AUSTRALIAN PRODUCT INFORMATION – COVERAM® PLUS SR (PERINDOPRIL ARGININE / AMLODIPINE / INDAPAMIDE) CAPSULES

1 NAME OF THE MEDICINE

Perindopril arginine / Amlodipine / Indapamide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each COVERAM PLUS 5/5/1.5 SR capsule contains 5 mg of perindopril arginine, 5 mg of amlodipine (as besilate[‡]) and 1.5 mg of indapamide

Each COVERAM PLUS 10/5/1.5 SR capsule contains 10 mg of perindopril arginine, 5 mg of amlodipine (as besilate[‡]) and 1.5 mg of indapamide

Each COVERAM PLUS 10/10/1.5 SR capsule contains 10 mg of perindopril arginine 10 mg of amlodipine (as besilate[‡]) and 1.5 mg of indapamide

Excipient with known effect: Contains lactose

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

3 PHARMACEUTICAL FORM

Modified release capsule.

COVERAM PLUS 5/5/1.5 SR is a light yellow, hard gelatin capsule, imprinted with '1' in black ink on the capsule containing one perindopril arginine immediate release film coated tablet, one indapamide sustained-release film coated tablet, and amlodipine immediate release coated granules.

COVERAM PLUS 10/5/1.5 SR is a yellow, hard gelatin capsule, imprinted with '2' in black ink on the capsule containing two perindopril arginine immediate release film coated tablets, one indapamide sustained-release film coated tablet, and amlodipine immediate release coated granules.

COVERAM PLUS 10/10/1.5 SR is a dark yellow, hard gelatin capsule, imprinted with '3' in black ink on the capsule containing two perindopril arginine immediate release film coated tablets, one indapamide sustained-release film coated tablet, and amlodipine immediate release coated granules.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

COVERAM PLUS SR is indicated as substitution therapy for treatment of hypertension, in patients already controlled with perindopril, amlodipine and indapamide, taken at the same dose level. Treatment should not be initiated with this combination.

[‡] Amlodipine doses are given as active base

4.2 DOSE AND METHOD OF ADMINISTRATION

COVERAM PLUS SR (perindopril arginine / amlodipine / indapamide) is available in strengths 5 mg/ 5 mg/ 1.5 mg, 10 mg/ 5 mg/ 1.5 mg, 10 mg/ 10 mg/ 1.5 mg as substitution therapy for patients already controlled with equivalent separate doses of perindopril, amlodipine and indapamide, given concurrently at the dose level as indicated in the table below. Treatment should not be initiated with this combination. If a change of the posology is required, titration should be done with the individual components.

Table 1. Dose conversion from perindopril, amlodipine and indapamide to COVERAM PLUS SR

perindopril		amlodipine	indapamide	COVERAM PLUS SR
arginine	erbumine			
5 mg	4 mg	5 mg	1.5 mg ⇒	COVERAM PLUS 5/5/1.5 SR
10 mg	8 mg	5 mg	1.5 mg ⇒	COVERAM PLUS 10/5/1.5 SR
10 mg	8 mg	10 mg	1.5 mg ⇒	COVERAM PLUS SR 10/10/1.5

Method of administration

COVERAM PLUS SR is for oral use.

Recommended treatment is one capsule per day as a single dose, preferably to be taken in the morning and before a meal.

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

Special populations

Patients with impaired Renal function

In severe renal impairment (creatinine clearance below 30 mL/min), treatment is contraindicated.

In patients with moderate renal impairment (creatinine clearance 30-60 mL/min), COVERAM PLUS SR at the doses 10 mg/5 mg /1. 5 mg and 10 mg/10 mg/1.5 mg are contraindicated. It is recommended to start treatment with the adequate dosage of the free combination.

Usual medical follow-up will include frequent monitoring of creatinine and potassium.

Concomitant use of perindopril with aliskiren is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2), *(see section 4.3 – Contraindications and section 4.4 – Special warnings and precautions for use)*.

Patients with impaired hepatic function

In severe hepatic impairment, COVERAM PLUS SR is contraindicated.

In patients with mild to moderate hepatic impairment, COVERAM PLUS SR should be administrated with caution, as dosage recommendations for amlodipine in these patients have not been established *(see section 4.3 – Contraindications, section 4.4 – Special warnings and precautions for use and section 5.2 – Pharmacokinetic properties).*

When liver function is impaired, thiazide-related diuretics may cause, particularly in the case of electrolyte imbalance, hepatic encephalopathy which can progress to hepatic coma. Administration of COVERAM PLUS

SR must be stopped immediately if this occurs.

Elderly Patients

Elimination of perindoprilat is decreased in the elderly *(see section 5.2 - Pharmacokinetic properties).*

Elderly patients can be treated with COVERAM PLUS SR according to renal function *(see section 4.3 – Contraindication and section 4.4 - Special warnings and precautions for use).*

In the small, frail and elderly, the starting dose of amlodipine is 2.5 mg and this dose is not available in the triple combination. Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients, particularly at the higher strengths of COVERAM PLUS SR, since available data in this patient population is limited.

Paediatric population

There is no data regarding the safety and efficacy of COVERAM PLUS SR in children and adolescents; therefore it is not recommended for this population.

4.3 CONTRAINDICATIONS

COVERAM PLUS SR is contraindicated in:

- Dialysis patients
- Patients with untreated decompensated heart failure
- Severe renal impairment (creatinine clearance below 30 mL/min)
- Moderate renal impairment (creatinine clearance below 60 mL/min) for COVERAM PLUS SR doses containing 10mg/1.5mg of perindopril/indapamide combination (i.e., COVERAM PLUS SR 10mg/5mg/1.5mg and 10mg/10mg/1.5mg)
- Hypersensitivity to the active substances, to other sulfonamides, to dihydropyridine derivatives, any other angiotensin converting enzyme (ACE) inhibitor or to any of the excipients *(see section 6.1 – list of excipients)*
- History of angioedema (Quincke's oedema) associated with previous ACE inhibitor therapy *(see section 4.4 - Special warnings and precautions for use)*
- Hereditary/ idiopathic angioedema
- Unstable angina pectoris (excluding Prinzmetal's angina)
- Pregnant and lactating women *(see section 4.4 - Special warnings and precautions for use and section 4.6 – Fertility, pregnancy & lactation)*
- Hepatic encephalopathy
- Hepatic coma
- Severe hepatic impairment
- Hypokalaemia
- Severe hypotension
- Shock, including cardiogenic shock
- Obstruction of the outflow-tract of the left ventricle (e.g. high-grade aortic stenosis)
- Haemodynamically unstable heart failure after acute myocardial infarction
- Concomitant use of COVERAM PLUS SR with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60mL/min/1.73m^2) *(see section 4.5 - Interactions with other medicines and other forms of interactions and section 5.1 – Pharmacodynamic properties)*
- Concomitant use with sacubitril/valsartan therapy. COVERAM PLUS SR 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 – Interaction with other medicines and other forms of interaction).*
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces *(see section 4.5 - Interaction with other medicines and other forms of interaction).*

- Significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney *(see section 4.4 - Special warnings and precautions for use).*

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

All warnings related to each component, as listed below, should apply also to the fixed combination of COVERAM PLUS SR.

Related to COVERAM PLUS SR

Potassium levels

The combination of indapamide with perindopril and amlodipine does not prevent the onset of hypokalaemia particularly in diabetic patients or in patients with renal failure. As with any antihypertensive agent in combination with a diuretic, regular monitoring of plasma potassium levels should be carried out.

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril, ACE inhibitors can cause hyperkalaemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. Risk factors for the development of hyperkalemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole) and especially aldosterone antagonists or angiotensin-receptor blockers. 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. Hyperkalemia 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. If concomitant use of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

Potassium depletion with hypokalaemia is a major risk with thiazide diuretics and thiazide-related diuretics. Hypokalaemia may cause muscle disorders. Cases of Rhabdomyolysis have been reported, mainly in the context of severe hypokalaemia. The risk of onset of lowered potassium levels (< 3.4 mmol/l) should be prevented in some high risk populations such as elderly and/or malnourished subjects, whether or not they are taking multiple medications, cirrhotic patients with oedema and ascites, coronary patients and patients with heart failure.

In such cases hypokalaemia increases the cardiac toxicity of cardiac glycosides and the risk of rhythm disorders. Hypokalaemia will be more common when combined with a steroid or adrenocorticotropic (ACTH) treatment and when electrolyte intake is inadequate.

Subjects presenting with a long QT interval are also at risk, whether the origin is congenital or iatrogenic. Hypokalaemia, as with bradycardia, acts as a factor which favours the onset of severe rhythm disorders, in particular torsades de pointes, which may be fatal.
In all cases more frequent testing of potassium levels is necessary. The first measurement of plasma potassium levels should be carried out during the first week following the start of treatment.

If low potassium levels are detected, correction is required. Hypokalaemia found in association with low serum magnesium concentration can be refractory to treatment unless serum magnesium is corrected.

Renovascular hypertension

The treatment for renovascular hypertension is revascularisation. Since treatment with diuretics may be a contributing factor, extreme caution should be exercised with strict medical supervision if a patient is to continue with COVERAM PLUS SR. There is an increased risk of severe hypotension and acute renal failure.

Atherosclerosis

The risk of hypotension exists in all patients, but particular care should be taken in patients with ischaemic heart disease or cerebral circulatory insufficiency, with treatment being started at a low dose.

Excipients

COVERAM PLUS SR contains less than 1 mmol sodium (23 mg) per capsule.

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

Related to Perindopril component

Lithium

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

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.

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) *(see section 4.8 – Adverse effects (undesirable effects)).*

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)*). Angioedema can occur immediately after starting ACE inhibitor treatment, however severe angioedema may also develop after months or years of long-term treatment with an ACE inhibitor. 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.

Healthcare professionals should review the response to treatment noting standard therapies for histamine-mediated angioedema may be ineffective for bradykinin-mediated angioedema.

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 perindopril 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 perindopril therapy. If treatment with sacubitril/valsartan fixed dose combinations is stopped, perindopril 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 ACE inhibitors 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 desensitisation

There have been isolated reports of patients experiencing sustained, life-threatening anaphylactoid reactions while receiving ACE inhibitors during desensitisation treatment with hymenoptera (bees, wasps) venom. ACE inhibitors should be used with caution in allergic patients treated with desensitisation and avoided in those undergoing venom immunotherapy. However, these reactions could be prevented by temporary withdrawal of ACE inhibitor for at least 24 hours before treatment in patients who require both ACE inhibitors and desensitisation.

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*).

Primary aldosteronism

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

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.

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.

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.

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.

Patients with Diabetes

In patients with insulin dependent diabetes mellitus (spontaneous tendency to increased levels of potassium), treatment should be started under medical supervision with a reduced initial dose.
The glycaemia levels should be closely monitored in diabetic patients previously treated with oral antidiabetic drugs or insulin, namely during the first month of treatment with an ACE inhibitor.
Monitoring of blood glucose is important in diabetic patients, particularly when potassium levels are low.

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.

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)*).

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*).

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.

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.

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.

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).

Cardiac failure/severe cardiac insufficiency

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.

Related to Indapamide component

Photosensitivity

Cases of photosensitivity reactions have been reported with thiazides and thiazide-related diuretics. It is recommended to stop treatment if a photosensitivity reaction occurs during treatment. If re-administration of the diuretic is deemed necessary, it is recommended that areas exposed to the sun or to artificial UVA are protected

Plasma sodium

This must be measured before starting treatment, then subsequently at regular intervals. The decrease in plasma sodium may initially be asymptomatic. Regular monitoring is therefore essential and should be more frequent in the elderly and in patients with cirrhosis (see *section 4.8 - Adverse effects (Undesirable effects*)). Treatment with any diuretic may cause hyponatraemia, sometimes with very serious consequences. Hyponatraemia with hypovolaemia may be responsible for dehydration and orthostatic hypotension. Concomitant loss of chloride ions may lead to secondary compensatory metabolic alkalosis.

Uric acid

Hyperuricaemia may occur during treatment with indapamide, and gout has been reported rarely. Tendency to gout attacks may be increased in patients with hyperuricaemia.

Lithium

Diuretics should not be given with lithium because they reduce its renal clearance and add a high risk of lithium toxicity (see *section 4.5 - Interactions with other medicines and other forms of interactions)*.

Water and electrolyte balance

Patients receiving indapamide should be monitored for signs and symptoms of fluid or electrolyte imbalance; namely hyponatraemia, hypochloraemia and hypokalaemia. Blood urea, nitrogen and uric acid should also be assessed during treatment. The signs of electrolyte imbalance are dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscle fatigue, hypotension, oliguria, gastrointestinal disturbances such as nausea and vomiting, tachycardia and ECG changes.

Plasma magnesium

Thiazides and related diuretics have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia (see *section 4.5 - Interactions with other medicines and other forms of interactions and 4.8 - Adverse effects (Undesirable effects*)).

Plasma calcium

Diuretic treatment should be withdrawn before the investigation of parathyroid function. Thiazide and related diuretics may decrease urinary calcium excretion and cause a slight and transitory rise in calcium. Frank hypercalcaemia may be due to previously unrecognised hyperparathyroidism.

Orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates, narcotics or concurrent therapy with other antihypertensives.

When indapamide SR is combined with other non-diuretic antihypertensive medicines, the effects on blood pressure are additive.

Sulfonamide derivatives have been reported to exacerbate or activate systemic lupus erythematosus. Serious allergic skin reactions (such as Stevens-Johnson syndrome) have also occasionally been reported with sulfonamides. This should be considered when using indapamide.

Although a indapamide SR dose of one tablet/ day can be used safely in patients with hypertension and renal impairment, treatment should be discontinued if there is an increase in azotaemia and oliguria.

A study in patients with impaired renal function demonstrated that patients with severe renal impairment (creatinine clearance 11-35 mL/min) had impaired clearance of indapamide and elevated plasma levels of the drug.

Blood glucose

Monitoring of blood glucose is important in patients with diabetes, in particular in the presence of hypokalaemia.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma

Sulfonamide, or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Use in hepatic impairment

Related to COVERAM PLUS SR

The effect of the combination COVERAM PLUS SR has not been tested in hepatic dysfunction. Taking into account the effect of each individual component of this combination, COVERAM PLUS SR is contraindicated in patients with severe hepatic impairment, and caution should be exercised in patients with mild to moderate 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*).

Related to Indapamide component

When liver function is impaired, thiazide-related diuretics may cause, particularly in case of electrolyte imbalance, hepatic encephalopathy which can progress to hepatic coma. Administration of the diuretic must be stopped immediately if this occurs.

Use in renal impairment

Related to COVERAM PLUS SR

In cases of severe renal impairment (creatinine clearance < 30 mL/min), treatment is contraindicated. For patients with a moderate renal impairment (creatinine clearance between 30 mL/min and 60 mL/min), treatment is contraindicated with COVERAM PLUS SR doses containing 10mg/1.5mg of perindopril/indapamide combination (i.e., COVERAM PLUS SR 10mg/ 5mg/ 1.5 mg and 10mg/10mg/ 1.5 mg).

In certain hypertensive patients without pre-existing apparent renal lesions and for whom renal blood tests show functional renal insufficiency, treatment should be stopped and possibly restarted either at a low dose or with one constituent only. In these patients usual medical follow-up will include frequent monitoring of potassium and creatinine, after two weeks of treatment and then every two months during therapeutic stability period. Renal failure has been reported mainly in patients with severe heart failure or underlying renal failure including renal artery stenosis.

The drug is usually not recommended in case of bilateral renal artery stenosis or a single functioning kidney.

Risk of arterial hypotension and/or renal insufficiency (in cases of cardiac insufficiency, water and electrolyte depletion, etc.): Marked stimulation of the renin-angiotensin-aldosterone system has been observed with perindopril particularly during marked water and electrolyte depletions (strict sodium restricted diet or prolonged diuretic treatment), in patients whose blood pressure was initially low, in cases of renal artery stenosis, congestive heart failure or cirrhosis with oedema and ascites.

Thiazide diuretics and thiazide-related diuretics are only fully effective when renal function is normal or only slightly impaired (creatinine levels lower than approximately 25 mg/l, i.e. 220 µmol/l for an adult).

Hypovolaemia, secondary to the loss of water and sodium caused by the diuretic at the start of treatment, causes a reduction in glomerular filtration. It may result in an increase in blood urea and creatinine levels. This transitory functional renal insufficiency is of no adverse consequence in patients with normal renal function but may however worsen a pre-existing renal impairment.

The effect of the combination COVERAM PLUS SR has not been tested in renal dysfunction. In renal impairment, COVERAM PLUS SR doses should respect those of the individual components taken separately.

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.

Related to Indapamide component

In the elderly, the plasma creatinine must be adjusted in relation to age, weight and gender. Elderly patients can be treated with indapamide when renal function is normal or only minimally impaired.

Ethnicity

Related to Perindopril component

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.

Athletes

Related to COVERAM PLUS SR

Athletes should note that this product contains an active substance which may cause a positive reaction in doping tests.

Paediatric use

Use of COVERAM PLUS SR 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.

Reported with Indapamide component

Hyperuricaemia (0.4 %). Hyperglycaemia (0.4 %) (see *section 4.8 - Adverse effects (Undesirable effects*)).

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Shared by Perindopril, Amlodipine and Indapamide

Drugs inducing Hyperkalaemia

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with COVERAM PLUS SR. Some drugs or therapeutic classes may increase the occurrence of hyperkalaemia: aliskiren, potassium salts, potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), ACE inhibitors, angiotensin-II receptor antagonists, NSAIDs, heparins, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole), as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. The combination of these drugs increases the risk of hyperkalaemia. Therefore, the combination of COVERAM PLUS SR with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Combined use which is CONTRAINDICATED:

Aliskiren

In diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increases.

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) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions (see section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Concomitant use to be taken into consideration:

Imipramine-like antidepressants (tricyclics), neuroleptics

Increased antihypertensive effect and increased risk of orthostatic hypotension (additive effect).

Other antihypertensive agents

Use of other antihypertensive medicinal products could result in additional blood pressure lowering effect.

Corticosteroids, tetracosactide

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

Shared by Perindopril and amlodipine

Combined use which requires SPECIAL CARE:

Baclofen

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

Concomitant 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*).

Shared by Perindopril and Indapamide

Combined use which is NOT RECOMMENDED:

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 combined with indapamide 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:

Baclofen

Increased antihypertensive effect. It is recommended that hydration and renal function be monitored at the start of treatment. Monitoring of blood pressure, renal function and adequate hydration is recommended with dose adaptation of the antihypertensive to occur if necessary.

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

Medicines with prostaglandin synthetase inhibitor properties (e.g. indometacin) or an NSAID (i.e. acetylsalicylic acid at anti-inflammatory dose regimens, non-selective NSAIDs or COX-2 inhibitors), may diminish the antihypertensive efficacy of concomitantly administered ACE inhibitors. However, clinical studies have not demonstrated any interaction between this fixed dose combination tablet containing 5 mg of perindopril arginine and 1.25 mg of indapamide hemihydrate 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. Due to the risk of acute renal failure in patients with dehydration as a result of decreased glomerular filtration, it is recommended that hydration, and serum potassium and renal function be monitored at the start of treatment, and periodically thereafter.

Combined use which requires SOME CARE:

Tricyclic antidepressants / Antipsychotics / Anaesthetics

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

Other antihypertensive agents

Combined use of other antihypertensive agents may increase hypotensive effects.

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:

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 perindopril 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 perindopril. Perindopril 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

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 perindopril 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*).

Racecadotril

Concomitant use of ACE inhibitors with racecadotril may lead to an increased risk for 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).

Concomitant use to be taken into consideration:

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 perindopril. 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.

Anaesthetic drugs

ACE inhibitors may enhance the hypotensive effects of certain anaesthetic drugs

Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide

Concomitant administration with ACE inhibitors may lead to an increased risk for leucopaenia.

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.

Diuretics (thiazide or loop diuretics)

Prior treatment with high dose diuretics may result in volume depletion and in a risk of hypotension when initiating therapy with perindopril.

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 which is 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.

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.

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.

Concomitant use to be taken into consideration:

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

Atorvastatin, Digoxin or Warfarin

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

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.

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.

Alcohol

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

Related to Indapamide component

No interactions have been reported between indapamide and anticoagulants, or between indapamide and uricosuric medicines. It is recommended that indapamide not be used in combination with a diuretic since the combination may cause hypokalaemia and hyperuricaemia.

Combined use which is NOT RECOMMENDED:

Lithium

The combined use of indapamide and lithium may result in increased plasma lithium levels and symptoms of overdose (due to decreased urinary lithium excretion). If diuretics are necessary, careful monitoring of plasma lithium and dose adjustment are required.

Combined use which REQUIRES SPECIAL CARE:

Torsades de pointes-inducing drugs

The combined use of indapamide and *Torsades de pointes*-inducing drugs, including the following, is not recommended due to the increased risk of ventricular arrhythmias, particularly *Torsades de pointes* (hypokalaemia is a risk factor). Medicines which induce *Torsade de pointes* include (but are not limited to):

- class Ia antiarrhythmic agents (e.g. disopyramide) and class Ic antiarrhythmic agents (e.g. flecainide)
- class III antiarrhythmic agents (e.g. amiodarone, sotalol)
- some antipsychotics : phenothiazines (e.g. chlorpromazine, trifluoperazine), benzamides (e.g. amisulpride, sulpiride), butyrophenones (e.g. droperidol, haloperidol) and other antipsychotics
- psychoanaleptic (e.g. donepezil)
- some antidepressants (e.g. citalopram, escitalopram)
- antimicrobial agents: fluoroquinolones (e.g. moxifloxacin, ciprofloxacin), macrolides (e.g. erythromycin IV, clarithromycin), azole antifungals (e.g. fluconazole)
- antiparasitics (e.g. chloroquine, pentamidine)
- antihistamines
- antiemetics (e.g. ondansetron, domperidone)
- antineoplastic and immunomodulating agents (e.g. vandetanib, oxaliplatin, anagrelide)
- anaesthetics (e.g. propofol, sevoflurane).
- others: diphemanil, methadone, papaverine, cilostazol

This list is indicative and not exhaustive.

Monitor (using plasma electrolytes and ECG) for hypokalaemia and correct, if required, before using indapamide and a *Torsades de pointes*-inducing drug in combination.

NSAIDs (systemic route) including COX-2 selective inhibitors, high dose acetylsalicylic acid (≥ 3 g/day)

Due to the risk of acute renal failure in patients with dehydration as a result of decreased glomerular filtration, it is recommended that hydration and renal function be monitored at the start of treatment. Combined use with NSAIDs may also result in a reduction in the antihypertensive effect of indapamide.

Other compounds causing hypokalaemia: amphotericin B (amphotericin) (IV), gluco- and mineralo-corticoids (systemic route), stimulant laxatives

Due to the increased risk of hypokalaemia (additive effect):

- monitoring, and correction if required, of plasma potassium (especially during treatment with digoxin) is recommended
- the use of non-stimulant laxatives is recommended.

Baclofen

Due to the increased risk of antihypertensive effects, it is recommended that hydration and renal function be monitored at the start of treatment.

Digitalis preparations

Monitoring of plasma potassium, plasma magnesium and ECG is recommended during treatment with digitalis, and if necessary, adjust the treatment as hypokalaemia and/or hypomagnesaemia predispose to the toxic effects of digitalis.

Allopurinol

Combined use with indapamide may increase the incidence of hypersensitivity reactions to allopurinol.

Concomitant use to be taken into consideration:

Potassium-sparing diuretics (amiloride, spironolactone, triamterene)

Due to the increased risk of either hyperkalaemia or hypokalaemia (particularly in patients with renal failure or diabetes), care should be taken when co-administering potassium-sparing diuretics. Plasma potassium and ECG should be monitored and, if necessary, treatment reviewed.

Metformin

Do not co-administer with metformin when plasma creatinine exceeds 15 mg/L (135 µmol/L) in men and 12 mg/L (110 µmol/L) in women due to the increased risk of metformin induced lactic acidosis as a result of the possibility of functional renal failure associated with diuretics and more particularly with loop diuretics.

Iodinated contrast media

Adequate hydration before administration of the iodinated compound is recommended due to an increased risk of acute renal failure resulting from dehydration, particularly when large doses of iodinated contrast media are used.

Imipramine-like antidepressants, neuroleptics

Caution is recommended with these combinations due to an increased antihypertensive effect and increased risk of orthostatic hypotension.

Calcium (salts)

Caution is recommended with this combination due to the risk of hypercalcaemia resulting from decreased urinary elimination of calcium.

Cyclosporin, tacrolimus

Caution is recommended with this combination due to the risk of increased plasma creatinine without any change in circulating cyclosporin levels, even in the absence of water/sodium depletion.

Corticosteroids, tetracosactide (tetracosactrin) (systemic route)

Caution is recommended with this combination due to the risk of decreased antihypertensive effect (water/sodium retention due to corticosteroids).

4.6 FERTILITY, PREGNANCY AND LACTATION

Given the effects of the individual components in this combination product on pregnancy and lactation, COVERAM PLUS SR is contraindicated during pregnancy and lactation.

Effects on fertility

No animal studies with COVERAM PLUS SR have been performed.

Related to Perindopril and Indapamide component

Reproductive toxicity studies showed no effect on fertility in female and male rats. No effects on human fertility are anticipated. 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 doses up to 10 mg/kg/day. A reproductive toxicity study in rats showed no impairment of male or female fertility at oral indapamide doses up to 25 mg/kg/day, however, the number of implantation sites was reduced at the highest dose.

Related to Amlodipine component

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. 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, COVERAM PLUS SR is contraindicated during pregnancy *(see section 4.3 – Contraindications).*

COVERAM PLUS SR 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 COVERAM PLUS SR 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 fetus in pregnant animals. There are no adequate and well-controlled studies of ACE inhibitors in pregnant women, but fetotoxicity 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 fetus.

The ACE inhibitor class has also been associated with fetal 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. Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended

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 fetus.

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.

Related to Indapamide component

Indapamide should be avoided in pregnant women and should not be used to treat oedema in pregnancy. There are limited data with the use of indapamide in pregnant women. Prolonged exposure to thiazides during the third trimester of pregnancy can reduce maternal plasma volume as well as uteroplacental blood flow, which may cause foetal-placental ischaemia and growth retardation.
No embryofetal toxicity or teratogenic potential were seen in rats (up to 150 mg/kg/day) and in rabbits (up to 180 mg/kg/day).Thiazides, related diuretics and loop diuretics enter the foetal circulation and may cause electrolyte disturbances. Loop diuretics like furosemide (frusemide) and bumetanide are probably also associated with this risk. During the latter part of pregnancy, medicines of this type should be used with caution and at the lowest effective dose. Neonatal thrombocytopaenia has been reported with thiazides and related diuretics.

No studies on the effect on embryofetal development have been conducted with the perindopril/amlodipine/indapamide combination.

Use in Lactation

COVERAM PLUS SR is contraindicated in lactating women. A risk to the newborns/infants cannot be excluded.

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 proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown.

Related to Indapamide component

Indapamide should not be used during breast-feeding. Indapamide is excreted in human breast milk and the possible effect on the newborn is unknown and cannot be excluded. Indapamide is closely related to thiazide diuretics which have associated with a decrease in, or even suppression of, lactation. Hypersensitivity to sulfonamide-derived medicines and hypokalaemia might occur.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of COVERAM PLUS SR 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 machines. If patients suffer from dizziness, headache, fatigue, weariness or nausea, the ability to react may be impaired.
As a result, the ability to drive or operate machinery may be impaired. Caution is recommended especially at the start of treatment.

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 www.tga.gov.au/reporting-problems.

Summary of safety profile

The most commonly reported adverse reactions with perindopril, amlodipine and indapamide given separately are: hypokalaemia, dizziness, headache, paraesthesia, somnolence, dysgeusia, visual impairment, diplopia, tinnitus, vertigo, palpitations, flushing, hypotension (and effects related to hypotension), cough,

dyspnoea, gastro-intestinal disorders (abdominal pain, constipation, diarrhoea, dyspepsia, nausea, vomiting, change of bowel habit), pruritus, rash, rash maculo-papular, muscle spasms, ankle swelling, asthenia, oedema and fatigue.

Tabulated list of adverse reactions

The following adverse effects have been observed with perindopril, amlodipine and indapamide during treatment 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: Tabulated list of adverse reactions

MedDRA System Organ Class	Undesirable Effects	Frequency		
		Perindopril	**Amlodipine**	**Indapamide**
Infections and infestations	Rhinitis	Very rare	Uncommon	-
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Rare	-	-
Blood and lymphatic system disorders	Eosinophilia	Uncommon*	-	-
	Agranulocytosis *(see section 4.4 - Special warnings and precautions for use)*	Very rare	-	Very rare
	Aplastic anaemia	-	-	Very rare
	Pancytopenia	Very rare	-	-
	Leukopenia *(see section 4.4 - Special warnings and precautions for use)*	Very rare	Uncommon	Very rare
	Neutropenia *(see section 4.4 - Special warnings and precautions for use)*	Very rare	Very rare	-
	Haemolytic anaemia	Very rare	-	Very rare
	Thrombocytopenia *(see section 4.4 - Special warnings and precautions for use)*	Very rare	Uncommon	Very rare
Immune system disorders	Hypersensitivity	Uncommon	Uncommon	-
Metabolism and nutrition disorders	Hypokalaemia *(see section 4.4 - Special warnings and precautions for use)*	-	-	Common
	Hypoglycaemia *(see section 4.4 - Special warnings and precautions for use and section 4.5 – Interaction with other medicines and other forms of interaction).*	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*		Uncommon
	Hypochloraemia	-	-	Rare
	Hypomagnesaemia	-	-	Rare
	Hyperglycaemia	-	Uncommon	-
	Hypercalcaemia	-	-	Very rare
Psychiatric disorders	Insomnia	-	Uncommon	Uncommon
	Mood altered (including anxiety)	Uncommon	Uncommon	-
	Depression	Uncommon*	Uncommon	-
	Sleep disorder	Uncommon	-	-

MedDRA System Organ Class	Undesirable Effects	Frequency		
		Perindopril	**Amlodipine**	**Indapamide**
	Confusional state	Very rare	Rare	-
Nervous system disorders	Dizziness	Common	Common	Common
	Headache	Common	Common	Common
	Paraesthesia	Common	Uncommon	Rare
	Somnolence	Uncommon*	Common	-
	Hypoaesthesia	-	Uncommon	-
	Dysgeusia	Common	Uncommon	-
	Tremor	-	Uncommon	-
	Syncope	Uncommon*	Uncommon	Not known
	Hypertonia	-	Rare	-
	Neuropathy peripheral	-	Uncommon	-
	Extrapyramidal disorder (extrapyramidal syndrome)	-	Not known	-
	Stroke possibly secondary to excessive hypotension in high-risk patients *(see section 4.4 - Special warnings and precautions for use)*	Very rare	-	-
	Possibility of onset of hepatic encephalopathy in case of hepatic insufficiency *(see section 4.3 – Contraindications and section 4.4 - Special warnings and precautions for use)*	-	-	Not known
Eye disorders	Acute angle-closure glaucoma	-	-	Not known
	Choroidal effusion	-	-	Not known
	Conjunctivitis		Uncommon	-
	Diplopia	-	Common	-
	Eye pain	-	Uncommon	-
	Myopia	-	-	Not known
	Vision blurred	-	-	Not known
	Visual impairment	Common	Common	Uncommon
Ear and labyrinth disorders	Tinnitus	Common	Uncommon	-
	Vertigo	Common	Uncommon	Rare
Cardiac disorders	Palpitations			Very rare
	Tachycardia	Uncommon*	-	-
	Angina pectoris *(see section 4.4 - Special warnings and precautions for use)*	Very rare	-	-
	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	Very rare	Uncommon	Very rare
	Myocardial infarction, possibly secondary to excessive hypotension in high risk patients *(see section 4.4 - Special warnings and precautions for use)*	Very rare	Very rare	-
	Torsade de pointes (potentially fatal) *(see section 4.4 - Special warnings and precautions for use and section 4.5 - Interactions with other medicines and other forms of interactions).*	-	-	Not known
	Cardiac failure	-	Rare	-
	Hear rate irregular	-	Rare	-

MedDRA System Organ Class	Undesirable Effects	Frequency		
		Perindopril	**Amlodipine**	**Indapamide**
	Extrasystoles	-	Rare	-
Vascular disorders	Flushing	Common	Common	-
	Hypotension (and effects related to hypotension) *(see section 4.4 - Special warnings and precautions for use)*	Common	Uncommon	Very rare
	Vasculitis	Common	Uncommon	-
	Raynaud's phenomenon	Not known	-	-
	Peripheral circulatory failure	Common	-	-
	Peripheral ischaemia	-	Uncommon	-
	Cold and clammy skin	-	Rare	-
	Peripheral coldness	Uncommon	Uncommon	Uncommon
	Epistaxis	Common	Uncommon	-
Respiratory, thoracic and mediastinal disorders	Cough *(see section 4.4 - Special warnings and precautions for use)*	Common	Uncommon	-
	Dyspnoea	Common	Common	-
	Bronchospasm	Uncommon	-	-
	Eosinophilic pneumonia	Very rare	-	-
Gastro-intestinal disorders	Abdominal pain	Common	Common	-
	Constipation	Common	Common	Rare
	Diarrhoea	Common	Common	-
	Dyspepsia	Common	Common	-
	Nausea	Common	Common	Rare
	Vomiting	Common	Uncommon	Uncommon
	Dry mouth	Common	Uncommon	Rare
	Change of bowel habit	-	Common	-
	Gingival hyperplasia	-	Uncommon	-
	Pancreatitis	Very rare	Uncommon	Very rare
	Gastritis	-	Rare	-
	Epigastric pain	Common	-	-
	Flatulence	-	Uncommon	-
	Dysphagia	-	Uncommon	-
Hepatobiliary disorders	Hepatitis *(see section 4.4 - Special warnings and precautions for use)*	Very rare	Rare	Not known
	Jaundice	-	Rare	-
	Hepatic function abnormal	-	-	Very rare
Skin and subcutaneous tissue disorders	Pruritus	Common	Uncommon	-
	Rash	Common	Uncommon	-
	Rash maculo-papular		-	Common
	Urticaria *(see section 4.4 - Special warnings and precautions for use)*	Uncommon	Uncommon	Very rare
	Angioedema *(see section 4.4 - Special warnings and precautions for use)*	Uncommon	Uncommon	Very rare
	Alopecia	-	Uncommon	-
	Purpura	-	Uncommon	Uncommon
	Skin discolouration	-	Uncommon	-
	Hyperhidrosis	Uncommon	Uncommon	-
	Exanthema	Common	Uncommon	-
	Photosensitivity reaction (see section 4.4 - Special warnings and precautions for use)	Uncommon*	Very rare	Not known

MedDRA System Organ Class	Undesirable Effects	Frequency		
		Perindopril	**Amlodipine**	**Indapamide**
	Psoriasis aggravation	Rare*	-	-
	Pemphigoid	Uncommon*	-	-
	Erythema multiforme	Very rare	Rare	-
	Stevens-Johnson Syndrome	-	Very rare	Very rare
	Exfoliative dermatitis	-	Very rare	-
	Toxic epidermal necrolysis	-	Not known	Very rare
	Quincke's oedema	-	Very rare	-
	Dry skin	-	Rare	-
Musculoskeletal and connective tissue disorders	Muscle spasms	Common	Common	Not known
	Ankle swelling	-	Common	-
	Arthralgia	Uncommon*	Uncommon	-
	Muscular weakness	-	-	Not known
	Myalgia	Uncommon*	Uncommon	Not known
	Rhabdomyolysis	-	-	Not known
	Back pain	-	Uncommon	-
	Possible worsening of pre-existing systemic lupus erythematosus	-	-	Not known
Renal and urinary disorders	Micturition disorder, pollakiuria, nocturia	-	Uncommon	-
	Anuria/oliguria	Rare*	-	-
	Acute renal failure	Rare	-	-
	Renal failure	Uncommon	-	Very rare
Reproductive system and breast disorders	Erectile dysfunction	Uncommon	Uncommon	Uncommon
	Gynaecomastia	-	Uncommon	-
General disorders and administration site conditions	Asthenia	Common	Common	-
	Fatigue	-	Common	Common
	Oedema	-	Very common	-
	Chest pain	Uncommon*	Uncommon	Very rare
	Pain	-	Uncommon	-
	Malaise	Uncommon*	Uncommon	-
	Oedema peripheral	Uncommon*	Common	-
	Pyrexia	Uncommon*	-	-
	Discomfort on exertion	Common	-	-
Investigations	Weight gain	-	Uncommon	-
	Weight decrease	-	Uncommon	-
	Blood urea increased	Uncommon*	-	-
	Blood creatinine increased	Uncommon*	-	-
	Blood bilirubin increased	Rare	-	-
	Hepatic enzyme increased	Rare	-	Not known
	Haemoglobin decreased and haematocrit decreased *(see section 4.4 - Special warnings and precautions for use)*	Very rare	-	-
	Electrocardiogram QT prolonged *(see section 4.4 - Special warnings and precautions for use and section 4.5 - Interactions with other medicines and*	-	-	Not known

MedDRA System Organ Class	Undesirable Effects	Frequency		
		Perindopril	Amlodipine	Indapamide
	other forms of interactions).			
	Blood glucose increased	-	-	Not known
	Blood uric acid increased	-	-	Not known
Injury, poisoning and procedural complications	Fall	Uncommon *	-	-

** Frequency calculated from clinical trials for adverse events detected from spontaneous report*

Description of selected adverse reactions:

During phase II and phase III studies comparing indapamide 1.5mg and 2.5mg, plasma potassium analysis showed a dose-dependent effect of indapamide:

Indapamide 1.5mg: Plasma potassium <3.4 mmol/l was seen in 10 % of patients and < 3.2 mmol/l in 4 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.23 mmol/l.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

There is no information on overdosage with COVERAM PLUS SR in humans.

For perindopril

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.

For amlodipine

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.

For indapamide

Signs of acute poisoning at higher doses take the form of water/electrolyte disturbances (hyponatraemia, hypokalaemia) and may include the possibility of nausea, vomiting, hypotension, cramps, vertigo, drowsiness, confusion, polyuria or oliguria possibly to the point of anuria (by hypovolaemia). In patients with cirrhosis, an overdose might precipitate hepatic coma.

Treatment

There is no specific antidote. Treatment is symptomatic and supportive. Discontinue drug; induce emesis or perform gastric lavage and/or administration of activated charcoal (activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected), correct dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

COVERAM PLUS SR is a combination of three antihypertensive components with complementary mechanisms to control blood pressure in patient with hypertension. Perindopril arginine salt is an ACE inhibitor, amlodipine is a calcium ion flux inhibitor of the dihydropyridine group and indapamide is a chlorosulphamoyl diuretic.

The pharmacological properties of COVERAM PLUS SR are derived from those of each of the components taken separately. In addition, the combination of perindopril/ indapamide produces an additive synergy of the antihypertensive effects of the two components.

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.

Pharmacology of Indapamide

Indapamide is an oral antihypertensive medicine. The mechanism whereby indapamide exerts its antihypertensive action has not been completely elucidated; both vascular and renal actions have been implicated.

The possible beneficial pharmacological effects of indapamide in the treatment of hypertension include a reduction in cardiac hypertrophy and a reduction in the thickening of arterial walls, a prevention of the accumulation of the embryonic isoform of fibronectin in coronary vessels, free radical scavenging leading to stimulation of vasodilator eicosanoid formation, and interaction with renal carbonic anhydrase.

The renal effects of indapamide are minimal and the antihypertensive effect of indapamide has been attributed to a reduction in vascular reactivity to pressor amines. The finding that indapamide retains its antihypertensive activity in patients who are functionally anephric lends support to this hypothesis.

The renal site of action of indapamide is the proximal segment of the distal tubule. Indapamide appears to have natriuretic properties (sodium and chloride being excreted in equivalent amounts) with less effect on kaliuresis or uric acid excretion. Only at doses greater than 1.5 mg indapamide hemihydrate sustained

release tablet / day is an appreciable increase in urinary volume observed in man. No significant changes in plasma sodium levels have been observed in clinical studies. Significant hypokalaemia (plasma potassium < 3.2 mmol/L) has been reported in 4 % of patients.
Indapamide does not adversely affect serum triglycerides, LDL cholesterol, the LDL-HDL cholesterol ratio, or glucose tolerance.

Clinical Trials

There have been no long-term, clinical outcome studies using COVERAM PLUS SR

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.

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)*.

Indapamide

No data available

Perindopril/amlodipine/indapamide

Three biopharmaceutical studies were performed to demonstrate bioequivalence (BE) of COVERAM PLUS SR against the free combination of perindopril arginine, amlodipine and indapamide SR administered

concomitantly.

Study PKH 5183-005 (NP42725) was a single dose crossover study with the primary objective of demonstrating bioequivalence of one capsule of the fixed dose combination product COVERAM PLUS SR 10/10/1.5 containing perindopril arginine 10 mg/amlodipine 10 mg/indapamide 1.5 mg versus the free combination of one tablet of perindopril arginine 10 mg film-coated tablet; and one amlodipine 10 mg film-coated tablet; and one indapamide 1.5 mg sustained release film coated tablet administered concomitantly in fasting conditions. The study was performed in 80 healthy, male and female volunteers from 18 and 65 years of age.

The secondary objectives included evaluation of the pharmacokinetics of the test drug and reference drugs with respect to the analytes perindopril, perindoprilat, amlodipine and indapamide.

The PK parameters for perindopril (AUC_t and C_{max}), amlodipine (AUC_{72} and C_{max}) and indapamide (AUC_t, AUC_{inf} and C_{max}) were analysed. The test treatments were considered bioequivalent if the 90% CI of geometric least squares mean ratio (GLSMR) for the three aforementioned parameters were within the acceptance range [80 – 125%] for perindopril, amlodipine, and indapamide.

Bioequivalence between COVERAM PLUS SR capsule and the free combination of perindopril arginine, and amlodipine and indapamide SR administered concomitantly, was demonstrated in healthy volunteers under fasting conditions. The bioequivalence analyses (i.e. geometric least squares mean ratio, 90% CI, CV%) are summarised in Table 3.

Table 3. Bioequivalence evaluation of amlodipine, indapamide and perindopril in study PKH-05183-005

Pharmacokinetic parameter	Geometricmean ratio test/reference	Confidence intervals*	Intra-subject Coefficient of Variation (CV%)
Amlodipine			
AUC_{72}	104.47	**102.44 - 106.53**	6.93
C_{max}	105.83	**103.41 - 108.30**	8.32
Indapamide			
AUC_t	101.71	**97.59 - 106.01**	15.26
AUC_{inf}	102.05	**97.92 - 106.35**	15.12
C_{max}	91.75	**87.22 - 96.50**	18.58
Perindopril			
AUC_t	106.73	**104.02 - 109.51**	9.45
C_{max}	116.61	**108.78 - 125.00**	25.73

Test Treatment: 1 × S5183 hard capsule containing 10/1.5/10 mg – perindopril arginine/indapamide/amlodipine Reference Treatment: 1 × 10 mg perindopril arginine (Coversyl◦) film-coated tablet, 1 × 1.5 mg Fludex◦ indapamide film-coated tablet and 1 × 10 mg Norvasc◦ amlodipine film-coated tablet administered concomitantly.
◦Comparisons where the 90%CI was within the standard bioequivalence acceptance criteria range of 80% to 125% are bolded.

Study PKH-05183-002 (NP42247) was a single dose crossover study with the primary objective of demonstrating bioequivalence of one capsule of the fixed dose combination product COVERAM PLUS SR 10/10/1.5 containing perindopril arginine 10 mg /amlodipine 10 mg/indapamide 1.5 mg versus the free combination of one tablet of perindopril arginine 10 mg film-coated tablet; and one amlodipine 10 mg film-coated tablet; and one indapamide sustained release film coated tablet administered concomitantly in fed conditions. The study was performed in 80 healthy, male and female volunteers from 18 and 65 years of age.

The secondary objectives were to evaluate other PK parameters of the test drug and reference drugs with respect to perindopril, perindoprilat, amlodipine and indapamide; and to assess the safety and tolerability of the test drug and the reference drugs based on the rate of Adverse Events.
The design was a single-dose, open label, randomized, two-period, two-sequence, two- treatment,

crossover, and laboratory-blinded study.

Bioequivalence between COVERAM PLUS SR capsule and the free combination of perindopril arginine, and amlodipine and indapamide SR administered concomitantly, was demonstrated in healthy volunteers under fed conditions. The bioequivalence analyses (i.e. geometric least squares mean ratio, 90% CI, CV%) of Test Product vs. Reference Product for amlodipine, indapamide, perindopril and perindoprilat are summarised in Table 4.

Table 4. Bioequivalence evaluation of amlodipine, indapamide, perindopril and perindoprilat in study PKH-05183-002

Pharmacokinetic parameter	Geometric mean ratio test/reference	Confidence intervals*	Intra-subject Coefficient of Variation (CV%)
Amlodipine			
AUC_t	98.85	**96.03 - 101.76**	9.14
C_{max}	94.68	**90.97 - 98.54**	12.67
Indapamide			
AUC_t	100.80	**97.35 - 104.38**	10.98
AUC_{inf}	101.21	**97.67 - 104.89**	11.23
C_{max}	93.75	**88.49 - 99.33**	18.35
Perindopril			
AUC_t	98.90	**96.42 - 101.45**	7.96
C_{max}	66.41	**60.38 - 73.06**	30.48
Perindoprilat			
AUC_t	100.85	**98.91 - 102.84**	6.13
C_{max}	98.24	**94.88 - 101.71**	11.00

Test Treatment: 1 × S5183 hard capsule containing 10/1.5/10 mg – perindopril arginine/indapamide/amlodipine Reference Treatment: 1 × 10 mg perindopril arginine (Coversyl◦) film-coated tablet, 1 × 1.5 mg Arifon◦ Retard indapamide film-coated tablet and 1 × 10 mg Norvasc® amlodipine film-coated tablet administered concomitantly.
*Comparisons where the 90%CI was within the standard bioequivalence acceptance criteria range of 80% to 125% are bolded.

Safety data from the healthy volunteers in the pivotal PK studies PKH-05183-005 and PKH-05183-002 showed that COVERAM PLUS SR was well tolerated and safe in the evaluated dosages, that correspond the higher proposed strength. The number of participants having reported at least one Treatment Emergent Adverse Event (TEAE) was similar in the different treatment groups in all studies. Overall, headache and hypotension were the most frequently observed TEAEs.

A real-world Italian study compared a three-drug fixed-dose combination (FDC) of perindopril/indapamide/amlodipine with regimens using an ACE inhibitor, calcium channel blocker, and diuretic administered as a two-drug FDC plus a separate third agent. High adherence (proportion of days covered [PDC] >75%) was observed in 59% of patients receiving the FDC and 25% of patients receiving the two-pill combination. Patients treated with the FDC were more likely to be highly adherent (RR 2.38; 95% CI 2.32–2.44; P<0.001) and had a markedly reduced likelihood of low adherence (PDC <25%; reduction 67%, 95% CI 66–69%; P<0.001). Treatment discontinuation was 41% lower with the FDC (RR 0.59; 95% CI 0.57–0.60; P<0.001). Compared with the two-pill regimen, the FDC was also associated with a lower risk of cardiovascular hospitalisation (HR 0.87; 95% CI 0.79–0.95; P=0.001).

Two additional retrospective studies using Italian administrative healthcare databases evaluated similar comparisons. In the first study (n=158), switching from perindopril/indapamide plus amlodipine (two pills) to the perindopril/indapamide/amlodipine FDC increased the proportion of adherent patients (PDC ≥80%) from 44.3% to 75.3% (P<0.05) and reduced the proportion with PDC <40% from 17.7% to 14.6% (P<0.001). The second study assessed adherence, cardiovascular outcomes, mortality, and healthcare costs. After propensity score matching, 12,150 patients received the FDC and 6105 received a multiple-pill regimen.

Adherence (PDC ≥80%) was higher with the FDC (59.9% vs 26.9%; P<0.001). During follow-up, mortality was lower in the FDC cohort (29.9 vs 33.7 per 1000 person-years; P<0.05). The incidence of a composite outcome of death and cardiovascular events was also lower with the FDC (105.8 vs 139.0 per 1000 person-years; P<0.001).

Paediatric population

No data are available with COVERAM PLUS SR in children.

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetics of COVERAM PLUS SR

The co-administration of perindopril, amlodipine and indapamide as sustained-release formulation does not change their pharmacokinetic properties by comparison to separate administration.

Pharmacokinetics of Perindopril

Absorption

After oral administration, the absorption of perindopril is rapid and the peak concentration is achieved within 1 hour (perindopril is a prodrug and perindoprilat the active metabolite). The plasma half-life of perindopril is equal to 1 hour. As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril arginine should be administered orally in a single daily dose in the morning before a meal.

Distribution

The volume of distribution is approximately 0.2 L/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent.

Metabolism

Perindopril is a prodrug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

Excretion

Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days, and perindoprilat does not accumulate.

Linearity/non-linearity
It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure.

Special Populations
- *Elderly:* Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure.
- *Renal impairment*: Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance).
- *In case of dialysis*: clearance of perindoprilat is equal to 70 mL/min.

- *In patients with cirrhosis*: Perindopril pharmacokinetics is modified, hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see sections 4.2 and 4.4).

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 %.
The bioavailability of amlodipine is not affected by food intake.

Distribution

The volume of distribution is approximately 21 L/kg. 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 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 %.

Indapamide as sustained-release (SR) formulation:

Indapamide SR 1.5 mg is supplied in a prolonged release dosage based on a matrix system in which the drug substance is dispersed within a support which allows sustained release of indapamide.

Absorption

The fraction of indapamide released is rapidly and totally absorbed via the gastrointestinal digestive tract. Ingestion with food slightly increases the rate and extent of absorption. These changes are unlikely to be clinically significant. Peak serum level following a single dose occurs about 12 hours after ingestion, repeated administration reduces the variation in serum levels between two doses. Intra-individual variability exists.

Distribution

Binding of indapamide to plasma proteins is 79 %. The plasma elimination half-life is 14 to 24 hours (mean 18 hours). The drug has a volume of distribution of approximately 60 L. Steady state is achieved after 7 days. Repeated administration does not lead to accumulation.

Metabolism and elimination

The drug is extensively metabolised in the liver, with only 5 to 7 % of the dose excreted in the urine as

unchanged drug. Elimination is essentially urinary (70 % of the dose) and faecal (22 %) in the form of inactive metabolites.

High risk individuals

In patients with severe renal impairment, plasma concentrations sometimes increase significantly.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies of perindopril in combination with amlodipine and indapamide 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

Amlodipine was not genotoxic in a battery of tests for gene mutations and clastogenicity.

Related to Indapamide component

Indapamide was negative in mutagenicity tests in bacteria, and bone marrow micronucleus tests in mice.

Carcinogenicity

No carcinogenicity or genotoxicity studies of perindopril in combination with indapamide and 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.

Related to Indapamide component

Carcinogenicity studies in mice and rats showed no evidence of tumourigenicity when indapamide was

administered in the diet at levels up to 100 mg/kg/day

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Perindopril arginine tablets
Core:
Calcium carbonate, pregelatinsed maize starch, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, colloidal anhydrous silica
Film coating:
Microcrystalline cellulose, hypromellose, magnesium stearate, iron oxide yellow

Amlodipine (as besilate) granules
microcrystalline cellulose, hypromellose, purified talc

Indapamide sustained release tablets
Core: hypromellose, lactose monohydrate, magnesium stearate, povidone, colloidal anhydrous silica
Film-coating: glycerol, hypromellose, macrogol 6000, magnesium stearate, titanium dioxide

Empty hard capsule shell
Gelatin, titanium dioxide, iron oxide yellow, Capsugel Ink 10A2 Black (ID: 109521).

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Keep the bottle tightly closed.

6.5 NATURE AND CONTENTS OF CONTAINER

Thirty (30) tablets supplied in a white HDPE bottle equipped with a polypropylene child resistant closure.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

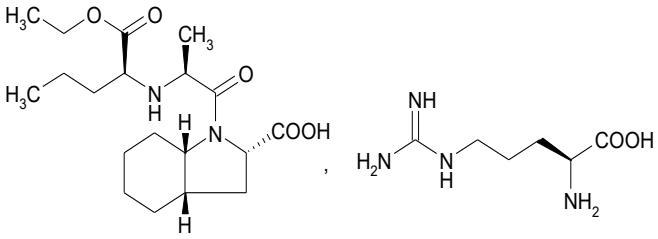
6.7 PHYSICOCHEMICAL PROPERTIES

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



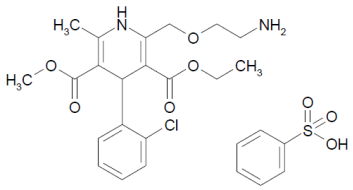
CAS number

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



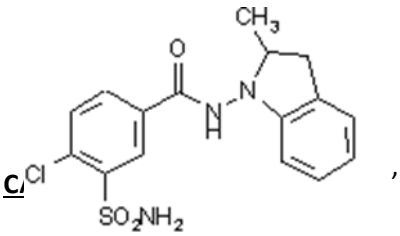
CAS number

111470-99-6

Indapamide

Indapamide hemihydrate (4-chloro-N(2-methyl-1-indolinyl)-3- sulfamoyl benzamide hemihydrate) is a non-thiazide indole derivative of chlorosulfonamide. The active ingredient is a racemic mixture. Indapamide is a white crystalline lipophilic powder, soluble in methanol, ethanol, acetic acid and ethyl acetate, very slightly soluble in ether, chloroform and benzene and practically insoluble in water.

Chemical structure



, ½ H_2O

26 807-65-8

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

25 August 2026

10 DATE OF REVISION

Not applicable

SUMMARY TABLE OF CHANGES

Section(s) Changed	Summary of new information