COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil 5 mg/1000 mg, soft capsules

(rosuvastatin calcium/omega-3-acid ethyl esters 90)

NL/H/4611/001/DC

Date: 29 July 2020

This module reflects the scientific discussion for the approval of Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil 5 mg/1000 mg, soft capsules. The procedure was finalised at 15 January 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
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
DHA	Docosahexaenoic Acid
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EPA	Eicosapentaenoic Acid
ERA	Environmental Risk Assessment
FDC	Fixed Dose Combination
HDL-C	High-Density Lipoprotein Cholesterol
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
O3FAs	Omega−3 Fatty Acids
O3FAEEs	Omega-3-acid Ethyl Esters
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TG	Triglycerides
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil 5 mg/1000 mg, soft capsules, from Oy Medfiles Ltd.

The product is indicated as substitution therapy for the treatment of mixed hyperlipidaemia (type IIb) in adult patients adequately controlled with rosuvastatin and omega-3-acid ethyl esters 90 given concurrently at the same dose level.

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

This decentralised procedure concerns a fixed dose combination (FDC) application. Fixed dose combinations (pursuant to article 10b of Directive 2001/83/EC) contain active substances from medicinal products already authorised in the EEA but not hitherto used in combination for therapeutic purposes. In these kind of applications pre-clinical and clinical data relating to that combination are provided. However, it is not necessary to provide pre-clinical and clinical data relating to each individual active substance.

The innovator product containing rosuvastatin is Crestor 5 mg, film-coated tablets (NL license RVG 30823) which has been registered in the Netherlands by AstraZeneca BV since 20 July 2004 by procedure NL/H/0343/004. Crestor is indicated for the treatment of hypercholesterolemia and the prevention of cardiovascular events.
The active substance omega-3-acid ethyl esters 90 is registered as Omacor 1000 mg soft capsules 460 mg/380 mg which has been registered by Pronova BioPharma Norge AS in France since 22 July 2001. In the Netherlands, Omacor (NL License RVG 28822) has been registered since 15 August 2003 by procedure FR/H/0105/001/MR. Omacor is indicated for hypertriglyceridemia.

The concerned member state (CMS) involved in this procedure was Italy.

II. QUALITY ASPECTS

II.1 Introduction

Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil is a white, oblong-shaped, film-coated soft capsule, filled with light yellow oil. Each soft capsule contains 5 mg rosuvastatin (as rosuvastatin calcium) and 1000 mg omega-3-acid ethyl esters 90 (O3FAEEs) comprising 460 mg eicosapentaenoic acid (EPA), 380 mg docosahexaenoic acid (DHA) and 4 mg alpha tocopherol.

The soft capsules are packed in oPA/Al/PVC – Al blisters or PVC/Al blisters in a pillow bag.

The excipients are:
Soft capsule core - gelatine and glycerol (E422)
Capsule coating - hypromellose 2910, poly(butyl methacrylate-co-(2-dimethyl-aminoethyl) methacrylate-co-methyl methacrylate) 1:2:1(=Eudragit® E PO), magnesium oxide (E530), triethyl citrate (E1505) and may contain traces of soybean oil.

II.2 Drug Substances

The active substances are rosuvastatin calcium and omega-3-acid ethyl esters 90, established active substances described in the European Pharmacopoeia (Ph.Eur.).

The CEP procedure is used for both active substances. 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.

Rosuvastatin calcium
Rosuvastatin calcium is a white or almost white slightly hygroscopic powder and soluble in water and methanol. Two pairs of isomers are possible; for this medicinal product R, S isomer is manufactured. Rosuvastatin calcium manufactured by the active substance manufacturer is the amorphous form.

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. and the CEP with an additional XRD test and a test for residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for six batches.

Stability of drug substance
The active substance is stable for 48 months when stored under the stated conditions. This re-test period is fully justified by stability results of three full scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months).

Omega-3-acid ethyl esters 90
The active substance is a hydrophobic light yellow oil and practically insoluble in water and very soluble in acetone, ethanol (96%), heptane and methanol. Omega-3-acid ethyl esters 90

are marine oil derived ethyl esters and are obtained by the transesterification of the body oil of fat fish species.

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. with an additional test for α- tocopherol Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 2 years when stored under the stated conditions. 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. No additional development information was necessary for the core soft capsules, as they are already registered in the EU. Compounded rosuvastatin calcium as a coating solution is sprayed on the surface of core soft capsule using a coating machine, so that the loss of the coating solution during the process is inevitable. The loss rate of the coating solution during the coating process was evaluated and the overage percentage of rosuvastatin calcium coating materials was confirmed necessary. Formulation development study to select excipients and to optimise excipient level was performed and the formulation in which a stabiliser in the 2nd coating process was confirmed to be suitable by the study. Based on this result comparative dissolution evaluation with the reference drug was carried out and batch formula for pilot scale batch and commercial scale production batch were established.
A bioequivalence study was performed concerning rosuvastatin calcium against innovator Crestor. As the Omega-3-acid ethyl esters are already in a liquid form, bio equivalence with the reference product is not an issue. Additional information has, however, been included on disintegration time. The limit set for QC dissolution, is deemed acceptable in view of the *in vitro* studies with the biobatch.

Manufacturing process
The critical part of the manufacturing process is the coating with rosuvastatin. This coating process has been validated on full-scale. The core soft capsules can be regarded as intermediate product. They are manufactured on a different site. An intermediate hold time of 18 weeks is established following a hold time study. As the release date of the finished

product may be later than 30 days after production of the core capsules, information and results of this hold time study have been provided. The 18 weeks hold time is acceptable, based on these studies. The start of shelf life is, however, set in line with the applicable guideline.

Control of excipients
The specifications for all excipients used for the production of the product 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 description, identification, uniformity of dosage units, disintegration, acid value, peroxide value, anisidine value, oligomers, α-tocopherol, assay, dissolution (for rosuvastatin), related substances, residual solvents and microbial limit. No release or shelf life requirement has been set for certain impurities. As these impurities will not increase during manufacturing or storage, this is no objection. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from a total of eighteen batches 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 full-scale batches in accordance with applicable European guidelines stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). A photostability study showed that the product met the acceptance criteria of the study when packed in the immediate packaging. On basis of the data submitted, a shelf life was granted of 3 years. The labelled storage conditions are: 'Store below 25°C. Store in the original package in order to protect from moisture.'

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Certificates of suitability issued by the EDQM have been provided, for the used gelatine of the capsules, 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 Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil 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 Pharmacology, pharmacokinetics and toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of omega-3-acid ethyl esters 90 and rosuvastatin are well known. As these esters and rosuvastatin are widely used, well-known active substances, only a combination study has been performed and further studies are not required. The 13-week repeat dose study in rats with the combination of omega-3-acid ethyl esters and rosuvastatin showed that no significant differences were seen in adverse events from the combination and the ethyl esters or rosuvastatin alone. When extrapolated to human, the fixed dose Rosuvastatin/Omega-3-acid ethyl esters 90 is not expected to cause adverse effects. Therefore, no pre-clinical safety concerns are identified.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil is intended for substitution of separately used rosuvastatin calcium and omega-3-acid ethyl esters 90 containing products, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Rosuvastatin calcium and omega-3-acid ethyl esters 90 are well-known active substances with established efficacy and tolerability.

To support this application, the MAH has provided two bioavailability studies and a phase 3 study to evaluate the efficacy and safety of Rosuvastatin/Omega-3-acid ethyl esters 90. Additionally, in the clinical overview the MAH has provided scientific literature on rosuvastatin and omega-3-acid ethyl esters.

IV.2 Pharmacokinetics

To support the application, the MAH submitted one pilot and one pivotal bioavailability/bioequivalence study.

Bioavailability/bioequivalence studies

Pilot study 150095

A pilot, single-center, randomised, open-label, three-way crossover comparative bioavailability study was carried out under fasted conditions in 18 healthy male (6) and

female (12) subjects. A single oral dose of either the Test or Reference study drugs was administered:

- Treatment A (Test): 4 x 5 mg/1000 mg Rosumega soft-gelatin capsules;
- Treatment B (Reference 1): Rosuvastatin (Crestor) 1 x 20 mg film-coated tablet;
- Treatment C (Reference 2): Omacor soft-gelatin capsule (O3EEs 1000 mg (containing ~460 mg EPA ethyl ester and ~380 mg DHA ethyl ester) 4 x 1000 mg.

The extent and rate of absorption of rosuvastatin from the Test product, Rosuvastatin/Omega-3-acid ethyl esters 90, 1000/5 mg capsule, was on average 19% and 22% higher, respectively, with 90% CI above the upper limit of 125% as compared to the Reference Crestor product. Rosuvastatin/Omega-3-acid ethyl esters 90, 1000/5 mg capsule was bioequivalent with the Reference Omacor product regarding the total EPA (baseline corrected) component, but the rate and extent of absorption of total baseline corrected DHA component was 18% and 43% lower, respectively, with 90% CI being outside the lower limit of 80%. The MAH clarified that the failure to demonstrate bioequivalence with regard to fatty acids content in the pilot study 150095 (n=18) was due to highly variable and erratic pharmacokinetics of the fatty acids, which also has been reported in literature. Based on the results from this pilot study, an appropriate sample size has been calculated for the pivotal study 150096 with expected CV of 48% for AUC and 30% for C_{max} for total DHA content. The MAH did not discuss the results of study 150095 for rosuvastatin. However, since this was an exploratory study and bioequivalence for rosuvastatin has been demonstrated in the pivotal study 150096, this issue was not pursued.

Pivotal study 150096

The MAH conducted a bioavailability/bioequivalence study in which the pharmacokinetic profile of the test product Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil 5 mg/1000 mg, soft capsules (Oy Medfiles Ltd, Finland) is compared with the pharmacokinetic profile of the reference products Omacor 1000 mg soft capsules 460 mg/380 mg (Pronova BioPharma Norge AS, Norway) simultaneously given with Crestor 20 mg film-coated tablets (AstraZeneca GmbH, Germany)

The choice of the reference products in the bioequivalence study has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioavailability study was carried out under fasted conditions in 100 healthy male (70) and female (30) subjects. In each period, each subject received a single dose of either the test of reference formulations:

- Treatment A (test): 4 x Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil 5 mg/1000 mg, soft capsules
- Treatment B (reference): 1 x Crestor 20 mg film-coated tablets and 4 x Omacor 1000 mg soft capsules 460 mg/380 mg

The tablet was orally administered 30 minutes after a high-fat, high caloric breakfast. The breakfast consisted of two eggs fried in butter, two slices of toast with butter, two strips of bacon, approximately 120 g of hash brown potatoes and 200 ml of whole milk.
There were 2 dosing periods, separated by a washout period of 14 days.

For rosuvastatin, 18 blood samples were drawn into blood collection tubes (1 x 4 mL) containing dipotassium ethylenediaminetetraacetic acid (K2 EDTA) prior to drug administration and 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 12.0, 24.0, 48.0 and 72.0 hours post-dose in each period.
For total EPA and total DHA, 23 blood samples were drawn into blood collection tubes (1 x 6 mL) containing tripotassium ethylenediaminetetraacetic acid (K3 EDTA) -1.00, -0.500, prior to drug administration (0.00),1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 9.00, 10.0, 11.0, 12.0, 14.0, 16.0, 20.0, 24.0, 28.0, 36.0, 48.0, and 72.0 hours post-dose in each period.

The design of the study is acceptable. The fed conditions are acceptable since the product should be taken with food.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject was withdrawn from the study due to not finishing the breakfast within 30 minutes and one subject withdrew from the study due to personal reasons. Therefore, 98 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1 **Rosuvastatin - Ratios (A/B), 90% Geometric Confidence Intervals, Intra- and Inter-Subject CVs.**

			90% Geometric C.I.[2]			
Parameter	Treatment Comparisons	Ratio[1]	Lower	Upper	Intra-Subject CV	Inter-Subject CV
AUC_{0-t}	Rosuvastatin/Omega-3-acid ethyl esters (A) - Crestor + Omacor (B)	110.46%	106.98%	114.07%	13.59%	41.81%
AUC_{0-inf}	Rosuvastatin/Omega-3-acid ethyl esters (A) - Crestor + Omacor (B)	108.38%	105.10%	111.76%	12.86%	42.89%
C_{max}	Rosuvastatin/Omega-3-acid ethyl esters (A) - Crestor + Omacor (B)	109.00%	103.38%	114.91%	22.56%	46.55%

[1] Calculated using least-squares means according to the formula: $e^{(DIFFERENCE)}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.
Treatment A (Test): Kuhnil Pharmaceutical Co. Ltd., South Korea, rosuvastatin (as rosuvastatin calcium)/omega-3-acid ethyl esters, 4 x 5 mg/1000 mg soft gelatin capsule.
Treatment B (References): AstraZeneca UK Ltd., United Kingdom (Crestor®) rosuvastatin (as rosuvastatin calcium), 1 x 20 mg film-coated tablet; Pronova BioPharma Norge AS, Norway (Omacor), omega-3-acid ethyl esters 4 x 1000 mg soft gelatin capsule.

Table 2. Total EPA (Baseline Corrected) - Ratios (A/B), 90% Geometric Confidence Intervals, Intra- and Inter-Subject CVs.

Parameter	Treatment Comparisons	Ratio[1]	90% Geometric C.I.[2] Lower	Upper	Intra-Subject CV	Inter-Subject CV
AUC_{0-72}	Rosuvastatin/Omega-3-acid ethyl esters (A) - Crestor + Omacor (B)	100.88%	96.67%	105.28%	18.12%	31.49%
C_{max}	Rosuvastatin/Omega-3-acid ethyl esters (A) - Crestor + Omacor (B)	99.60%	95.05%	104.37%	19.91%	28.92%

[1] Calculated using least-squares means according to the formula: $e^{(DIFFERENCE)}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.
Treatment A (Test): Kuhnil Pharmaceutical Co. Ltd., South Korea, rosuvastatin (as rosuvastatin calcium)/omega-3-acid ethyl esters, 4 x 5 mg/1000 mg soft gelatin capsule.
Treatment B (References): AstraZeneca UK Ltd., United Kingdom (Crestor®) rosuvastatin (as rosuvastatin calcium), 1 x 20 mg film-coated tablet; Pronova BioPharma Norge AS, Norway (Omacor), omega-3-acid ethyl esters 4 x 1000 mg soft gelatin capsule.

Table 3. Total DHA (Baseline Corrected) - Ratios (A/B), 90% Geometric Confidence Intervals, Intra- and Inter-Subject CVs.

Parameter	Treatment Comparisons	Ratio[1]	90% Geometric C.I.[2] Lower	Upper	Intra-Subject CV	Inter-Subject CV
AUC_{0-72}	Rosuvastatin/Omega-3-acid ethyl esters (A) - Crestor + Omacor (B)	108.37%	97.48%	120.49%	46.42%	74.78%
C_{max}	Rosuvastatin/Omega-3-acid ethyl esters (A) - Crestor + Omacor (B)	104.39%	96.94%	112.41%	31.60%	42.59%

[1] Calculated using least-squares means according to the formula: $e^{(DIFFERENCE)}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.
Treatment A (Test): Kuhnil Pharmaceutical Co. Ltd., South Korea, rosuvastatin (as rosuvastatin calcium)/omega-3-acid ethyl esters, 4 x 5 mg/1000 mg soft gelatin capsule.
Treatment B (References): AstraZeneca UK Ltd., United Kingdom (Crestor®) rosuvastatin (as rosuvastatin calcium), 1 x 20 mg film-coated tablet; Pronova BioPharma Norge AS, Norway (Omacor), omega-3-acid ethyl esters 4 x 1000 mg soft gelatin capsule.

<u>Conclusion on bioequivalence study</u>

Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil was shown to be bioequivalent to Crestor 20 mg film-coated tablet co-administered with the Omacor 1000 mg soft capsules, with respect to each component of the formulation, i.e. rosuvastatin, EPA and DHA with 90% CI being within 80-125% limits.

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

The pharmacodynamics of rosuvastatin are well-established, while the pharmacodynamics with respect to the mechanism of action of the Omega−3 fatty acids (O3FAs) are not fully understood. The two mono-components have different main pharmacodynamic effects, i.e. reduction in LDL-C and reduction in triglyceridemia for rosuvastatin and O3FAs, respectively.

IV.4 Clinical efficacy

In support of the combination of O3FA/rosuvastatin in the treatment of mixed hyperlipidaemia, the MAH has provided an overview of 6 clinical studies, including the pivotal ROMANTIC trial, conducted by the MAH.

ROMANTIC study
The ROMANTIC study is a multi-centre, randomised, double-blind, parallel phase III study performed in South Korea to evaluate the efficacy and safety of Rosuvastatin/Omega-3-acid ethyl esters 90 in patients whose triglycerides (TG) level is not adequately controlled with rosuvastatin calcium monotherapy while low-density lipoprotein cholesterol (LDL-C) is properly controlled.

Eligible participants underwent a 4-week run-in period. During the run-in period, all participants received 20 mg/d of open-label rosuvastatin calcium and discontinued use of other lipid-lowering agents. After the run-in period, the levels of LDL-C and TGs were measured repeatedly.

After a 4-week run-in period of treatment with rosuvastatin, the patients with residual hypertriglyceridemia were randomised to receive rosuvastatin 20 mg/day + O3FAEEs 4 g/d (Rosuvastatin/Omega-3-acid ethyl esters 90 group) or rosuvastatin 20 mg/day (rosuvastatin group) with a 1:1 ratio and were administered each medication for 8 weeks.

The primary efficacy endpoint is percent change in non- high-density lipoprotein cholesterol (HDL-C) at week 8 from baseline. Secondary endpoints were percent change in non-HDL-C at week 4 from baseline and percent change in total cholesterol, triglycerides, LDL-C, HDL-C, very LDL-C, Apolipoprotein A1 and Apolipoprotein B at week 4 and 8 from baseline. A total of 201 patients were analysed.

The results are at baseline and 8 weeks after treatment are presented below (table 3).

Table 4 Lipid and lipoprotein levels at baseline and 8 weeks after treatment

	ROSUMEGA (n = 97)			Rosuvastatin (n = 104)			
Variable	Baseline, Mean (SD), mg/dL	Week 8, Mean (SD), mg/dL	Percent Change, Mean (SEM)	Baseline, Mean (SD), mg/dL	Week 8, Mean (SD), mg/dL	Percent Change, Mean (SEM)	*P* for Percent Change Between Groups
Triglycerides	284.0 (68.6)	205.9 (91.4)	−26.3 (3.1)	279.6 (64.2)	241.7 (97.7)	−11.4 (3.4)	<0.001
Non-HDL-C	99.1 (23.7)	86.0 (25.4)	−10.7 (2.9)	96.7 (22.0)	94.1 (30.7)	−2.2 (2.5)	0.001
Total cholesterol	141.2 (24.5)	128.3 (27.2)	−8.1 (1.9)	139.4 (24.0)	137.2 (31.9)	−1.2 (1.7)	<0.001
LDL-C	61.9 (19.6)	61.5 (22.2)	1.8 (3.1)	62.5 (18.4)	64.7 (25.5)	4.3 (2.9)	0.335
HDL-C	42.1 (7.5)	42.3 (8.8)	0.9 (1.5)	42.6 (10.1)	43.1 (8.9)	2.8 (1.6)	0.377
VLDL-C	37.2 (16.4)	24.6 (15.1)	−28.5 (4.4)	34.2 (13.4)	29.4 (19.5)	−12.2 (4.9)	0.004
Apolipoprotein A1	140.1 (23.0)	133.8 (24.5)	−1.5 (4.1)	139.9 (23.8)	138.0 (22.7)	−0.5 (1.2)	0.009
Apolipoprotein B	75.4 (20.5)	71.1 (18.3)	−3.4 (2.5)	75.7 (16.5)	75.3 (20.4)	0.3 (2.0)	0.049

Clinical studies with the combination of O3FAs and other statins

Several studies have evaluated the efficacy of combining O3FAs with statins on controlling TG levels. One of the early large trials investigating combination therapy was the 2007 Combination of prescription O3FA with Simvastatin (COMBOS) study (Davidson 2007[1]). This was a multicentre RCT in adults who had received ≥8 weeks of stable statin therapy and had mean fasting TG levels of ≥2.2 and <5.5 mmol/l and mean LDL levels ≤10% above their goal and dietary counselling, followed by 8 weeks of randomised treatment with double-blind O3FAEEs (Lovaza/Omacor) 4 g/day + simvastatin 40 mg/day or placebo + simvastatin 40 mg/day. Significant improvement was observed in non-HDL with TG-lowering from the addition of O3FAEE to simvastatin compared to simvastatin alone. Results showed significant reductions in TG and very-LDL levels in the O3FAEE + simvastatin group compared to simvastatin alone after 8 weeks with nonsignificant changes in LDL levels in either group.

The Epanova Combined with a Statin in Patients with Hypertriglyceridemia to Reduce non-HDL Cholesterol (ESPRIT) study (Maki 2013[2]) was similar to COMBOS. The study showed improvements in cardiovascular risk profiles in patients with persistent hypertriglyceridemia (TG ≥2.2 mmol/l and <5.5 mmol/l) despite statin therapy using either 2 or 4 g of daily O3FA free fatty acids compared to olive oil and placebo. Results showed significant reductions in non-HDL by 3.9% and 6.9% in the 2 and 4 g/day doses, respectively, compared to 0.9% reduction with olive oil (p<0.05 and <0.001, respectively), significant reductions in TG by 14.6% and 20.6%, respectively, compared to 5.9% in olive oil (p<0.001 for both), and significant reductions in total cholesterol and VLDL compared to olive oil (all at least p<0.05)

[1] Davidson MH, Stein EA, Bays HE, Maki KC, Doyle RT, Shalwitz RA, Ballantyne CM, Ginsberg HN; COMBination of prescription Omega-3 with Simvastatin (COMBOS) Investigators. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clin Ther. 2007;29(7):1354-67.

[2] Maki KC, Orloff DG, Nicholls SJ, et al. A highly bioavailable omega-3 free fatty acid formulation improves the cardiovascular risk profile in high-risk, statin-treated patients with residual hypertriglyceridemia (ESPRIT trial). Clin Ther. 2013;35(9):1400-11.e1-3.

(Maki 2013]). A later analysis of ESPRIT (Dunbar 2015[3]) found that small LDL particles were significantly reduced in those taking the 4 g/d dose compared to olive oil. Furthermore, the 4 g/d dose brought significant reductions in Lipoprotein-associated phospholipase A2 and both O3FA doses brought significant reductions in apolipoprotein CIII compared to placebo.

In the ANCHOR study (Ballantyne 2012[4]), 4 g/day of icosapent ethyl, the ethyl ester of EPA, combined with several kinds of statins also reduced TG levels by a greater amount than statin alone (18% vs 6%).
A randomised control trial (Ng 2014[5]) tested the effect of atorvastatin (40 mg/day) and atorvastatin + O3FAEEs (4 g/day) on very-LDL metabolism in obese, insulin resistant men. Compared with placebo, atorvastatin significantly decreased very-LDL concentration (-40%, $p < 0.001$) by increasing very-LDL fractional catabolic rate. Atorvastatin + O3FAEE lowered very-LDL-TG concentration to a greater degree compared with placebo (-46%, $p < 0.001$) or atorvastatin monotherapy (-13%, $p = 0.04$).
Also outcome data have shown a benefit of adding O3FA to statins. In the Japan EPA Lipid Intervention Study (JELIS) (Yokoyama 2007 [6]), 18645 Japanese patients with hypercholesterolemia (LDL-C ≥ 4.4 mmol/l) with or without coronary artery disease received either 1.8 g/day EPA + a statin (simvastatin or pravastatin) or a statin only. After a mean of 4.6 years, the rate of major cardiovascular events was reduced by 19% in the EPA + statin group, in which 2.8% experienced an event over a follow-up of 5 years, compared with 3.5% in controls (p=0.011). When analysing groups based on the presence of baseline coronary artery disease, those receiving EPA + statin for primary prevention had lower major cardiovascular event rates compared to controls; however, this was not statistically significant. In contrast, those receiving EPA + statin for secondary prevention had a statistically significant reduction in major cardiovascular events. Baseline TG's in both groups was 1.7 mmol/l, HDL was 1.5 mmol/l, and LDL was 4.7 mmol/l. A separate analysis of data from this study found that the EPA supplementation did not affect total stroke incidence but did reduce the risk of recurrent stroke by 20% in patients who had previously experienced a stroke (Tanaka 2008[7]).

[3] Dunbar RL, Nicholls SJ, Maki KC, et al. Effects of omega-3 carboxylic acids on lipoprotein particles and other cardiovascular risk markers in high-risk statin-treated patients with residual hypertriglyceridemia: a randomized, controlled, double-blind trial. Lipids Health Dis. 2015;14:98.
[4] Ballantyne CM, Bays HE, Kastelein JJ, et al. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR study). Am J Cardiol. 2012;110(7):984-92.
[5] Ng TW, Ooi EM, Watts GF, Chan DC, Barrett PH. Atorvastatin plus omega-3 fatty acid ethyl ester decreases very-low-density lipoprotein triglyceride production in insulin resistant obese men. Diabetes Obes Metab. 2014;16(6):519-26.
[6] Yokoyama M, Origasa H, Matsuzaki M, et al. Japan EPA lipid intervention study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007;369(9567):1090-8.
[7] Tanaka K, Ishikawa Y, Yokoyama M et al. JELIS Investigators, Japan. Reduction in the recurrence of stroke by eicosapentaenoic acid for hypercholesterolemic patients: subanalysis of JELIS trial. Stroke. 2008;39(7):2052-8.

Co-prescription data of O3FA and rosuvastatin
In addition to the provided data on the co-prescription of 03FA with other statins, the MAH provided co-prescription data from 5 European countries (United Kingdom, Germany, Italy, France and Spain). This has been considered acceptable.

IV.5 Clinical safety

The safety of O3FA and rosuvastatin has already been established during the clinical development of each substance.

Omega-3 fatty acids
Commonly reported adverse effects of O3FA products are usually mild. The most common adverse effects of O3FA preparations are gastrointestinal disturbances, particularly at high doses, including nausea, eructation, vomiting, abdominal distension, dyspepsia, gastroesophageal reflux disease, flatulence, diarrhoea, and constipation. There have been rare reports of acne and eczema. Moderate increases in hepatic transaminases, alanine aminotransferase and aspartate aminotransferase, have been reported in patients with hypertriglyceridemia (EFSA 2012[8], Sweetman 2017b[9]).

Rosuvastatin
The safety of rosuvastatin has been comprehensively reviewed. The adverse reactions seen with rosuvastatin are generally mild and transient. The most frequent adverse events (AEs) associated with rosuvastatin in placebo-controlled studies were pharyngitis (9.0%), headache (5.5%), diarrhoea (3.4%), dyspepsia (3.4%), nausea (3.4%), and myalgia (2.8%). These rates are similar to those of other currently marketed statins and did not differ from the AEs documented in patients receiving placebo. Withdrawal rates due to an AE, arguably one of the most revealing measures of a drug's tolerability, with rosuvastatin, atorvastatin, simvastatin, and pravastatin were similar.

Combination omega-3 fatty acids and rosuvastatin
ROMANTIC trial
213 subjects were included in the safety set. Mean dose was 210.75±38.06 capsules of Rosuvastatin/Omega-3-acid ethyl esters 90 (1000 mg O3FA/ 5 mg rosuvastatin) in the test group and 53.96±8.36 tablets of Crestor 20 mg (rosuvastatin) in the control group. Mean total duration of administration was 55.22±9.19 days in the test group and 55.65±7.03 days in the comparator group; there was no significant inter-group difference (p=0.8223).

The provided safety data provided from the ROMANTIC trial are summarised below in table 5.

[8] EFSA, European Food Safety Authority. Scientific Opinion on the Tolerable Upper Intake Level of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA). EFSA Journal 2012;10(7):2815.
[9] Sweetman SC, Editor. Martindale The Complete Drug Reference. Omega-3 fatty acids. 39th Edition, Pharmaceutical Press 2017b.

Table 5 Summary of adverse events

Summary of Adverse Events	Test Group N=103 n◆ (%)	[#]	Comparator Group N=110 n◆ (%)	[#]	*p*-value
Treatment-Emergent Adverse Event (TEAE)	16 (15.53)	[22]	19 (17.27)	[25]	0.7322†
Adverse Drug Reaction (ADR)€	2 (1.94)	[2]	0 (0.00)	[0]	0.2327‡
Serious Adverse Event (SAE)	2 (1.94)	[2]	2 (1.82)	[2]	1.0000‡
Suspected Unexpected Serious Adverse Reaction (SADR)	0 (0.00)	[0]	0 (0.00)	[0]	—
Suspected Unexpected Serious Adverse Reaction(SUSAR)	0 (0.00)	[0]	0 (0.00)	[0]	—

€: definitely related, likely, possible, or 'unknown' for causal relationship
†: Pearson's chi-square test
‡: Fisher's exact test

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 Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil.

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

Important identified risks	- Muscle injury (rhabdomyolysis/myopathy) - Abnormal liver function
Important potential risks	None
Missing information	None

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

The pharmacokinetic studies were designed to demonstrate bioequivalence between the recognised reference formulations of the individual mono-components with the proposed fixed-dose combination as well as to investigate a possible pharmacokinetic interaction of the components. Results were satisfactory: the fixed dose combination can be used instead of the separate mono-components. Overall, the provided clinical overview is considered sufficient to justify the rationale of this particular combination when used to substitute patients already on stable doses of the separate agents. According to the MAH, the main advantage of using Rosuvastatin/Omega-3-acid ethyl esters 90 FDC is that instead of using capsules of O3FAEE and one tablet of rosuvastatin the FDC would reduce the number of medicinal products to be taken which may lead to an improved adherence to therapy. Data from clinical practice do not suggest any substantial different safety profile from that which is known for the mono-components.

V. USER CONSULTATION

The package leaflet has not been evaluated via a user consultation study. Bridging is proposed to other parent leaflets. Rosuvastatin/Omega-3-acid ethyl esters 90 is a fixed combination medicinal product, combining rosuvastatin and omega-3-acid ethyl esters in the same capsule. Therefore, there are two separate parent leaflets for testing the key safety messages. Reference is made to the package leaflet of Omacor (FR/H/0105/001) and Rosuvastatin DSM Sinochem (NL/H/3486/001-004/DC). A user test has been performed and approved for the package leaflet of Omacor and Rosuvastatin. Regarding the layout and design of the package leaflet the MAH refers to the leaflets of Valganciclovir film-coated tablets (NL/H/3315/001/DC). In the bridging report the MAH compared the design and lay out on several points with the design and layout of this product. Overall, 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

Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil 5 mg/1000 mg, soft capsules has a proven chemical-pharmaceutical quality and are considered an approvable fixed dose combination. Rosuvastatin calcium and omega-3-acid ethyl esters 90 are well known, established active substances which are used as a combination in clinical practice.

The proposed combination product was demonstrated to be bioequivalent with co-administration of the separate components. The results two bioavailability studies and a phase 3 study demonstrate that there is no significant pharmacokinetic interaction between the co-administered components of the reference products Omacor and Crestor. The efficacy and safety profile is considered the same as for the mono-components.

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, have granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 January 2020.

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