LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Rosuvastatin/Amlodipin/Ramipril Adamed
(rosuvastatin calcium, ramipril, amlodipine besilate)

SE/H/2412/001-006/DC

This module reflects the scientific discussion for the approval of Rosuvastatin/Amlodipin/Ramipril Adamed. The procedure was finalised at 2026-05-13. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Rosuvastatin/Amlodipin/Ramipril Adamed, 10 mg/5 mg/5 mg, 10 mg/5 mg/10 mg, 10 mg/10 mg/10 mg, 20 mg/5 mg/5 mg, 20 mg/5 mg/10 mg, 20 mg/10 mg/10 mg, Capsule, hard.

The active substance is rosuvastatin calcium, rosuvastatin, ramipril, amlodipine, amlodipine besilate. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 Rationale for the product

High blood pressure (BP), cigarette smoking, diabetes mellitus, and lipid abnormalities are major modifiable risk factors for cardiovascular disease (CVD). Among these, high BP is associated with the strongest evidence for causation and has a high prevalence of exposure. Patients with hypertension often have atherogenic dyslipidaemia characterized by elevated triglycerides and LDL cholesterol (LDL-C), and low HDL cholesterol (HDL-C). Therefore, hypertension and dyslipidaemia are two most commonly co-occurring cardiovascular risk factors. Coronary artery disease (CAD) or more generally cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide. It is a multi-factorial disease, emphasis is to treat overall cardiovascular risk, rather than single risk factors in isolation. Hypertension and dyslipidaemia can act multiplicatively or synergistically to increase the risk of a cardiovascular disease event. Current guidelines for management of hypertension recommend statin treatment in patients with hypertension and elevated CV risk (I class of recommendation; A level of evidence). Moreover, statin treatment at maximum tolerated dose is recommended as the first-line drug class to achieve LDL-cholesterol targets in patients with hypertension and high CV risk (I class of recommendation; A level of evidence). Use of a polypill containing two BP lowering drugs and a statin for LDL-cholesterol lowering can be considered in hypertensive patients for primary prevention (II class of recommendation; A level of evidence) [Mancia 2023].

The proposed FDC contains active substances with different - but related - therapeutic indications and different pharmacological targets, i.e. is a fixed combination medicinal product for treating patients at high cardiovascular risk due to hypertension and elevated cholesterol levels, containing rosuvastatin as a lipid-modifying agent and ramipril and amlodipine as antihypertensive agents.

This application follows provisions of the Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017).

To be in line with requirements for FDC products, established in EMA/CHMP/158268/2017 guideline the Applicant has conducted a bioequivalence (BE) study of 3 reference products (Crestor: rosuvastatin, Norvasc: amlodipine besylate, Tritace: ramipril) and the test product, i.e. a FDC of rosuvastatin + amlodipine + ramipril in the same strengths. In addition, a drug-drug interaction (DDI) study has been conducted confirming absence of clinically relevant pharmacokinetic interaction between components.

The application is further based on published clinical data providing rational for the combined use of rosuvastatin, amlodipine and ramipril in the treatment of hypertension associated with dyslipidaemia.

II.2 About the product

Rosuvastatin is a statin, indicated in the treatment of hyperlipidaemia. Amlodipine is a long-acting calcium channel blocker (CCB). Ramipril is a prodrug and non-sulfhydryl angiotensin converting enzyme (ACE) inhibitor. Amlodipine and ramipril are indicated in the treatment of hypertension.

The claimed indication is:
[Invented name] is indicated as substitution therapy for treatment of essential hypertension associated with primary hypercholesterolaemia or combined (mixed) hyperlipidaemia in adult patients already adequately controlled with Ramipril, Amlodipine and Rosuvastatin given concurrently at the same dose level as in the combination.

The recommended dose of [Invented name] is one capsule per day.
The fixed dose combination is not suitable for initial therapy.
Before switching to [Invented name] patients should be controlled on stable doses of the monocomponents taken at the same time. The dose of [Invented name] should be based on the doses of the individual components of the combination at the time of switching.

II.3 General comments on the submitted dossier

The application for Rosuvastatin/Amlodipin/Ramipril Adamed, 10 mg/5 mg/5 mg, 10 mg/5 mg/10 mg, 10 mg/10 mg/10 mg, 20 mg/5 mg/5 mg, 20 mg/5 mg/10 mg, 20 mg/10 mg/10 mg, capsule, hard, is a Combination Art. 10b application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and EL, PL and PT as concerned member states (CMS).

ES was initially a CMS in the procedure, but the applicant has withdrawn the application in ES in connection with the day 106 response (2026-01-27).

The active substances are not considered to be new active substances.

European Reference Product (ERP)
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

Paediatric Regulation
Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision [EMA/PE/0000224486] on the granting of a product specific waiver.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with

which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU. The QP-declaration is acceptable.

GCP aspects
A statement on the application of appropriate GCP standards in the submitted studies has been provided. No issues regarding GCP have been identified. The clinical and the bioanalytical facilities were inspected by the CZ authority in 2020 and 2023, without any critical findings. No inspection of the submitted bioequivalence studies is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

Drug Product
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

Pharmacology
In vivo pharmacology studies have been conducted in multiple species and reported beneficial effects in the treatment of hypertension, hypercholesterolaemia and hyperlipidaemia using Amlodipine, Ramipril or Rosuvastatin. The combination of Amlodipine, a calcium-channel blocker, and Ramipril, an ACE-inhibitor, has been used within EU for a long time to establish an effective therapy for hypertension. Rosuvastatin, an HMG-CoA reductase inhibitor, has been used for the treatment of

hypercholesterolemia and hyperlipidaemia. Each of the single components has been approved in EU for more than 15 years.

In conclusion, the beneficial effects and the safety profile of Amlodipine, Ramipril and Rosuvastatin are well-established in the treatment of cardio-vascular diseases involving hypertension and hypercholesterolemia/hyperlipidaemia.

Pharmacokinetics

Rosuvastatin

Rosuvastatin has a prolonged action and a low inhibitory concentration (IC50) for HMG-CoA reductase with poor penetration in extrahepatic tissues. Micro-autoradiography showed that rosuvastatin was selectively distributed to the intracellular space in liver. The uptake, studied in isolated rat hepatocytes, occurs by both active transport and passive diffusion, with a Km of 9.17 µM. The hepatic uptake involves OATP-C. Only about 10% of a radiolabelled dose is recovered as metabolites, and the major metabolite N-desmethyl-rosuvastatin, which exhibits a low inhibitory effect accounts, for 4.9%. The CYP450 enzymes involved in the metabolism are CYP 2C9 and to a minor extent CYP2C19. After oral administration of [^{14}C]rosuvastatin to rat, 98% was recovered in faeces and 0.4% in urine.

Amlodipine

Oral bioavailability was 63, 88, 100, and 100% in humans, dogs, mice, and rats, respectively and plasma half-life 35, 30, 11 and 3h in the respective specie. The volume of distribution was 25 L/kg in dogs and 21 L/kg in humans with high plasma protein binding (98%). Amlodipine is extensively metabolised in liver and the metabolic pathways appear to be similar to either rat or dog. Most of the radiolabelled drug was recovered in urine after IV administration and with a similar pattern as after oral administration, i.e. 62, 45, 38 and 25% in human, dog, rat and mice respectively.

Ramipril

The kinetics of Ramipril was studied in rat, cat and dog. Tmax ranged between 0.25-1h. Ramipril was rapidly distributed into tissues. After oral administration to rats, high concentrations were detected in liver, kidney and lungs. Ramipril passes into breast milk in rat and presence of ACE inhibitors have been reported in human milk. Excretion has been studied in cats with 87% excretion in faeces and 11% in urine.

In conclusion, the pharmacokinetic studies presented in the non-clinical overview were of limited value and some references included product monographs and product information, which is not considered appropriate. However, based on the long clinical experience with treatment of rosuvastatin, ramipril and amlodipine, deficits in the non-clinical pharmacokinetic data is acceptable. For pharmacokinetic evaluation regarding the combination of all three substances, see clinical pharmacokinetics.

Toxicology

Acute toxicity studies

Single dose toxicity studies were conducted in mice, rats, dogs and for rosuvastatin, also in monkeys. The risk for acute toxicity following oral administration of rosuvastatin and ramipril is very low and a particular target for toxicity was not clear. High doses of Amlodipine in dog identified cardiac toxicity such as oedema and haemorrhage in the right atrial wall as a toxicological target, which also was confirmed in repeated dose toxicity studies.

Repeat dose toxicity studies

Repeated dose toxicity studies were conducted in mice, rats, dogs, monkeys and rabbits. Most information in this section were cited from product monographies or SmPC's, only a few literature references were cited. However, the substances concerned has been marketed for a long time period and the use of each substance are well established with a well-known clinical benefit-risk.

Targets for toxicity following repeated administration of rosuvastatin in respective specie were; Rat: liver (including gallbladder and bile duct), stomach, musculoskeletal and connective tissue disorder (rhabdomyolysis with acute renal failure secondary to myoglobinuria starting approximately ten days after treatment initiation) and uterus; Dog: liver (including gallbladder), vascular lesions in CNS affecting the eyes such as corneal opacity, cataracts, retinal dysplasia and retinal loss at systemic exposures from x20 times the human exposure based on AUC comparisons to a dose of 40 mg, and testis; Monkey: kidney and testis; Rabbit: muscle. The length of the studies is not mentioned for the respective adverse event.

Amlodipine was studied in mice, rats and dogs up to 6 and/or 12 months. The most common side effects in the lower dose range but above human equivalent doses were related to renal dysfunction (increased urine volume, changes in urine composition, increased BUN), and cardiac effects; increased heart weight, and in dog only, reduced blood pressure and compensatory increase in heart rate. In addition, inflammatory lesion in right atrial wall was observed as a result of the haemodynamic changes.

Ramipril was studied in mice, rats, dogs and monkeys up to 2-6 and/or 12-18 months. The most common side effects in the lower dose range but above human equivalent doses were decreased body weight, anaemia, histopathological kidney findings and increased BUN.

Genotoxicity

No genotoxic concerns were reported for either rosuvastatin, amlodipine or ramipril.

Carcinogenicity

Animal data does not suggest that any of the test substances are carcinogenic.

Reproductive toxicity

Reproductive studies have been conducted in rats and rabbits, for ramipril, also in Cynomolgus monkey.

<u>Rosuvastatin</u>
Rosuvastatin is contraindicated during pregnancy and breast feeding due to inhibition of the cholesterol synthesis important for fetal development including synthesis of steroids and cell membranes. Rat studies have shown that rosuvastatin is excreted in milk. Rosuvastatin did not affect fertility.

<u>Amlodipine</u>
Amlodipine has shown to induce adverse effects on reproductive parameters in male rats. The safety of amlodipine in human pregnancy has not been established. Studies in amlodipine-treated rats have shown adverse effects in the offspring at high dose levels.

<u>Ramipril</u>
No literature studies on reproductive toxicity were submitted on ramipril. Angiotensin converting enzyme (ACE) inhibitors may cause injury or death of the developing foetus. Ramipril is not recommended the first trimester of pregnancy and contraindicated from the second trimester.

The adverse risks are reflected in the SmPC proposed by Applicant. Since this is a fixed combination product, Applicant has suggested a contraindication in pregnancy and lactation in line with previous recommendation for rosuvastatin. This is agreed.

Environmental Risk Assessment (ERA)
The applicant has agreed to provide a new variation with an updated ERA within 5 years after the end of procedure. The ERA will be in line with both the active legislation and active ERA-guideline at submission.

Conclusions:
There are no objections to approval of Rosuvastatin/Amlodipine/Ramipril Adamed from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing fixed combination product Rosuvastatin/Amlodipine/Ramipril (Rosuvastatin/Amlodipin/Ramipril Adamed) with the individual active substance products Crestor, Norvasc and Tritace taken concomitantly and one drug-drug interaction study.

Pharmacokinetic properties of the individual active substances
Rosuvastatin: Maximum rosuvastatin plasma concentrations are achieved approximately 5 hours after oral administration. The absolute bioavailability is approximately 20%. Systemic exposure of rosuvastatin increases in proportion to dose. There are no changes in pharmacokinetic parameters following multiple daily doses. The plasma elimination half-life is approximately 19 hours. Rosuvastatin may be given at any time of day, with or without food.

Amlodipine: After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The bioavailability of amlodipine is not affected by food intake. The terminal plasma elimination half-life is about 35-50 hours.

Ramipril: After oral administration, ramipril is rapidly absorbed from the gastrointestinal tract: the maximum plasma concentration of ramipril is reached within one hour. The extent of absorption is at least 56% and is not significantly influenced by the presence of food in the gastrointestinal tract. The bioavailability of the active metabolite, ramiprilat, after oral administration of 2.5 mg and 5 mg ramipril is 45%. Due to its saturable, strong ACE binding and slow enzyme dissociation, ramiprilat has a prolonged terminal elimination phase at very low plasma concentrations. The effective half-life of ramiprilat concentrations was 13-17 hours for 5-10 mg doses and longer for lower doses of 1.25-2.5 mg.

Bioequivalence study 903/22 (20 mg/10 mg/10 mg)
Methods
This was a single-dose, two-way crossover study conducted in 60 healthy volunteers, comparing fixed combination Rosuvastatin/Amlodipine/Ramipril, 20 mg/10 mg/10 mg, hard capsule with individual active substance products taken concomitantly under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of rosuvastatin, amlodipine and ramipril were determined with LC-MS/MS methods. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t}, AUC_{0-72h} and C_{max}. The study was conducted between 14 January and 23 February 2023.

Results

The results from the pharmacokinetic and statistical analysis are presented below.

Table 1. Pharmacokinetic Data for Amlodipine, Ramipril and Rosuvastatin in study 903/22 (ROS-AML-RAM-BIO-01-22)

Amlodipine						
Pharmacokinetic parameter	Arithmetic Means ±SD					
	Test			R1+R2+R3		
$AUC_{(0-72h)}$	242.808	±	59.779	236.519	±	53.971
Cmax	6.549	±	1.348	6.193	±	1.156
Tmax[1]	7.00 h (5.00 – 8.05 h)			7.00 h (5.00 – 10.00 h)		
Ramipril						
Pharmacokinetic parameter	Arithmetic Means ±SD					
	Test			R1+R2+R3		
$AUC_{(0-t)}$	20.42	±	11.14	18.26	±	10.73
$AUC_{(0-\infty)}$	21.05	±	11.38	19.03	±	11.22
Cmax	36.12	±	21.27	32.24	±	17.02
Tmax[1]	0.50 h (0.33 – 2.50 h)			0.50 h (0.33 – 1.00 h)		
Rosuvastatin						
Pharmacokinetic parameter	Arithmetic Means ±SD					
	Test			R1+R2+R3		
$AUC_{(0-t)}$	101.676	±	50.427	95.960	±	50.686
$AUC_{(0-\infty)}$	104.815	±	51.134	99.540	±	50.719
Cmax	12.994	±	7.420	12.108	±	8.014
Tmax[1]	3.00 h (1.00 – 5.00 h)			4.50 h (1.00 – 5.00 h)		

[1] Median (Min, Max)

Table 2. Summary Table of Bioequivalence Data of T/R

Parameter	GEOMETRIC LEAST SQUARES MEANS				RATIO T/R (%)	90 % CONFIDENCE LIMITS (%)		BE	CV_{intra} (%)
	N	Test	N	Ref.		Lower	Upper		
Amlodipine									
$AUC_{(0-72h)}$ (ng·h/mL)	24	235.817	24	230.512	102.30	99.58	105.10	YES	5.45
C_{max} (ng/mL)	24	6.419	24	6.092	105.38	102.20	108.65	YES	6.18
Ramipril									
$AUC_{(0-t)}$ (ng·h/mL)	54	17.61	54	15.84	111.17	103.76	119.11	YES	21.64
C_{max} (ng/mL)	54	30.14	54	27.99	107.68	96.20	120.54	YES	36.09
Rosuvastatin									
$AUC_{(0-t)}$ (ng·h/mL)	54	90.752	54	85.643	105.97	99.41	112.96	YES	20.02
C_{max} (ng/mL)	54	11.137	54	10.385	107.25	97.42	118.06	YES	30.48

Note: Subjects No. **04**, **05**, **13**, **22**, **37**, and **44** were excluded from statistical assessment

For AUC_{0-t} (ramipril and rosuvastatin), AUC_{0-72h} (amlodipine) and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Bioequivalence study 925/22 (10 mg/5 mg/5 mg)

Methods

This was a single-dose, two-way crossover study conducted in 60 healthy volunteers, comparing fixed combination Rosuvastatin/Amlodipine/Ramipril, 10 mg/5 mg/5 mg, hard capsule with the individual active substance products taken concomitantly under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of rosuvastatin, amlodipine and ramipril were determined with LC-MS/MS methods. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t}, AUC_{0-72h} and C_{max}. The study was conducted between 29 July and 22 August 2023.

Results

The results from the pharmacokinetic and statistical analysis are presented below.

Table 3. Pharmacokinetic Data for Amlodipine, Ramipril and Rosuvastatin in study 925/22 (ROS-AML-RAM-BIO-02-23)

Amlodipine		
Pharmacokinetic parameter	Arithmetic Means ±SD	
	Test	R1+R2+R3
$AUC_{(0-72h)}$	98.589 ± 26.159	100.081 ± 25.780
Cmax	2.503 ± 0.571	2.573 ± 0.630
Tmax[1]	8.00 h (5.00 – 12.00 h)	7.50 h (5.00 – 10.02 h)
Ramipril		
Pharmacokinetic parameter	Arithmetic Means ±SD	
	Test	R1+R2+R3
$AUC_{(0-t)}$	7.87 ± 3.32	7.50 ± 3.59
$AUC_{(0-\infty)}$	8.25 ± 3.38	7.83 ± 3.60
Cmax	12.49 ± 6.39	12.72 ± 5.99
Tmax[1]	0.50 h (0.33 – 1.67 h)	0.50 h (0.33 – 1.00 h)
Rosuvastatin		
Pharmacokinetic parameter	Arithmetic Means ±SD	
	Test	R1+R2+R3
$AUC_{(0-t)}$	60.206 ± 25.492	59.211 ± 26.347
$AUC_{(0-\infty)}$	62.700 ± 26.122	61.590 ± 26.389
Cmax	6.862 ± 3.222	6.379 ± 2.977
Tmax[1]	4.50 h (0.50 – 5.50 h)	4.50 h (2.00 – 5.00 h)

[1] Median (Min, Max)

Table 4. Summary Table of Bioequivalence Data of T/R

Parameter	GEOMETRIC LEAST SQUARES MEANS				RATIO T/R (%)	90 % CONFIDENCE LIMITS (%)		BE	CV_{intra} (%)
	N	Test	N	Ref.		Lower	Upper		
Amlodipine									
$AUC_{(0-72h)}$ (ng·h/mL)	28	95.194	28	97.089	98.05	94.68	101.54	YES	7.69
C_{max} (ng/mL)	28	2.439	28	2.500	97.56	92.64	102.74	YES	11.39
Ramipril									
$AUC_{(0-t)}$ (ng·h/mL)	60	7.20	60	6.73	107.01	99.82	114.72	YES	23.10
C_{max} (ng/mL)	60	11.06	60	11.27	98.21	90.03	107.14	YES	29.10
Rosuvastatin									
$AUC_{(0-t)}$ (ng·h/mL)	60	55.180	60	53.712	102.73	96.53	109.34	YES	20.63
C_{max} (ng/mL)	60	6.214	60	5.747	108.13	100.06	116.86	YES	25.85

For AUC_{0-t} (ramipril and rosuvastatin), AUC_{0-72h} (amlodipine) and C_{max} the 90% confidence interval

for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strengths of 10 mg/5 mg/10 mg, 10 mg/10 mg/10 mg, 20 mg/5 mg/5 mg and 20 mg/5 mg/10 mg.

Drug-drug interaction study 927/22

Methods

This was a single dose, four-period, cross-over drug-drug interaction study comparing individual active substance products Crestor, 20 mg, film-coated tablets, Norvasc, 10 mg, tablets and Tritace, 10 mg, tablets administrated concomitantly versus each drug administrated alone in 60 healthy volunteers under fasting conditions.

Results

The results from the pharmacokinetic and statistical analysis are presented below.

Table 5. Summary Table of the Comparative Data

Amlodipine								
Parameter	GEOMETRIC LEAST SQUARES MEANS				RATIO T/A (%)	90% CONFIDENCE LIMITS (%)		CV_{intra} (%)
	N	Trt. T	N	Trt. A		Lower	Upper	
$AUC_{(0-72h)}$ (ng·h/mL)	26	259.801	26	248.110	104.71	101.52	108.00	6.48
C_{max} (ng/mL)	26	6.933	26	6.402	108.30	104.27	112.48	7.95
Ramipril								
Parameter	GEOMETRIC LEAST SQUARES MEANS				RATIO T/B (%)	90% CONFIDENCE LIMITS (%)		CV_{intra} (%)
	N	Trt. T	N	Trt. B		Lower	Upper	
$AUC_{(0-t)}$ (ng·h/mL)	55	15.55	55	13.07	118.99	108.55	130.44	29.33
C_{max} (ng/mL)	55	26.43	55	21.57	122.53	107.00	140.31	44.35
Rosuvastatin								
Parameter	GEOMETRIC LEAST SQUARES MEANS				RATIO T/C (%)	90% CONFIDENCE LIMITS (%)		CV_{intra} (%)
	N	Trt. T	N	Trt. C		Lower	Upper	
$AUC_{(0-t)}$ (ng·h/mL)	55	99.119	55	93.361	106.17	100.67	111.97	16.70
C_{max} (ng/mL)	55	10.815	55	9.362	115.52	106.92	124.82	24.48
Ramiprilat								
Parameter	GEOMETRIC LEAST SQUARES MEANS				RATIO T/B (%)	90% CONFIDENCE LIMITS (%)		CV_{intra} (%)
	N	Trt. T	N	Trt. B		Lower	Upper	
$AUC_{(0-72h)}$ (ng·h/mL)	55	199.47	55	194.60	102.50	99.29	105.82	9.97
C_{max} (ng/mL)	55	18.27	55	20.32	89.91	83.31	97.03	24.16

The results revealed that the 90% confidence intervals for co-administered versus each drug alone ratios of the geometric least squares means for AUC_{0-72h} and C_{max} of amlodipine and AUC_{0-t} and C_{max} of rosuvastatin were within the conventional bioequivalence acceptance range of 80.00-125.00%. The confidence limits for ramipril were found above acceptance range for AUC_{0-t} and C_{max}; however, AUC_{0-72h} and C_{max} parameters for ramiprilat were within this range.

Discussion and overall conclusion

One therapeutic scenario is applied for: substitution therapy. Bridging studies comparing PK data between the fixed combination product and the individual active substances taken simultaneously is essential.

The bioequivalence studies and the statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence

(CPMP/EWP/QWP/1401/98 Rev 1/Corr) and ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms (EMA/CHMP/ICH/953493/2022). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence studies with highest (20 mg/10 mg/10 mg) and lowest (10 mg/5 mg/5 mg) strengths, the proposed fixed-dose combination product Rosuvastatin/Amlodipin/Ramipril Adamed is considered bioequivalent with the individual active substance products taken simultaneously.

A bracketing approach has been applied. The results of study 903/22 with 20 mg/10 mg/10 mg formulation and study 925/22 with 10 mg/5 mg/5 mg formulation CAN be extrapolated to other strengths 10 mg/5 mg/10 mg, 10 mg/10 mg/10 mg, 20 mg/5 mg/5 mg and 20 mg/5 mg/10 mg, according to conditions in the Guideline on the investigation of Bioequivalence; CPMP/EWP/QWP/1401/98 Rev. 1, section 4.1.6.

A possible drug-drug interaction for ramipril was observed in the drug-drug interaction study. It can be agreed with the applicant that pharmacokinetic results for the active metabolite ramiprilat are not changed by the co-administration with rosuvastatin and amlodipine and that this indicates that metabolism of ramipril is not affected by the two other substances rosuvastatin and amlodipine. From a clinical point of view, the pharmacokinetic parameters of the active metabolite ramiprilat are more relevant than those for ramipril (inactive prodrug). Furthermore, since only the substitution therapy is applied for no concern regarding the results for ramipril is raised.

The applicant has not presented any new PK studies with the proposed FDC to study distribution, elimination, dose-proportionality, intra- and inter-individual variability, pharmacokinetics in target population or special populations and refers to already available data for the individual active substances. As neither of the monocomponents are NCE and the co-administration of rosuvastatin, amlodipine and ramipril is established, the absence of dedicated studies is considered acceptable.

The proposed SmPC wording is based on the individual active substance products SmPCs, which is acceptable.

Pharmacodynamics
No specific clinical pharmacological studies are needed in line with the requirements stated in the Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017).

The rationale for use of each monocomponent has been adequately discussed in the clinical overview and these are acceptable. The substitution indication is considered to have been justified adequately in terms of Pharmacodynamics.

Clinical efficacy
The proposed Rosuvastatin/Amlodipine/Ramipril combination is indicated for the treatment of essential hypertension in association with primary hypercholesterolaemia or mixed hyperlipidaemia, as substitution therapy in adult patients adequately controlled with rosuvastatin, amlodipine and ramipril given concurrently at the same dose level as in the combination, but as separate products.

No efficacy clinical studies have been conducted with the fixed-dose combination. Since the fixed-dose combination is expected to improve therapeutic compliance over the three active substances administered separately no efficacy and safety trials are deemed necessary, in accorance with the Guideline on Clinical Development of Fixed Combination Medicinal products

(EMA/CHMP/158268/2017). Co-prescription data for rosuvastatin, amlodipine and ramipril separated by strengths has been provided, supporting the use of the triple combination.

The efficacy of all three active components of the fixed-dose combination for the treatment of essential hypertension in association with primary hypercholesterolaemia or mixed hyperlipidaemia is fully documented and evidence-based as supported by the recommendations of the main European Guidelines.

Published data supporting the efficacy of each of the respective monocomponents has been provided.

In addition, data supporting the combination of amlodipine and ramipril, the combination of rosuvastatin with either amlodipine or ramipril as well as data on the triple combination of rosuvastatin, amlodipine and ACEis/ARB (other than ramipril) has been provided.

The selected doses for amlodipine and ramipril are consistent with the innovators SmPC and the recommendations by the available guidelines for hypertension. For statins, there is not a specific dose recommendation. The choice of the statin dose should be based on the cholesterol target levels to be reached. However, the selected doses for the monocomponents are considered adequate, since the indication is a substitution therapy in patients adequately controlled with the monocomponents given concomitantly at equivalent therapeutic doses. Relevant justifications for the chosen doses have been provided.

Several studies have showed that fixed-dose combinations improve therapeutic compliance in comparison with separate pills treatments. Evidence suggests that reducing dosage demands is an effective single approach to enhancing medication adherence, so the fixed combination is expected at least from a theoretical point of view to improve therapeutic compliance over the three drugs administered separately.

Clinical safety

No specific studies to investigate the safety of the fixed-dose combination have been performed. Taking into account that the intended indication of the fixed-dose combination is a mere substitution indication and that the FDC contains active substances with a wide therapeutic experience in the claimed indication at the proposed dosing schedule, a safety database based on the available experience on the free combination is deemed sufficient and therefore the need of additional safety data is precluded, according to the Guideline on Clinical Development of Fixed Combination Medicinal products (EMA/CHMP/158268/2017). It is not expected that the switch from the concomitant use of the three individual tablets as a free combination to the fixed-dose combination would lead to a potentially different safety profile.

Pharmacovigilance system

Proposed MAH: Adamed Pharma S.A.

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Proposed MAH: Adamed Laboratorios S.L.U.

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Rosuvastatin/Amlodipin/Ramipril Adamed.

Part II Safety specification

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	– None
Important potential risks	– None
Missing information	– None

The safety specification is in line with the safety specifications for the monocomponents.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.1 signed 25 Nov 2024 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

Active substance is currently not listed in the published EURD list
The MAH shall submit the first/next periodic safety update report for this product with a period of 3 years (i.e. DLP of 3 years after authorisation) following authorisation. Further, MAHs shall continuously check the European medicines web-portal if the active substance has been included in the list of Union reference dates (EURD list). If yes, after publication in the EURD list the PSURs shall be submitted in accordance with the requirements set out in the EURD list.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

From a clinical point of view, the fixed-dose combination is justified as a substitution therapy. The efficacy of all three active components of the fixed-dose combination for the treatment of essential hypertension in association with primary hypercholesterolaemia or mixed hyperlipidaemia is fully documented and evidence-based as supported by the recommendations of the main European Guidelines. The safety profiles of the three monocomponents are well known and it is not expected that the switch from the concomitant use of the three individual tablets as a free combination to the fixed-dose combination would lead to a potentially different safety profile.

Bioequivalence between the fixed combination product and the individual active substances taken simultaneously has been adequately demonstrated.

The quality of the product(s), Rosuvastatin/Amlodipin/Ramipril Adamed, is found adequate.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments

Description	Due date
Environmental Risk Assessment (ERA)	5 years from end of current procedure

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**

  N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**

  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**

  N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was Polish.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-