Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Coveram Plus SR

Active ingredients: Perindopril arginine, amlodipine, indapamide

Sponsor: Servier Laboratories (Aust.) Pty Ltd

November 2026

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About AusPARs

- The Australian Public Assessment Report (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. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

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List of abbreviations

Abbreviation	Meaning
ACE	Angiotensin-converting enzyme inhibitor
ACM	Advisory Committee on Medicines
ARB	Angiotensin II receptor blocker
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
ASH	American Society of Hypertension
AUC_t	Area under the plasma concentration-time curve from time zero to the last measurable concentration or last sampling time t, whichever occurs first
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
BP	Blood Pressure
C_{max}	Maximum plasma concentration
CMI	Consumer Medicines Information
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DLP	Data lock point
EAEs	Emergent adverse events
EU	Europe Union
FDC	Fixed dose combinations
HDPE	High-Density Polyethylene
PI	Product Information
PK	Pharmacokinetic
PSUR	Periodic safety update report
PT	Preferred term
PY	Patient years
RMP	Risk management plan
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System Organ Class
SR	Sustained release
SS	Safety set
TGA	Therapeutic Goods Administration
T_{max}	Time to reach maximum plasma concentration

Product submission

Submission details

Type of submission:	New fixed combination medicine
Product names:	Coveram Plus 5/5/1.5 SR Coveram Plus 10/5/1.5 SR Coveram Plus 10/10/1.5 SR
Active ingredients:	Perindopril arginine, amlodipine, indapamide
Decision:	Approved
Date of decision:	18 August 2026
Date of entry onto ARTG:	25 August 2026
ARTG numbers:	485985, 485986, 485987
▼*Black Triangle Scheme for the current submission:*	No
Sponsor's name and address:	Servier Laboratories (Aust.) Pty Ltd Level 4, Building 9 588A Swan Street Burnley, 3121, Victoria
Dose form:	Capsule, modified release
Strengths:	Coveram Plus 5/5/1.5 SR – each capsule contains 5 mg of perindopril arginine, 5 mg of amlodipine (as besilate‡) and 1.5 mg of indapamide Coveram Plus 10/5/1.5 SR – each capsule contains 10 mg of perindopril arginine, 5 mg of amlodipine (as besilate‡) and 1.5 mg of indapamide Coveram Plus 10/10/1.5 SR - each capsule contains 10 mg of perindopril arginine 10 mg of amlodipine (as besilate‡) and 1.5 mg of indapamide ‡ Amlodipine doses are given as active base
Container:	White HDPE, child resistant bottle
Pack size:	30 tablets
Approved therapeutic use for the current submission:	*Coveram Plus SR is indicated as substitution therapy for treatment of hypertension, in patients already controlled with perindopril, amlodipine and indapamide, taken at the same dose level. Treatment should not be initiated with this combination.*
Route of administration:	Oral use
Dosage:	Coveram Plus SR (perindopril arginine, amlodipine, indapamide) is recommended as a daily, single dose available as substitution therapy for patients already controlled with equivalent separate doses of perindopril, amlodipine and indapamide, given concurrently at the dose level as indicated in the table below.

Table 1. Dose conversion from perindopril, amlodipine and indapamide to Coveram Plus SR.

Perindopril		amlodipine	indapamide	Coveram Plus SR
arginine	erbumine			
5 mg	4 mg	5 mg	1.5 mg	Coveram Plus 5/5/1.5 SR
10 mg	8 mg	5 mg	1.5 mg	Coveram Plus 10/5/1.5 SR
10 mg	8 mg	10 mg	1.5 mg	Coveram Plus 10/10/1.5 SR

For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.

Pregnancy category: **Category D**

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

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Servier Laboratories (Australia) (the sponsor) to register:

- Coveram Plus 10/10/1.5 SR perindopril arginine 10 mg/amlodipine (as besilate) 10 mg/ indapamide 1.5 mg modified release capsule bottle
- Coveram Plus 10/5/1.5 SR perindopril arginine 10 mg/amlodipine (as besilate) 5 mg/ indapamide 1.5 mg modified release capsule bottle
- Coveram Plus 5/5/1.5 SR perindopril arginine 5 mg/amlodipine (as besilate) 5 mg/ indapamide 1.5 mg modified release capsule bottle

for the following proposed indication:[1]

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

The new fixed dose combination (FDC) products proposed in this application contain perindopril arginine, amlodipine (as besilate), and indapamide hemihydrate sustained release (SR) in three different strength combinations. Each of the mono-components has a well-established history of use in the treatment of hypertension. The strengths of the FDC products

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

have been selected based on approved dosages for each active substance as a mono-component product (Coversyl, Norvasc, Natrilix SR).

The FDC products are proposed as substitution therapy in patients already controlled with perindopril, amlodipine and indapamide at the same dose level. Combination therapy, including triple combination of ACE inhibitor (or angiotensin receptor blocker), calcium channel blocker, and diuretic, is supported by international clinical practice guidelines for the management of hypertension.[2]

The clinical development of the proposed FDC products was informed by regulatory guidance in the *Guideline on clinical development of fixed combination medicinal products*,[3] the *Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms,* and *Clinical investigation of medicinal products for long-term use*.

The FDC products proposed in this application were also submitted, and approved, under the tradenames Reaptan Plus SR and Triplixam SR. The corresponding AusPARs are available on the TGA website.

Disease or condition

Hypertension is an important and treatable cause of cardiovascular disease (CVD) morbidity and mortality. High systolic blood pressure contributed to 53% of ischaemic heart disease deaths, 53% of stroke deaths and 62% of deaths from chronic kidney disease, according to the World Health Organisation's *Global report on hypertension: the race against a silent killer*. [4]

Furthermore, hypertension is an independent risk factor for myocardial infarction, chronic kidney disease, ischaemic and haemorrhagic stroke, heart failure and premature death. If left uncontrolled or untreated, hypertension is associated with increasing CVD risk, and the onset of vascular and renal damage.

Globally, the prevalence of hypertension was slightly higher among males (34%) than females (32%). This female advantage is age-related: the global age standardised prevalence of hypertension among people aged 30–49 years is 19% for women versus 24% for men. This pattern of lower hypertension prevalence among women aged under 50 years holds in most countries worldwide. However, for people aged 50–79 years, both men and women globally are estimated to have equivalent hypertension prevalence of 49%.[4]

In Australia, over one in ten (11.6%) or 3 million people reported having hypertension in 2022.[5] Prevalence of reported hypertension was similar for males and females (11.7% and 11.6%, respectively) with prevalence increasing with age and almost tripling between the 35-44 years (4.7%) and 45-54 years (12.4%) age groups.[5]

Current treatment options

There are several classes of antihypertensives routinely used in Australia. These include ACE inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers (dihydropyridine and non-dihydropyridine), thiazide-like diuretics, and beta-blockers. There are other less

[2] McEvoy et al. (2024). 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. Eur Heart Journal; 45(38): 3912-4018 https://doi.org/10.1093/eurheartj/ehae178

[3] Committee for Medicinal Products for Human Use (CHMP) (2009) Guideline on clinical development of fixed combination medicinal products. EMA Doc. Ref. CHMP/EWP/240/95 Rev. 1

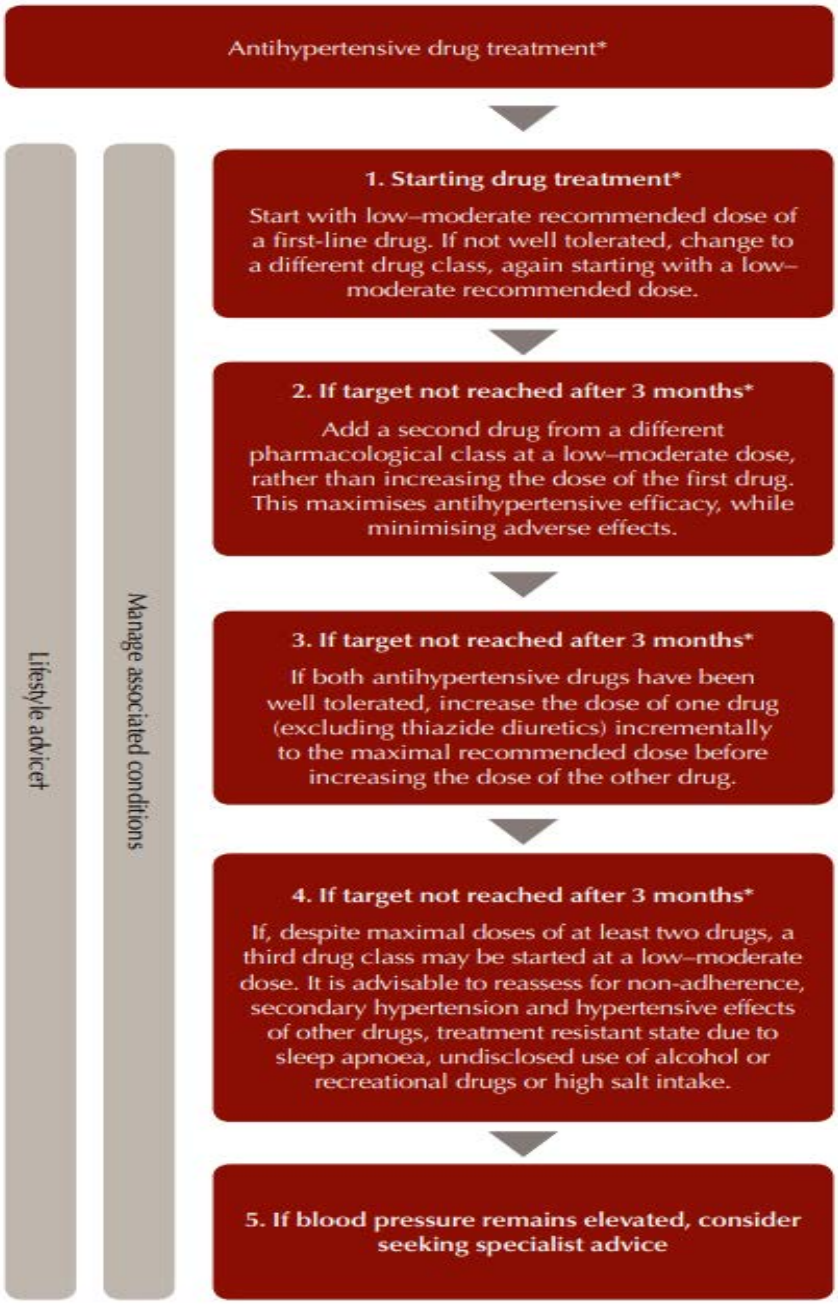
[4] Global report on hypertension: the race against a silent killer. Geneva: World Health Organization; 2023. Licence: CC BY-NC-SA 3.0 IGO. *Global report on hypertension: the race against a silent killer*

[5] Hypertension and high measured blood pressure, 2022 | Australian Bureau of Statistics

commonly prescribed antihypertensive agents, including amiloride, clonidine, hydralazine, methyldopa, moxonidine, prazosin, and spironolactone.

The current guideline for the diagnosis and management of hypertension in adults,[6] published in 2016, is currently undergoing a review. Commencing in 2025, the Heart Foundation is leading the development of critical updates of the clinical guideline for managing hypertension (high blood pressure). The following chart provides a general strategy in Australia for the treatment of hypertension using medicines (Figure 1).

Figure 1. Antihypertensive drug treatment strategy.[6]



*Maximum effect of drug likely to be seen in 4–6 weeks. If baseline blood pressure is severely elevated earlier reviews may be considered. For steps 1–4, review every 4–6 weeks for tolerance, efficacy and adverse effects. †All patients should receive lifestyle advice with follow-up based on clinical context.

Source: National heart Foundation (2016) Guidelines for the diagnosis and management of hypertension in adults, pg. 36

[6] National heart Foundation (2016) Guidelines for the diagnosis and management of hypertension in adults. Hypertension-guideline-2016_WEB.pdf

Clinical rationale

Coveram Plus SR is a combination of three antihypertensive components with complementary mechanisms to control blood pressure in patient with hypertension. The components include perindopril arginine salt, amlodipine and indapamide is a chlorosulphamoyl diuretic.

Perindopril 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 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.

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. 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 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.

Indapamide is an oral antihypertensive medicine whose mechanism of action has not been fully elucidated; both vascular and renal effects have been implicated. The possible beneficial pharmacological effects of indapamide in the treatment of hypertension include a reduction in cardiac hypertrophy and a reduction in the thickening of arterial walls, a prevention of the accumulation of the embryonic isoform of fibronectin in coronary vessels, free radical scavenging leading to stimulation of vasodilator eicosanoid formation, and interaction with renal carbonic anhydrase.

Combining a renin-angiotensin system blocker, calcium channel blocker, and a thiazide diuretic agent is in line with the recommended combinations of classes by most current international and national guidelines for the management of hypertension, including:

- European Society of Cardiology (ESC) guidelines,
- European Society of Hypertension (ESH) guidelines,
- American Society of Hypertension (ASH) guidelines,
- International Society of Hypertension (ISH) guidelines.

These international guidelines indicate that combination therapy is safe and effective, and provides a synergistic effect based on their pharmacological mode of action. Further, the American Society of Hypertension's Position Papers on combination therapy in management of hypertension report that an appropriate combination of antihypertensive agents may improve the reaching of target blood pressure control and tolerability since each agent in the combination can lessen the adverse effects of other components.[7] In addition, it is suggested that the reduced pill load for patients can potentially help with long-term adherence to the treatment.[7]

[7] Gradman, A. H., Basile, J. N., Carter, B. L., Bakris, G. L., & American Society of Hypertension Writing Group (2011). Combination therapy in hypertension. *Journal of clinical hypertension (Greenwich, Conn.)*, *13*(3), 146–154. https://doi.org/10.1111/j.1751-7176.2010.00397.x

Regulatory status

Australian regulatory status

This product is considered a new fixed dose combination (FDC) medicine for Australian regulatory purposes. This is the first application to register a triple-component FDC of perindopril, amlodipine, and indapamide in Australia.

The Australian monotherapy reference products relevant to this submission are:

- Coversyl perindopril arginine 5 mg and 10 mg tablet bottle [8,9] by Servier Laboratories (Aust) Pty Ltd
- Norvasc amlodipine (as besilate) 5mg and 10 mg tablet blister [10,11] by Aspen Pharmacare Australia Pty Ltd
- Natrilix SR indapamide hemihydrate 1.5 mg tablet blister [12] by Servier Laboratories (Aust) Pty Ltd.

FDC products containing perindopril arginine and amlodipine (Coveram) and perindopril arginine and immediate release indapamide (Coversyl Plus 5/1.25, Coversyl Plus LD 2.5/0.625) are well established. Coveram has a substitution indication and is registered in 4 strengths of 5/5, 5/10, 10/5, and 10/10. Coversyl Plus is indicated for the treatment of hypertension. Treatment can be initiated with Coversyl Plus LD 2.5/0.625, with an option to up-titrate to Coversyl Plus 5/1.25.

Other triple-component FDC products for the treatment of hypertension registered on the Australian Register of Therapeutic Goods (ARTG), include Exforge-HCT (valsartan/ amlodipine/ hydrochlorothiazide) and Sevikar-HCT (olmesartan/amlodipine/hydrochlorothiazide). Exforge-HCT has a substitution indication, whereas Sevikar-HCT has substitution and add-on indications.

International regulatory status

A FDC of perindopril, amlodipine, and *immediate release* indapamide (Triplixam) has had marketing approval in the Europe Union (EU) since 2013. It has been approved in 96 countries and is currently marketed in 83 countries. Triplixam has a substitution indication for the treatment of hypertension, and is marketed in four strengths: 5 mg/5 mg/1.25 mg, 5 mg/10 mg/1.25 mg, 10 mg/5 mg/2.5 mg, and 10 mg/10 mg/2.5 mg.

At the time the TGA considered this submission, a similar submission for Triplixam SR was under consideration in France, Latvia, Lithuania and Poland (decentralised procedure-submitted on 3 March 2025). The proposed indication is a substitution indication similar to that proposed in Australia.

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

[8] COVERSYL 5 perindopril arginine 5 mg tablet bottle (101568) | Therapeutic Goods Administration (TGA)
[9] COVERSYL 10 perindopril arginine 10 mg tablet bottle (101569) | Therapeutic Goods Administration (TGA)
[10] NORVASC amlodipine 5mg (as besilate) tablet blister pack (42902) | Therapeutic Goods Administration (TGA)
[11] NORVASC amlodipine 10mg (as besilate) tablet blister pack (42903) | Therapeutic Goods Administration (TGA)
[12] NATRILIX SR Indapamide hemihydrate 1.5mg tablet blister pack (66849) | Therapeutic Goods Administration (TGA)

Table 1. Timeline for Submission PM-2025-00787-1-3.

Description	Date
Submission dossier accepted and first round evaluation commenced	30 June 2025
Evaluation completed (End of round 2)	7 August 2026
Registration decision (Outcome)	18 August 2026
Registration in the ARTG completed	25 August 2026
Number of working days from submission dossier acceptance to registration decision*	189

*Statutory timeframe for standard submissions is 255 working days

Assessment overview

A summary of the TGA's assessment for this submission is provided below.

Quality evaluation summary

Drug substance

Perindopril is a prodrug that is hydrolysed in the liver to its active metabolite perindoprilat. Perindopril is present as an arginine salt in the drug substance. The perindopril arginine drug substance is produced by chemical synthesis. It is manufactured as a crystalline Form-α which is stable and highly soluble across the physiological pH range. Perindopril has low permeability and is accordingly considered a BCS class III substance. The proposed specification adequately controls the identity, potency, purity and chemical and physical properties of the drug substance relevant to the dose form. The analytical methods used to analyse perindopril arginine were adequately described and validated. Risk evaluations on the potential presence of nitrosamines and elemental impurities were performed and no significant risk was identified.

Amlodipine is present as the besilate salt. Amlodipine besilate is produced by chemical synthesis. It is manufactured as the anhydrous crystalline form which is stable in the drug product. Amlodipine besilate is slightly soluble across the pH range and highly permeable. It is considered a BCS class I substance. The proposed specification adequately controls the identity, potency, purity and chemical and physical properties of the drug substance relevant to the dose form. The analytical methods used to analyse the product were adequately described and validated. Risk evaluations on the potential presence of nitrosamines and elemental impurities were performed and no significant risk was identified.

Indapamide has one stereo centre and is present in the racemic form. Indapamide is produced by chemical synthesis. It is manufactured as the semi-hydrated crystalline Form I which is stable in the drug product. Indapamide is practically insoluble across the pH range and highly permeable. However, based on the maximum daily dose, indapamide is classified as a BCS class I substance in the context of the proposed product. The proposed specification adequately controls the identity, potency, purity and chemical and physical properties of the drug substance relevant to the dose form. Risk evaluations on the potential presence of nitrosamines and elemental impurities were performed.

Drug product

The perindopril arginine drug substance is used to manufacture a yellow perindopril arginine 5 mg immediate release film-coated tablet. The amlodipine besilate drug substance is used to manufacture light yellowish green amlodipine besilate immediate release lubricated granules, while the indapamide drug substance is used to manufacture a white indapamide 1.5 mg sustained release film-coated tablet. Each of the above intermediates are conventionally formulated with no novel excipients.

The drug product consists of a yellow coloured 'size 0' hard, gelatin capsule. The three different strengths include:

- Each Coveram Plus 5/5/1.5 SR capsule contains 5 mg of perindopril arginine, 5 mg of amlodipine (as besilate‡) and 1.5 mg of indapamide
- Each Coveram Plus 10/5/1.5 SR capsule contains 10 mg of perindopril arginine, 5 mg of amlodipine (as besilate‡) and 1.5 mg of indapamide
- Each Coveram Plus 10/10/1.5 SR capsule contains 10 mg of perindopril arginine 10 mg of amlodipine (as besilate‡) and 1.5 mg of indapamide

‡ Amlodipine doses are given as active base

The strengths are differentiated based on capsule colour using different shades of yellow, and a number imprinted on the capsule. As the capsule contains a sustained release indapamide tablet, the dosage form is considered a 'modified release capsule'. The capsules are packaged in a high-density polyethylene (HDPE) bottle with a polypropylene child-resistant closure. The pack size is 30 capsules.

The drug product specifications adequately control the quality of the drug product at release and throughout the shelf-life if stored below 25°C. The data support a maximum shelf life of 24 months when stored below 25°C. The in-use shelf life is 60 days.

The drug product formulation used in the clinical studies is the same as the formulation proposed for registration. The studies evaluating the proposed FDC were conducted for the highest proposed strength (10 mg/10 mg/1.5 mg) and the application included an acceptable *Additional strength biowaiver* for not providing biopharmaceutic studies for the two lower strength formulations (5 mg/5 mg/1.5 mg, 10 mg/5 mg/1.5 mg), as well as an acceptable justification for use of overseas reference products.

Nonclinical evaluation summary

The nonclinical evaluation was of adequate scope and consistent with the EU Guideline on the non-clinical development of fixed combinations of medicinal products. The proposed doses and indications for the FDC are within those already approved for the individual components or other combinations with these components and therefore no increase in risk is anticipated and animal safety assessments are not required. The module consisted of pharmacokinetic interaction studies and studies on impurities. Clinically relevant drug interactions are not anticipated based on *in vitro* study findings.

The proposed specifications for impurities in the drug substances and impurities/degradants in the drug product have been qualified for mutagenicity and general safety and are acceptable.

The proposed Pregnancy Category D is appropriate, as perindopril and amlodipine are both Pregnancy Category D and indapamide is Pregnancy Category C.

There are no objections on non-clinical grounds to the registration of Coveram Plus SR for the proposed indication.

Clinical evaluation summary

Summary of clinical studies

The FDC products are proposed as substitution therapy in patients already controlled with perindopril, amlodipine and indapamide, taken at the same dose level. The regulatory strategy for this application is based primarily on demonstration of bioequivalence of the FDC to the mono-component reference products. The application included three key bioequivalence (BE) studies:

- Study PKH-05183-005: A single-dose BE study of the FDC formulation and the reference products (perindopril arginine, indapamide SR and amlodipine) administered simultaneously as mono-components under fasting conditions.
- Study PKH-05183-002: A single-dose BE study of the FDC formulation and the reference products (perindopril arginine, indapamide SR and amlodipine) administered simultaneously as mono-components under fed conditions.
- Study PKH-05182-004: A multiple-dose BE study of indapamide SR 1.5 mg tablets used in the FDC versus the reference indapamide SR 1.5 mg tablets (Arifon Retard) under fasting conditions.

Study PKH-05183-002 and an additional BE study PKH-05183-001 evaluated a test product with an older formulation of perindopril arginine which was subsequently re-formulated to address nitrosamine risk, whereas Study PKH-05183-005 evaluated the formulation proposed for marketing.

The application presented additional clinical studies, published literature, and clinical practice guidelines to support the efficacy and safety of the triple combination, including:

- sponsored studies and published studies supporting the clinical rationale for the triple combination therapy and the contribution of each of the components to the overall efficacy of the FDC
- sponsored studies and published studies addressing the risk of PK drug-drug interactions
- published real-world data from France, Hungary and Poland describing rates of co-prescription of perindopril, amlodipine, and indapamide SR at the strengths proposed in the FDC
- international clinical practice guideline recommendations on the role of combination therapy for the treatment of hypertension, including, but not limited to, Williams et al. 2018,[13] Mancia et al. 2023,[14] and McEvoy et a. 2024.[2]

[13] Williams, B., Mancia, G., et al. …ESC Scientific Document Group (2018). 2018 ESC/ESH Guidelines for the management of arterial hypertension. *European heart journal*, *39*(33), 3021–3104. https://doi.org/10.1093/eurheartj/ehy339;
[14] Mancia, G., Kreutz, R., et al., … Kjeldsen, S. E. (2023). 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *Journal of Hypertension*, *41*(12), 1874-2071. https://doi.org/10.1097/HJH.0000000000003480

- published data supporting improved medication adherence with FDC products compared to mono-components.[2,15,16]

Safety of the FDC was also supported by an analysis of long-term safety data for the triple combination in at least 100 patient-years of treatment. A post hoc analysis was conducted on safety data from the Phase 3 Study CL3-05985-018 and a pooled analysis of the Phase 3 studies CL3-16257-056, CL3-18886-012, CL3-16257-063, CL3-16257-083.

Pharmacology

Pharmacokinetics

The key pharmacokinetic (PK) studies were a single-dose BE study of the proposed FDC compared to the mono-component EU reference products under fasted conditions, a single-dose BE study of a FDC compared to the mono-component EU reference products under fed conditions, and a multiple-dose BE study of the indapamide SR component only against the EU reference product (Table 3).

Table 3. Summary of *in vivo* bioequivalence studies.

Study code	Primary objective	Design (number of subjects)	Treatments
PKH-05183-005	BE in healthy subjects	Single-dose, randomized, open-label, laboratory-blinded, two-period, two-sequence, two-treatment, single-centre, crossover, under fasting conditions (n=80 randomised, n=75 completed))	Test Product 1 x Per 10mg/Ind SR 1.5mg/Aml 10mg FDC capsule Reference Products 1 x Coversyl® 10 mg film-coated tablet + 1 x Fludex® Retard 1.5 mg film-coated tablet + 1 x Norvasc® 10 mg film-coated tablet
PKH-05183-002	BE in healthy subjects	Open-label, single-dose, randomised, two-period, two-treatment, two-sequence crossover, under fed conditions, laboratory-blinded (n=80 randomised, n=74 completed))	Test Product 1 x Per 10mg/Ind SR 1.5mg/Aml 10mg FDC capsule Reference Products 1 x Coversyl® 10 mg film-coated tablet + 1 x Arifon® Retard 1.5 mg tablet + 1 x Norvasc® 10 mg tablet
PKH-05182-004	BE in healthy subjects	Open-label, multiple-dose, randomised, two-period, two-treatment, two-sequence, crossover, laboratory-blinded (n=50 n=47 completed)	Test Product 1 x Indapamide SR 1.5 mg mini-tablet* once a day for 7 days Reference Products 1 x Arifon® Retard 1.5 mg tablet once a day for 7 days

* Product intermediate within the hard capsule of the Per/Ind SR/Aml FDC (S05183)
BE: bioequivalence, FDC: fixed dose combination, SR: sustained release

The single-dose bioequivalence (BE) study under fed conditions and the multiple-dose BE study were required for the indapamide SR component based on the *Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms*. The conduct of the multiple-dose BE study with indapamide SR component only against the EU indapamide reference product (Arifon Retard 1.5 mg tablets) under fasting conditions was agreed during a Scientific Advice procedure.

[15] Sherrill, B., Halpern, M., Khan, S., Zhang, J., & Panjabi, S. (2011). Single-pill vs free-equivalent combination therapies for hypertension: a meta-analysis of health care costs and adherence. *Journal of clinical hypertension (Greenwich, Conn.)*, *13*(12), 898–909. https://doi.org/10.1111/j.1751-7176.2011.00550.x

[16] Rea, F., Morabito, G., Savaré, L., Pathak, A., Corrao, G., & Mancia, G. (2023). Adherence and related cardiovascular outcomes to single pill vs. separate pill administration of antihypertensive triple-combination therapy. *Journal of hypertension*, *41*(9), 1466–1473. https://doi.org/10.1097/HJH.0000000000003497

The two BE studies of the FDC product were performed with the highest proposed strength, and a biowaiver for the lower strengths was assessed in the Module 3 evaluation. The justification for use of overseas reference products was assessed in the Module 3 evaluation.

Study PKH-05183-005

Bioequivalence between Test Product A (S5183 hard capsule containing perindopril arginine 10 mg, indapamide SR 1.5 mg, amlodipine 10 mg) and Reference Products B (co-administration of Coversyl perindopril arginine 10 mg film-coated tablet, Fludex indapamide 1.5 mg film-coated tablet, and Norvasc amlodipine 10 mg film-coated tablet) was demonstrated in healthy volunteers under fasting conditions (Table 4).

Table 4. Pharmacokinetic results Study PKH-05183-005.

Pharmacokinetic Results

BE Analysis Results for Plasma Amlodipine

Parameter (N_A/N_B)[0]	Geometric Means Arithmetic Means (CV %) TRT A	TRT B	Ratio of Geometric Means	90% CI	Intra-subject Coefficient of Variation (CV) (%)
AUC_{72} (pg.h/mL) (70/70)	223847.68 231073.25 (25.55)	214278.36 221046.80 (25.21)	104.47	102.44 - 106.53	6.93
C_{max} (pg/mL) (72/72)	6607.84 6806.55 (25.56)	6243.94 6473.15 (27.46)	105.83	103.41 - 108.30	8.32

BE Analysis Results for Plasma Indapamide

Parameter (N_A/N_B)[0]	Geometric Means Arithmetic Means (CV %) TRT A	TRT B	Ratio of Geometric Means	90% CI	Intra-subject CV (%)
AUC_t (pg.h/mL) (75/75)	363130.59 380716.16 (31.55)	357024.47 375106.43 (32.48)	101.71	97.59 - 106.01	15.26
AUC_{inf} (pg.h/mL) (74/74)	388738.61 410822.18 (33.78)	380926.40 402692.82 (34.69)	102.05	97.92 - 106.35	15.12
C_{max} (pg/mL) (74/74)	11536.80 11979.89 (28.09)	12574.60 13257.86 (32.48)	91.75	87.22 - 96.50	18.58

BE Analysis Results for Plasma Perindopril

Parameter (N_A/N_B)[*]	Geometric Means Arithmetic Means (CV %) TRT A	TRT B	Ratio of Geometric Means	90% CI	Intra-subject CV (%)
AUC_t (pg.h/mL) (75/75)	95012.30 100051.88 (30.89)	89021.55 93669.86 (29.53)	106.73	104.02 - 109.51	9.45
C_{max} (pg/mL) (74/74)	87102.89 92800 (35.73)	74697.50 79565.37 (34.18)	116.61	108.78 - 125.00	25.73

Note: N_A/N_B are the number of observations for Treatments A and B, respectively.

Study PKH-05183-002

The *Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms* requires a fed study to evaluate bioequivalence of the indapamide SR component. In the fed study, bioequivalence between the Test Product A (S05183 hard capsule containing perindopril arginine 10 mg, indapamide SR 1.5 mg, amlodipine 10 mg) and Reference Products B (co-administration of Coversyl Perindopril arginine 10 mg, Arifon Retard Indapamide 1.5 mg, and Norvasc Amlodipine 10 mg) was demonstrated for indapamide, amlodipine, and perindoprilat, but not for perindopril (Table 5).

Perindopril is an inactive prodrug which is rapidly metabolised in the liver to the active metabolite, perindoprilat. Perindopril AUC_t was equivalent but C_{max} was lower for the test product compared to Coversyl. This was attributed to a reduced rate of absorption of the pellet formulation (T_{max} 2.5 h) compared to Coversyl tablet (T_{max} 1.5 h). The pellet formulation of

perindopril arginine used in this study is not proposed for marketing, as it has been re-formulated to address nitrosamine levels.

Table 5. PK results Study PKH-05183-002.

Bioequivalence Analysis Results for Plasma Amlodipine:

STUDY 2615 FED (01MAR2022 - 15:08)
TREATMENT A vs TREATMENT B

Parameter (N_A /N_B)	Geometric Means Arithmetic Means (CV %) TRT A	TRT B	Ratio of Geometric Means	90% Confidence Interval	Intra-Subject CV (%)
AUCt (pg.h/mL) (74 /73)	237124.35 235394.01 (21.76)	239882.41 241455.89 (23.78)	98.85	96.03 - 101.76	9.14
Cmax (pg/mL) (74 /74)	6055.92 6037.51 (21.72)	6396.26 6506.83 (24.82)	94.68	90.97 - 98.54	12.67

Bioequivalence Analysis Results for Plasma Indapamide:

STUDY 2615 FED (01MAR2022 - 15:49)
TREATMENT A vs TREATMENT B

Parameter (N_A /N_B)	Geometric Means Arithmetic Means (CV %) TRT A	TRT B	Ratio of Geometric Means	90% Confidence Interval	Intra-Subject CV (%)
AUCt (pg.h/mL) (73 /72)	369085.32 379068.42 (26.15)	366143.86 376700.31 (26.09)	100.80	97.35 - 104.38	10.98
AUCinf (pg.h/mL) (73 /72)	389965.07 401209.24 (27.30)	385293.09 396916.82 (27.17)	101.21	97.67 - 104.89	11.23
Cmax (pg/mL) (73 /73)	16858.99 17675.37 (32.81)	17982.41 18847.62 (28.52)	93.75	88.49 - 99.33	18.35

Bioequivalence Analysis Results for Plasma Perindopril:

STUDY 2615 FED (02MAR2022 - 09:21)
TREATMENT A vs TREATMENT B

Parameter (N_A /N_B)	Geometric Means Arithmetic Means (CV %) TRT A	TRT B	Ratio of Geometric Means	90% Confidence Interval	Intra-Subject CV (%)
AUCt (pg.h/mL) (73 /73)	107296.26 110885.01 (23.88)	108485.13 112703.13 (24.56)	98.90	96.42 - 101.45	7.96
Cmax (pg/mL) (73 /73)	39852.71 41825.96 (29.19)	60006.63 66682.31 (40.84)	66.41	60.38 - 73.06	30.48

Bioequivalence Analysis Results for Plasma Perindoprilat:

TREATMENT A vs TREATMENT B

Parameter (N_A /N_B)	Geometric Means Arithmetic Means (CV %) TRT A	TRT B	Ratio of Geometric Means	90% Confidence Interval	Intra-Subject CV (%)
AUCt (pg.h/mL) (74 /73)	180017.23 184962.82 (30.39)	178493.73 182503.05 (31.11)	100.85	98.91 - 102.84	6.13
Cmax (pg/mL) (74 /74)	11186.90 12675.29 (56.10)	11387.88 12750.68 (52.39)	98.24	94.88 - 101.71	11.00

Note: N_A/N_B are the number of observations for Treatments A and B, respectively.

The lower C_{max} for perindopril in Test Product A compared to Coversyl in PKH-05183-002 does not preclude a conclusion of bioequivalence of the proposed FDC product to the mono-components because:

- this study evaluated a pellet formulation of perindopril arginine which is not proposed for marketing as it was reformulated to address nitrosamine levels. The formulation proposed for marketing was evaluated in Study PKH-05183-005 and bioequivalence was established for perindopril, amlodipine and indapamide.
- the fed study was required specifically to evaluate the modified release formulation of indapamide SR and bioequivalence was demonstrated for indapamide C_{max} and AUC.
- the fed study also demonstrated bioequivalence for amlodipine and perindoprilat, the active metabolite of the prodrug perindopril.
- the FDC is proposed to be taken in the morning before a meal, the same posology as Coveram and Coversyl Plus. Natrilix is to be taken in the morning with no specific guidance regarding meals.

Study PKH-05182-004

The multiple-dose study demonstrated bioequivalence between Test Product A (prolonged-release film-coated tablet containing 1.5 mg of indapamide) and Reference Product B (Arifon Retard prolonged-release film-coated tablet containing 1.5 mg of indapamide) in healthy, non-smoking volunteers under fasting steady state conditions (Table 6).

Table 6. PK results Study PKH-05182-004.

Bioequivalence Analysis Results for Plasma Indapamide:

TREATMENT A vs TREATMENT B

Parameter (N_A/N_B)	Geometric Means Arithmetic Means (CV %) TRT A	TRT B	Ratio of Geometric Means	90% Confidence Interval	Intra-Subject CV (%)
AUCtau,ss (pg.h/mL) (47/47)	374667.20 397862.99 (37.10)	375825.59 403619.50 (39.76)	99.69	95.14 - 104.46	13.54
Cmax,ss (pg/mL) (47/47)	18596.44 19620.55 (34.80)	19627.31 20985.71 (37.64)	94.75	90.01 - 99.73	14.88
Ctau,ss (pg/mL) (47/47)	13546.28 14777.51 (44.29)	12344.46 13654.59 (50.22)	109.74	103.70 - 116.12	16.44

Note: N_A/N_B are the number of observations for Treatments A and B, respectively.

Drug-drug interactions

No new PK interaction studies were conducted for the clinical development of the new FDC as previous studies have demonstrated the absence of a clinically relevant interaction between perindopril *tert*-butylamine 8 mg and indapamide IR 2.5 mg (Study PKH-05597-002), between perindopril arginine 10 mg and amlodipine 10 mg (Study PKH-05985-004), between indapamide SR 1.5 mg and amlodipine 10 mg (Study PKH-05520-001) and between perindopril 10 mg, indapamide IR 2.5 mg, and amlodipine 10 mg (Study PKH-06593-004).

Efficacy

The new FDC products are proposed as substitution therapy in patients already controlled on the same doses of each of the components. No efficacy studies of this FDC have been conducted. Efficacy of each of the components of the FDC in the treatment of hypertension is well

established (registered products Coversyl, Norvasc, and Natrilix SR). Efficacy of the three components used in combination is supported by sponsored studies (Studies CL3-05985-018, CL3-06593-006, CL3-06593-018) and published studies.[17,18, 19,20] The formulations and strengths of the triple combination of perindopril, amlodipine, and indapamide varied across these studies, but overall, they support the rationale for triple combination therapy and the contribution of each of the components to the efficacy of the triple FDC.

Study CL3-05985-018 was a randomised, double-blind, controlled trial which compared perindopril/amlodipine FDC plus indapamide SR versus a valsartan/amlodipine FDC regimen over 6 months in patients with hypertension. The study included 4 titration steps, the last being the addition of indapamide SR 1.5 mg from Month 3. The addition of indapamide SR 1.5 mg in patients uncontrolled on the previous treatment with perindopril 14 mg + amlodipine 10 mg resulted in a mean decrease in SBP of -14.8 mmHg and in DBP of -7.2 mmHg, and 82.5% BP normalisation (SBP<140 mmHg and DBP<90 mmHg).

Study CL3-06593-006 was a Phase 3, multicentre, randomised, double-blind study which primarily assessed the superiority of triple FDC (perindopril 5 mg/amlodipine 5 mg/indapamide 1.25 mg) versus dual FDC (perindopril 5 mg/indapamide 1.25 mg) in patients uncontrolled on perindopril 5mg /indapamide 1.25 mg over 1 month, and assessed the benefit of up-titration in terms of BP lowering effect over 4 months. After 1-month, superior SBP (-3.1 mmHg, P = 0.02) and DBP (-2.8 mmHg, P < 0.001) reductions were observed with the triple FDC. Up-titration was effective at each visit in both treatment arms (P < 0.001), with more than 80% of the patients achieving BP control at the end of the study.

Study CL3-06593-018 was a Phase 3, multicentre, randomised, double-blind, non-inferiority study evaluating the efficacy and safety of a triple Per/Ind/Aml FDC compared to Per/Ind FDC plus amlodipine in Chinese adults with mild-to-moderate hypertension. Similar decreases in SBP were observed in both groups at 2 months from baseline (-14.99±14.46 mmHg Per/Ind/Aml FDC versus -14.49±12.87 mmHg Per/Ind + Aml).

Safety

The safety profiles of the three components of the FDC, and dual FDC products, are well established in Australia. The safety of the proposed triple FDC is based on the established safety profiles of the three components (as monotherapy and dual combination therapy) supported by safety data for the triple combination. The safety evaluation presented safety data from:

- three bioequivalence studies in healthy volunteers (single-dose studies PKH-05183-005 and PKH-05183-002; and multiple-dose study PKH-05182-004),
- Study CL3-05985-018 which evaluated the safety of the free combination of perindopril (up to 14 mg), amlodipine (up to 10 mg), and indapamide SR 1.5 mg,

[17] Páll, D., Szántó, I., & Szabó, Z. (2014). Triple combination therapy in hypertension: the antihypertensive efficacy of treatment with perindopril, amlodipine, and indapamide SR. *Clinical drug investigation*, *34*(10), 701–708. https://doi.org/10.1007/s40261-014-0223-0

[18] Sirenko, Y. & Radchenko, G. (2013) Antihypertensive effectiveness of indapamide-retard adding to fixed dose combination perindopril/ amlodipine in a hypertensive population. Journal of Hypertension, 31:e334.

[19] Snyman JR, Bortolotto LA, Degli Esposti L, et al. (2024) A real-world analysis of outcomes and healthcare costs of patients on perindopril/indapamide/amlodipine single-pill vs. multiple-pill combination in Italy. Journal of Hypertension, Jan;42(1):136-142. https://doi.org/10.1097/HJH.0000000000003570

[20] Rea, F., Morabito, G., Savaré, L., Pathak, A., Corrao, G., & Mancia, G. (2023). Adherence and related cardiovascular outcomes to single pill vs. separate pill administration of antihypertensive triple-combination therapy. *Journal of hypertension*, *41*(9), 1466–1473. https://doi.org/10.1097/HJH.0000000000003497

- Study CL3-06593-006 which evaluated the safety of the triple FDC containing perindopril, amlodipine and indapamide IR,
- post-marketing safety data for the triple FDC containing perindopril, amlodipine and indapamide IR.

A post-hoc analysis of Viacoram (Study CL3-05985-018) and Cardiovascular pool (Studies CL3-16257-056 BEAUTIFUL, CL3-18886-012 PERFORM, CL3-16257-063 SHIFT, and CL3-16257-083 SIGNIFY) was conducted to provide long-term safety data of the triple combination of perindopril, amlodipine and indapamide for at least 100 patient years (PY) of exposure to address requirements of the TGA-adopted EU Directive 75/318/EEC *Clinical Investigation of Medicinal Products for Long-Term Use (1987)*.

Study CL3-05985-018

This Phase 3 Study evaluated the safety of the free combination of perindopril (up to 14 mg), amlodipine (up to 10 mg), and indapamide SR 1.5 mg, with Step 4 providing safety data following the addition of indapamide SR 1.5 mg to the combination of perindopril 14 mg and amlodipine 10 mg (Table 7, Table 8, Table 9).

Table 7. Rate of patients reporting at least one EAE within each step (Study CL3-05985-018).

		N patients exposed	N patients with EAE	% patients with EAE	NEAE
Step 1	**Per 3.5 mg + Aml 2.5 mg**	887	165	18.6%	264
	Val 80 mg	884	153	17.3%	224
Step 2	**Per 7 mg + Aml 5 mg**	718	125	17.4%	181
	Val 160 mg	741	129	17.4%	187
Step 3	**Per 14 mg + Aml 10 mg**	495	119	24.0%	180
	Val 160 mg + Aml 5 mg	564	130	23.0%	185
Step 4	**Per 14 mg + Aml 10 mg + Ind 1.5 mg**	202	51	25.2%	76
	Val 160 mg + Aml 10 mg	273	69	25.3%	100

Per: perindopril; Aml: amlodipine; Ind: indapamide; Val: valsartan; NEAE: Number of emergent adverse events

Table 8. Most frequently reported EAEs in step 4 as compared to step 3 in at least 1% of patients in any group – Safety Set (CL3-05985-018).

Preferred term	Step 4 (Per 14 + Aml 10 + Ind 1.5) (N=202)			Step 3 (Per 14 + Aml 10) (N=495)		
	NEAE	n	%	NEAE	n	%
Oedema peripheral	9	9	4.5	28	28	5.7
Type 2 diabetes mellitus	3	3	1.5	4	4	0.8
Blood glucose increased	3	3	1.5	3	3	0.6
Hyperuricaemia	3	3	1.5	-	-	-
Hypokalaemia	3	3	1.5	-	-	-
Nasopharyngitis	2	2	1.0	8	8	1.6
Cough	2	2	1.0	7	7	1.4
Hypertriglyceridaemia	2	2	1.0	7	7	1.4
Hypercholesterolaemia	2	2	1.0	6	6	1.2
Dizziness	2	2	1.0	3	3	0.6
Erectile dysfunction	2	2	1.0	1	1	0.2
Asthenia	2	2	1.0	-	-	-
Headache	0	0	0.0	1	1	0.2
ALL	**76**	**51**	**25.2**	**180**	**119**	**24.0**

NEAE: number of emergent adverse events – N: total number of exposed patients in the considered treatment group – n: number of affected patients - %: n/N x 100
Per: perindopril; Aml: amlodipine; Ind: indapamide

Table 9. Analysis of EAEs leading to treatment discontinuation at step 4 versus step 3 (CL3-05985-018).

Adverse Event	Step 4 (Per 14 + Aml 10 + Ind 1.5) (N=202)			Step 3 (Per 14 + Aml 10) (N=495)		
	NEAE	n	%	NEAE	n	%
Oedema peripheral	4	4	2.0	14	14	2.8
Cough	1	1	0.5	3	3	0.6
Acute myocardial infarction	1	1	0.5	-	-	-
Sinus tachycardia	-	-	-	1	1	0.2
Nausea	1	1	0.5	-	-	-
Abdominal pain upper	-	-	-	1	1	0.2
Erectile dysfunction	1	1	0.5	-	-	-
Dizziness	-	-	-	1	1	0.2
Ischaemic stroke	-	-	-	1	1	0.2
Creatinine renal clearance decreased	-	-	-	1	1	0.2
Hypotension	-	-	-	1	1	0.2
ALL	**8**	**8**	**4.0**	**23**	**23**	**4.6**

Per: perindopril; Aml: amlodipine; Ind: indapamide
N: total number of exposed patients in the considered treatment group
NEAE: number of emergent adverse events
n: number of patients affected%: n/N x 100

Post-hoc analysis of long-term safety data

The analysis included patients in the original Safety Sets who received perindopril, amlodipine and indapamide continuously for at least 10 months and at least at the highest dose of the FDC. Patients in Study CL3-05985-018 had essential hypertension and received a higher dose of perindopril (14 mg) than proposed for the FDC. Patients in the Cardiovascular pool provided safety data for a population with hypertension and at higher risk of CVD. The mean (SD) duration of exposure was 10.8 (0.3) months for Study CL3-05985-018 and 24.7 (7.3) months for the Cardiovascular pool. The total exposure to the combination was 122 patient years for Study CL3-05985-018 and 144 PY for the Cardiovascular pool (Table 10). The findings of this analysis of long-term safety data for combination therapy with perindopril, amlodipine, and indapamide are consistent with the established safety profiles of the three components.

Table 10. Source of long-term safety data.

Source	Doses (per/ind SR or IR/amlo)	N of patients	Mean length of therapy (years)	Exposure (patient years)
CL3-05985-018 study	14 mg/1.5 SR mg/10 mg	135	0.9	122
Cardiovascular pool (SS4)	10 mg/1.5 SR mg/10 mg	37	2.1	77
Cardiovascular pool (SS5)	10 mg/2.5 IR mg/10 mg	33	2.0	67
Total		**205**		**266**

Study CL3-05985-018

The profile of emergent adverse events (EAEs) by System Organ Class (SOC) and Preferred Term (PT) is shown in Table 11. In Study CL3-05985-018, 64.2% of total EAEs were rated as mild, 30.2% as moderate, and 5.7% as severe. Four patients reported 6 severe EAEs comprising of one event each of increased gamma-glutamyltransferase, increased transaminases, acute myocardial infarction, metastatic squamous cell carcinoma, renal failure, and benign prostatic hyperplasia. Twelve serious EAEs were reported in 7 (5.2%) patients. No fatal EAEs were reported. There were 17 treatment-related EAEs in 13 (9.6%) patients; the most frequently

reported were hypokalaemia (3 EAEs in 3 [2.2 %] patients), cough (3 EAEs in 3 [2.2 %] patients), and oedema peripheral (2 EAEs in 2 [1.5 %] patients).

Table 11. Emergent adverse events reported under the combination by System Organ Class (cut-off 5%) and Preferred Term (cut-off 1%) – CL3-05985-018.

System organ class *Preferred term*	SS (N=135) NEAE	 n (%)
All	**106**	**47 (34.8)**
Metabolism and nutrition disorders	**17**	**15 (11.1)**
Hypokalaemia	*5*	*5 (3.7)*
Hyperuricaemia	*4*	*4 (3.0)*
Hypercholesterolaemia	*3*	*3 (2.2)*
Type 2 diabetes mellitus	*3*	*3 (2.2)*
Infections and infestations	**15**	**11 (8.1)**
Nasopharyngitis	*5*	*4 (3.0)*
Pharyngitis	*4*	*3 (2.2)*
Nervous system disorders	**10**	**9 (6.7)**
Dizziness	*2*	*2 (1.5)*
Sciatica	*2*	*2 (1.5)*
General disorders and administration site conditions	**8**	**8 (5.9)**
Oedema peripheral	*5*	*5 (3.7)*
Investigations	**11**	**8 (5.9)**
Gamma-glutamyltransferase increased	*2*	*2 (1.5)*
Musculoskeletal and connective tissue disorders	**9**	**8 (5.9)**
Arthralgia	*2*	*2 (1.5)*
Back pain	*2*	*2 (1.5)*
Pain in extremity	*2*	*2 (1.5)*

N: number of patients in SS; NEAE: number of emergent adverse events; n: number of patients with at least one emergent adverse event; SS: safety set.
%: (n/N) x 100.

Cardiovascular pool

In total, 191 EAEs were reported in 54 (77.1%) patients. The most frequently reported EAEs by PT were hypertension (13 EAEs in 10 [14.3 %] patients), decreased heart rate (7 EAEs in 5 [7.1 %] patients), diabetes mellitus (5 EAEs in 5 [7.1 %] patients), hypercholesterolaemia (5 EAEs in 5 [7.1 %] patients), type 2 diabetes mellitus (5 EAEs in 5 [7.1 %] patients).

Hyperuricaemia (4 EAEs in 4 [5.7 %] patients), angina pectoris (3 EAEs in 3 [4.3 %] patients), angina unstable (3 EAEs in 3 [4.3 %] patients), bradycardia (3 EAEs in 3 [4.3 %] patients), cardiac failure (3 EAEs in 3 [4.3 %] patients), benign prostatic hyperplasia (3 EAEs in 3 [4.3 %] patients), fall (3 EAEs in 3 [4.3 %] patients).

Osteoarthritis (3 EAEs in 3 [4.3 %] patients). 70.2% of EAEs were rated as mild, 27.2% as moderate, and 2.1% as severe. 38 serious EAEs were reported in 23 (32.9%) patients. No fatal EAEs were reported.

Post-marketing data

The proposed product is not yet marketed globally, but the application referenced the extensive post-marketing safety experience with perindopril/amlodipine/indapamide FDC products containing an IR indapamide formulation. The estimated cumulative exposure to perindopril/amlodipine/indapamide FDC products since the first Marketing Authorisation and up to 25 November 2022 (period ending for the most recent EU PBRER) is 10,402,989 patient

years. During the period of this PBRER, there were no significant actions taken for safety reasons regarding investigational uses and marketing experiences in any country. No new safety signals were validated for the FDC. The type and frequency of adverse events from the FDC were accounted from the mono-components perindopril, amlodipine, indapamide. No specific risks related to the FDC product were detected from post-marketing data.

Risk management plan

The sponsor is required to comply with product vigilance and risk minimisation requirements.

A risk management plan (RMP) is **not** required for this Category-1 Type B application for perindopril arginine, amlodipine besilate and indapamide hemihydrate. The risk profile of the individual components is well established as they have been registered in Australia for many years.

The indication states this treatment is for patients already controlled with perindopril, amlodipine and indapamide, taken at the same dose level, and treatment should not be initiated with this combination. This mitigates the risk of any new safety concerns that this new combination may have.

See TGA's guidance on when an RMP is required.

The TGA may request an updated RMP at any stage of a product's life cycle, during both the pre-approval and post-approval phases. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach. Information on the Australia-specific annex (ASA) can be found on the TGA website.

Risk-benefit analysis

Delegate's considerations

Efficacy

The new FDC products are proposed as substitution therapy in patients already stabilised on the same doses of each of the components. The clinical development program was aligned with regulatory guidance in the *Guideline on clinical development of fixed combination medicinal products*. The efficacy of each of the components of the FDC in the treatment of hypertension is well established (registered products Coversyl, Norvasc and Natrilix SR) and bioequivalence of the FDC to the individual components has been satisfactorily demonstrated (including justification for use of overseas reference products, and biowaivers for the lower strengths). Sponsored studies and published studies support the clinical rationale for the triple combination therapy and demonstrate that each of the components of the triple combination contribute to the efficacy of the FDC. The submitted PK and efficacy data are consistent with the requirements for a substitution indication for a new FDC.

Safety

The safety of the proposed triple FDC is based on the established safety profiles of the three components (as monotherapy and dual combination therapy) supported by safety data for the triple combination, including a post hoc analysis of long-term safety data covering more than 100 patient-years of treatment with triple combination therapy and extensive post-marketing safety data for the FDC of perindopril/amlodipine/indapamide. The safety profile of the triple

combination is consistent with the known safety profiles of the three components, with no new safety signals being identified.

Proposed Indications

The indication for the proposed FDC products is a substitution indication:

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

The data presented in support of the substitution indication are consistent with the *Guideline on clinical development of fixed combination medicinal products*. The dosing guidance in the draft Product Information is consistent with the proposed substitution indication.

Uncertainties and limitations of the data

There is extensive clinical experience with the three active substances, as monotherapy and in combination, but safety data for the triple combination in the elderly, and in patients with renal or hepatic impairment, are more limited. Increased caution is advised in these populations. This has been adequately addressed in the Product Information.

A bioequivalence study in the fed state was required to assess the SR formulation of indapamide. Study PKH-05183-002 demonstrated bioequivalence of indapamide SR, amlodipine, and perindoprilat (which is the active metabolite of the prodrug perindopril) but failed to show bioequivalence of perindopril due to lower C_{max} observed with the FDC. The formulation of perindopril in the FDC evaluated in that study differed from the formulation proposed for marketing. Bioequivalence of all components of the proposed FDC was demonstrated in the fasted BE study PKH-05183-005. The FDC is recommended to be taken in the morning before a meal.

Conclusion

The FDC products are proposed as substitution therapy in patients already controlled with perindopril, amlodipine, and indapamide, taken at the same dose level. The role for triple combination therapy for the treatment of hypertension is well established in clinical practice, as referenced in international clinical practice guidelines.

The efficacy of each of the components of the proposed FDC products in the treatment of hypertension is well established and the efficacy of the three components used in combination is supported by a large body of clinical data, including sponsored studies and published studies.

The safety of the three components of the FDC, both alone and in combination, has been extensively characterised. A post-hoc safety analysis of more than 100 PY of exposure to perindopril, amlodipine and indapamide at doses at least as high as the highest strength of the FDC was consistent with the established safety profiles of the three components.

There are no outstanding issues requiring advice from the Advisory Committee on Medicines (ACM).

The Sponsor has confirmed that the draft Product Information has been updated to address all issues. No additional changes to the Product Information are required.

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register:

- COVERAM PLUS 10/10/1.5 SR perindopril arginine 10 mg/amlodipine (as besilate) 10 mg/indapamide 1.5 mg modified release capsule bottle
- COVERAM PLUS 10/5/1.5 SR perindopril arginine 10 mg/amlodipine (as besilate) 5 mg/indapamide 1.5 mg modified release capsule bottle
- COVERAM PLUS 5/5/1.5 SR perindopril arginine 5 mg/amlodipine (as besilate) 5 mg/indapamide 1.5 mg modified release capsule bottle

indicated for:

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

Product Information and Consumer Medicine Information

For the most recent Product Information (PI) and Consumer Medicine Information (CMI), please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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Reference/Publication #