



Australian Government

Department of Health and Ageing  
Therapeutic Goods Administration

# Australian Public Assessment Report for Perindopril arginine/amlodipine (as besylate)

Proprietary Product Name: Coveram

Sponsor: Servier Laboratories (Aust) Pty Ltd

**December 2009**

**TGA** Health Safety  
Regulation

## About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

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- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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## I. Introduction to Product Submission

### Product Details

<i>Type of Submission</i>	New Combination
<i>Decision:</i>	Approved
<i>Date of Decision</i>	13 November 2009
<i>Active ingredient(s):</i>	Perindopril arginine / amlodipine (as besylate)
<i>Product Name(s):</i>	Coveram 5mg/5mg, Coveram 5mg/10mg, Coveram 10mg/5mg, Coveram 10mg/10mg
<i>Sponsor's Name and Address</i>	Servier Laboratories (Australia) Pty Ltd 8 Cato Street Hawthorn Vic 3122
<i>Dose form(s):</i>	Tablet
<i>Strength(s):</i>	5/5mg, 5/10mg, 10/5mg and 10/10mg perindopril arginine / amlodipine (as besylate) uncoated tablets.*
<i>Container(s):</i>	PP tube
<i>Pack size(s):</i>	30 tablets
<i>Approved therapeutic use:</i>	Coveram is indicated as substitution therapy for the treatment of hypertension and/or stable coronary heart disease in patients already controlled with separate doses of perindopril and amlodipine, given concurrently at the same dose level. Treatment should not be initiated with this combination
<i>Route(s) of administration:</i>	Oral
<i>Dosage:</i>	The same dose level as the individual components

\* The strength of amlodipine refers to the base and not to the besylate salt

### Product Background

Perindopril and amlodipine have both been widely used for more than 15 years in countries worldwide. The combination of a calcium channel blocker with an ACE inhibitor is one of the fixed-dose combinations recommended by the medical practice guidelines as being safe and effective (ESC, 2003; ESH/ESC, 2003; JNC7, 2003). Thus the combination of perindopril and amlodipine may be justified on the basis of their synergistic effects on several pathophysiological mechanisms leading to cardiovascular disease as well as their compatibility from a pharmacokinetic point of view (same dose interval and timing, i.e. once daily in the morning). A further justification may be sought in the volume of co-prescriptions

of perindopril and amlodipine: in France, 8.6% (150 000) and in UK, 12% (620 000) of the total prescriptions of perindopril are co-prescriptions with amlodipine.

This submission by Servier Laboratories (Aust) Pty Ltd seeks to register a new fixed dose combination of perindopril arginine with amlodipine (as besylate) as a substitution therapy for patients who are currently controlled on both monotherapies given at the same dose level. It is designed to simplify treatment for patients by switching from their current two tablets to one tablet. The approved indication includes the currently approved indications common to each monotherapy.

Perindopril is an angiotensin converting enzyme inhibitor that is registered in Australia as an erbumine salt (Perindo) and an arginine salt (Coversyl) by Servier and by various generic sponsors (erbumine only). It is currently registered for the treatment of hypertension, heart failure and for patients with coronary artery disease. Amlodipine is a dihydropyridine calcium channel antagonist that is registered in Australia as the besylate salt by Pfizer (Norvasc) and various generic sponsors, but not by Servier.

This perindopril / amlodipine combination has not been previously considered by the TGA. However perindopril and amlodipine have separately been considered by ADEC from Servier and Pfizer respectively.

### **Regulatory Status at the Time of Submission**

This submission has not been sent to the USA, Canada or New Zealand. It is currently approved in the European Union with the following indication.

- as substitution therapy for treatment of essential hypertension and/or stable coronary artery disease, in patients already controlled with perindopril and amlodipine given concurrently at the same dose level.

### **Product Information**

The approved product information current at the time this AusPAR was developed is contained at attachment 1.

## **II. Quality Findings**

### **Drug Substance (active ingredient)**

Perindopril arginine is the arginine salt of perindopril. It is manufactured and controlled as for the Servier monotherapy products. The arginine salt is freely soluble in water. Perindopril (itself) is a dipeptide related to many other drugs with the “pril” suffix. It is a prodrug of perindoprilat which is quickly formed *in vivo* by hydrolysis of the ethyl ester.

Amlodipine besylate is the besylate salt of amlodipine. There is an EP/BP monograph for amlodipine besylate and this material meets these requirements. The material is only slightly soluble in water. According to the synthesis used, appropriate tests and limits were added to ensure that the non-pharmacopoeial impurities complied with current guidance. The route of synthesis could also give rise to by-products which are potentially genotoxic and were therefore limited to 20 ppm (each). The Medicines Toxicology Evaluation Section of OPM (MTES) advised that these limits were acceptable.

According to the manufacturing process of the drug product, appropriate limits on particle size distribution have been set for perindopril arginine and amlodipine besylate. Amlodipine besylate will be referred to as amlodipine for the remainder of this document except where the discussion relates to the relationship between the free base and the salt.

## Drug Product

The tablets are to be manufactured by Les Laboratoires Servier Industrie in France or Servier (Ireland) Industries Ltd in Ireland. The same method of manufacture (simple dry compression) is used at both sites. The tablets contain no unusual excipients and the quality of the excipients is adequately controlled. The lactose used in the tablets is from an acceptable source.

The tablets are well controlled with satisfactory expiry limits and release limits that allow for the changes observed on storage. The 10/10, 5/10 and 10/5 tablets are all the same mass and the same colour (white). However they are distinguished by shape and embossing (being round, square and triangular, respectively). The 5/5 tablet is a direct scale of the 10/10 tablet and rod shaped.

Stability data was provided to support the proposed shelf lives of 15 months when stored below 30°C in white PP tubes with white LDPE stoppers containing a desiccant and a flow reducer. The storage condition 'protect from light' also applies.

## Pharmacokinetics

Five pharmacokinetic studies were provided together with a justification for not providing other pharmacokinetic data. Appropriately validated test analytical methods for the determination of perindopril, perindoprilat and amlodipine were used in the studies.

### Study PKH-05985-001/NP 23343

In a 2-way cross-over, this study compared the relative bioavailability of the proposed 10/10 tablet to the bioavailability from a dose consisting of a 8 mg perindopril erbumine tablet and a 10 mg amlodipine tablet.

Study 001 Parameter	Geometric Mean Ratio (T/R)* and [90% Confidence Intervals]		
	Perindopril	Perindoprilat	Amlodipine
C <sub>max</sub>	1.09 [1.00-1.18]	1.08 [0.99-1.17]	1.03 [0.99-1.07]
AUC <sub>0-t</sub>	1.10 [1.07-1.14]	0.99 [0.96-1.03]	1.00 [0.97-1.04]
AUC <sub>0-∞</sub>	1.10 [1.07-1.14]	0.99 [0.93-1.05]	1.00 [0.97-1.04]

\* T : Test (S5985); R : Reference (S 9490 + Amlodipine)

The results (see above) indicate that the pharmacokinetic profiles of perindopril, perindoprilat and amlodipine from the proposed "10/10" fixed dose combination tablet are bioequivalent to those from the co-administration of separate 8 mg perindopril erbumine and 10 mg amlodipine tablets supplied overseas.

### Study PKH-05985-002/NP 23360

In a 2-way cross-over, this study compared the relative bioavailability of the proposed 10/5 tablet to the bioavailability from a dose consisting of an 8 mg perindopril erbumine tablet and a 5 mg amlodipine tablet.

Study 002 Parameter	Geometric Mean Ratio (T/R)* and [90% Confidence Intervals]		
	Perindopril	Perindoprilat	Amlodipine
C <sub>max</sub>	1.04 [0.98-1.10]	1.05 [0.98-1.12]	0.98 [0.95-1.03]

AUC <sub>0-t</sub>	1.07 [1.04-1.10]	1.01 [0.97-1.06]	0.99 [0.95-1.03]
AUC <sub>0-∞</sub>	1.07 [1.04-1.10]	1.03 [0.97-1.10]	0.98 [0.94-1.02]

\* T : Test (S5985); R : Reference (S 9490 + Amlodipine)

The results (see above) indicate that the pharmacokinetic profiles of perindopril, perindoprilat and amlodipine from the proposed “10/5” fixed dose combination tablet are bioequivalent to those from the co-administration of separate 8 mg perindopril erbumine and 5 mg amlodipine tablets supplied overseas.

### Study PKH-05985-003/NP 23361

In a 2-way cross-over, this study compared the relative bioavailability of the proposed 5/10 tablet to the bioavailability from a dose consisting of a 4 mg perindopril erbumine tablet and a 10 mg amlodipine tablet.

Study 003 Parameter	Geometric Mean Ratio (T/R)* and [90% Confidence Intervals]		
	Perindopril	Perindoprilat	Amlodipine
C <sub>max</sub>	1.08 [0.98-1.18]	1.08 [0.98-1.19]	1.05 [1.01-1.10]
AUC <sub>0-t</sub>	1.06 [1.02-1.10]	1.01 [0.94-1.08]	1.02 [0.99-1.06]
AUC <sub>0-∞</sub>	1.06 [1.02-1.10]	not calculated**	1.02 [0.99-1.06]

\* T : Test (S5985); R : Reference (S 9490 + Amlodipine)

\*\* Due to low number of results (only 9) meeting criteria that AUC<sub>extra</sub> must be <20%.

The results (see above) indicate that the pharmacokinetic profiles of perindopril, perindoprilat and amlodipine from the proposed “5/10” fixed dose combination tablet are bioequivalent to those from the co-administration of separate 4 mg perindopril erbumine and 10 mg amlodipine tablets supplied overseas.

### Study PKH-05985-008

The bioequivalence of the amlodipine tablets used in these studies to amlodipine tablets available in Australia was determined in a bioavailability study.

In a 2-way cross-over, this study compared the relative bioavailability of a 10 mg amlodipine tablet purchased in Australia and the 10 mg amlodipine tablet used in studies 001 and 003 mentioned above.

Study 008 Parameter	Geometric Mean Ratio (T/R)* and [90% Confidence Intervals]	
	Amlodipine	
C <sub>max</sub>	1.01	[0.96-1.07]
AUC <sub>0-t</sub>	0.98	[0.93-1.03]
AUC <sub>0-∞</sub>	0.98	[0.92-1.03]

\* T: Test (Amlodipine 10 mg AUS); R : Reference (Amlodipine 10 mg NLD)

The results (see above) indicate that the pharmacokinetic profiles of amlodipine from the 10 mg amlodipine tablets supplied overseas are bioequivalent to those from a 10 mg amlodipine tablet supplied in Australia.

**Study PKH-05985-004/NP 23342**

A 3-way cross-over PK interaction study where a 10 mg perindopril arginine tablet and a 10 mg amlodipine tablet were administered separately or in combination.

<b>Study 004</b> Parameter	Geometric Mean Ratio (T/R or T/Q)* and [90% Confidence Intervals]		
	<b>Perindopril</b>	<b>Perindoprilat</b>	<b>Amlodipine</b>
$C_{max}$	0.92 [0.83-1.02]	1.06 [0.98-1.14]	1.07 [1.00-1.14]
$AUC_{0-t}$	1.01 [0.97-1.04]	1.01 [0.97-1.05]	1.06 [0.98-1.14]
$AUC_{0-\infty}$	1.01 [0.97-1.04]; n=34	1.07 [0.99-1.16]; n=8	1.06 [0.98-1.14]

\* T : Test (S 6490 + amlodipine); R : Reference (S 6490); Q : Reference (amlodipine)

The results (see above) indicate that amlodipine does not affect the pharmacokinetic profiles of perindopril or perindoprilat and vice versa.

**Justification submitted for non-supply of bioavailability/bioequivalence data**

No data comparing the proposed 5/5 tablet to either of the proposed 10/10 tablet or to a dose consisting of a 4 mg perindopril erbumine tablet and a 5 mg amlodipine (as besylate) tablet has been provided. A justification for this omission was provided. The chemistry and quality control aspects were acceptable and the clinical aspects were acceptable to the Delegate.

**Other bioavailability comments**

No data on the absolute bioavailability of the tablets has been provided. However, given the results of the studies provided, it will be accepted that results for the proposed fixed-dose combination tablets are similar to those for the relevant monotherapy tablets.

No data relating to the affect on food on the bioavailability of the proposed tablets has been provided. However, given the results of the studies provided, it will be accepted that results for the proposed fixed-dose combination tablets are similar to those for the relevant monotherapy tablets.

Finally, the proposed indication in the draft Product Information document (PI) does not stipulate if the monotherapy perindopril dose is from a perindopril arginine tablet or a perindopril erbumine tablet. It therefore allows for switching from taking both perindopril erbumine and amlodipine tablets and both perindopril arginine and amlodipine tablets to the proposed perindopril arginine and amlodipine fixed-dose combination tablets. In addition, the first three bioavailability studies mentioned above used monotherapy perindopril erbumine tablets and not monotherapy perindopril arginine tablets.

The issue of bioequivalence of the single entity tablets containing perindopril arginine and tablets containing perindopril erbumine has been addressed previously. The evaluator's conclusions were as follows:

*A single bioequivalence study comparing the proposed 10 mg tablet with the registered 4 mg (x2) erbumine tablet was provided. The evaluator concurs with the company's conclusion that the two salts of perindopril (arginine and tert-butylamine) are bioequivalent with regard to both perindopril and perindoprilat on the basis that the 90% confidence intervals for*



*geometric mean ratios for both  $C_{max}$  and  $AUC_{0-\infty}$  fall within the recommended range of 0.80-1.25 for both analytes.<sup>1</sup>*

*A justification for not providing bioequivalence data for the proposed 2.5 mg and 5 mg tablets has been provided and has been assessed as satisfactory from a pharmaceutical chemistry perspective”.*

However, the draft PI does not make this clear or include any statement that the dose of perindopril erbumine monotherapy and perindopril arginine monotherapy will have to differ to give the same perindopril response as that observed from the combination tablets. This was brought to the attention of the Delegate.

### **Previous Consideration by the Pharmaceutical Subcommittee of ADEC (PSC)**

Details of this submission were presented at the 126<sup>th</sup> meeting of the Pharmaceutical Subcommittee of ADEC (PSC) in May 2009. The PSC endorsed all question raised by the quality evaluator and had no objections to approval of these products provided all issues were addressed to the satisfaction of the TGA. This was the case for all issues apart from the issue of the PI clearly stating that monotherapy doses of perindopril arginine and perindopril erbumine differ.

### **Quality Summary and Conclusions**

Approval of the company's application is recommended with respect to chemistry and quality control.

With respect to bioavailability, data was provided (in this or earlier submissions) that demonstrated bioequivalence of perindopril, perindoprilat and amlodipine when administered as the combination perindopril arginine and amlodipine tablets to perindopril, perindoprilat and amlodipine when administered as a co-administration of perindopril erbumine and amlodipine monotherapy tablets or as a co-administration of perindopril arginine and amlodipine monotherapy tablets.

However, though the draft PI allows from switching to the proposed fixed dose combination products from amlodipine tablets and, either perindopril erbumine tablets or perindopril arginine tablets, it was not clearly written in respect to the fact that doses of perindopril erbumine and perindopril arginine are different.

## **III. Non-Clinical Findings**

### **Introduction**

No nonclinical data on potential pharmacodynamic, pharmacokinetic or toxicological interactions were submitted. Only brief summaries of the toxicological profiles of the individual components were provided. Information regarding amlodipine was obtained by the sponsor from a published FDA review, as the sponsor does not have access to the original data. A justification for omission of new nonclinical data was provided by the sponsor:

- Based on the TGA-adopted Guideline CHMP/EMEA/CHMP/SWP/258498/2005 (Guideline on the non-clinical development of fixed combinations of medicinal products);  
“when the fixed combination under development includes compounds for which there is

<sup>1</sup> Tertbutylamine is a synonym for erbumine and will be referred to as erbumine for the remainder of this document.

*sufficiently documented human experience of their individual and combined use, safety studies in animals are in general not required”;*

- Frequency of prescription and co-prescription of an ACE inhibitor and of a calcium-channel blocker, and more precisely perindopril and amlodipine;
- A lack of adverse effects attributed to the perindopril/amlodipine combination from pharmacovigilance data;
- A study in human volunteers demonstrated no pharmacokinetic interactions between the two components.

A similar dossier was submitted in Europe to the Concerned Member States within the European Union, with France being the Reference Member State. European marketing approval for the product was granted in March 2008.

In the absence of nonclinical data with perindopril/amlodipine combinations, potential interactions were considered based on pharmacodynamic, pharmacokinetic and toxicological profiles of the individual components.

## **Pharmacology**

### ***Potential pharmacodynamic interactions***

Perindopril and amlodipine have complementary, yet distinct, mechanisms of action; perindopril reduces blood pressure indirectly via ACE inhibition and amlodipine works directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and a reduction in blood pressure. Synergistic pharmacodynamic effects would be expected and this was the rationale for combination therapy with these two active ingredients.

## **Pharmacokinetics**

### ***Potential pharmacokinetic interactions***

Perindopril is a prodrug that is converted hepatically to the diacid product, perindoprilat; the major drug-related material excreted in urine. Though perindopril, as a result of exaggerated pharmacological action on tissue-associated ACE, can cause renal function impairment, this will not have an effect on amlodipine pharmacokinetics as amlodipine is extensively metabolised in the liver by CYP3A. There is no information regarding interactions of perindopril with CYP450 enzymes. Theoretically, these two drugs are not expected to have any significant pharmacokinetic interactions with other drugs. However, such interactions will need to be assessed from clinical data

## **Toxicology**

### ***Potential toxicological effects***

Previous toxicological studies with perindopril identified exaggerated pharmacological effects with renal impairment (tubulonephritis and increased urinary volumes) and reduced heart and liver weights. Renal, adrenal and cardiovascular toxicity were observed in nonclinical studies with amlodipine with increased kidney weights and increased urinary excretion, thickening of the adrenal zona glomerulosa and necrosis in the sub-endocardium and papillary muscles in the left ventricle, with pigment laden macrophages and haemorrhage of the right atria. With the kidney as a common target organ for perindopril and amlodipine, the potential for renal toxicity maybe expected to be greater with the perindopril/amlodipine combination compared to the individual components.

## Non-Clinical Summary and Conclusions

There were no non-clinical objections to the registration of this product. No new nonclinical data were submitted to support this application. This is acceptable and consistent with *Guideline on the Non-clinical Development of Fixed Combinations of Medicinal Products* (CHMP/EMEA/CHMP/SWP/258498/2005).

Based on previous nonclinical studies performed separately with perindopril arginine and amlodipine, synergistic pharmacological effects, with the potential for greater renal and reproductive toxicity would be expected with combination therapy compared to monotherapy.

In the absence of nonclinical data with the fixed combination product, potential safety issues will need to be addressed by the clinical data.

## IV. Clinical Findings

### Introduction

The clinical data relies on 4 bioequivalence studies and one pharmacokinetic drug interaction study which were also evaluated by the pharmaceutical chemistry evaluator. There are no other clinical trials. The trials are summarised in Table 1 below.

**TABLE 1: Bioequivalence Studies with Perindopril (PERIN) and Amlodipine (AMLOD) and their Combination**

Study	Subjects, Dose	Objectives, Design of Study	Results, Safety
PKH-05985-001	18M, 18F (18-40y) PERIN Arginine 10mg / AMLOD 10mg fixed combination tablet PERIN erbumine 8mg and AMLOD 10mg	Objectives: To demonstrate bioequivalence of perindopril / amlodipine combination with perindopril erbumine plus amlodipine in healthy volunteers.  Design: randomised, open, two-way crossover study; single of fixed combination tablet or both tablets together; 3 week washout between doses; bloods to 240hours after each administration; drug and metabolite levels by LC/MS/MS; non-compartment kinetic parameters; data compared by ANOVA and 90%CI of ratios for kinetic data; safety data throughout study.	Results: Bioequivalence established (AUC, Cmax ratios in 80-125% range) between the combination and individual tablets for perindopril and metabolite as well as amlodipine.  Safety: headache main side effects; nausea, vomiting malaise other effects; no clinically significant effects on vital signs, ECG or clinical lab tests.
PKH-05985-002	19M, 19F (18-39y). PERIN Arginine 10mg / AMLOD 5mg fixed combination tablet PERIN erbumine 8mg and AMLOD 5mg co-administered.	Objectives: To demonstrate bioequivalence of one fixed tablet of perindopril arginine 10mg / amlodipine 5mg with one tablet of perindopril erbumine 8mg plus amlodipine 5mg in healthy volunteers.  Design: randomised, open, two-way crossover study; single dose of combination tablet or both tablets together; 3 week washout between doses; bloods to 240hours after each administration; drug and metabolite levels by LC/MS/MS; non-compartment kinetic parameters; data compared by ANOVA and 90%CI of ratios for kinetic data; safety data throughout study.	Results: Bioequivalence established (AUC, Cmax ratios in 80-125% range) between the combination and individual tablets for perindopril and metabolite as well as amlodipine.  Safety: headache main side effect with dizziness, syncope; no clinically significant effects on vital signs, ECG or clinical lab tests.

PKH-05985-003	17M, 20 F (19-40y).  PERIN Arginine 5mg/ AMLOD 10mg combination tablet  PERIN erbumine 4mg and AMLOD 10mg co-administered	Objectives: To demonstrate bioequivalence of one fixed tablet of perindopril arginine 5mg / amlodipine 10mg with one tablet of perindopril erbumine 4mg plus amlodipine 10mg in healthy volunteers.  Design: randomised, open, two-way crossover study; single dose of combination tablet or both tablets together; 3 week washout between doses; bloods to 240hours after each administration; drug and metabolite levels by LC/MS/MS; non-compartment kinetic parameters; data compared by ANOVA and 90%CI of ratios for kinetic data; safety data throughout study.	Results: Bioequivalence established (AUC, Cmax ratios in 80-125% range) between the combination and individual tablets for perindopril and metabolite as well as amlodipine.  Safety: headache main side effect with asthenias, malaise, feelings of heaviness; no clinically significant effects on vital signs, ECG or clinical lab tests.
PKH-05985-004	18M, 19F (19-40y)  PERIN arginine 10mg;  AMLOD 10 mg; and PERIN arginine 10mg and AMLOD 10mg co-administered	Objectives: To examine the potential interaction between perindopril and amlodipine administered alone and together in healthy volunteers.  Design: randomised, open study; three-way crossover; single dose of each drug and co-administered; 3 week washout between doses; bloods to 240hours after each dose; drugs determined by LC/MS/MS; non-compartment kinetic parameters; data compared by ANOVA and 90%CI of ratios for kinetic data; safety data throughout study.	Results: No difference in perindopril metabolite and amlodipine kinetic parameters administered alone or co-administered; similarly for amlodipine.  Safety: headache main side effect; no clinically significant effects on vital signs, ECG or clinical lab tests.
PKH-05985-008	9M, 9F (18-45y).  AMLOD 10mg (NLD)  AMLOD 10mg (AUS)	Objectives: To demonstrate bioequivalence of amlodipine 10mg marketed in the Netherlands with 10mg tablet marketed in Australia in healthy volunteers.  Design: randomised, open, two-way crossover study; single dose of amlodipine; 3 week washout between doses; bloods to 240hours after each administration; drug and metabolite levels by LC/MS/MS; non-compartment kinetic parameters; data compared by ANOVA and 90%CI of ratios for kinetic data; safety data throughout study.	Results: Formulations were deemed to be bioequivalent based on the 90%CIs for the ratio of AUC, AUCt and Cmax.  Safety: headache main side effect; no clinically significant effects on vital signs, ECG or clinical lab tests.

## Pharmacokinetics

### Bioequivalence

#### *Perindopril-Amlodipine Combination*

Three studies summarised in Table 1 were presented to evaluate the bioequivalence of fixed tablet combinations of perindopril arginine and amlodipine (10mg/10mg; 10mg/5mg and 5mg/10mg) with perindopril erbumine and amlodipine when administered simultaneously as separate tablets. All of the studies were performed as open, crossover studies in healthy male and female volunteers. Plasma concentrations of perindopril, its major metabolite, perindoprilat and amlodipine were determined by validated LC/MS/MS methods. No bioequivalence data was presented comparing the administration of the combined tablet formulation containing 5mg perindopril arginine and 5mg amlodipine to that of perindopril

erbumine 4mg and amlodipine 5mg administered simultaneously as separate tablets. This was justified by the sponsor on the basis that:

- The ratio between active substances and excipients is the same for the two different dose strengths 5/5mg and 10/10mg;
- Linearity has been demonstrated over the therapeutic dose range for both compounds;
- The qualitative composition for the two combinations is the same;
- The different strength tablets are manufactured by the manufacturer using the same manufacturing process;
- The dissolution profiles for perindopril and amlodipine are similar for the two strengths

The information provided by the sponsor would thus appear to conform to the guidelines CPMP/EWP/QWP/1401/98 Note for the Guidance on the investigation of bioavailability and bioequivalence.

Study **PKH-05985-001** examined pharmacokinetic parameters following a single oral dose of the combination of perindopril arginine 10mg and amlodipine 10mg in 36 healthy volunteers and compared these with the pharmacokinetic parameters obtained in the same volunteers following a single dose of perindopril erbumine 8mg taken with amlodipine 10mg. The dose of perindopril amino-acid was equivalent to 6.79mg for the arginine salt and 6.67mg for the erbumine salt. In the case of amlodipine 13.9mg of the besylate salt was administered equivalent to 10mg of the free base. Pharmacokinetic parameters for perindopril, its main active metabolite perindoprilat and amlodipine were determined by a non-compartmental analysis and compared using ANOVA as well as determining the 90% confidence intervals (90% CI) for the ratio of  $AUC_{0-t}$ ,  $AUC_{0-\infty}$  and  $C_{max}$  for the test and reference compounds.

The results are shown in the table below. All pharmacokinetic parameters were within the accepted confidence interval of 80% to 125% for bioequivalence.

Study 001 Parameter	Geometric Mean Ratio (T/R)* and [90% Confidence Intervals]		
	Perindopril	Perindoprilat	Amlodipine
$C_{max}$	1.09 [1.00-1.18]	1.08 [0.99-1.17]	1.03 [0.99-1.07]
$AUC_{0-t}$	1.10 [1.07-1.14]	0.99 [0.96-1.03]	1.00 [0.97-1.04]
$AUC_{0-\infty}$	1.10 [1.07-1.14]	0.99 [0.93-1.05]	1.00 [0.97-1.04]

\* T : Test (S5985); R : Reference (S 9490 + Amlodipine)

Further the plasma concentration time curves for the three analytes produced almost identical profiles in the volunteers following the combination drug or the two individual components administered together. Thus it was concluded that the combination of perindopril arginine 10mg and amlodipine 10mg produced the same systemic availability as perindopril erbumine 8mg and amlodipine 10mg as individual components taken together. In this study there was no clinically significant effect of the combination on vital signs or electro-cardiographic parameters.

In a similar two-way, crossover design study **PKH-05985-002** investigated the bioequivalence of the combined tablet formulation of perindopril arginine 10mg and amlodipine 5mg in 38 healthy volunteers and compared pharmacokinetic parameters after

single doses obtained in the same volunteers following perindopril erbumine 8mg taken with amlodipine 5mg. The dose of perindopril free amino-acid was equivalent to 6.79mg for the arginine salt and 6.67mg for the erbumine salt. In the case of amlodipine 6.94mg of the besylate salt was administered equivalent to 5mg of the free base. Pharmacokinetic parameters for perindopril, its main active metabolite perindoprilat and amlodipine were determined by a non-compartmental analysis and compared using ANOVA and by determining the 90% confidence intervals (90% CI) for the ratio of AUC<sub>0-t</sub>, AUC<sub>0-∞</sub> and C<sub>max</sub> for the test and reference compounds.

The results are shown in the table below. All pharmacokinetic parameters were within the accepted confidence interval of 80% to 125% for bioequivalence.

Study 002 Parameter	Geometric Mean Ratio (T/R)* and [90% Confidence Intervals]		
	Perindopril	Perindoprilat	Amlodipine
C <sub>max</sub>	1.04 [0.98-1.10]	1.05 [0.98-1.12]	0.98 [0.95-1.03]
AUC <sub>0-t</sub>	1.07 [1.04-1.10]	1.01 [0.97-1.06]	0.99 [0.95-1.03]
AUC <sub>0-∞</sub>	1.07 [1.04-1.10]	1.03 [0.97-1.10]	0.98 [0.94-1.02]

\* T : Test (S5985); R : Reference (S 9490 + Amlodipine)

Thus it was concluded that the combination of perindopril arginine 10mg and amlodipine 5mg administered as a fixed combination tablet produced the same systemic availability as the individual components taken together as perindopril erbumine 8mg and amlodipine 5mg. Both supine systolic (SBP) and supine diastolic (DBP) blood pressure were decreased from baseline to a similar extent over first 24 hours after the combined tablet or the individual tablets taken together. There were no clinically significant changes in ECG parameters following either administration.

The final study **PKH-05985-003** assessed the bioequivalence of a fixed combination tablet containing 5mg perindopril arginine and 10mg amlodipine with that of individual tablets containing 4mg perindopril erbumine and 10mg amlodipine taken together. A two way, randomised crossover study was performed in 35 healthy volunteers. The dose of perindopril free base was equivalent to 3.4mg for the arginine salt and 3.34mg for the erbumine salt. In the case of amlodipine 13.9mg of the besylate salt was administered equivalent to 10mg of the free amino-acid. As in the previous studies pharmacokinetic parameters for perindopril, its main active metabolite perindoprilat and amlodipine were determined by a non-compartmental analysis and compared using ANOVA, while the 90% CIs for the ratio of AUC<sub>0-t</sub>, AUC<sub>0-∞</sub> and C<sub>max</sub> for the test and reference compounds were calculated.

The results are shown in the table below. All pharmacokinetic parameters were within the accepted confidence interval of 80% to 125% for bioequivalence.

The values for AUC<sub>0-∞</sub> were not available for perindoprilat as this is a derived parameter (AUC<sub>0-t</sub> + C<sub>last</sub> / λ<sub>z</sub>) based on the last measured concentration and the elimination rate constant. Where extrapolation exceeds 20% of the total value the data, by convention, are regarded as unreliable. The situation arises due to the slow and non-linear dissociation of perindoprilat from plasma angiotensin converting enzyme. This is a characteristic of the pharmacokinetics of ACE inhibitor drugs (Toutain and Lefebvre, 2004). In the view of the evaluator it does not represent a serious issue in the pharmacokinetic considerations as bioequivalence can be established from the more reliable measurements of AUC<sub>0-t</sub>.

Study 003 Parameter	Geometric Mean Ratio (T/R)* and [90% Confidence Intervals]		
	Perindopril	Perindoprilat	Amlodipine
C <sub>max</sub>	1.08 [0.98-1.18]	1.08 [0.98-1.19]	1.05 [1.01-1.10]
AUC <sub>0-t</sub>	1.06 [1.02-1.10]	1.01 [0.94-1.08]	1.02 [0.99-1.06]
AUC <sub>0-∞</sub>	1.06 [1.02-1.10]	not calculated**	1.02 [0.99-1.06]

\* T : Test (S5985); R : Reference (S 9490 + Amlodipine)

\*\* Due to low number of results (only 9) meeting criteria that AUC<sub>extra</sub> must be <20%.

Thus it was concluded that the fixed combination of perindopril arginine 5mg and amlodipine 10mg administered as a fixed combination tablet produced the same systemic availability as the individual components taken together as perindopril erbumine 4mg and amlodipine 10mg.

A secondary objective of the study was to evaluate changes in blood pressure after the two regimens. As with the previous studies, there was a mean decline in supine SBP and DBP for both the combined treatment and the two individual treatments taken together. Maximum effects occurred between 6 and 8 hours after the dose. The mean maximum decreases in SBP and DBP were 4.2 and 6.6mmHg for the combined tablet and 7.6 and 5.7mmHg for the individual tablets taken together. No clinically relevant changes were reported in the ECG for the administration of either regimen.

### *Amlodipine*

A single study **PKH-05985-008**, examined the bioequivalence of amlodipine 10mg tablets manufactured in the Netherlands and Australia. The study was conducted as a single dose, randomised, open label, two-way, crossover study in healthy volunteers with a three week washout period between doses. Pharmacokinetic parameters were determined by a non-compartmental analysis from plasma concentrations determined after 240 hours after each dose. Bioequivalence was examined using the ratio of the pharmacokinetic parameters  $AUC_{0-\infty}$ ,  $AUC_{0-t}$  and  $C_{max}$  determined for the two formulations and their 90% CI. These ratios are shown in the table below and are within the generally accepted 80-125% range for bioequivalence. There were no clinically relevant safety issues during administration of either formulation.

Study 008 Parameter	Geometric Mean Ratio (T/R)* and [90% Confidence Intervals]	
	<b>Amlodipine</b>	
$C_{max}$	1.01	[0.96-1.07]
$AUC_{0-t}$	0.98	[0.93-1.03]
$AUC_{0-\infty}$	0.98	[0.92-1.03]

\* T: Test (Amlodipine 10 mg AUS); R : Reference (Amlodipine 10 mg NLD)

With respect to Section 7 of Appendix 15 of the Australian Regulatory Guidelines for Prescription Medicines, the sponsor does not seem to have justified the choice of the Dutch-registered amlodipine in the formulation of the combination product. Given that amlodipine has been registered for clinical use for several years and its efficacy, safety, pharmacokinetic and drug interaction potential are well recognised, coupled with the demonstration that the product to be used is bioequivalent with that of an Australian product (no information could be found which specifically identified the brand name of the Australian product nor that of the Dutch product) it would not appear to be a serious deficiency in the application from a clinical point of view.

### **Drug Interactions**

A single study **PKH-05985-004**, also reported in Table 1, investigated, as its primary objective, the potential interaction between perindopril and amlodipine in 37 healthy volunteers. The study was conducted as an open label, three-way, crossover study. Each subject received in randomised order 10mg perindopril arginine corresponding to 6.79mg of perindopril free amino-acid, 13.9mg of amlodipine besylate corresponding to 10mg of amlodipine free base and both tablets together. Doses were separated by a three week washout period. Pharmacokinetic parameters determined for perindopril and its metabolite, perindoprilat, as well as for amlodipine taken alone or in combination are compared in the table below.



Study 004 Parameter	Geometric Mean Ratio (T/R or T/Q)* and [90% Confidence Intervals]		
	Perindopril	Perindoprilat	Amlodipine
$C_{max}$	0.92 [0.83-1.02]	1.06 [0.98-1.14]	1.07 [1.00-1.14]
$AUC_{0-t}$	1.01 [0.97-1.04]	1.01 [0.97-1.05]	1.06 [0.98-1.14]
$AUC_{0-\infty}$	1.01 [0.97-1.04]; n=34	1.07 [0.99-1.16]; n=8	1.06 [0.98-1.14]

\* T : Test (Perindopril arginine + Amlodipine); R : Reference (Perindopril arginine); Q : Reference (Amlodipine)

The pharmacokinetic interaction effect was assessed by the comparison of the 90% CIs for the ratios of  $AUC_{0-t}$ ,  $AUC_{0-\infty}$  and  $C_{max}$  for each analyte alone and in the presence of the other. As shown in the table there was a lack of pharmacokinetic interaction for perindopril, perindoprilat and amlodipine as the 90% CI values were within the accepted 80-125% bioequivalence range. The secondary objective of the study was to examine the safety of the combination. As such information was available for blood pressure (BP) under each treatment regimen. The change in SBP and DBP from baseline to last study visit was reported as not clinically significant. Since the main objective was to investigate a potential drug interaction in healthy volunteers, no statistical analysis was applied to examine the effect of the three treatments on the change in BP over time nor was an analysis performed to examine the potential differences between treatments. Given that this was a single dose study in a healthy population differences may not be expected to emerge given the sample size. Maximum change in SBP and DBP from baseline for the three conditions was perindopril arginine alone  $-7.4 \pm 7.8$  mmHg (at 8 hours) and  $-9.2 \pm 7.5$  mmHg (at 8 hours); for amlodipine alone  $-3.6 \pm 6.6$  mmHg (at 4 hours) and  $-5.7 \pm 7.5$  mmHg (at 8 hours); for the combination it was  $-9.4 \pm 6.9$  mmHg (at 8 hours) and  $-12 \pm 6.2$  mmHg (at 6 hours). With respect to the ECG there were no clinically significant changes from baseline to the end of study visit. Similarly biochemical and haematological tests suggested no clinically significant changes throughout the course of the study.

### Pharmacodynamics

No new studies were presented.

### Efficacy

No new studies were presented.

### Safety

#### Adverse Events

Between 35% and 81% of subjects reported one or more adverse events during the studies. The events were classified as nervous system disorders and generally were headache (39.0 - 73.1%), syncope vasovagal (5.2 - 16.7%), nausea (2.6 - 5.3%) and asthenia (11.1 - 27.2%). There did not appear to be any differences between the combination tablet or the individual components taken together with regard to the incidence or type of adverse event. Further the incidence of events did not appear to depend on the order in which the treatments were administered. All reported adverse events were of mild to moderate severity. There were no serious adverse events. There were no deaths. The types of adverse events noted in these healthy subjects did not appear to differ from those observed in hypertensive patients taking either medication as monotherapy.

#### Clinical Laboratory Tests

The results for biochemistry, haematology and urinalysis were reported as the changes from baseline to the follow-up after the last study visit. For each of these parameters there were no clinically relevant changes over time nor were there differences between the treatment groups. For some individual subjects there were changes which fell outside of the normal range. None of these was regarded as clinically significant and there was no pattern of changes which emerged. There were no differences between the combination tablet and the individual tablets taken together for the occurrence of these abnormal values. Thus the combination therapy appears to be equivalent to the two agents taken together with respect to effects on clinical laboratory tests.

### *ECG Recordings*

Standard 12-lead ECG was recorded at selection and final visit. The calculated parameters were heart rate, PR interval, QRS duration, QRS interval and QT interval. No clinically relevant changes were observed in either of the two treatment groups and there were no differences between groups. Some participants presented with ECG abnormalities such as first degree atrioventricular block, supraventricular extrasystoles and shortened PR intervals at the beginning of treatment but none was clinically significant. Further these abnormalities were present at the end of the study.

### *BP and Physical Examinations*

Full physical examinations were conducted at selection, inclusion of subjects and end of study visits. All values were normal and no relevant changes were observed. Blood pressure and heart rate were measured in healthy volunteers prior to drug administration and for up to 24 hours after each dose regimen in the supine position. A decrease was observed in systolic and diastolic BP over time with the maximum change generally occurring between 6 and 8 hours after the dose. Data were reported as change from the baseline value. Since the main objective of these studies performed in healthy volunteers was to investigate bioequivalence and pharmacokinetic interaction, there was no attempt to analyse the results statistically or to compare results between treatment regimens. The table below reports the maximum decrease (and range of values) in SBP and DBP observed under each of the treatment regimens for each of the three bioequivalence studies. The asymptomatic changes in BP have been reported before in patients after perindopril and amlodipine and were not unexpected. There did not appear to be any clinically relevant differences between regimens.

Comparative Blood Pressure Lowering Effects of Perindopril and Amlodipine Administered as a Fixed Combination Tablet or as Co-administered Individual Tablets in Healthy Volunteers		
Study	Maximum SBP Change*	Maximum DBP Change*
PKH-05985-001		
Fixed Combination (10mg/10mg)	-9.8 (-35 to +17)	-12 (-33 to +3)
Co-administered Individual Tablets	-8.6 (-23 to +4)	-12 (-34 to +2)
PKH-05985-002		
Fixed Combination	-8.3 (-28 to +16)	-7.3 (-25 to +11)

(10mg/5mg)		
Co-administered Individual Tablets	-7.5 (-25 to +7)	-8.6 (-20 to +2)
PKH-05985-003		
Fixed Combination (5mg/10mg)	-4.2 (-29 to +15)	-6.6 (-21 to 9)
Co-administered Individual Tablets	-7.6 (-23 to +10)	-5.7 (-19 to +3)

\*Data are maximum change of BP (mmHg) and the range of values observed.

### Clinical Summary and Conclusions

1. Bioequivalence was established for perindopril and amlodipine when the two drugs were administered as a combined tablet or taken together as individual tablets.
2. There was no evidence for a pharmacokinetic interaction between perindopril and amlodipine.
3. The formulation of amlodipine used in The Netherlands was bioequivalent with that used in Australia.
4. The combination treatment was well tolerated.
5. In comparison to perindopril and amlodipine administered together as separate tablets the combination tablet did not appear to be associated with any increase in safety issues.

The evaluators recommend that the proposed indication that “Coveram is indicated as substitution therapy in patients adequately controlled with separate doses of perindopril and amlodipine given concurrently at the same dose level” be accepted.

### V. Pharmacovigilance Findings

There were no pharmacovigilance data presented.

### VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the Delegate’s overview and recommendation.

#### Quality

Approval is recommended from a chemistry, quality control and bioavailability aspect. The bioequivalence studies showed:

- 10/10mg was bioequivalent to 8mg perindopril erbumine and 10mg amlodipine (overseas).
- 10/5mg was bioequivalent to 8mg perindopril erbumine and 5mg amlodipine (overseas).
- 5/10mg was bioequivalent to 4mg perindopril erbumine and 10mg amlodipine (overseas).
- 10mg of amlodipine from overseas used in the first and third studies above was bioequivalent to 10mg amlodipine from Australia.

A pharmacokinetic interaction study using 10mg perindopril arginine and 10mg amlodipine indicated there was no interaction between perindopril (and perindoprilat) and amlodipine or vice versa. There was no study using the 5/5mg presentation but an acceptable justification was provided. No food effect study was provided but this was considered acceptable as it should be similar to the monotherapies.

### Non-Clinical

There were no non-clinical objections to the registration of this product. No new non-clinical data were submitted which was considered acceptable and consistent with the EU guideline. Greater renal toxicity is expected being a common target organ and greater reproductive toxicity is expected with such a combination compared to monotherapy.

### Clinical

The clinical data relies on 4 bioequivalence studies and one pharmacokinetic drug interaction study which were also evaluated by the pharmaceutical chemistry evaluator. There are no clinical trials. The clinical evaluator has recommended approval. The clinical evaluator concluded:

- Bioequivalence was demonstrated between the combination tablet and the co-administered monotherapies.
- No evidence of a pharmacokinetic drug interaction.
- The formulation of amlodipine used in the studies was bioequivalent to Norvasc in Australia.
- Treatment was well tolerated in the studies
- There did not appear to be an increase in safety concerns from the combination product.
- The bioequivalence studies and pharmacokinetic interaction study demonstrated the same findings as noted by the pharmaceutical chemistry evaluator.
- There were no new efficacy data.
- Safety was similar between the combination and the co-administered monotherapy tablets, including adverse events, laboratory tests and ECGs. Decreases in BP were observed for both combination and co-administered monotherapies as expected, with slight differences that were not deemed clinically significant.

### Risk-Benefit Analysis

**Product's purpose:** The sponsor has stated that this product is designed to simplify treatment for patients on both drugs. However, no data have been submitted to support the concept that compliance or convenience is improved by this product. The clinical evaluator has cited a paper showing fixed dose combinations decrease non-compliance by 24% and the EU guideline on substitution indications, which has not been adopted by the TGA, discusses this type of submission and notes that improved compliance might be expected.

**Lack of clinical trial data:** Servier has not submitted any new clinical trials to demonstrate the efficacy and safety of this combination of medicines and such a combination is not currently registered in Australia as a fixed dose product. Fixed dose combination products are usually second line products in the treatment of hypertension when a patient has failed one of the components and then a second agent is added to the regimen in the form of the fixed combination product. Such indications require clinical trial data to demonstrate the benefit of adding a second agent to the treatment protocol and that data support dose titration. In this submission, the sponsor is requesting a different indication whereby a patient must

already be on both component medicines as individual products and then only when stable on those treatments could the doctor then substitute the two products for this single fixed combination product at the same dose level. This is known as a substitution indication and does not usually require clinical data to support it according to the EU guideline. This guideline notes the data requirements are usually pharmacokinetic and occasionally pharmacodynamic if needed. Depending on the dose interval (for example, both once daily or twice daily) and dose timing (for example, mane or nocte) for each component, then this will present different data requirements. In this case, perindopril is generally recommended once daily mane before meals and amlodipine is generally recommended once daily with or without meals. Therefore it is reasonable for this combination product to be administered once daily before meals in the morning, as is recommended in the proposed PI. To support the lack of clinical data, the sponsor has justified this by stating that both drugs have complementary and different mechanisms of action, compatible pharmacokinetic properties (once daily dosing), demonstrated safety and efficacy profiles as monotherapies and clinical benefit as seen in the ASCOT and CAFÉ studies. The PI for amlodipine also states in the dosage instructions that amlodipine has been safely administered with ACE inhibitors and that no dose adjustment is required for concomitant administration. The perindopril PI makes no mention of combined use with calcium channel blockers.

**Indication and heart failure:** Both perindopril and amlodipine are indicated for overlapping indications of hypertension treatment and established coronary artery disease / chronic stable angina. However, perindopril is also indicated for heart failure treatment whereas amlodipine is not. Although this in itself is not an objection, the concern is that the PI for Norvasc specifically advises caution in the use of amlodipine in patients with heart failure, being a calcium channel blocker. The maximum dose of perindopril in heart failure is also less than for the other indications (i.e. maximum of 5mg perindopril arginine or 4mg perindopril erbumine). The EU approved indication for this product only includes hypertension and / or stable coronary artery disease and not heart failure. Given that amlodipine is not contraindicated in heart failure, the Delegate expressed an inclination to include it in the indication. ADEC's advice was requested on this matter.

**Switching from Perindopril erbumine to the perindopril arginine in this product:**

Perindopril is registered as the erbumine salt by Servier and various generic sponsors and as the arginine salt by only Servier. Perindopril erbumine is registered in strengths of 2mg, 4mg and 8mg. Perindopril arginine is registered in strengths of 2.5mg, 5mg and 10mg. Bioequivalence has been previously demonstrated or justified by Servier between:

- 2mg perindopril erbumine and 2.5mg perindopril arginine
- 4mg perindopril erbumine and 5mg perindopril arginine
- 8mg perindopril erbumine and 10mg perindopril arginine.

The actual amount of perindopril is almost the same in both products (for example, the 8mg of perindopril erbumine contains 6.675mg of free perindopril and the 10mg of perindopril arginine contains 6.790mg of free perindopril). The submitted bioequivalence studies used the perindopril erbumine monotherapies and there were no data submitted using the perindopril arginine monotherapy. However given previous studies submitted by Servier comparing perindopril erbumine with arginine, then this would be acceptable. Since the intent of this submission is to switch from perindopril monotherapy, be that erbumine or arginine, to the perindopril arginine in this product, then the PI should include a clear statement, similar to the three dot points above, that 2mg perindopril erbumine is equivalent to 2.5mg perindopril arginine, etc, to avoid confusion from the different doses.

**Dose adjustments:** Related to the above issue is how to handle dose adjustments for such a product if it was required. Given the wording of the indication is a substitute for patients stable on both monotherapies, then if there was a need to adjust up or down, the indication would imply that a patient would be required to return to separate component drugs, with one or both of them at the new dose, be that higher or lower. Only then once re-established at the new dose level could the fixed dose combination product be substituted. It should also be remembered there is no clinical data to support dose titration with this product, although there is with each monotherapy. Therefore the PI should be clear that any dose adjustments, including for those with renal impairment or elderly, should be using the separate component products.

**Summary:** The sponsor has submitted sufficient data to support a substitution indication for this product. The main issues are the indication wording and whether heart failure should be included, addressing dose adjustments and potential for confusion when switching from perindopril erbumine to perindopril arginine in this product. The last issue was addressed in the product information.

**Advisory Committee Recommendation:** The Australian Drug Evaluation Committee (ADEC), having considered the evaluations and the Delegate's overview, recommended approval of the application for the indication:

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

The ADEC did not consider it appropriate to include heart failure as an indication for Coveram, as this indication is only TGA approved in Australia for the perindopril component but not for the amlodipine component of the combination.

ADEC also agreed with the Delegate that changes to the product information which should be made prior to approval include a statement to the effect that, in the absence of any clinical studies supporting dose adjustments with combined treatment, any dose adjustments conducted while receiving treatment with Coveram should be done using the individual components of the combination.

## Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of the fixed dose combination of perindopril arginine with amlodipine in strengths of Coveram 5mg/5mg, Coveram 5mg/10mg, Coveram 10mg/5mg, Coveram 10mg/10mg as a substitution therapy indication, based on the quality, safety and efficacy of the product being satisfactorily established for the indication below and for the reasons stated above:

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

## Attachment 1. Product Information

## PRODUCT INFORMATION

### NAME OF THE DRUG

#### COVERAM 5MG/5MG

perindopril arginine 5 mg/amlo地平ine besylate<sup>†</sup> 5 mg

#### COVERAM 5MG/10MG

perindopril arginine 5 mg/amlo地平ine besylate<sup>†</sup> 10 mg

#### COVERAM 10MG/5MG

perindopril arginine 10 mg/amlo地平ine besylate<sup>†</sup> 5 mg

#### COVERAM 10MG/10MG

perindopril arginine 10 mg/amlo地平ine besylate<sup>†</sup> 10 mg

### DESCRIPTION

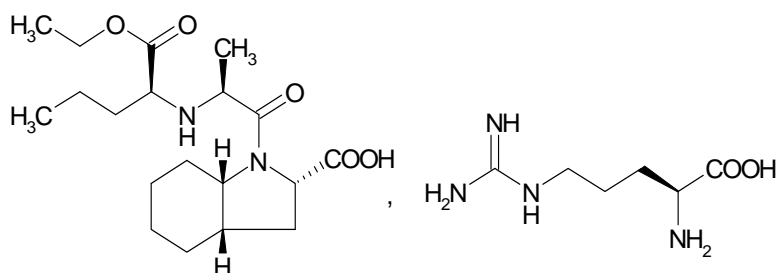
#### Active Ingredients

**Perindopril arginine** has the chemical name, L-arginine (2S, 3aS, 7aS) - 1 - N - [ (S) -1 - ethoxycarbonyl butyl ] - L - alanyl) perhydroindole-2 - carboxylate. It is a dipeptide monoacid monoester with a perhydroindole group and no sulphhydryl 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).

CAS Registry Number: 612548-45-5

Molecular formula: C<sub>19</sub>H<sub>32</sub>N<sub>2</sub>O<sub>5</sub>, C<sub>6</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>

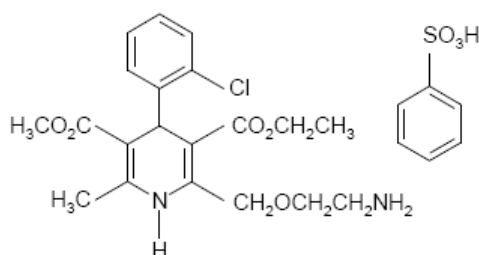
Chemical structure:



**Amlodipine besylate** is a dihydropyridine derivative, and has the following chemical name: 3-ethyl 5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzene sulphonate. Amlodipine besylate is chiral and present as a racemate. It is a white crystalline powder and is slightly soluble in water and sparingly soluble in ethanol. It has a molecular weight of 567.1 (free base 408.9).

CAS Registry Number: 111470-99-6

Molecular formula: C<sub>20</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>5</sub>·C<sub>6</sub>H<sub>6</sub>O<sub>3</sub>S

Chemical structure:**Excipients**

Lactose, cellulose microcrystalline, silica colloidal anhydrous, magnesium stearate.

**PHARMACOLOGY****Mechanism of Action**Related to 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 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.

Related to 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:

1. 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.
2. Amlodipine has been shown to block constriction in main coronary arteries and coronary arterioles, induced by calcium, potassium, adrenaline, serotonin and thromboxane A<sub>2</sub> analogue both in normal and in ischaemic regions.

### **Pharmacokinetics and Metabolism**

#### **Related to COVERAM**

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

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

A pharmacokinetic interaction study between perindopril arginine 10 mg and amlodipine 10 mg revealed that the extent and rate of bioavailability of perindopril, perindoprilat and amlodipine are similar for perindopril arginine 10 mg or amlodipine 10 mg administered alone or within a co-administration. No pharmacokinetic interaction exists between these two formulations.

#### **Related to perindopril**

Following oral administration, perindopril is rapidly absorbed with bioavailability of 24%. Elimination is rapid, occurring predominantly via the urine. Plasma half-life is approximately 1 hour. Bioavailability of the active metabolite perindoprilat is approximately 27%. Peak plasma concentrations of perindoprilat occur 3 to 4 hours after oral administration of perindopril. Protein binding of perindoprilat is 20%, principally to angiotensin converting enzyme. Perindoprilat binds to plasma and tissue ACE, and free perindoprilat is eliminated through the urine. The terminal half-life of the unbound fraction is approximately 17 hours. When perindopril is administered chronically, steady state of perindoprilat is reached within 4 days, and perindoprilat does not accumulate. Food intake may reduce hepatic biotransformation to perindoprilat. The elimination of perindoprilat is reduced in elderly patients and in patients with cardiac and renal failure. Apart from perindoprilat, the administration of perindopril leads to the formation of 5 other metabolites, all of which are inactive and exist in very low quantities. One of these is the glucuronoconjugate of perindoprilat, which is formed by a hepatic first-pass effect. This effect does not appear to have any influence on the kinetics of perindoprilat.

#### **Related to amlodipine**

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours postdose. This may reflect significant initial uptake by the liver, followed by a phase of redistribution. This interval is shorter (2-8 hours) in patients with hepatic insufficiency. Absolute bioavailability has been estimated to be between 64 and 90%.

The bioavailability of amlodipine is not altered by the presence of food. The volume of distribution is approximately 20 L/kg. The terminal plasma elimination half life is about 35- 50 hours and is

consistent with once daily dosing. Steady state plasma levels are reached after 7-8 days of consecutive dosing.

In elderly hypertensive patients (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%.

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

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

In hypertensive patients with 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.

## **Pharmacodynamics**

### **Related to perindopril**

#### ***Hypertension***

Studies carried out in animal models of hypertension have shown that perindopril is a specific competitive angiotensin I converting enzyme inhibitor. The administration of perindopril to patients with essential hypertension results in a reduction in supine and standing blood pressure without any significant effect on heart rate. Abrupt withdrawal of perindopril has not been associated with a rebound rise in blood pressure. Single dose studies have demonstrated that peak inhibition of ACE activity and peak reduction in blood pressure occurs 4-6 hours after administration. The durations of these effects are dose related and at the recommended dose range, both effects have been shown to be maintained over a 24-hour period.

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

In one study of 48 patients where 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 10 hours of regular observation. The possibility of late hypotensive response cannot be ruled out with perindopril.

### **Related to amlodipine**

#### ***Hypertension***

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 agents possessing significant negative inotropic effects.

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

## **CLINICAL TRIALS**

Clinical trials using COVERAM consist of three bioequivalence studies and a pharmacokinetic interaction study (see *PHARMACOKINETICS*).

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

### **Related to 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 (EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease) study was a multicentre, international, randomised, double blind, placebo-controlled clinical trial lasting 4 years. 12218 patients aged over 18 were randomised: 6110 patients to high dose perindopril, equivalent to perindopril arginine 10 mg and 6108 patients to placebo.

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

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

Study medication was added to conventional therapy, including medication used for the management of hyperlipidaemia, hypertension and diabetes mellitus. Patients randomised to perindopril were initiated on doses of perindopril equivalent to perindopril arginine 2.5 mg or perindopril arginine 5 mg for 2 weeks, and then titrated up to a dose of perindopril equivalent to

perindopril arginine 10 mg during the 2 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 agents and beta-blockers. At the end of the study, the proportions of patients on these concomitant medications were 91%, 69% and 63% respectively.

The 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 3 years of continuous treatment on perindopril

### **Related to 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 concomitant beta-blockers. 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 therapy 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 1 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 1153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin and diuretics. Follow-up was at least 6 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 8-12 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 **PRECAUTIONS**).

## **INDICATIONS**

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

## **CONTRAINDICATIONS**

COVERAM is contraindicated:

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

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

### Related to Perindopril component

- in patients with bilateral or unilateral renal artery stenosis.
- in patients with a history of hereditary and/or idiopathic angio-oedema or angio-oedema associated with previous ACE-inhibitor treatment, and
- in patients haemodialysed using high-flux polyacrylonitrile ("AN69") membranes who are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. This combination should therefore be avoided, either by use of alternative antihypertensive drugs or alternative membranes (e.g. cuprophane or polysulphone PSF).

### Related to Amlodipine component

- severe hypotension.
- shock, including cardiogenic shock.
- obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis).
- unstable angina pectoris (excluding Prinzmetal's angina).
- heart failure after acute myocardial infarction (during the first 28 days).

## **PRECAUTIONS**

**Related to COVERAM****Lactose intolerance**

Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, glucose galactose malabsorption, or the Lapp lactase deficiency should not take this medicinal product.

**Related to perindopril component****Hyperkalaemia**

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

**Angio-oedema**

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

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

Angio-oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients with ACE inhibitors and has been reported uncommonly with perindopril. 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. Angio-oedema associated with laryngeal oedema may be fatal or near fatal. In most cases symptoms occurred during the first week of treatment and the incidence appears to be similar in both sexes or those with heart failure or hypertension.

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

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

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

Patients may have multiple episodes of angio-oedema with long symptom-free intervals.

Angio-oedema may occur with or without urticaria.

Intestinal angio-oedema 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 angio-edema and C-1 esterase levels were normal. The angio-oedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angio-edema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

There are reports when changing a patient to another ACE inhibitor was followed by recurrence of angio-oedema and others where it was not. Because of the potential severity of this rare event, another ACE inhibitor should not be used in patients with a history of angio-oedema, to a drug of this class (see **CONTRAINDICATIONS**).

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

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

### Hypotension

Hypotension has been reported in patients commencing treatment with ACE inhibitors. Excessive hypotension is rarely seen in uncomplicated hypertension but is a potential consequence of perindopril use in severely salt/volume-depleted patients with impaired renal function, those treated vigorously with diuretics, after severe diarrhoea or patients on dialysis. 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 severe congestive heart failure, with or without associated renal impairment, excessive hypotension has been observed. 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, therapy should be started at low doses under very close supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dosage is increased, or diuretic therapy is commenced or increased.

Patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident should be closely followed for the first two weeks of treatment and whenever the dose of perindopril and/or diuretic is increased.

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

### Impaired renal function

As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on RAAS activity, treatment with ACE inhibitors may be

associated with oliguria and/or progressive increase in blood nitrogen, and rarely with acute renal failure and/or death.

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

Some hypertensive patients with no apparent pre-existing renovascular disease have developed increases in blood urea, nitrogen and serum creatinine, which are usually minor and transient. This is more likely to occur in patients with pre-existing renal impairment or in those on diuretics. Dosage reduction of the ACE inhibitor and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. If deterioration in renal function has occurred after treatment with one ACE inhibitor, then it is likely to be precipitated by another and in these patients usage of another class of antihypertensive agent would be preferable. Patients with unilateral renal artery disease present a special problem as deterioration of function may not be apparent from measurement of blood urea and serum creatinine.

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

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

### Hepatic failure

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

### Impaired hepatic function

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



### Race

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.

### Cough

A persistent dry (non-productive) irritating cough has been reported with most of the ACE inhibitors. The frequency of reports has been increasing since cough was first recognised as a class-effect of ACE inhibitor therapy with the incidence of cough varying between 2-15% depending upon the drug, dosage and duration of use.

The cough is often worse when lying down or at night, and has been reported more frequently in women (who account for 2/3 of the reported cases). Patients who cough may have increased bronchial reactivity compared with those who do not. The observed higher frequency of this side-effect in non-smokers may be due to a higher level of tolerance of smokers to cough.

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

### Proteinuria

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

### Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever).

### Dermatological reactions

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

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

### Taste disturbances (dysgeusia)

Taste disturbances were reported to be common (prevalence up to 12.5%) with high doses of one ACE inhibitor. The actual incidence of taste disturbance is probably low (<0.5%) but data are scarce and difficult to interpret.

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

### Agents causing renin release

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

### Surgery and anaesthesia

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

### Valvular stenosis

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

### Diabetic patients

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

## **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 therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

### Use in Patients with Congestive Heart Failure

Patients with cardiac failure should be treated with caution.

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 *CLINICAL TRIALS*).

### Use in Patients with Impaired Hepatic Function

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.

#### Use in Impaired renal function:

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.

#### Peripheral Oedema

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

#### Use in Pregnancy – Category D

No animal studies with COVERAM have been performed.

COVERAM 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 should be stopped immediately, and, if appropriate, alternative therapy should be started.

#### Related to perindopril component

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. If a patient intends to become pregnant, treatment with ACE inhibitors must be discontinued and replaced by another form of treatment. If a patient becomes pregnant while on ACE inhibitors, she must immediately inform her doctor to discuss a change in medication and further management.'

There are no adequate and well-controlled studies of ACE inhibitors in pregnant women, but foetotoxicity is well documented in animal models. Data, however, show that ACE inhibitors cross the human placenta. Post marketing experience with all ACE inhibitors suggests that exposure *in utero* may be associated with hypotension and decreased renal perfusion in the foetus. ACE inhibitors have also been associated with foetal death *in utero*.

A historical cohort study in over 29,000 infants born to non-diabetic mothers has shown 2.7 times higher risk for congenital malformations in infants exposed to 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 hypotension, renal failure, skull hypoplasia and death.

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

Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalaemia. If such complications arise, appropriate medical treatment should be initiated to support blood pressure and renal perfusion. While small amounts of perindopril are found in the breast milk of animals, there is no human data.

#### Related to amlodipine component

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

Safety of Amlodipine in human pregnancy or lactation has not been established. In animal studies, amlodipine did not affect fertility in rats at oral doses up to 18 mg/kg (base) and had no teratogenic effects in rats (18 mg/kg) or rabbits (10 mg/kg). Amlodipine (10 mg/kg as besylate salt, 7 mg/kg base), administered orally to rats at or near parturition induced a prolongation of gestation time, an increase in the number of stillbirths and a decreased postnatal survival.

#### Use in Lactation

No animal studies with COVERAM have been performed.

#### Related to perindopril component

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

It is not known whether amlodipine is excreted in human milk. In the absence of this information, breast-feeding should be discontinued during treatment with amlodipine.

#### Paediatric Use

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

#### Use in the Elderly

##### Related to perindopril component

Care should be taken when prescribing perindopril to elderly patients.

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

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

##### 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.

### **Carcinogenicity, Genotoxicity, Impairment of Fertility**

No animal studies with COVERAM have been performed.

#### **Related to perindopril component**

Carcinogenicity studies have not been conducted with perindopril arginine. 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 2 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 ACE inhibitors to cause this effect in man is unknown. Moreover, the progression of oxyphilic cells to oncocytomas is rare in humans and when it does occur, it is considered to be benign.

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

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

#### **Related to Amlodipine component**

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.

### **Interactions With Other Medicines**

#### **Related to perindopril component**

##### **Concomitant use not recommended:**

##### ***Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:***

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

##### ***Lithium:***

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

##### **Concomitant use which requires special care:**

*Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin  $\geq 3$  g/day:*

The administration of a non-steroidal anti-inflammatory drug 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 renal function after initiation of concomitant therapy, and periodically thereafter.

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

*ACE inhibitors, anti-inflammatory drugs and thiazide diuretics:*

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

*Antidiabetic agents (insulin, hypoglycaemic sulphonamides):*

Reported with captopril and enalapril.

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

*Concomitant use to be taken into consideration:**Diuretics:*

When a diuretic is added to the therapy of a patient receiving an ACE inhibitor, the antihypertensive effect is usually additive. Patients receiving diuretics, especially those in whom diuretic therapy was recently instituted or in those with intravascular volume depletion, may sometimes experience an excessive reduction of blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects may be minimised by ensuring adequate hydration and salt intake prior to commencing ACE inhibitor therapy. The starting dose of the ACE-inhibitor should be reduced and the patient closely observed for several hours following the initial dose of the ACE inhibitor and until the blood pressure has stabilised.

*Gold:*

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

*Tetracycline and other drugs that interact with magnesium:*

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

*Agents Affecting Sympathetic Activity:*

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

Concomitant use not recommended :*Dantrolene (infusion):*

In animals, lethal ventricular fibrillations are observed after administration of verapamil and dantrolene I.V. By extrapolation, the combination of amlodipine and dantrolene should be avoided.

Concomitant use which requires special care :*CYP3A4 inducers (rifampicin, Hypericum perforatum, anticonvulsant agents i.e carbamazepine, phenobarbitone, phenytoin, primidone):*

Co-administration 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 the dose of amlodipine should be adjusted if necessary.

*CYP3A4 inhibitors (itraconazole, ketoconazole):*

Co-administration may increase the plasma concentration of amlodipine and consequently its adverse effects. Caution should be exercised when combining amlodipine with itraconazole or ketoconazole and the dose of amlodipine should be adjusted if necessary.

*Baclofen:*

Potential of antihypertensive effect. Monitoring of blood pressure and renal function, and dose adaptation of the antihypertensive if necessary.

Concomitant use to be taken into consideration:*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 haemodynamic repercussion.

*Antihypertensive agents (such as beta-blockers) and vasodilators:*

Concomitant use of these agents may increase the hypotensive effects of perindopril and amlodipine.

Concomitant use with nitroglycerine and other nitrates or other vasodilators, may further reduce blood pressure and therefore should be considered with caution.

*Corticosteroids:*

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

*Alpha-blockers (prazosin, tamsulosin, terazosin):*

Increased antihypertensive effect and increased risk of orthostatic hypotension.

*Amifostine:*

May potentiate the antihypertensive effect of amlodipine.

*Tricyclic antidepressants/antipsychotics/anaesthetics:*

Increased antihypertensive effect and increased risk of orthostatic hypotension.

Other concomitant use:

Specific studies conducted with other drugs 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 agent independently exerted its own blood pressure lowering effect.

*Aluminium/magnesium (antacid):*

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

*Grapefruit juice:*

Grapefruit juice is known to inhibit the cytochrome P450 system, thereby affecting the pharmacokinetics of drugs such as calcium channel blockers.

In a study of 20 healthy volunteers, co-administration of 240ml 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 drugs have shown that amlodipine has no influence on the pharmacokinetics parameters of those drugs:

*Atorvastatin:*

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

*Digoxin:*

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

*Warfarin:*

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

*Cyclosporin:*

Pharmacokinetic studies with cyclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of cyclosporin. Patients in these studies were not taking corticosteroids.

*Alcohol:*

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

Effects on the ability to drive or operate machinery

No studies on the effects of COVERAM on the ability to drive and use machines have been performed. When driving or operating machines it should be taken into account that occasionally dizziness or weariness related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication.

Effects on laboratory tests

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Reported with perindopril component

Elevation of liver enzymes and serum bilirubin have been reported rarely. Increases in blood urea, serum creatinine and hyperkalaemia have also been reported.

Reported with amlodipine component

Amlodipine therapy 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.

**ADVERSE EFFECTS**

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

The following undesirable effects have been observed with an amlodipine/perindopril treatment regimen; with perindopril monotherapy; and with amlodipine monotherapy, and ranked under the following frequency:

Very common (>10%); common (>1%, <10%); uncommon (>0.1%, <1%); rare (>0.01%, <0.1%), very rare (>0.001%, <0.01%), not known (cannot be estimated from the available data).

**Reported with amlodipine/perindopril treatment regimen (see PHARMACOLOGY-pharmacodynamics):**Nervous System disorders:

*Very common:* dizziness

*Common:* vertigo

Cardiac disorders:

*Common:* chest pain

*Uncommon:* bradycardia

Vascular Disorders:

*Uncommon:* peripheral coldness

Respiratory, Thoracic and Mediastinal Disorders:

*Very common:* cough

*Common:* dyspnoea

Gastro-intestinal disorders:

*Common:* diarrhoea

Skin and Subcutaneous Tissue Disorders:

*Common:* eczema

Musculoskeletal And Connective Tissue Disorders:

*Very common:* joint swelling

Reproductive System and Breast Disorders:

*Common:* erectile dysfunction

General Disorders and Administration Site Condition:

*Very common:* oedema peripheral

*Common:* fatigue, lethargy

Reported with perindopril:Blood and the lymphatic System Disorders:

*Very rare:* leucopenia/neutropenia (see PRECAUTIONS), agranulocytosis or pancytopenia (see PRECAUTIONS), thrombocytopenia (see PRECAUTIONS), haemolytic anaemia in patients with a congenital deficiency of G-6PDH (see PRECAUTIONS), decrease in hemoglobin and haematocrit

Immune system Disorders:

*Uncommon:* allergic reaction; urticaria

Metabolism and nutrition disorders:

*Not known:* hypoglycaemia (see PRECAUTIONS)

Psychiatric disorders:

*Uncommon:* mood changes, sleep disturbances (insomnia, dream abnormality)

*Very rare:* depression

Nervous System disorders:

*Common:* dizziness, headache, drowsiness, paresthaesia, vertigo

*Very rare:* confusion, hallucinations

Eye disorders:

*Common:* visual disturbances

Ear and labyrinth disorders:

*Common:* tinnitus

Cardiac disorders:

*Common:* palpitations, impaired peripheral circulation

*Very rare:* angina pectoris, myocardial infarction and stroke, possibly secondary to excessive hypotension in high risk patients (see PRECAUTIONS), arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)

Vascular Disorders:

*Common:* flushing, hypotension (and effects related to hypotension)

*Very rare:* stroke possibly secondary to excessive hypotension in high-risk patients (see PRECAUTIONS), vasculitis

Respiratory, Thoracic and Mediastinal Disorders:

*Common:* dyspnoea, epistaxis, discomfort on exertion, cough

*Uncommon:* bronchospasm

*Very rare:* rhinitis, eosinophilic pneumonia

Gastro-intestinal disorders:

*Common:* abdominal pain, nausea, vomiting, dyspepsia, dysgeusia, diarrhoea, constipation

*Uncommon:* dry mouth

*Very rare:* pancreatitis

Hepato-biliary Disorders:

*Very rare:* hepatitis either cytolytic or cholestatic (see PRECAUTIONS)

Skin and Subcutaneous Tissue Disorders:

*Common:* pruritis, rash

*Uncommon:* angio-edema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see PRECAUTIONS), sweating

*Very rare:* erythema multiform

Musculoskeletal And Connective Tissue Disorders:

*Common:* muscle cramps

Renal and Urinary Disorders:

*Uncommon:* renal impairment

*Very rare:* acute renal failure

Reproductive System and Breast Disorders:

*Uncommon:* impotence

General Disorders and Administration Site Condition:

*Common:* asthenia

*Uncommon:* atypical chest pain

Withdrawals

In total 56 of 1275 patients studied (4.4%) stopped treatment because of adverse reactions. In a specific study of 632 patients in which 36 (5.7%) patients withdrew because of adverse events, a plausible or probable relationship with perindopril treatment was considered to exist in 19 (3%) cases.

Reported with amlodipine:Blood and the lymphatic System Disorders:

*Uncommon:* leucopenia, thrombocytopenia

*Very rare:* neutropenia (see PRECAUTIONS)

Immune system Disorders:

*Uncommon:* allergic reaction

*Rare:* urticaria

Metabolism and Nutrition Disorders:

*Uncommon:* weight gain, weight decrease, thirst, hyperglycaemia

*Rare:* increased appetite

Psychiatric disorders:

*Uncommon:* insomnia, mood changes, sexual dysfunction (male and female), nervousness, depression, dream abnormality, anxiety, depersonalisation

*Rare:* apathy, agitation, amnesia

Nervous System disorders:

*Common:* somnolence, dizziness, headache

*Uncommon:* tremor, hypoesthesia, paresthesia, vertigo, peripheral neuropathy

*Rare:* migraine, parosmia

*Very rare:* hypertonia

Eye disorders:

*Uncommon:* visual disturbances, conjunctivitis, diplopia, eye pain

*Rare:* dry eyes, abnormal visual accommodation

Ear and labyrinth disorders:

*Uncommon:* tinnitus

Cardiac disorders:

*Common:* palpitations

*Uncommon:* syncope, peripheral ischaemia, postural dizziness, postural hypotension, tachycardia

*Rare:* myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see PRECAUTIONS), angina pain, cardiac failure, pulse irregularity, extrasystoles, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)

Vascular Disorders:

*Common:* flushing

*Uncommon:* hypotension (and effects related to hypotension), vasculitis

*Rare:* cold and clammy skin

Respiratory, Thoracic and Mediastinal Disorders:

*Uncommon:* dyspnoea, rhinitis, epistaxis

*Very rare:* cough

Gastro-intestinal Disorders:

*Common:* abdominal pain, nausea

*Uncommon:* vomiting, dyspepsia, altered bowel habits, dry mouth, taste perversion, dysgeusia, anorexia, dysphagia, flatulence, constipation, diarrhoea, gingival hyperplasia, pancreatitis

*Rare:* loose stools, gastritis

Hepato-biliary Disorders:

*Rare:* hepatitis, cholestatic jaundice, hepatic enzyme elevations

Skin and Subcutaneous Tissue Disorders:

*Uncommon:* alopecia, purpura, increased sweating, pruritis, rash, rash erythematous, rash maculopapular, skin discolouration, angio-edema

*Rare:* skin dryness, erythema multiform, dermatitis

*Very rare:* Quincke's oedema, Stevens-Johnson syndrome

Musculoskeletal And Connective Tissue Disorders:

*Uncommon:* arthralgia, arthrosis, myalgia, muscle cramps, back pain

*Rare:* muscle weakness, twitching, ataxia, hypertonia

Renal and Urinary Disorders:

*Uncommon:* micturition disorder, nocturia, increased urinary frequency

*Rare:* dysuria

Reproductive System and Breast Disorders:

*Uncommon:* impotence, gynaecomastia

General Disorders and Administration Site Condition:

*Common:* oedema, peripheral oedema, fatigue

*Uncommon:* chest pain, asthenia, pain, malaise, rigors

**DOSAGE AND ADMINISTRATION**

COVERAM (perindopril arginine/ amlodipine) is available in strengths of 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg as substitution therapy for patients already controlled with separate doses of perindopril (5 or 10 mg) and amlodipine (5 or 10 mg), given concurrently at the dose level as indicated in the table below. Treatment should not be initiated with this combination.

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

perindopril arginine	and or erbumine	amlodipine	COVERAM
5 mg	4 mg	5 mg	COVERAM 5MG/5MG
5 mg	4 mg	10 mg	COVERAM 5MG/10MG
10 mg	8 mg	5 mg	COVERAM 10MG/5MG
10 mg	8 mg	10 mg	COVERAM 10MG/10MG

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

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

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

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

### **Patients with impaired renal function and elderly patients**

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

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

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

### **Patients with impaired hepatic function**

A dosage regimen for patients with hepatic impairment has not been established. Therefore, COVERAM should be administered with caution.

## **OVERDOSAGE**

There is no information on overdosage with COVERAM in humans.

### **Related to perindopril component**

Limited data are available for overdosage in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. Perindopril may be

removed from the general circulation by haemodialysis (See PRECAUTIONS). Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

#### Related to amlodipine component

Available data suggest that overdose 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 1- to 5 hours following overdose. Hypotension can persist for longer than 24 hours despite treatment. Cardiac rhythm disturbances have been noted to persist for up to 7 days. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.


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 2 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.

Advice on overdose management can be obtained from the national Poisons Information Centre by telephoning 131126.


## **PRESENTATION AND STORAGE CONDITIONS**

### **Presentation**


#### **COVERAM 5MG/5MG**

White, rod-shaped tablet engraved with 5/5 on one face and  on the other face, containing 5 mg perindopril arginine and 5 mg amlodipine. Supplied in a polypropylene container equipped with a low density polyethylene flow reducer and a low density polyethylene stopper containing a desiccant gel. Supplied in a tube of 30 tablets<sup>#</sup>


#### **COVERAM 5MG/10MG**

White, square-shaped tablet engraved with 5/10 on one face and  on the other face, containing 5 mg perindopril arginine and 10 mg amlodipine. Supplied in a polypropylene container equipped with a low density polyethylene flow reducer and a low density polyethylene stopper containing a desiccant gel. Supplied in a tube of 30 tablets<sup>#</sup>

#### **COVERAM 10MG/5MG**

White, triangular-shaped tablet engraved with 10/5 on one face and  on the other face, containing 10 mg perindopril arginine and 5 mg amlodipine. Supplied in a polypropylene container equipped with a low density polyethylene flow reducer and a low density polyethylene stopper containing a desiccant gel. Supplied in a tube of 30 tablets<sup>#</sup>

#### **COVERAM 10MG/10MG**

White, round tablet engraved with 10/10 on one face and  on the other face, containing 10 mg perindopril arginine and 10 mg amlodipine. Supplied in a polypropylene container equipped with a

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low density polyethylene flow reducer and a low density polyethylene stopper containing a desiccant gel. Supplied in a tube of 30 tablets<sup>#</sup>

**Storage Conditions**

Store in a dry place below 30°C. Keep the container tightly closed and protect from light.

**NAME AND ADDRESS OF THE SPONSOR**

Servier Laboratories (Australia) Pty Ltd  
8 Cato Street  
PO Box 196  
HAWTHORN VIC 3122  
ABN 54 004 838 500

**POISONS SCHEDULE**

S4

**DATE OF TGA APPROVAL**

13 November, 2009

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<sup>†</sup> Amlodipine doses are given as active base

<sup>#</sup> A 10- tablet presentation is also available for hospital pharmacy use only

## **Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia

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