should be considered until clinical stability is re-established. Please consult the product information of the individual perindopril or amlodipine products.

Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment.

Amlodipine is not dialysable.

In elderly patients, adjustments using amlodipine and perindopril as separate products should be considered. Small, fragile or elderly individuals should be started on amlodipine 2.5 mg once daily and care should be taken when increasing the dosage of amlodipine. The initial dose of perindopril in the elderly should always be a dose equivalent to perindopril arginine 2.5 mg daily and patients should be monitored closely during the initial stages of treatment.

Patients with impaired hepatic function

Dosage recommendations have not been established in patients with mild to moderate hepatic impairment therefore REAPTAN should be administered with caution and treatment should start at the lower end of the dosing range (*see section 4.4 - Special warnings and precautions for use* and *section 5.2 - Pharmacokinetic properties*). Dose adjustments can be made by decreasing or increasing the dose of either perindopril and/or amlodipine using separate perindopril and/or amlodipine products within the recommended dose range until an optimal starting and maintenance dose is found. Patients with hepatic impairment should be started on amlodipine 2.5 mg once daily.

4.3 CONTRAINDICATIONS

REAPTAN is contraindicated:

- In patients with a history of previous hypersensitivity to either of the active ingredients; perindopril or amlodipine, ACE inhibitors, dihydropyridines or excipient ingredients present in REAPTAN
- During pregnancy and for lactating women.

All contraindications related to the individual components, as listed below, should also apply to the fixed combination of REAPTAN.

Related to Perindopril component

- In patients with bilateral or unilateral renal artery stenosis (*see section 4.4 - Special warnings and precautions for use*)
- In patients with a history of hereditary and/or idiopathic angioedema or angioedema associated with previous ACE inhibitor treatment (*see section 4.4 - Special warnings and precautions for use*)
- In patients receiving extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitrile membranes such as "AN69") and low density lipoprotein apheresis with dextran sulfate due to increased risk of severe anaphylactoid reactions following treatment with ACE inhibitors. This combination should therefore be avoided, either by use of alternative antihypertensive medicines or alternative membranes (e.g. cuprophane or polysulfone (PSF)) (*see section 4.4 - Special warnings and precautions for use* and *section 4.5 - Interactions with other medicines and other forms of interactions*)
- In combination with aliskiren-containing products in patients with diabetes or renal impairment (GFR < 60 mL/min/1.73 m²) (*see section 4.4 - Special warnings and precautions for use* and *section 4.5 - Interactions with other medicines and other forms of interactions*)
- Combined use with sacubitril/valsartan fixed dose combinations- REAPTAN must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (*see section 4.4 - Special warnings and precautions for use* and *section 4.5 - Interactions with other medicines and other forms of interactions*).

Related to Amlodipine component

- Severe hypotension.
- Shock, including cardiogenic shock.
- Obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis).
- Unstable angina pectoris (excluding Prinzmetal's angina).
- Heart failure after acute myocardial infarction.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Related to REAPTAN

Lactose intolerance

As REAPTAN contains lactose monohydrate, patients with rare hereditary problems of galactose intolerance, glucose galactose malabsorption, or total lactase deficiency should not take REAPTAN.

Related to Perindopril component

Hyperkalaemia

Since ACE inhibitors reduce angiotensin II formation resulting in decreased production of aldosterone, increases in serum potassium have been observed in some patients treated with ACE inhibitors including perindopril. The effect is usually not significant in patients with normal renal function. Serum electrolytes (including sodium potassium and urea) should be measured from time to time when ACE inhibitors are given especially in combination with diuretics.

Hyperkalaemia can cause serious, sometimes fatal, arrhythmias. Risk factors for the development of hyperkalaemia include those with renal impairment, worsening of renal function, age (> 70 years), diabetes, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and combined use with potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other medicines associated with increases in serum potassium (e.g. heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole, other ACE-inhibitors, angiotensin receptor blocker, acetylsalicylic acid ≥ 3 g/day, COX-2 inhibitors and other non-selective NSAIDs, immunosuppressant medicines such as ciclosporin or tacromilus). 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. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored. Combined use of the above-mentioned medicines should be used with caution in combination with ACE inhibitors. Frequent monitoring of serum potassium is needed (*see section 4.5 - Interactions with other medicines and other forms of interactions*). In some patients hyponatraemia may co-exist with hyperkalaemia.

Patients with diabetes

Glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor in patients with diabetes treated with oral medicines or insulin (*see section 4.5 - Interactions with other medicines and other forms of interactions*).

Lithium

The combination of lithium and perindopril is not recommended (*see section 4.5 - Interactions with other medicines and other forms of interactions*).

Potassium sparing medicines, potassium supplements or potassium-containing salt substitutes

The combination of perindopril and potassium sparing medicines, potassium supplements or potassium-containing salt substitutes is not recommended (*see section 4.5 - Interactions with other medicines and other forms of interactions*).

Dantrolene

The combination of dantrolene and perindopril is not recommended (*see section 4.5 - Interactions with other medicines and other forms of interactions*).

Angioedema

ACE inhibitors should not be used in patients with a history of angioedema related to any other medicine as these patients may be at increased risk of angioedema while treated with an ACE inhibitor (*see section 4.3 – Contraindications*).

Life-threatening angioedema 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 angioedema is non-pitting oedema of the skin mucous membrane and subcutaneous tissue.

Angioedema of the face, extremities, lips, tongue, mucous membranes, glottis and/or larynx has been reported in patients with ACE inhibitors and has been reported uncommonly with perindopril (*see section 4.8 - Adverse effects (Undesirable effects)*). This may occur at any time during treatment. In such cases treatment 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 in those with heart failure or hypertension.

Where there is involvement of the tongue, glottis or larynx likely to cause airway obstruction, appropriate treatment (e.g. adrenaline (epinephrine) and oxygen) should be given promptly. Treatment of progressive angioedema should be aggressive and failing a rapid response to medical treatment, 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 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 during 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.

The combined use of REAPTAN with sacubitril/valsartan fixed dose combinations is contraindicated due to the increased risk of angioedema (*see section 4.3 – Contraindications*). Sacubitril/valsartan fixed dose combinations must not be initiated until 36 hours after taking the last dose of REAPTAN. If treatment with sacubitril/valsartan fixed dose combinations is stopped, REAPTAN must not be initiated until 36 hours after the last dose of sacubitril/valsartan fixed dose combination (*see section 4.3 – Contraindications* and *section 4.5 - Interactions with other medicines and other forms of interactions*).

The combined use of REAPTAN with NEP inhibitors, mammalian target of rapamycin (mTOR) inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin, alogliptin) may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (*see section 4.5- Interactions with other medicines and other forms of interactions*). Caution should be used when commencing treatment with these above-mentioned medicines in a patient already taking an ACE inhibitor.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis and haemodialysis

Rarely, patients treated with ACE inhibitors during apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor treatment prior to each apheresis.

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes, who are treated with an ACE inhibitor. Extracorporeal treatments leading to contact of blood with negatively charged surfaces (e.g. polyacrylonitril membranes such as “AN69”) are contraindicated. If such treatment is required, consideration should be given to using a different type of dialysis membrane (e.g. cuprophane or polysulfone (PSF)) or a different class of antihypertensive medicines (*see section 4.3 – Contraindications* and *section 4.5 - Interactions with other medicines and other forms of interactions*).

Anaphylactic reactions during desensitisation

Patients treated with ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced life-threatening 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. Symptomatic hypotension is rarely seen in uncomplicated hypertension but is a potential consequence of perindopril use in patients with salt/volume depletion, for example, in patients vigorously treated with diuretics, in patients on dialysis, with impaired renal function, following severe diarrhoea or vomiting, in patients on dietary

restrictions or in those with severe renin-dependent hypertension (*see section 4.4 - Special warnings and precautions for use* and *section 4.8 - Adverse effects (Undesirable effects)*).

Administration of a dose of perindopril equivalent to perindopril arginine 2.5 mg to patients with mild-moderate heart failure was not associated with any significant reduction in blood pressure. In patients with symptomatic heart failure, with or without associated renal impairment, symptomatic hypotension has been observed. This is more likely to occur in those patients with severe heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. This may be associated with 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, treatment 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 dose is increased, or diuretic treatment 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 the diuretic is increased.

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with perindopril. This is anticipated and is usually not a reason to discontinue treatment. If symptomatic hypotension occurs, a reduction of dose or discontinuation of perindopril may be necessary.

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.

Renovascular hypertension

If renovascular hypertension is also present, treatment should be started under close medical supervision with low doses and careful dose titration. There is an increased risk of severe hypotension and renal impairment. Since treatment with diuretics may be a contributing factor to the above, they should be discontinued and renal function should be monitored during the first weeks of perindopril treatment. Loss of renal function may occur with only minor changes in serum creatinine even in patients with unilateral renal artery stenosis.

Kidney transplantation

There is no experience regarding the administration of REAPTAN in patients with a recent kidney transplantation.

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 treated with ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (*see section 4.8 - Adverse effects (Undesirable effects)*).

Ethnicity

ACE inhibitors cause a higher rate of angioedema in patients of indigenous African origin than in patients of other racial origin. As with other ACE inhibitors, perindopril may be less effective in lowering blood pressure in people of indigenous African origin than in people of other racial origin, possibly because of a higher prevalence of low-renin states in this population. It is unknown if the same observations have been made in patients of indigenous Australian origin.

Patients with Diabetes

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with any ACE inhibitor.

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 treatment with the incidence of cough varying between 2-15 % depending upon the ACE inhibitor, dose 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 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 medicines may be required in severe cases.

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 potential to delay the progression of nephropathy in patients with diabetes or hypertension.

Neutropaenia/Agranulocytosis/Thrombocytopaenia/Anaemia

Neutropaenia, agranulocytosis, thrombocytopaenia and anaemia have been reported in patients treated with an ACE inhibitor. In patients with normal renal function and no other complicating factors, neutropaenia occurs rarely. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant treatment, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing renal impairment. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic treatment. 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 (e.g. sore throat, fever).

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.) have been reported following administration of perindopril and may therefore occur. A causal relationship is difficult to assess. Patients who develop a cutaneous reaction with one ACE inhibitor might not when switched to another medicine 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. Dysgeusia usually occurs in the first weeks of treatment and may disappear in most cases within one to three months.

Medicines causing renin release

The effects of perindopril may be enhanced when administered with antihypertensive medicines which cause renin release.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

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 RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (*see section 4.3 – Contraindications* and *section 4.5 - Interactions with other medicines and other forms of interactions*). If dual blockade treatment is considered absolutely necessary, this should be limited to individually defined cases with frequent close monitoring of renal function, electrolytes and blood pressure.

The combination of perindopril with aliskiren is contraindicated in patients with diabetes or renal impairment (GFR < 60 mL/min/1.73m²) (*see section 4.3 – Contraindications* and *section 4.5 - Interactions with other medicines and other forms of interactions*).

ACE inhibitors and angiotensin II receptor blockers should not be used in combination in patients with diabetic nephropathy.

Surgery and anaesthesia

Perindopril may block angiotensin II formation secondary to compensatory renin release in patients undergoing major surgery or during anaesthesia with medicines that produce hypotension and cause further reduction in blood pressure. Treatment should be discontinued one day prior to the surgery. Perioperative hypotension can be corrected with volume expansion.

Aortic or mitral valve Stenosis / hypertrophic cardiomyopathy

There has been some concern on theoretical grounds that patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or with hypertrophic cardiomyopathy

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.

Stable coronary artery disease

If an episode of unstable angina pectoris, regardless of severity, occurs during the first month of perindopril treatment, a careful appraisal of the benefits/risks of continuing treatment should be performed.

Primary aldosteronism

Patients with primary hyperaldosteronism will generally not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin system. Therefore, treatment with REAPTAN is not recommended.

Related to Amlodipine component

Increased angina

Rarely patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina on starting calcium channel blocker treatment or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Outflow obstruction (Aortic Stenosis)

Amlodipine should be used with caution in the presence of a fixed left ventricular outflow obstruction (aortic stenosis).

Use in patients with congestive heart failure

Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure. In a long-term, placebo-controlled study of amlodipine in patients with NYHA III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo (*see section 5.1 - Pharmacodynamic properties*).

Peripheral oedema

Mild to moderate peripheral oedema was the most common adverse event in clinical trials. The incidence of peripheral oedema was dose-dependent and ranged in frequency from 3.0 to 10.8 % in 5 to 10 mg dose range. Care should be taken to differentiate this peripheral oedema from the effects of increasing left ventricular dysfunction.

Use in hepatic impairment

Related to Perindopril component

Biotransformation of perindopril to perindoprilat mainly occurs in the liver. Studies in patients with hepatic impairment 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 Tmax) were also unchanged. The increase in bioavailability could be due to inhibition of the formation of perindopril metabolites other than perindoprilat (*see section 5.2 - Pharmacokinetic properties*). 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 in the kinetics of perindoprilat do not justify the need to change the usual dose in most patients with hepatic failure.

Related to Amlodipine component

There are no adequate studies in patients with liver dysfunction and dosage recommendations have not been established. In a small number of patients with mild to moderate hepatic impairment given single doses of 5 mg, amlodipine half-life has been prolonged. Worsening of liver function test values may occur. Amlodipine should, therefore, be administered with caution in these patients and careful monitoring should be performed. A lower starting dose of amlodipine may be required (*see section 4.2 - Dose and method of administration*).

Use in renal impairment

Related to Perindopril component

As a consequence of inhibiting the 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 patients with symptomatic heart failure, hypotension following the initiation of treatment with ACE inhibitors may lead to further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

ACE inhibitors should be avoided in patients with known or suspected renal artery stenosis (*see section 4.3 – Contraindications*).

In clinical studies in patients with hypertension with unilateral or bilateral renal artery stenosis, increases in blood urea, nitrogen and serum creatinine were observed in 20 % of patients. Acute renal impairment may also occur. These increases are usually reversible upon discontinuation.

Renal function may also be reduced 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. ACE inhibitors can lead to the thrombotic occlusion of a stenosed renal artery.

Some patients with hypertension and with no apparent pre-existing renovascular disease have developed increases in blood urea, nitrogen and serum creatinine, which are usually minor and transient, particularly when perindopril has been combined with a diuretic. However, increases in blood urea, nitrogen and serum creatinine are more likely to occur in patients with pre-existing renal impairment or in those on diuretics. Dose reduction of the ACE inhibitor and/or discontinuation of the diuretic may be required.

Renal function should always be assessed (*see section 4.2 - Dose and method of administration*). In the case of renal impairment, the initial perindopril dose should be adjusted according to the patient's creatinine clearance (*see section 4.2 - Dose and method of administration*). Routine monitoring of potassium and

creatinine are part of normal medical practice for these patients (*see section 4.8 - Adverse effects (Undesirable effects)*). If a deterioration in renal function has occurred after treatment with one ACE inhibitor, then it is likely to be precipitated by another and in these patients use of another class of antihypertensive medicines 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, combined use with potassium-sparing diuretics or high doses of other diuretics, limited cardiac reserve, or treatment with a non-steroidal anti-inflammatory medicine (NSAID).

Anaemia has been observed in patients who have had a kidney transplant or have been undergoing dialysis. The reduction in haemoglobin levels is more apparent as initial values were high. This effect does not seem to be dose-dependent but may be linked to the mechanism of action of angiotensin converting enzyme inhibitors. This reduction in haemoglobin is slight, occurs within one to six months, and then remains stable. It is reversible when treatment is stopped. Treatment can be continued with regular haematological testing.

Perindopril is dialysable with a clearance of 70 mL/min.

Related to Amlodipine component

Amlodipine is extensively metabolised to inactive metabolites with 10 % excreted as unchanged drug in the urine. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine may be used in such patients at normal doses. Amlodipine is not dialysable.

Use in the elderly

Related to Perindopril component

Renal impairment is commonly observed in elderly people. Care should be taken when prescribing perindopril-containing medicines to elderly patients with hypertension. The initial daily dose in the elderly should always be at a low dose or with one component only, and patients should be monitored closely during the initial stages of treatment (*see section 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 impairment.

Related to Amlodipine component

In elderly patients (> 65 years) clearance of amlodipine is decreased with a resulting increase in AUC. In clinical trials the incidence of adverse reactions in elderly patients was approximately 6 % higher than that of younger population (< 65 years). Adverse reactions include oedema, muscle cramps and dizziness. Amlodipine should be used cautiously in elderly patients.

Paediatric use

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

Effects on laboratory tests

Reported with Perindopril component

- Reduced sodium levels.
- Slight increase in urea and in plasma creatinine levels, reversible when treatment is stopped- this increase is more frequent in cases of renal artery stenosis, arterial hypertension treated with diuretics, renal impairment.
- Increased levels of potassium, usually transitory.
- Elevation of liver enzymes and serum bilirubin have been reported rarely.

Reported with Amlodipine component

Amlodipine treatment has not been associated with clinically significant changes in routine laboratory tests. Hepatic enzymes elevations: ALT, AST (mostly consistent with cholestasis) have been reported very rarely.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Shared by Perindopril and amlodipine

Combined use which requires SPECIAL CARE:

Baclofen

Baclofen may increase the antihypertensive effect of REAPTAN. Monitor blood pressure and renal function and adjust the dose of REAPTAN if necessary.

Combined use to be taken into CONSIDERATION:

Antihypertensive medicines (such as beta-blockers) and vasodilators

Combined use of these medicines may increase the hypotensive effects of perindopril and amlodipine. Combined use with nitroglycerine and other nitrates or other vasodilators, may further reduce blood pressure and therefore should be considered with caution.

Corticosteroids, tetracosactide

Reduction in antihypertensive effect (salt and water retention due to corticosteroids).

Alpha-blockers (prazosin, alfuzosin, doxazosin, tamsulosin, terazosin)

Increased antihypertensive effect and increased risk of orthostatic hypotension.

Amifostine

May potentiate the antihypertensive effect of amlodipine.

Tricyclic antidepressants/antipsychotics/anaesthetics

Combined use of certain anaesthetics, tricyclic antidepressants and antipsychotics with ACE inhibitors or amlodipine may result in further reduction of blood pressure (*see section 4.4 - Special warnings and precautions for use*).

Related to Perindopril component

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (*see section 4.3 – Contraindications* and *section 4.4 - Special warnings and precautions for use*).

Combined use which is CONTRAINDICATED (*see section 4.3 – Contraindications and section 4.4 - Special warnings and precautions for use*):

Aliskiren

Patients with diabetes or renal impairment (GFR < 60 mL/min/1.73 m²), may be at risk of hypotension, syncope, stroke, hyperkalaemia and changes in renal function (including acute renal failure).

Extracorporeal treatments

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes such "AN69") and low density lipoprotein apheresis with dextran sulfate are contraindicated due to increased risk of severe anaphylactoid reactions (*see section 4.3 – Contraindications* and *section 4.4 - Special warnings and precautions for use*). If such treatment is required, consideration should be given to using a different type of dialysis membrane (e.g. cuprophane or polysulfone (PSF)) or a different class of antihypertensive agent.

Sacubitril-valsartan

The combined use of REAPTAN with sacubitril/valsartan fixed dose combinations is contraindicated as the concomitant inhibition of neprilysin and ACE may increase the risk of angioedema. Sacubitril/valsartan fixed dose combinations must not be started until 36 hours after taking the last dose of REAPTAN. REAPTAN must not be started until 36 hours after the last dose of sacubitril/valsartan fixed dose combination (*see section 4.3 – Contraindications* and *section 4.4 - Special warnings and precautions for use*)

Combined use which is NOT RECOMMENDED (*see section 4.4 - Special warnings and precautions for use*):

Aliskiren

Patients other than those with diabetes or renal impairment may be at risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity, and an increase in mortality (*see section 4.3 – Contraindications*).

ACE inhibitor and angiotensin-receptor blocker

It is reported in the literature that in patients with established atherosclerosis, heart failure, or diabetes with end organ damage, combined use with an ACE inhibitor and an angiotensin-receptor blocker is associated with a higher frequency of hypotension, syncope, hyperkalaemia, and worsening renal function (including acute renal failure) as compared to use of a single RAAS medicine. Dual blockade (e.g. by

combining an ACE inhibitor with an angiotensin receptor blocker) should be limited to individually defined cases with close monitoring of renal function, serum potassium, and blood pressure.

Co-trimoxazole (trimethoprim/sulfamethoxazole)

Patients on combined treatment with co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk of hyperkalaemia (*see section 4.4 - Special warnings and precautions for use*).

Potassium-sparing diuretics (e.g. triamterene, amiloride, potassium salts)

The combined use of REAPTAN and potassium sparing diuretics may result in potentially lethal hyperkalaemia especially in patients with renal impairment (additive hyperkalaemic effects). The combination of perindopril with these drugs is not recommended (*see section 4.4 Special warnings and precautions for use*). If the combination is required, it should be used with caution and with frequent monitoring of serum potassium. For use of spironolactone and eplerenone in heart failure, see *Combined use which requires SPECIAL CARE*.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during combined administration of lithium with ACE inhibitors. Combined 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 (*see section 4.4 - Special warnings and precautions for use*).

Combined use which requires SPECIAL CARE:

Non-steroidal anti-inflammatory medicines (NSAIDs) including acetylsalicylic acid ≥ 3 g/day

Medicines with prostaglandin synthetase inhibitor properties (e.g. indometacin) or non-steroidal anti-inflammatory drug (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, non-selective NSAIDs or COX-2 inhibitor), may diminish the antihypertensive efficacy of co-administered ACE inhibitors. However, clinical studies have not demonstrated any interaction between perindopril or indometacin or other NSAIDS. Treatment with an NSAID may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring serum potassium and renal function after initiation of concomitant therapy, and periodically thereafter.

Antidiabetic agents (insulin, hypoglycaemic sulfonamides)

Reported with captopril and enalapril. The use of ACE inhibitors may increase the hypoglycaemic effect in diabetics receiving treatment with insulin or with hypoglycaemic sulfonylureas. The onset of hypoglycaemic episodes is very rare (improvement in glucose tolerance with a resulting reduction in insulin requirements) and appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Non-potassium-sparing Diuretics

Patients treated with diuretics, especially those who are volume and/or salt depleted, may sometimes experience an excessive reduction of blood pressure after initiation of treatment with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic or by increasing volume or salt intake prior to commencing treatment with a low and progressive dose of the ACE inhibitor. If it is not possible to discontinue the diuretic, the starting dose of the ACE inhibitor should be reduced. The

patient should be closely observed for several hours following the initial dose of the ACE inhibitor and until the blood pressure has stabilised.

In arterial hypertension, when prior diuretic treatment has caused salt/volume depletion, the diuretic must be discontinued before commencing treatment with the ACE inhibitor. The ACE inhibitor must be commenced at a low dose and progressively increased prior to a non-potassium-sparing diuretic being commenced.

In diuretic-treated congestive heart failure, the ACE inhibitor should be initiated at a very low dose, possibly after reducing the dose of the non-potassium-sparing diuretic.

In all cases, renal function (creatinine levels) must be monitored during the first few weeks of ACE inhibitor treatment.

Potassium-sparing diuretics (eplerenone, spironolactone)

As the combination of perindopril and potassium sparing medicines (e.g. eplerenone and spironolactone), potassium supplements or potassium-containing salt substitutes is not recommended:

- Ensure patients do not have hyperkalaemia or renal impairment before commencing treatment with this combination.
- There is a risk of potentially lethal hyperkalaemia with this combination in patients treated for NYHA Class II-IV heart failure with a reduced ejection fraction, who have been previously treated with ACE inhibitors and loop diuretics. This risk is particularly high when recommendations for use of this combination have not been followed.
- Weekly monitoring of serum potassium and creatinine levels is recommended in the first month of the treatment and, monthly thereafter.

Combined use of ACE inhibitors, anti-inflammatory medicines and thiazide diuretics

The combined use of an ACE inhibiting medicine (ACE inhibitor or angiotensin receptor blocker), an anti-inflammatory medicine (NSAID or COX-2 inhibitor) and a thiazide diuretic increases the risk of renal impairment. This includes use in fixed-combination products. The combination of medicines from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment. Combined use of these medicines should be accompanied by increased monitoring of serum creatinine, particularly at initiation.

Ciclosporin

Hyperkalaemia may occur during the combined use of ACE inhibitors with ciclosporin. Frequent monitoring of serum potassium is recommended.

Heparin

Hyperkalaemia may occur during the combined use of ACE inhibitors with heparin. Frequent monitoring of serum potassium is recommended.

Mammalian target of rapamycin (mTOR) inhibitor (e.g. temsirolimus, sirolimus, everolimus)

Patients on combined treatment with an ACE inhibitor and an mTOR inhibitor may be at increased risk of angioedema (*see section 4.4 - Special warnings and precautions for use*).

Gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin, alogliptin)

When an ACE inhibitor and a gliptin are used in combination, there is an increased risk of angioedema due to the decreased activity of the dipeptidyl peptidase IV (DPP-IV).

Combined use which requires SOME CARE:

Antihypertensive medicines and vasodilators

Combined use of these medicines may increase the hypotensive effects of perindopril. Combined use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Medicines Affecting Sympathetic Activity

As the sympathetic nervous system plays an important part in physiological blood pressure regulation, caution should be exercised with combined administration of a medicine with sympathetic activity and REAPTAN. Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients treated with injectable gold (sodium aurothiomalate) and ACE inhibitors including perindopril.

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates

Perindopril may be combined with thrombolytics, acetylsalicylic acid (when used as a thrombolytic), beta-blockers and/or nitrates.

Tetracycline and other medicines 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 medicines that interact with magnesium.

Related to Amlodipine component

Amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerine, non-steroidal anti-inflammatory medicines, antibiotics and oral hypoglycaemic medicines.

Combined use NOT RECOMMENDED:

Dantrolene (infusion)

In animals, lethal ventricular fibrillations and CV collapse are observed after administration of verapamil, and intravenous dantrolene. By extrapolation, the combination of calcium channel blockers such as amlodipine, and dantrolene should be avoided especially in patient susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Combined use which requires SPECIAL CARE:

CYP3A4 inducers (rifampicin, Hypericum perforatum (St John's Wort), anticonvulsant medicines i.e. carbamazepine, phenobarbitone, phenytoin, primidone)

Co-administration of known inducers of the CYP3A4 may lead to reduced plasma concentration of amlodipine due to an increase of the hepatic metabolism of amlodipine by these inducers. Caution should

be exercised with this combination and blood pressure should be monitored. The dose of amlodipine should be adjusted if necessary during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

CYP3A4 inhibitors (erythromycin in young patients, clarithromycin, verapamil or diltiazem in elderly patients)

Co-administration with strong or moderate CYP3A4 inhibitors (including but not limited to: protease inhibitors like ritonavir, azole antifungals like fluconazole and itraconazole, macrolides like erythromycin or clarithromycin, calcium channel blockers like verapamil or diltiazem) may significantly increase the plasma concentration of amlodipine and consequently its adverse effects. The clinical translation of these PK variations may be more pronounced in the older people. Caution should be exercised when combining amlodipine with strong or moderate CYP3A4 inhibitors and the dose of amlodipine should be adjusted if necessary. Clinical monitoring and dose adjustment may thus be required. There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine. Close observation of patients is recommended when amlodipine is co administered with clarithromycin.

Combined use which requires SOME CARE:

Combined use of amlodipine with other medicines with antihypertensive properties may further reduce blood pressure.

Tacrolimus

There is a risk of increased tacrolimus blood levels when co administered with amlodipine. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Rapamycin (mTOR) Inhibitors

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With combined use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Ciclosporin

No drug interaction studies have been conducted with ciclosporin and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable increases of trough concentrations of ciclosporin were observed. Consideration should be given to monitoring ciclosporin levels in patients who have undergone renal transplantation and are treated with amlodipine, and ciclosporin dose reductions should be made as necessary.

Simvastatin

Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in an increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Beta-blockers used in heart failure (bisoprolol, carvedilol, metoprolol)

Risk of hypotension, heart weakness in patients with cardiac heart failure, be it latent or uncontrolled (addition of negative inotrope effect). Furthermore, the beta-blocker may minimise the sympathetic reflex in the case of excessive heamodynamic repercussion.

Antihypertensive medicines (such as beta-blockers) and vasodilatators

Combined use of these medicines may increase the hypotensive effects of perindopril and amlodipine. Combined use with nitroglycerine and other nitrates or other vasodilatators, may further reduce blood pressure and therefore should be considered with caution.

Corticosteroids, tetracosactide

Reduction in antihypertensive effect (salt and water retention due to corticosteroids).

Alpha-blockers (prazosin, tamsulosin, terazosin, alfuzosin, doxazosin)

Increased antihypertensive effect and increased risk of orthostatic hypotension.

Amifostine

May potentiate the antihypertensive effect of amlodipine.

Other combined use:

Specific studies conducted with other medicines have shown no influence on amlodipine.

Cimetidine

Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Sildenafil

A single 100 mg dose of sildenafil in 16 patients with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each medicine independently exerted its own blood pressure lowering effect.

Aluminium/magnesium (antacid)

Co-administration of an aluminium/magnesium antacid with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Grapefruit juice

Grapefruit juice is known to inhibit the cytochrome P450 system, thereby affecting the pharmacokinetics of medicines such as calcium channel blockers. In a study of 20 healthy volunteers, co-administration of 240 mL of grapefruit juice with a single oral dose of 10 mg amlodipine had no significant effect on the pharmacokinetics of amlodipine. Specific studies conducted with other medicines have shown that amlodipine has no influence on the pharmacokinetics parameters of those medicines.

Atorvastatin

Co-administration of multiple doses of 10 mg amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady-state pharmacokinetics parameters of atorvastatin.

Digoxin

Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Warfarin

In healthy male volunteers, the co-administration of amlodipine did not significantly alter the effect of warfarin on prothrombin response time. Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

Alcohol

Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No animal studies with REAPTAN have been performed.

Related to Perindopril component

The effects of perindopril arginine on fertility have not been investigated. Studies in rats showed no impairment of male or female fertility at oral perindopril erbumine doses up to 10 mg/kg/day.

Related to Amlodipine component

In animal studies, amlodipine did not affect fertility in rats at oral doses up to 18 mg/kg (base).

Use in pregnancy

Australian Pregnancy Categorisation: D.

As this combination contains an ACE-inhibitor, REAPTAN is contraindicated during pregnancy (see section 4.3 – Contraindications).

No animal studies with REAPTAN have been performed.

REAPTAN should not be initiated during pregnancy. Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with REAPTAN should be stopped immediately, and, if appropriate, alternative treatment should be started.

Related to Perindopril component

The use of ACE inhibitors is contra-indicated during pregnancy (*see section 4.3 – Contraindications*).

As with all ACE inhibitors, perindopril should not be taken during pregnancy. Pregnancy should be excluded before starting treatment with perindopril and avoided during the treatment. Unless continued treatment with an ACE inhibitor is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. 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.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded.

A historical cohort study in over 29,000 infants born to mothers without diabetes has shown 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.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of foetal and neonatal toxicity, hypotension, hyperkalaemia, renal failure, skull hypoplasia, oligohydramnios 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. Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. If such complications arise, appropriate medical treatment should be initiated to support blood pressure and renal perfusion.

Related to Amlodipine component

Calcium channel blockers carry the potential to produce foetal hypoxia associated with maternal hypotension. Accordingly they should not be used in pregnant women unless the potential benefit outweighs the risk to the foetus.

The safety of amlodipine in human pregnancy or lactation has not been established. Amlodipine (10 mg/kg as besilate salt, 7 mg/kg base), administered orally to rats at or near parturition induced a prolongation of gestation time, an increase in the number of stillbirths and a decreased postnatal survival.

Use in Lactation

No animal studies with REAPTAN have been performed.

Related to Perindopril component

Alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or pre-term infant.

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.

Related to Amlodipine component

Amlodipine is excreted in human milk. The effect of amlodipine on infants is unknown. Breast-feeding should be discontinued during treatment with amlodipine.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of REAPTAN on the ability to drive and use machines have been performed. The antihypertensive effect in individual cases may be symptomatic. Treatment with any blood pressure lowering medicine 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. Amlodipine can have minor or moderate influence on the ability to drive and use machinery. If patients suffer from dizziness, headache, fatigue, weariness or nausea, the ability to react may be impaired. Caution is recommended particularly at initiation of treatment with REAPTAN.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

Summary of safety profile

The most commonly reported adverse reactions with perindopril and amlodipine given separately are: oedema, somnolence, dizziness, headache (especially at the beginning of the treatment), dysgeusia, paraesthesia, visual impairment (including diplopia), tinnitus, vertigo, palpitations, flushing, hypotension (and effects related to hypotension), dyspnoea, cough, abdominal pain, nausea, vomiting, dyspepsia, change of bowel habit, diarrhoea, constipation, pruritus, rash, exanthema, joint swelling (ankle swelling), muscle spasms, fatigue, asthenia.

Tabulated list of adverse reactions

Three bioequivalence studies using doses equivalent to REAPTAN 5/10, REAPTAN 10/10 and REAPTAN 10/5, and one pharmacokinetic interaction study between perindopril arginine 10 mg and amlodipine 10 mg revealed no serious adverse effects. All the reported adverse effects were mild or moderate in intensity.

The following adverse effects have been observed during clinical trials and/or post-marketing use with an amlodipine/perindopril treatment regimen; with perindopril monotherapy, and with amlodipine monotherapy and ranked under the following frequency: Very common (> 10 %); common (> 1 %, < 10 %); uncommon (> 0.1 %, < 1 %); rare (> 0.01 %, < 0.1 %), very rare (> 0.001 %, < 0.01 %), not known (cannot be estimated from the available data).

Table 2. Reported with amlodipine/perindopril treatment regimen (*see section 5.1 - Pharmacodynamic properties*):

MedDRASystem organ class Adverse Effects	Frequency		
	Perindopril	Amlodipine	REAPTAN
Infections and infestations			
Conjunctivitis	-	Uncommon	-
Rhinitis	Very rare	Uncommon	-

MedDRASystem organ class Adverse Effects	Frequency Perindopril	Amlodipine	REAPTAN
Blood and lymphatic system disorders			
Eosinophilia	Uncommon[#]	-	-
Leukopenia (*see section 4.4 - Special warnings and precautions for use*)	Very rare	Uncommon	-
Agranulocytosis (*see section 4.4 - Special warnings and precautions for use*)	Very rare	-	-
Pancytopenia (*see section 4.4 - Special warnings and precautions for use*)	Very rare	-	-
Neutropenia (*see section 4.4 - Special warnings and precautions for use*)	Very rare	Very rare	-
Haemolytic anaemia in patients with a congenital deficiency of G-6PDH (*see section 4.4 - Special warnings and precautions for use*)	Very rare	-	-
Thrombocytopenia (*see section 4.4 - Special warnings and precautions for use*)	Very rare	Uncommon	-
Immune system disorders			
Hypersensitivity	Uncommon	Uncommon	-
MedDRASystem organ class **Adverse Effects**	**Frequency** **Perindopril**	**Amlodipine**	**REAPTAN**
Endocrine disorders			
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Rare	-	-
Metabolism and nutrition disorders			
Hypoglycaemia (*see section 4.4 - Special warnings and precautions for use* and *section 4.5 - Interactions with other medicines and other forms of interactions*).	Uncommon[#]	-	-
Hyperkalaemia, reversible on discontinuation (*see section 4.4 - Special warnings and precautions for use*)	Uncommon[#]	-	-
Hyponatraemia (*see section 4.4 - Special warnings and precautions for use*)	Uncommon[#]	-	-
Hyperglycaemia	-	Uncommon	-
Decreased appetite	-	Uncommon	-
Increased appetite	-	Rare	-
Thirst	-	Uncommon	-
Psychiatric disorders			
Sleep disorder	Uncommon		-
Insomnia	-	Uncommon	-
Mood altered	Uncommon	Uncommon	-
Depression	Uncommon[#]	Uncommon	-
Hallucination	Very rare	-	-
Nervousness	-	Uncommon	-
Anxiety	-	Uncommon	-
Depersonalisation	-	Uncommon	-
Apathy	-	Rare	-
Agitation	-	Rare	-
Nervous system disorders			
Amnesia	-	Rare	-

MedDRASystem organ class **Adverse Effects**	**Frequency** **Perindopril**	**Amlodipine**	**REAPTAN**
Ataxia	-	Rare	-
Lethargy	Common	Common	Common
Postural dizziness	-	Uncommon	-
Somnolence (especially at the beginning of treatment)	Uncommon[#]	Common	-
Dizziness (especially at the beginning of treatment)	Common	Common	Very common
Headache (especially at the beginning of treatment)	Common	Common	-
Dysgeusia	Common	Uncommon	-
Tremor	-	Uncommon	-
Hypoaesthesia	-	Uncommon	-
Paresthaesia	Common	Uncommon	
Drowsiness	Common	-	-
Syncope	Uncommon[#]	Uncommon	-
Confusional state	Very rare	Rare	-
Hypertonia	-	Rare	-
Neuropathy peripheral	-	Uncommon	-
Cerebrovascular accident possibly secondary to excessive hypotension in high-risk patients (*see section 4.4 - Special warnings and precautions for use*)	Very rare	-	-
Extrapyramidal disorder (extrapyramidal syndrome)	-	Not known	-
MedDRASystem organ class **Adverse Effects**	**Frequency** **Perindopril**	**Amlodipine**	**REAPTAN**
Nervous system disorders continued			
Migraine	-	Rare	-
Parosmia	-	Rare	-
Eye disorders			
Visual impairment	Common	Common	-
Diplopia	-	Common	
Eye pain	-	Uncommon	-
MedDRASystem organ class **Adverse Effects**	**Frequency** **Perindopril**	**Amlodipine**	**REAPTAN**
Eye disorders continued			
Dry eye	-	Rare	-
Accommodation disorder	-	Rare	-
Ear and labyrinth disorders		Rare	-
Tinnitus	Common	Uncommon	-
Vertigo	Common	Uncommon	Common
Cardiac disorders			
Bradycardia	-	-	Uncommon
Cardiac failure	-	Rare	-
Heart rate irregular		Rare	
Extrasystoles	-	Rare	-
Chest pain	-	-	Common
Vascular disorders			
Flushing	Common	Common	-

MedDRASystem organ class **Adverse Effects**	**Frequency**		
	Perindopril	**Amlodipine**	**REAPTAN**
Hypotension (and effects related to hypotension) (*see section 4.4 - Special warnings and precautions for use*)	Common	Uncommon	-
Vasculitis	Common	Uncommon	-
Peripheral circulatory failure	Common	-	-
Cold and clammy skin	-	Rare	-
Peripheral coldness	Uncommon	Uncommon	Uncommon
Peripheral ischaemia	-	Uncommon	-
Orthostatic hypotension	-	Uncommon	-
Raynaud's phenomenon	Not known	-	-
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Common	Common	Common
Cough (*see section 4.4 - Special warnings and precautions for use*)	Common	Uncommon	Very common
Bronchospasm	Uncommon	-	-
Eosinophilic pneumonia	Very rare	-	-
Epistaxis	Common	Uncommon	-
Discomfort on exertion	Common	-	-
MedDRASystem organ class **Adverse Effects**	**Frequency**		
	Perindopril	**Amlodipine**	**REAPTAN**
Gastrointestinal disorders			
Gingival hyperplasia	-	Uncommon	-
Abdominal pain	Common	Common	-
Nausea	Common	Common	-
Vomiting	Common	Uncommon	-
Dyspepsia	Common	Common	-
Changes of bowel habits	-	Common	-
Dry mouth	Common	Uncommon	-
Diarrhoea	Common	Common	Common
Constipation	Common	Common	-
Pancreatitis	Very rare	Uncommon	-
Gastritis	-	Rare	-
Epigastric pain	Common	-	-
Dysphagia	-	Uncommon	-
Flatulence	-	Uncommon	-
Hepato-biliary disorders			
Hepatitis (*see section 4.4 - Special warnings and precautions for use*)	Very rare	Rare	-
Hepatitis either cytolitic or cholestatic (*see section 4.4 - Special warnings and precautions for use*)	Very rare	-	-
Hepatic enzymes increased (mostly consistent with cholestasis)	-	Very rare	-
Jaundice	-	Rare	-
Skin and subcutaneous tissue disorders			

MedDRASystem organ class **Adverse Effects**	**Frequency**		
	Perindopril	**Amlodipine**	**REAPTAN**
Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (*see section 4.4 - Special warnings and precautions for use*)	Uncommon	Uncommon	-
Quincke's oedema	-	Very rare	-
Erythema multiforme	Very rare	Rare	-
Alopecia	-	Uncommon	-
Purpura	-	Uncommon	-
Skin discolouration	-	Uncommon	-
Hyperhidrosis	Uncommon	Uncommon	-
Pruritus	Common	Uncommon^	-
Rash erythematous	-	Uncommon	-
Urticaria (*see section 4.4 - Special warnings and precautions for use*)	Uncommon	Uncommon	-
Photosensitivity reactions	Uncommon#	Very rare	-
Pemphigoid	Uncommon#	-	-
Psoriasis aggravation	Rare#	-	-
Stevens-Johnson syndrome	-	Very rare	-
Toxic epidermal necrolysis	-	Not known	-
Dermatitis Exfoliative	-	Very rare	-
Dermatitis	-	Rare	-
Eczema	Uncommon#	-	Common
MedDRASystem organ class **Adverse Effects**	**Frequency**		
	Perindopril	**Amlodipine**	**REAPTAN**
Skin and subcutaneous tissue disorders continued			
Rash	Common	Uncommon	-
Rash maculopapular	-	Uncommon	-
Dry skin	-	Rare	
Exanthema	Common	Uncommon	-
Musculoskeletal and connective tissue disorders			
Joint swelling (ankle swelling)	-	Common	Very common
Arthralgia	Uncommon#	Uncommon	-
Myalgia	Uncommon#	Uncommon	-
Muscle spasms	Common	Common^	-
Back pain	-	Uncommon	-
Muscular weakness	-	Rare	-
Osteoarthritis	-	Uncommon	-
Muscle twitching	-	Rare	-
Renal and urinary disorders			
Renal failure	Uncommon	-	-
Renal failure acute kidney injury	Rare#	-	-
Micturition disorder, pollakiuria, nocturia	-	Uncommon	-
Dysuria	-	Rare	-
Anuria/Oliguria	Rare#	-	-
Reproductive system and Breast disorders			
Erectile dysfunction	Uncommon	Uncommon	Common
Gynaecomastia	-	Uncommon	-

MedDRASystem organ class Adverse Effects	Frequency		
	Perindopril	**Amlodipine**	**REAPTAN**
Sexual dysfunction (male^ and female)	-	Uncommon	-
General disorders and administration site conditions			
Oedema	-	Very common	-
Oedema peripheral	Uncommon#	Common	Very common
Fatigue	-	Common	Common
Atypical chest pain	Uncommon#	Uncommon	Common
Asthenia	Common	Common^	-
Pain	-	Uncommon	-
Malaise	Uncommon#	Uncommon	-
Pyrexia	Uncommon#	-	-
Chills	-	Uncommon	-
Investigations			
Weight gain	-	Uncommon	-
Weight decrease		Uncommon	-
Blood urea increased	Uncommon#	-	-
Blood creatinine increased	Uncommon#	-	-
Blood bilirubin increased	Rare	-	-
Hepatic enzyme increased	Rare	-	-
Haemoglobin decreased and haematocrit decreased (*see section 4.4 - Special warnings and precautions for use*)	Very rare	-	-
MedDRASystem organ class **Adverse Effects**	**Frequency**		
	Perindopril	**Amlodipine**	**REAPTAN**
Injury, Poisoning and Procedural Complications			
Fall	Uncommon#	-	-

Frequency calculated from clinical trials for adverse effects detected from spontaneous report

^ These events occurred in less than 1 % of patients in placebo-controlled trials, but the incidence of these adverse effects was between 1 % and 2 % in all multiple dose studies.

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 (5.7 %) patients withdrew because of adverse events, a plausible or probable relationship with perindopril treatment was considered to exist in 19 (3 %) cases.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

There is no information on overdosage with REAPTAN in humans.

Related to perindopril component

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. If available, treatment with Angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis (*see section 4.4 - Special warnings and precautions for use)*. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously. Pacemaker therapy is indicated for treatment resistant bradycardia.

Related to amlodipine component

Available data suggest that overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. Dysrhythmias may occur following overdose with any calcium antagonists. Hypotension and bradycardia are usually seen within one to five hours following overdose. Hypotension can persist for longer than 24 hours despite treatment. Cardiac rhythm disturbances have been noted to persist for up to seven days. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Rarely, non-cardiogenic pulmonary oedema has been reported as a consequence of amlodipine overdose, that may manifest with a delayed onset (24-48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine), should be considered with attention to circulating volume and urine output. Intravenous calcium may help to reverse the effects of calcium entry blockade. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine 10 mg has been shown to significantly decrease amlodipine absorption. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. Ipecac-emesis is not recommended since haemodynamic instability and CNS depression may rapidly develop. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pharmacology of Perindopril

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 visco-elastic

properties of large vessels and in compliance. Studies in animals and humans suggest that specific and competitive suppression of the renin-angiotensin-aldosterone system (RAAS) 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.

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 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 perinodpril 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 equivalent to perindopril arginine 2.5 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, whilst 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 possibility of a late hypotensive response are not available for perindopril.

Pharmacology of Amlodipine

Amlodipine is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterised by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces the total ischaemic burden by the following two actions:

- Amlodipine dilates peripheral arterioles and thus reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
- Amlodipine has been shown to block constriction in main coronary arteries and coronary arterioles, induced by calcium, potassium, adrenaline, serotonin and thromboxane A2 analogue both in normal and in ischaemic regions.

Following administration of therapeutic doses to patients with hypertension, Amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients.

Amlodipine has shown no harmful effect on lipid levels and is suitable for use in patients with asthma, diabetes and gout.

As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normal or well-compensated patients with heart failure with medicines possessing significant negative inotropic effects.

In patients with hypertension and normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

Clinical trials

Clinical trials using REAPTAN consist of three bioequivalence studies and a pharmacokinetic interaction study (*see section 5.2 - Pharmacokinetic properties*).

No other clinical trials have been conducted with REAPTAN, including trials to assess its long-term effects on cardiovascular morbidity or mortality. However the effects of the individual components of REAPTAN have been assessed in clinical trials as detailed below. The combined use of perindopril and amlodipine has been studied in patients with hypertension who have additional cardiovascular risk factors in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA).

Clinical Trials of Perindopril

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 (**EU**ropean trial on **R**eduction **O**f cardiac events with **P**erindopril in stable coronary **A**rtery disease) study was a multicentre, international, randomised, double blind, placebo-controlled clinical trial lasting four years. 12,218 patients aged over 18 were randomised: 6,110 patients to high dose perindopril, equivalent to perindopril arginine 10 mg and 6,108 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 three months before screening, coronary revascularisation at least six 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 treatment, including medication used for the management of hyperlipidaemia, hypertension and diabetes mellitus. Patients randomised to perindopril were initiated on doses of perindopril equivalent to perindopril arginine 2.5 mg or perindopril arginine 5 mg for two weeks, and then titrated up to a dose of perindopril equivalent to perindopril arginine 10 mg during the two following weeks. A dose of perindopril equivalent to perindopril arginine 10 mg was then maintained for the whole duration of the study. If this dose was not well tolerated, it could be reduced to a dose of perindopril equivalent to perindopril arginine 5 mg once daily.

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

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 a dose of perindopril equivalent to perindopril arginine 10 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 three years of continuous treatment on perindopril.

Clinical Trials of Amlodipine

Electrophysiologic Effects

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg of amlodipine and a further 10 mg of amlodipine after a 30-minute interval produced peripheral vasodilation and afterload reduction, but did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and beta-blockers in combination. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either

hypertension or angina, no adverse events on electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine treatment did not alter electrocardiographic intervals or produce higher degrees of AV block.

Effects in Hypertension

In patients with hypertension once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24-hour interval post dose. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration. The blood pressure effect is maintained over the 24-hour dosing interval, with little difference in peak and trough effect. Tolerance has not been demonstrated in patients studied for up to one year. Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure.

Effects in Chronic Stable Angina

In patients with angina, once daily administration of amlodipine increases total exercise time to angina onset and total work time to 1 mm ST segment depression and decreases both angina attack frequency and nitroglycerine tablet consumption. The sustained efficacy of amlodipine in angina patients has been demonstrated over long-term dosing. In patients with angina there were no clinically significant reductions in blood pressure (4/1 mmHg) or changes in heart rate (+0.3 bpm).

Studies In Patients With Congestive Heart Failure

Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1,153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin and diuretics. Follow-up was at least six months, with a mean of about 14 months. There was no effect on the primary endpoint of the study of all-cause mortality and cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalisation for worsened heart failure), or on NYHA classification or symptoms of heart failure.

Amlodipine has been compared to placebo in four eight-to-twelve-week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, efficacy in regard to the primary and secondary endpoints was not demonstrated and there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF (*see section 4.4 - Special warnings and precautions for use)*.

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetics of REAPTAN

Three studies have demonstrated bioequivalence between one tablet of the fixed combination of perindopril / amlodipine and the co-administration of one tablet of perindopril plus one tablet of amlodipine, at dose ranges equivalent to REAPTAN 5/10, REAPTAN 10/5 and REAPTAN 10/10.

The results of these studies were similar across the different doses and demonstrated that the rate and extent of absorption of perindopril and amlodipine in REAPTAN are not significantly different, respectively, from the rate and extent of absorption of perindopril and amlodipine in individual tablet formulations.

A pharmacokinetic interaction study between perindopril arginine 10 mg and amlodipine 10 mg revealed that the extent and rate of bioavailability of perindopril, perindoprilat and amlodipine are similar for

perindopril arginine 10 mg or amlodipine 10 mg administered alone or within a co-administration. No pharmacokinetic interaction exists between these two formulations.

Pharmacokinetics of Perindopril

Absorption

Following oral administration, perindopril is rapidly absorbed with 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 %.

Distribution

Peak plasma concentrations of perindoprilat occur three to four hours after oral administration of perindopril. When perindopril is administered chronically, steady state perindoprilat concentration is reached within four days, and perindoprilat does not accumulate.

Metabolism

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. Food intake may reduce hepatic biotransformation to perindoprilat.

Excretion

Protein binding of perindoprilat is 20 %, principally to angiotensin converting enzyme. 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 elimination of perindoprilat is reduced in elderly patients and in patients with cardiac and renal failure

Pharmacokinetics of Amlodipine

Absorption

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between six to twelve hours post-dose. This may reflect significant initial uptake by the liver, followed by a phase of redistribution. This interval is shorter (two to eight hours) in patients with hepatic impairment. Absolute bioavailability has been estimated to be between 64 and 90 %.

Distribution

In vitro studies have shown that approximately 97.5 % of circulating amlodipine is bound to plasma proteins.

Metabolism

Amlodipine is extensively metabolised by the liver to inactive metabolites with 10 % of the parent compound and 60 % of metabolites excreted in the urine.

Excretion

The bioavailability of amlodipine is not altered by the presence of food. The volume of distribution is approximately 20 L/kg. The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Steady state plasma levels are reached after seven to eight days of consecutive dosing. In elderly patients with hypertension (mean age 69 years) there was a decrease in clearance of amlodipine from plasma as compared to young volunteers (mean age 36 years) with a resulting increase in the area under the curve (AUC) of about 60 %.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies of perindopril in combination with amlodipine have been conducted.

Related to Perindopril component

Results from a broad set of assays for gene mutation and chromosomal damage with perindopril suggest no genotoxic potential at clinical doses.

Perindopril showed no evidence of genotoxicity potential in assays for gene mutation (Ames reverse mutation test, mouse lymphoma thymidine kinase assay), chromosomal damage (mouse micronucleus test, Chinese hamster bone marrow cells in vivo, human lymphocytes in vitro) and other genotoxic effects (gene conversion assay in *Saccharomyces cerevisiae*, unscheduled DNA synthesis in rat hepatic cells).

Related to Amlodipine component

In animal studies, amlodipine had no teratogenic effects in rats (18 mg/kg) or rabbits (10 mg/kg).

Carcinogenicity

No carcinogenicity or genotoxicity studies of perindopril in combination with amlodipine have been conducted.

Related to Perindopril component

No evidence of carcinogenic activity was observed in mice and rats when perindopril erbumine was administered via drinking water at levels up to 7.5 mg/kg/day for two years.

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.

Related to Amlodipine component

The carcinogenic potential of amlodipine has not been fully elucidated. Amlodipine did not induce any tumours when tested in rats at oral doses up to 2.5 mg/kg. This dose gave rise to plasma levels that are similar to those achieved clinically.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Lactose monohydrate
- Microcrystalline cellulose
- Colloidal anhydrous silica
- Magnesium stearate

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

3 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a dry place below 25 ^{o}C. Keep the container tightly closed and protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Thirty (30) tablets supplied in a white HDPE bottle equipped with a white induction-sealed child resistant-closure and desiccant sachets. REAPTAN 5/5 only, is also supplied in a 10-tablet bottle.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

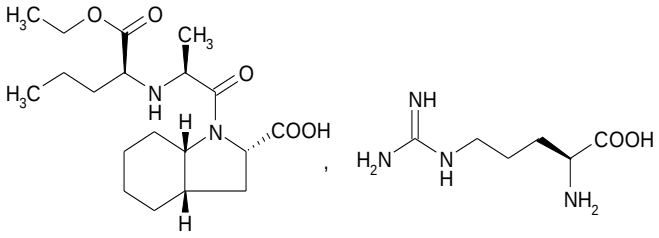
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Perindopril arginine

Perindopril arginine has the chemical name, L-arginine (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)butyl]amino] propanoyl]octahydro-1H-indole-2-carboxylate. It is a dipeptide monoacid monoester with a perhydroindole group and no sulfydryl radical. Perindopril arginine is a white powder, readily soluble in purified water, slightly soluble in 95% ethanol and practically insoluble in chloroform. Perindopril has five asymmetric centres. The drug is synthesised stereoselectively so that it is a single enantiomer (all S stereochemistry).

Chemical structure



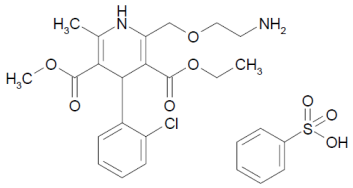
CAS number

612548-45-5

Amlodipine besilate

Amlodipine besilate is a dihydropyridine derivative, and has the following chemical name: 3-Ethyl 5-methyl (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonate. Amlodipine besilate is chiral and present as a racemate. It is a white crystalline powder and is slightly soluble in water and sparingly soluble in ethanol.

Chemical structure



CAS number

111470-99-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription only medicine

8 SPONSOR

Servier Laboratories (Aust.) Pty Ltd
www.servier.com.au
Level 4, Building 9
588A Swan Street
Burnley, 3121, Victoria

9 DATE OF FIRST APPROVAL

4 November 2010

10 DATE OF REVISION

07 September 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.9	**4.9 additional information regarding Non-cardiogenic pulmonary oedema has been reported under overdose relating to amlodipine component**