COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Crosuvo Plus 5 mg/10 mg, 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg, film-coated tablets (rosuvastatin calcium and ezetimibe)

NL/H/5139/001-004/DC

11 May 2022

This module reflects the scientific discussion for the approval of Crosuvo Plus. The procedure was finalised at 2 March 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AE	Adverse Event
ADR	Adverse Drug Reaction
ALT	Alanine Aminotransferase
ASMF	Active Substance Master File
AST	Aspartate Aminotransferase
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
EZE	Ezetimibe
FDC	Fixed Dose Concentration product
ICH	International Conference of Harmonisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RSV	Rosuvastatin
SmPC	Summary of Product Characteristics
SAE	Serious Adverse Event
TSE	Transmissible Spongiform Encephalopathy
ULN	Upper Limit of Normal value
USP	United States Pharmacopoeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Crosuvo Plus 5 mg/10 mg, 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg, film-coated tablets, from Bausch Health Ireland Limited.

Crosuvo Plus is indicated as adjunct to diet for treatment of primary hypercholesterolemia substitution therapy in adult patients adequately controlled with the individual substances given concurrently at the same dose level as in the fixed combination medicinal product but as separate products.

A comprehensive description of the indications and posology is given in the SmPC.

The current application combines two active substances which have well-established clinical use and well-known safety and efficacy profiles when prescribed individually as well as concomitantly. Apart from this well-established use, there is a further rationale for the development of this product. Hence there is a large number of patients that do not reach target lipid goals and a fixed combination product may improve adherence to medication.

Fixed dose combination products (FDCs) of ezetimibe with other statins are authorised within the EU, such as Inegy (ezetimibe/simvastatin combination) with procedure number DE/H/0496/001 and, very recently, Atozet (ezetimibe/ atorvastatin) with procedure number DE/H/3895/001, both authorised by Merck Sharp & Dohme B.V. A 'formal' reference product does not exist within the EU for the specific rosuvastatin/ezetimibe combination but similar combination products have been already authorised in EU recently (Rosuvastatin/Ezetimibe egis with procedure number NL/H/3016/001 , Rosuvastatin /Ezetimibe zentiva Rosuvastatin/Ezetimibe adamed), claiming a substitution indication.

This decentralised procedure concerns a FDC of rosuvastatin as calcium salt and ezetimibe. Rosuvastatin and ezetimibe are both approved medicinal products, marketed worldwide for many years. The innovator product Crestor film-coated tablets (rosuvastatin) was first registered in the Netherlands by AstraZeneca BV (NL Licence RVG 26873) through a national procedure on 6 November 2002. Crestor is currently registered through mutual recognition procedure NL/H/0343/MR since 7 March 2003. Ezetrol 10 mg tablets (ezetimibe) is registered in the Netherlands by Merck Sharp & Dohme Ltd. since 18 April 2003 (NL Licence RVG 28626) through mutual recognition procedure DE/H/0396/001.

The concerned member states (CMS) involved in this procedure were Czech Republic and Poland.

The marketing authorisation has been granted pursuant to Article 10b of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Crosuvo Plus 5 mg/10 mg, film-coated tablets
Light yellow, round, biconvex film coated tablets with "EL 5" embossed on one side.

Crosuvo Plus 10 mg/10 mg, film-coated tablets
Beige, round, biconvex film coated tablets with "EL 4" embossed on one side.

Crosuvo Plus 20 mg/10 mg, film-coated tablets
Yellow, round, biconvex film coated tablets with "EL 3" embossed on one side

Crosuvo Plus 40 mg/10 mg, film-coated tablets
White, round, biconvex film coated tablets with "EL 2" embossed on one side

And contains as active substances 5.20 mg, 10.40 mg, 20.80 mg or 41.60 mg of rosuvastatin calcium equivalent to 5 mg, 10 mg, 20 mg or 40 mg of rosuvastatin and 10 mg of ezetimibe.

The film-coated tablets are packed in cold blisters (OPA/AL/PVC/Al).

The excipients are:

All strengths
Tablet core – cellulose – microcrystalline (E460), silica – colloidal anhydrous (E551), magnesium stearate (E572), povidone K30 (E1201), croscarmellose sodium (E468), sodium laurilsulfate (E487), lactose monohydrate and hypromellose 2910 (E464).

Crosuvo Plus 5 mg/10 mg, film-coated tablets
Tablet coating – (Opadry Yellow) hypromellose 2910 (E464), titanium dioxide (E171), macrogol 4000 (E1521), iron oxide yellow (E172), talc (E553b) and iron oxide red (E171).

Crosuvo Plus 10 mg/10 mg, film-coated tablets
Tablet coating – (Opadry Beige) hypromellose 2910 (E464), titanium dioxide (E171), macrogol 4000 (E1521), iron oxide yellow (E172) and talc (E553b).

Crosuvo Plus 20 mg/10 mg, film-coated tablets
Tablet coating – (Vivacoat Yellow) hypromellose 2910 (E464), titanium dioxide (E171), macrogol 4000 (E1521), iron oxide yellow (E172) and talc (E553b).

Crosuvo Plus 40 mg/10 mg, film-coated tablets
Tablet coating – hypromellose 2910 (E464), titanium dioxide (E171), macrogol 4000 (E1521) and lactose monohydrate.

The four tablet strengths are dose proportional.

II.2 Drug Substance

Ezetimibe
The active substance is ezetimibe, an established substance not described in the European Pharmacopoeia (Ph.Eur.), but is described in the United States Pharmacopoeia (USP). Ezetimibe is a white to off-white crystalline powder, which is freely soluble in ethanol and methanol but practically insoluble in water. Ezetimibe contains three asymmetric carbon atoms and therefore exhibits optical isomerism. Ezetimibe exhibits polymorphism, the anhydrous form is consistently produced by the manufacturer.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process consists of several sieving, mixing and granulation steps after which the product is milled, tableted and coated. The synthesis description is in sufficient detail and sufficient chemical transformation steps are part of the regulatory synthesis route. Specifications of starting materials and intermediates are acceptable.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. The analytical procedures have been described in sufficient detail and are adequately validated. Sufficient information has been provided on the reference standards. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance has been provided for three lower scale and three higher scale batches stored at long-term (25°C/60% RH) for 60 months and accelerated (40°C/75% RH) conditions for six months in accordance with applicable European guidelines demonstrating the stability of the active substance for 48 months. Based on the data submitted, a retest period could be granted of 48 months with no special storage conditions.

Rosuvastatin calcium

The active substance is rosuvastatin calcium, an established substance described in the Ph.Eur. Rosuvastatin calcium is slightly soluble in water and practically insoluble in anhydrous ethanol. Rosuvastatin calcium exhibits polymorphism, the amorphous form is consistently produced by the manufacturer.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. The analytical procedures have been described in sufficient detail and are adequately validated. Sufficient information has been provided on the reference standards. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

The active substance is stable for 36 months when stored in an airtight container, protected from light, at a temperature of 2°C to 8°C. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies were the characterisation of the reference product, formulation development, dissolution methods development, manufacturing process development and the performance of comparative dissolution studies complementary to the bioequivalence (BE) study with the 40 mg/ 10 mg and 5 mg/ 10 mg strengths. In general all those parts of the drug development were appropriately performed and described. An extensive discussion has been provided by the MAH on the subject of dissolution studies, which are considered to be adequate.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. For the 10 mg/10 mg, 20 mg/10 mg, 40 mg/10 mg (rosuvastatin/ezetimibe) strengths the manufacturing process is considered to be a standard process, however, the 5 mg/10 mg strength does not correspond to a standard process as the drug load of rosuvastatin is below 2%. Process validation data on the product have been presented for three batches per strength in accordance with the relevant European guidelines.

Control of excipients

Specifications for all excipients have been provided. Except for coating agents, the specifications for all other excipients are in line with Ph. Eur., with additional testing for some excipients. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, uniformity of dosage units, water, disintegration, mean weight, identification of rosuvastatin and ezetimibe, assay, related substances, dissolution, microbiological tests, and identification of colourants. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life limits are identical except for the limits of water content and related substances. The specification is acceptable based on batch analysis results, available stability results and European guidance. Analytical methods have been adequately described. Satisfactory validation data of the analytical in-house methods have been presented.

Batch analytical data from three batches for each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches per strength with an exception of 40 mg/10 mg (rosuvastatin/ezetimibe) strength for which four batches were placed in stability. Stability information from accelerated (40 2ºC / 75 ± 5%RH, up to six months), intermediate (30 ± 2ºC / 75 ± 5%RH, 24 months) and long term (25 ± 2ºC / 60 ± 5% RH, 24 months) is provided. This is in accordance with applicable European guidelines and demonstrates the stability of the product for 36 months. On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage conditions are: “This medicinal product does not require any special temperature storage conditions” and “Store in the original package in order to protect from light and moisture”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided for lactose monohydrate and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Crosuvo has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Crosuvo is intended to be a FDC product, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a FDC product of rosuvastatin and ezetimibe based on Crestor and Ezetrol which are available on the European market. Reference is made to the preclinical data obtained with Crestor and Ezetrol. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

For this FDC product application, the MAH has submitted two bioequivalence studies which are discussed below. Furthermore, the MAH has submitted an extensive literature review, making reference to scientific studies relevant to this fixed combination product.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies:

- Study I: single dose study with the 40/10 mg tablet under fasting conditions.
- Study II: single dose study with the 5/10 mg tablet under fasting conditions.

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Rosuvastatin/Ezetimibe 40 mg/10 mg and 5 mg/10 mg tablets (Elpen S.A.

Pharmaceutical Industry, Greece) are compared with the pharmacokinetic profile of the reference products Ezetrol 10 mg tablets (MSD Greece for study II, Schering-Plough Labo N.V., Belgium for study I) and Crestor 5 mg and 40 mg tablets (AstraZeneca Osterreich GmbH for 5 mg strength, AstraZeneca GmbH, Germany for 40 mg strength).

The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in these studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

The design of the studies is acceptable.

Biowaiver

Two bioequivalence studies have been carried, one with the lowest strength and one with the highest strength. The formulations can be considered proportional, based upon the 5% rule and the fixed formulation rule, in which in this case ezetimibe can be considered as an inert excipient. Considering the linear pharmacokinetics of rosuvastatin, in principle one bioequivalence study would have been sufficient. Dissolution data at pH 1.2, 4.5 and 6.8 showed comparable dissolution between the 5mg/10mg, 10mg/10mg, 20mg/10mg, 40mg/10mg tablets. Therefore, the conclusions of the bioequivalence studies with the rosuvastatin/ezetimibe 40/10 and 5/10 mg strengths can be extrapolated to the intermediate 10/10mg and 20/10 mg tablet strengths.

Bioequivalence studies

Study I: single dose study with the 40/10 mg tablet under fasting conditions.

Design

An open label, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 62 healthy male subjects, aged 18-44 years. Each subject received a single dose (40/10 mg: 1 x 40/10 mg tablet or 1 x 40 mg tablet + 1 x 10 mg tablet) of both the test and the reference rosuvastatin and ezetimibe formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of 10 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

Results

Out of a total of 62, 58 subjects were eligible for pharmacokinetic analysis. One subject was withdrawn due to an adverse event following period one (accident, physical injury), one subject was found positive in alcohol breath test during admission of period two and two subjects did not report to the facility during admission of period two.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of total ezetimibe of the test and reference product under fasting conditions

Treatment N=58	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test: Rosuvastatin/Ezetimibe 40/10 mg tablet	1192 ± 553	1291 ± 633	169 ± 91	1.0 (0.33 – 5.0)
Reference: Ezetrol 10 mg tablet	1211 ± 494	1294 ± 520	169 ± 79	1.0 (0.67 – 4.0)
***Ratio (90% CI)**	0.97 (0.92 – 1.03)	--	0.98 (0.91 - 1.06)	--
CV (%)	17.6	--	25.0	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of total rosuvastatin of the test and reference product under fasting conditions

Treatment N=58	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test: Rosuvastatin/Ezetimibe 40/10 mg tablet	414 ± 184	427 ± 185	49 ± 25	3.67 (0.67 – 4.67)
Reference: Crestor 40 mg tablet	432 ± 209	445 ± 209	52 ± 30	2.5 (0.67 – 6.0)
***Ratio (90% CI)**	0.98 (0.93 – 1.03)	--	1.00 (0.92 - 1.09)	--
CV (%)	17.8	--	27.9	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Study II: single dose study with the 5/10 mg tablet under fasting conditions.

Design

An open label, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 62 healthy male subjects, aged 18-44 years. Each subject received a single dose (5/10 mg: 1 x 5/10 mg tablet or 1 x 5 mg tablet + 1 x 10 mg tablet) of both the test and the reference rosuvastatin and ezetimibe formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of 11 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

Results
Out of a total of 62, 62 subjects were eligible for pharmacokinetic analysis. One subject withdrew its consent before study initiation and was therefore replaced by the reserve subject.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of total rosuvastatin of the test and reference product under fasting conditions

Treatment N=62	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test: Rosuvastatin/Ezetimibe 5/10 mg tablet	58 ± 24	61 ± 25	6.6 ± 3.0	4.33 (0.67 – 5.0)
Reference: Crestor 10 mg tablet	63 ± 27	66 ± 27	6.8 ± 3.2	4.33 (0.67 – 6.0)
***Ratio (90% CI)**	0.93 (0.88 – 0.98)	--	0.97 (0.91 - 1.04)	--
CV (%)	17.6	--	23.1	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of total rosuvastatin of the test and reference product under fasting conditions

Treatment N=62	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**

Test: Rosuvastatin/Ezetimibe 5/10 mg tablet	1049 ± 466	1101 ± 499	168 ± 65	0.67 (0.33 – 2)
Reference: Ezetrol 5 mg tablet	1041 ± 427	1107 ± 463	154 ± 73	0.68 (0.67 – 2.7)
***Ratio (90% CI)**	1.00 (0.95 – 1.04)	--	1.11 (1.04 – 1.19)	--
CV (%)	15.0	--	21.6	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Rosuvastatin/Ezetimibe is considered bioequivalent with Crestor and Ezetrol.

The results of the bioequivalence studies with the 40 mg/10 mg and 5 mg/10 mg formulations respectively, can be extrapolated to the additional strengths of 10 mg/10 mg and 20 mg/10 mg as all the requirements in the bioequivalence study guideline (Doc. Ref.:CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, 2010) for granting such a biowaiver are fulfilled.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Pharmacodynamics

Rosuvastatin

Rosuvastatin belongs to the pharmacotherapeutic group of lipid modifying agents and HMG-CoA –reductase inhibitors (statins). This active substance is a selective and competitive inhibitor of HMG-CoA reductase which lowers the intracellular cholesterol level, converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol and upregulates the low density lipoprotein (LDL) receptors, resulting in increased clearance of LDL from the circulation. Rosuvastatin reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases high density lipoprotein (HDL)-cholesterol (C). It also lowers apoliprotein B (ApoB), non HDL-C, very low density lipoprotein cholesterol (VLDL-C), very low density lipoprotein triglycerides (VLDL-TG) and increases in apoliprotein A1 (ApoA-I) (see table 5). It also lowers the LDL-C/HDL-C, total C/HDL-C and non-HDL-C/HDL-C and the ApoB/ApoA-I ratios (AstraZeneca, 2017; AstraZeneca UK Limited, 2016; MHRA, 2017b).

Table 5. dose response to rosuvastatin 5, 10, 20 and 40 mg in patients with hypercholesterolemia.

Dose	N	LDL-C	Total-C	HDL-C	TG	nonHDL-C	Apo B	ApoA-I
Placebo	13	-7	-5	3	-3	-7	-3	0
5	17	-45	-33	13	-35	-44	-38	4
10	17	-52	-36	14	-10	-48	-42	4
20	17	-55	-40	8	-23	-51	-46	5
40	18	-63	-46	10	-28	-60	-54	0

Ezetimibe

Ezetimibe inhibits intestinal uptake of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients. By inhibiting cholesterol absorption at the level of the brush border of the intestine [by interaction with the Niemann- Pick C1-like protein 1 (NPC1L1)], ezetimibe reduces the amount of cholesterol delivered to the liver. Ezetimibe is orally active, and has a mechanism of action that differs from other classes of cholesterol-reducing compounds (e.g. statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols) (Merck Sharp & Dohme Limited, 2016; MHRA, 2017a; Sandoz Canada Inc., 2013). Ezetimibe has been shown to reduce LDL concentrations by 20%, but in adults it is used in combination with statins (Merck Sharp & Dohme Limited, 2016; MHRA, 2017a; Sandoz Canada Inc., 2013).

IV.4 Clinical efficacy

According to the guideline on clinical development of FDC products [EMA/CHMP/158268/2017] the requirements 1, 2 and 3 have to be fulfilled, i.e. justification of the medical rationale of the combination, establishment of the evidence base for the relevant contribution of all active substances to the desired therapeutic effect and demonstration that the evidence presented, if based on combined administration of separate active substances, is relevant to the FDC product for which the application is made.

a. Justification of the medical rationale of the combination

The combination of statin with ezetimibe is a widely used double combination for the treatment of hypercholesterolemia. The addition of ezetimibe in statin therapy (e.g. rosuvastatin) is recommended from the relevant guidelines and their therapeutic benefit and their clinical use have been demonstrated through a series of clinical studies.

The combination of ezetimibe plus a statin has the potential to effectively lower LDL-C levels by two independent and complementary pathways: inhibition of cholesterol absorption and inhibition of cholesterol synthesis. The specific combination has not only synergistic effects on the lowering of LDL-C levels and decreasing cholesterol absorption compared with a statin administered alone (Bays et al., 2011; Catapano et al., 2005; Daskalopoulou and Mikhailidis, 2004) but also this combination has a positive influence on the reduction of adverse events (Catapano et al., 2005; Daskalopoulou and Mikhailidis, 2004). In addition, some studies report

that a greater proportion of patients reached their target LDL level with rosuvastatin and ezetimibe than those with up-titration of rosuvastatin alone (Ballantyne et al., 2007; Bays et al., 2011). Moreover, a FDC is expected to improve medication compliance in patients with chronic diseases such as hypercholesterolemia (Bangalore et al., 2007). Based on a study conducted by Kosoglou and his co-scientists, there is no clinically significant interaction between the two active substances (Kosoglou et al., 2004b). Therefore, a FDC tablet of rosuvastatin/ezetimibe has been developed aimed to improve patient compliance and clinical outcomes.

b. Relevant contribution of all active substances to the desired therapeutic effect
The claimed therapeutic indication for the rosuvastatin/ezetimibe combination is a substitution indication for patients that are already used to be on dual concurrent therapy of the two mono components at the same dose level as in the FDC, since mono – or double treatment was not effective in the control of the disease.
The FDC product is intended to be used in patients who are already stabilised on an optimal dose of the mono-components, where the monocomponents will be discontinued and the FDC product started. It may be possible that those components belong to different therapeutic classes. The clinical use of statin (rosuvastatin) and cholesterol absorption inhibitors (ezetimibe) concurrently is recommended in the relative guidelines for the management of hypercholesterolemia and for prevention of cardiovascular disease.
The MAH has presented studies on the combined use of statins (including rosuvastatin) with ezetimibe including the EASE study of Sweeney and Johnson, 2007, a study of Hamilton-Craig et al., 2010, a study of Morrone et al., 2012, a pooled analysis of Ambegaonkar et al., 2014, a study specifically in HeFH of Pitsavos et al., 2009, a publication of Foody et al., 2013, a study of Inoue et al., 2010, and a study of Okada et al., 2012.

Moreover, the MAH has presented studies on the specific combined use of rosuvastatin with ezetimibe. These included the following studies:

- I-ROSETTE (Ildong ROSuvastatin & ezETimibe for hypercholesTErolemia) was an eight-week, double-blind, multicentre, Phase III randomised controlled trial conducted at 20 hospitals. Patients were randomly assigned to receive ezetimibe 10 mg/rosuvastatin 20 mg, ezetimibe 10 mg/rosuvastatin 10 mg, ezetimibe 10 mg/rosuvastatin 5 mg, rosuvastatin 20 mg, rosuvastatin 10 mg, or rosuvastatin 5 mg in a 1:1:1:1:1:1 ratio (Hong et al., 2018).
- A 12-week, randomised, double-blind, placebo-controlled, multicentre study in 245 patients with high cardiovascular risk. Patients received one of six regimens for eight weeks as follows: (1) rosuvastatin 5 mg, (2) rosuvastatin 5 mg/ezetimibe 10 mg, (3) rosuvastatin 10 mg, (4) rosuvastatin 10 mg/ ezetimibe 10 mg, (5) rosuvastatin 20 mg, or (6) rosuvastatin 20 mg/ezetimibe 10 mg (Yang et al., 2017).
- A study in 135 patients who were enrolled within 24 hours of Acute Myocardial Infarction (AMI), and were randomised to receive 10 mg rosuvastatin or 10 mg rosuvastatin plus 10 mg ezetimibe daily. HsCRP, Lp- PLA2, total cholesterol (TC), triglycerides (TG), LDL-C and HDL-C were determined at baseline and after one, three, six and 12 months of treatment (Ren et al., 2017).

- A clinical study in which 60 eligible patients were randomly assigned into 3 groups (20 subjects in each) and were treated for a period of 14 days with rosuvastatin 10 mg/d (R group), ezetimibe 10 mg/d (E group), and rosuvastatin 10 mg/d plus ezetimibe 10 mg/d (R+E group), respectively (Zhang et al., 2017).
- A study in which a total of 125 patients were randomly assigned to an intermediate intensity rosuvastatin group (rosuvastatin 10 mg/d, n = 42), high-dose rosuvastatin group (rosuvastatin 20 mg/d, n = 41) or combination therapy group (ezetimibe 10 mg/d and rosuvastatin 10 mg/d, n = 42) with a 12-week follow-up (Ran et al., 2017).
- A multicentre eight-week randomised double-blind phase III study (MRSROZE_ Multicenter Randomised Study of ROsuvastatin and eZEtmibe) which evaluated the efficacy of fixed-dose combinations of ezetimibe 10 mg plus rosuvastatin, compared with rosuvastatin alone in patents with primary hypercholesterolemia in 407 patients with primary hypercholesterolemia (Kim et al., 2016).
- A study including 106 patients with coronary atherosclerotic heart disease and hyperlipidaemia who were randomly assigned to one of two groups: (1) ezetimibe (10 mg, once a night) plus rosuvastatin (10 mg, once a night) (n = 55) or (2) rosuvastatin alone (10 mg, once a night) (n = 51) for 12 months (Wang et al., 2016).
- In a 12-week, prospective, randomised, open-label clinical study, Saeedi et al examined the efficacy of combination treatment with rosuvastatin and the cholesterol transport blocker, ezetimibe, vs. monotherapy with rosuvastatin in patients not achieving lipid goal (Saeedi et al., 2015).
- In a prospective randomised open-label study, a total of 51 patients with stable coronary artery disease requiring percutaneous coronary intervention were enrolled, and assigned to a combination group (n = 26, rosuvastatin 5 mg/day + ezetimibe 10 mg/day) or a monotherapy group (n = 25, rosuvastatin 5 mg/day) (Masuda et al., 2015).
- In a randomised clinical study (GRAVITY study), adult patients (n = 833) were randomised to rosuvastatin (RSV)10 mg/ezetimibe (EZE)10 mg, RSV20 mg/EZE10 mg, SIM40 mg/EZE10 mg or SIM80 mg/EZE10 mg for 12 weeks (Ballantyne et al., 2014)
- In a randomised open-label study, diabetic patients under treatment with rosuvastatin (2.5 mg daily), who had LDL-C levels ≥80 mg/dL (n = 79) were randomly allocated to two groups: the add-on ezetimibe group (combination group) that received 2.5 mg/day of rosuvastatin and 10 mg/day of ezetimibe (n = 40), and the rosuvastatin dose escalation group that received 5 mg/day of rosuvastatin (n = 39) for 12 weeks (Torimoto et al., 2013).
- A prospective randomised, open-label study for a 12-month prognosis after vascular surgery. Patients were randomly assigned to receive rosuvastatin (RSV) 10 mg/d or rosuvastatin 10 mg/d plus ezetimibe (RSV/EZE) 10 mg/d, starting prior to scheduled surgical procedure (Kouvelos et al., 2013).
- A prospective open randomised study, in which 17 patients with heterozygous familial hypercholesterolemia and single LDL receptor gene mutations were enrolled. Study subjects were divided into two groups: rosuvastatin 20 mg/day (group 1) versus rosuvastatin 10 mg/day coadministered with ezetimibe 10 mg/day (group 2) (Kawashiri et al., 2012).

- A multicentre, six-week, randomised, double-blind, parallel-group, clinical trial (ACTE study) evaluated the efficacy of ezetimibe (10 mg) added to stable rosuvastatin therapy versus uptitration of rosuvastatin from 5 to 10 mg or from 10 to 20 mg. The study population included 440 subjects at moderately high/high risk of coronary heart disease with low-density lipoprotein (LDL) (Bays et al., 2011).
- In a prospective study one group of patients (n=33) were administered with ezetimibe 10 mg/day alone for 12 weeks. In the other two groups, ezetimibe was given with an HMG-CoA reductase inhibitor (statin) to 13 patients for 12 weeks: pravastatin 10 mg/day (n = 7) or rosuvastatin 2.5 mg/day (n = 6) for 12 weeks. (Sawayama et al., 2010)
- In an open-label, 12-week sub study within a larger trial, ezetimibe 10 mg was added to stable therapy with rosuvastatin 40 mg (± bile acid sequestrant/niacin) in 107 patients with severe hypercholesterolemia (Stein et al., 2007).
- Another clinical study (EXPLORER study) aimed to investigate the efficacy of rosuvastatin 40 mg alone or in combination with ezetimibe 10 mg. Four hundred sixty-nine patients were randomly assigned to rosuvastatin alone or in combination with ezetimibe for six weeks (Ballantyne et al., 2007).

Furthermore, the MAH mentions that a more pronounced LDL-C reduction when adding ezetimibe to a statin should reduce the risk for major cardiovascular events which has been shown in the IMPROVE-IT trial (Cannon et al., 2015). When added to statin therapy, ezetimibe resulted in incremental lowering of LDL cholesterol levels and improved cardiovascular outcomes. In various other studies, add-on ezetimibe was significantly more effective in reducing LDL-C levels than doubling the statin dose, enabling more patients to achieve LDL-C goals (Mikhailidis et al., 2011). Further, reference is made to the JUPITER study.

c. Demonstration that the evidence presented - if based on combined administration of separate active substances - is relevant to the FDC product for which the application is made
Bridging studies comparing pharmacokinetic data between the FDC product and authorised active substances taken simultaneously is essential and bioequivalence should be demonstrated. Bioequivalence of the FDC product is in general required to bridge existing clinical data obtained from the combined use of mono-components with those from the FDC formulation. In order to support the clinical equivalence of the product, bioequivalence studies have been performed on the highest strength of the current application, 40 mg/10 mg (Rosuvastatin/Ezetimibe) versus Crestor (Rosuvastatin) film-coated tablets of AstraZeneca B.V Netherlands and Ezetrol (Ezetimibe) 10 mg Tablets of Merck Sharp & Dohme Ltd. Greece). In addition, two pilot bioequivalence studies in the same strength (40 mg/10 mg) were conducted, in order to decide the design and sample size for the pivotal study.

IV.5 Clinical safety

Rosuvastatin
Data has been presented based on information in the SmPC of AstraZeneca, 2017; AstraZeneca UK Limited, 2016; MHRA, 2017b. Safety information based on publication has also been presented.

Ezetimibe

Data has been presented based on information in the SmPC of Merck Sharp & Dohme Limited, 2016; MHRA, 2017a. Safety information based on publication has also been presented.

Rosuvastatin and ezetimibe

Several studies have been presented. These studies have also been included in the efficacy section. The largest studies are mentioned below:

- In an eight-week, double-blind, multicentre, Phase III randomised controlled trial (IROSETTE) conducted at 20 hospitals, patients with hypercholesterolemia were randomly assigned to receive ezetimibe 10 mg/rosuvastatin 20 mg, ezetimibe 10 mg/rosuvastatin 10 mg, ezetimibe 10 mg/rosuvastatin 5 mg, rosuvastatin 20 mg, rosuvastatin 10 mg, or rosuvastatin 5 mg in a 1:1:1:1:1:1 ratio. Among the 392 patients in the safety profile set, 44 (11.2%) experienced at least one adverse event (AE) after randomization. The most common AEs were gastrointestinal disorders, followed by investigations and musculoskeletal and connective tissue disorders. There were no significant differences in the overall incidence of AEs, adverse drug reactions (ADRs), or serious AEs. The observed AEs and frequency of drug-related AEs experienced by ≥2% of patients are the following ones (Hong et al., 2018).
- A multicentre eight-week randomised double-blind phase III study evaluated the safety of fixed-dose combinations of ezetimibe 10 mg plus rosuvastatin, compared with rosuvastatin alone in patents with primary hypercholesterolemia. 407 patients with primary hypercholesterolemia who required lipid-lowering treatment according to the ATP III guideline were randomised to one of the following six treatments for eight weeks: fixed dose combinations with ezetimibe 10 mg daily plus rosuvastatin (5, 10, or 20 mg daily) or rosuvastatin alone (5, 10, or 20 mg daily). No serious drug-related AEs were reported. There were three serious AEs, including one in the monotherapy group (breast cancer) and two in the combo therapy group (left ulnar fracture and epigastric pain), although these were not considered drug-related AEs by the investigators. The incidence of prespecified AEs was generally comparable between the two groups, with no clinically meaningful differences or statistical significance. Consecutive elevations ≥three times the upper normal limits in alanine aminotransferase or aspartate aminotransferase occurred in one (0.5%) of 204 patients receiving monotherapy and one (0.5%) of 206 patients receiving combo therapy. Elevations ≥five-times the upper normal limits in creatine kinase occurred only in one (0.5%) of 204 patents receiving combo therapy, with no significant differences between the groups (Kim et al., 2016).
- In a 12-week, randomised, double-blind, placebo-controlled, multicentre study, a total of 337 patients were screened. After a four-week run-in period, 245 of these patients with high or moderately high risk as defined by the National Cholesterol Education Program Adult Treatment Panel III guidelines were randomly assigned. Patients received one of six regimens for eight weeks as follows: (1) rosuvastatin 5 mg, (2) rosuvastatin 5 mg/ezetimibe 10 mg, (3) rosuvastatin 10 mg, (4) rosuvastatin 10 mg/ ezetimibe 10 mg, (5) rosuvastatin 20 mg, or (6) rosuvastatin 20 mg/ezetimibe 10 mg. The proportions of patients who experienced any AE in the rosuvastatin monotherapy and the rosuvastatin/ezetimibe combination groups were similar (26 patients [21.5%]

and 26 patients [21.1%], respectively). Patients with serious AEs or discontinued drugs for AEs were not common in either group. No individuals reported rhabdomyolysis, liver enzyme elevation, or muscle enzyme elevation above predefined levels (Yang et al., 2017).

- A study conducted by Ballantyne investigated the safety of rosuvastatin 40 mg alone or in combination with ezetimibe 10 mg in patients at high risk of coronary heart disease. 469 patients were randomly assigned to rosuvastatin alone or in combination with ezetimibe for 6 weeks. Both treatments were well tolerated, and the overall frequency and type of AEs were similar between treatment groups. Adverse events were experienced by 31.5% and 33.5% of patients receiving combination therapy or monotherapy, respectively. Frequencies of liver, muscle, and renal AEs were low in both groups. Myalgia was the most frequently reported AE in both treatment groups. Most AEs were mild to moderate in intensity. The most frequently reported treatment-related AE was increased ALT in the combination therapy group (n = 6 [2.5%]) and myalgia in the monotherapy group (n=5 [2.2%]) (Ballantyne et al., 2007).
- Adult patients (n= 833) were randomised to rosuvastatin (RSV) 10 mg/ezetimibe (EZE) 10 mg, RSV20/EZE10, SIM40/EZE10 or SIM80/EZE10. Following a six-week dietary lead-in, patients received six weeks' statin monotherapy followed by same statin dose plus ezetimibe for six more weeks. AEs were experienced by 32.7% and 31.4% of patients overall during monotherapy and combination therapy, respectively. Overall incidence of liver, muscle and renal AEs was low in all treatment groups during monotherapy and combination therapy: one case of myopathy was reported in the rosuvastatin 10 mg group; one case of myopathy was reported in the rosuvastatin 20 mg/ezetimibe 10 mg group during combination therapy. No cases of rhabdomyolysis were reported. 19 patients discontinued due to an AE during monotherapy. The most common AE leading to withdrawal was myalgia, occurring in one patient each in the rosuvastatin 10 mg and simvastatin 40 mg groups and three patients in the rosuvastatin 20 mg group. Twelve patients discontinued due to an AE during combination therapy. The most frequent AEs leading to withdrawal were fatigue, muscle spasms and dizziness, with each occurring in no more than one patient in any group and no notable differences in the frequency of AEs between groups. During monotherapy, 12 patients (1.4%), distributed across all groups, experienced serious adverse events (SAEs). Two patients in the rosuvastatin 20 mg group experienced a cerebrovascular accident, and all other SAEs occurred in no more than one patient. 16 patients (2.1%) experienced an SAE during combination therapy. The most frequent SAE was unstable angina occurring in two patients receiving rosuvastatin 10 mg plus ezetimibe and three patients receiving simvastatin 40 mg plus ezetimibe. All other SAEs were isolated reports. No deaths occurred during the study (Ballantyne et al., 2014).
- A multicentre, six-week, randomised, double-blind, parallel-group, clinical trial evaluated the safety of ezetimibe (10 mg) added to stable rosuvastatin therapy versus up-titration of rosuvastatin from 5 to 10 mg or from 10 to 20 mg. The study population included 440 subjects at moderately high/high risk of coronary heart disease with LDL cholesterol levels higher than the National Cholesterol Education Program Adult Treatment Panel III recommendations. All doses of rosuvastatin (10, 20 mg) and rosuvastatin (5, 10 mg) plus ezetimibe 10 mg add-on were generally well tolerated

during the six-week study. Analysis of the pooled rosuvastatin (5 mg and 10 mg) plus ezetimibe add-on and pooled rosuvastatin up-titration (10 and 20 mg) showed a similar incidence of one AE, drug related AE, and serious AE. No serious drug-related AEs were observed during the present study. Drug-related discontinuations that occurred during rosuvastatin plus ezetimibe add-on therapy included mild or moderate arthralgia, constipation, myalgia, dermatitis allergic, or eczema. The incidence of prespecified AEs of special interest was low, with no significant differences seen between the pooled groups. Only one subject in the rosuvastatin 5-mg plus ezetimibe 10-mg group experienced an elevation in alanine aminotransferase of three times the upper limit of normal, but it was not related to treatment. No patient experienced elevations in aspartate aminotransferase of three times the upper limit of normal. Only one subject in the rosuvastatin 20 mg group experienced an asymptomatic elevation in creatine kinase of 10 times the upper limit of normal. It was judged by the site investigator to not be related to drug therapy. The most common AE was gastrointestinal related. Ten subjects experienced the following drug-related clinical AEs while receiving ezetimibe added to rosuvastatin 5 mg or 10 mg: abdominal distension in one, abdominal pain in one, constipation in two, dry mouth in one, nausea in one, arthralgia in one, myalgia in two, dermatitis in one, and eczema in one patient. Six subjects who received rosuvastatin up-titrated to 10 or 20 mg experienced the following drug-related clinical AEs: constipation in two, asthenia in one, fatigue in one, myalgia in one, and skin exfoliation in one patient. The safety endpoints are presented in the following tables (Bays et al., 2011).

- Ran and his co-researchers randomly assigned 125 patients to an intermediate intensity rosuvastatin group (rosuvastatin 10 mg/d, n = 42), high-dose rosuvastatin group (rosuvastatin 20 mg/d, n = 41) or combination therapy group (ezetimibe 10 mg/d and rosuvastatin 10 mg/d, n = 42) with a 12-week follow-up. The incidence of drug-related adverse events was much higher in the rosuvastatin 20 mg group than the rosuvastatin 10 mg group and the combination therapy group (17.0% vs 2.4% vs 4.8%, $P < 0.05$). A total of ten patients experienced ADRs during the 12-week follow-up period. One patient in the rosuvastatin 20 mg group withdrew from our trial due to an elevated CK ≥five times the upper limit of normal values (ULN) on day five after the initiation of therapy. Patients in the rosuvastatin/ ezetimibe group and the rosuvastatin 10 mg group tolerated the treatments well and completed the study. One patient in the rosuvastatin 10 mg group experienced muscle pain. Seven patients in the rosuvastatin 20 mg group experienced adverse effects (one patient developed a rash and five patients had muscle pain), and two patients in the rosuvastatin/ezetimibe group reported AEs (one patient had muscle pain, and the other patient experienced gastrointestinal discomfort). No patients experienced rhabdomyolysis or obvious liver enzymes elevation. The total percent of ADRs in the rosuvastatin 20 mg group was significantly higher than those in the rosuvastatin 10 mg group and the rosuvastatin/ezetimibe group (17.0% vs. 2.4% vs. 4.8%, $P< 0.05$) (Ran et al., 2017).

In a clinical study by Wang et al comprised of a study group with 106 patients with coronary atherosclerotic heart disease and hyperlipidaemia. Each patient was randomly assigned to one of two groups: (1) Ezetimibe (10 mg, once a night) plus rosuvastatin (10 mg, once a night) (n =

55) or (2) Rosuvastatin alone (10 mg, once a night) (n = 51). The primary endpoint was new or recurrent myocardial infarction, unstable angina pectoris, cardiac death, and stroke. In the rosuvastatin group, one patient was withdrawn due to AEs, one patient was withdrawn because of poor compliance and one patient was lost to follow-up. In the combination of ezetimibe plus rosuvastatin group, two patients were withdrawn due to AEs, one patient was withdrawn because of poor compliance and two patients were lost to follow-up. The major AEs were recorded during 12 months. AEs occurred in two groups: One case of abnormality of laboratory value Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) > three times ULN; one case of myalgia in the rosuvastatin group; two cases of abnormality of laboratory value AST or ALT > three times ULN, one case of myalgia in the ezetimibe plus rosuvastatin group. Two cases of myalgia in the two groups occurred in older patients (Wang et al., 2016).

IV.6 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 Crosuvo.

Table 6. Summary table of safety concerns as approved in RMP

Important identified risks	- Rhabdomyolysis/myopathy including immune-mediated necrotizing myopathy. - Abnormal liver function: increased transaminases, jaundice and hepatitis.
Important potential risks	- None
Missing information	- Use in pregnancy and during lactation.

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator products Crestor and Ezetrol. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Rosuvastatine/ezetimibe EGIS,

(NL/H/3016/001-003/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Crosuvo Plus 5 mg/10 mg, 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg, film-coated tablets have a proven chemical-pharmaceutical quality and can be used as a substitute for Ezetrol and Crestor. Ezetrol and Crestor are well-known medicinal products with established favourable efficacy and safety profiles.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. Crosuvo Plus film-coated tablets were shown to be bioequivalent to the concomitant use of Crestor film-coated tablets and Ezetrol 10 mg film-coated tablets. The pharmacodynamic effects as well as the safety profile were shown to be similar. It is adequately shown that Crosuvo Plus can be used as substitution therapy in adult patients adequately controlled with the individual substances given concurrently at the same dose level as in the FDC, but as separate products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Crosuvo Plus with the reference product, and have therefore granted a marketing authorisation. The decentralised was finalised with a positive outcome on 2 March 2022.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse