Public Assessment Report

Scientific discussion

Ridutrin 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg capsules, hard

(rosuvastatin zinc/ezetimibe)

NL/H/3017/001-003/DC

Date: 14 October 2014

This module reflects the scientific discussion for the approval of Ridutrin 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg capsules, hard. The procedure was finalised on 30 June 2014. For information on changes after this date please refer to the module 'Update'.

This report includes a summary, on pages 16-18.

List of abbreviations

ASMF	Active Substance Master File
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{72}	Area under the plasma concentration-time curve from time zero to t=72
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EAS	European Atherosclerosis Society
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ESC	European Society of Cardiology
EU	European Union
FDC	Fixed Dose Combination
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HoFH	Homozygous Familial Hypercholesterolaemia
ICH	International Conference of Harmonisation
LDL-C	Low-Density Lipoprotein Cholesterol
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
NOEAL	No Observed Adverse Effect Level
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SD	Standard Deviation
SmPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP/NF	United States Pharmacopoeia/National Formulary

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ridutrin 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg capsules, hard from Egis Pharmaceuticals Plc.

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

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

This decentralised procedure concerns an application is based on Article 8(3) of Directive 2001/83/EC, a full-mixed application, where the individual active substances (monocomponents) have established clinical use as well as regulatory approval.

Both active substances are approved as monotherapy in the management of (different types of) hypercholesterolaemia. The innovator products Crestor (rosuvastatin) and Ezetrol (ezetimibe) were first registered in the EU in 2002 through procedures NL/H/0343/001-004/DC and Ezetrol DE/H/0396/001/MR, respectively. The proposed product is the first rosuvastatin-ezetimibe fixed dose combination (FDC). Co-therapy of statins and ezetimibe is currently only available as the FDC Inegy (DE/H/0496/001-004/MR), which contains simvastatin and ezetimibe in the strengths of 10/10 mg, 20/10 mg, 40/10 mg and 80/10 mg.

The use of rosuvastatin and ezetimibe monotherapy as well as ezetimibe + statin combination therapy is supported by the guideline of the European Society of Cardiology (ESC), based on the pharmacological synergistic mechanisms of action (combining rosuvastatin with ezetimibe reduces LDL-C by an additional 15 to 20%). Furthermore, ezetimibe is approved for combined treatment with statins as adjunct to diet for patients with homozygous familial hypercholesterolaemia (HoFH) and for patients with primary hypercholesterolaemia not sufficiently controlled on statin alone. The registered simvastatin/ezetimibe containing fixed dose combination Inegy is indicated as adjunct to diet in the treatment of primary (familial and non-familial) hypercholesterolemia or mixed hyperlipidaemia as add-on or substation therapy and as adjunct to diet in the treatment of HoFH. This is considered a justification for the combined use of rosuvastatin and ezetimibe.
The MAH further argued that in general FDCs could increase therapeutic adherence, and that compliance and the use of less packaging material would result in less waste production and a more protected environment.

Instead of the already in the EU approved calcium salt, the MAH has chosen zinc salt for rosuvastatin development. Rosuvastatin zinc has not yet been approved in the EU. According to Directive 2001/83/EC, as amended, products containing different salts of the same active substance may be considered essentially similar, if bioequivalence has been proven. It should further be proven that the safety profile of the new zinc salt is similar to the already approved calcium salt.

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

The marketing authorisation has been granted pursuant to Article 8(3), full-mixed application, of Directive 2001/83/EC. According to Part II of Annex I to the Directive mixed marketing authorisations shall mean: *marketing authorisation application dossiers where Module 4 and/or 5 consists of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references. All other Module(s) are in accordance with the structure described in Part I of this Annex. The competent authority shall accept the proposed format presented by the applicant on a case by case basis.*

No dedicated studies in the target population have been performed with this product. This is however not necessary taking into account the substitution indication. No new non-clinical studies were performed in support of this application. Non-clinical evaluation of the pharmacology, pharmacokinetics and toxicology of this medicinal product was based on literature references.

The submission includes a bioequivalence study comparing Ridutrin 40/10 mg capsules to the single component innovator products Crestor 40 mg with Ezetrol 10 mg, concomitantly dosed. For the lower strengths a biowaiver has been granted.
Further clinical evaluation of Rosuvastatin/ezetimibe EGIS was based on the presented literature data relevant to each active substance and references to the combinations of statins and ezetimibe published in the scientific literature with the aim of proving the clinical benefit provided by the combination and supporting the proposed indication

No Paediatric Investigation Plan (PIP) has been submitted. A product specific waiver has been granted by the EMA for Ridutrin for the treatment of hypercholesterolemia in all subsets of the paediatric population, on the grounds that rosuvastatin/ezetimibe FDC does not represent a significant therapeutic benefit over existing treatments for paediatric patients (EMEA-001447-PIP01-12, waiver decision number P/0131/2013).

II. QUALITY ASPECTS

II.1 Introduction

Ridutrin 10 mg/10 mg is an unmarked, self-closing Coni Snap type, size 0, hard gelatin capsule with yellow coloured cap and yellow coloured body filled with two tablets.
Ridutrin 20 mg/10 mg is an unmarked, self-closing Coni Snap type, size 0, hard gelatin capsule with caramel coloured cap and yellow coloured body filled with two tablets.
Ridutrin 40 mg/10 mg is an unmarked, self-closing Coni Snap type, size 0, hard gelatin capsule with red coloured cap and yellow coloured body filled with two tablets.

The capsules contain 10 mg, 20 mg or 40 mg rosuvastatin (as zinc) and 10 mg of ezetimibe.

The capsules are packed in cold OPA/AL/PVC//Al blisters.

The excipients are:
Core - Silicified microcryistalline cellulose (Microcrystalline cellulose (E460) and Colloidal Anhydrous Silica (E551)), Colloidal Anhydrous Silica (E551), Magnesium stearate (E572), Povidone (E1201)
Croscarmellose Sodium (E468), Microcrystalline Cellulose (E460), Mannitol (E421), Sodium laurilsulfate (E514), Low-substituted hydroxypropyl cellulose (E463)

Capsule shell
Cap and body 10/10 mg: Yellow iron oxide (E172), Titanium dioxide (E171), Gelatine
Cap 20 mg/10 mg and 40 mg/10 mg: Red iron oxide (E172), Titanium dioxide (E171), Yellow iron oxide (E172), Gelatine
Body 20 mg/10 mg and 40 mg/10 mg: Gelatine, Yellow iron oxide (E172), Titanium dioxide (E171)

The uncoated 10-20-40 mg rosuvastatin zinc tablets are dose-proportional.

II.2 Drug Substances

Rosuvastatin zinc
The active substance rosuvastatin zinc is not described in any pharmacopoeia. It is a white powder, which is freely soluble in ethanol, methylene chloride and dimethylformamide and slightly soluble in water and 2-propanol. Rosuvastatin zinc has two chiral centers, thus theoretically four diastereoisomers exist. Rosuvastatin zinc salt produced by the manufacturer has a 3R,5S geometry. Form I is used. The substance is hygroscopic, and sensitive to light and humidity.

The Active Substance Master File (ASMF) procedure is used for rosuvastatin zinc. 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 synthesis from rosuvastatin tert-butylammonium salt intermediate covers several synthetic steps. Sufficient information on the manufacturers and specifications has been provided. Specifications of the intermediates, critical process parameters and in-process control tests from the starting materials have been laid down. The carry over of potential impurities and residual solvents has been adequately discussed.

Quality control of drug substance
The drug substance specification has been established in-house. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for at least three batches of rosuvastatin zinc.

Stability of drug substance
Three batches have been stored for 18 months at 25°C/60% RH and 6 months at 40°C/75% RH. Three batches have been stored for 3 months at 25°C/60% RH and 3 months at 40°C/75% RH.
The MAH has demonstrated that the polymorphic form of the drug substance does not change during storage. All stability results were in accordance with the set drug substance specification. Based on the provided stability data a re-test period of 18 months if stored in the proposed packaging at 2-8°C can be accepted.

Ezetimibe
The active substance ezetimibe is not described in any pharmacopoeia. It is a white to off-white crystalline powder which is practically insoluble in water. Ezetimibe has three chiral centers in the molecule and hence it exhibits optical isomerism. The anhydrous crystalline polymorphic form is used.
The Active Substance Master File (ASMF) procedure is used for both manufacturers of ezetimibe.

Manufacturing process
The first manufacturer produces ezetimibe in seven stages. For all steps numerous and adequate in-process controls are applied. Appropriate specifications are applied for all intermediary stages.
The process of the second manufacturer includes three chemical synthesis steps and one final purification step, which have been described in sufficient detail.

Quality control of drug substance
All proposed drug substance specifications are acceptable. For all analytical methods full descriptions and validation data have been provided. For the drug substances from both manufacturers at least three batches have been analyzed, demonstrating compliance with the specification.

Stability of drug substance
For the first supplier, three lower scale batches have been stored for 5 years at 2-8°C and 6 months at 40°C/75% RH, and three larger scale batches for 4 years at 2-8°C and 6 months at 40°/75% RH. All stability results were in accordance with the set drug substance specification. Based on the provided stability data the claimed re-test period of 4 years if stored at 2-8°C in the proposed packaging can be accepted.
For the second manufacturer three batches have been stored for 60 months at 25°C/60% RH, 12 months at 30°C/65% RH and 6 months at 40°C/75% RH. All stability results met the set requirements. Based on these data a re-test period of 5 years without specific storage temperature can be granted.

II.3 Medicinal Product

Pharmaceutical development
The pharmaceutical development for the proposed product is well described. The aim of formulation development was to obtain a hard gelatine capsule containing two unique tablets of the two separate active ingredients in order to guarantee the rapid dissolution of ezetimibe and to ensure the best stability for both drug substances. The development of the rosuvastatin zinc 10-20-40 mg tablets and ezetimibe 10 mg uncoated tablets has been adequately described. The MAH chose to compress both ezetimibe and rosuvastatin zinc final granule blends into tablets before inclusion into the capsules. The bioequivalence study was performed between the proposed 40 mg rosuvastatin zinc/10 mg ezetimibe hard capsule and the separate originator products Crestor 40 mg and Ezetrol 10 mg from Hungary dosed concomitantly. Comparative dissolution studies have been performed for the test bio-batch (40 mg/10 mg hard capsule) and two separate reference bio-batches. Sufficient details on the pharmaceutical development have been provided.

Manufacturing process
Rosuvastatin zinc 10-20-40 mg tablets: The manufacturing process consists of usual steps of weighing and sieving, pre-blending, granulation, blending, sieving of external phase, final blending, and compression. For the 10 mg & 20 mg tablets two pilot-scale batches and for the 40 mg tablets three pilot-scale batches have been prospectively validated, and all prospective validation results were satisfactory, meeting the acceptance criteria. Because the manufacturing process is considered a standard process, the available data can be accepted.

Ezetimibe 10 mg tablets: A crystalline ezetimibe suspension is prepared by precipitating an alcoholic solution of ezetimibe with an anti-solvent in the presence of a binder and a surfactant. The inner phase granules are coated with this suspension. The coated granulate is then blended. The manufacturing process for ezetimibe tablets is considered a non-standard process. The validation results from three batches showed compliance with the set acceptance criteria.
Bulk rosuvastatin 10-20-40 mg film-coated tablets and ezetimibe 10 mg tablets are subsequently packed with an automatic encapsulating machine. The proposed in-process controls are considered adequate and acceptable.

Control of excipients
Adequate specifications are applied for all excipients. The colourants used in the hard gelatin capsule, yellow iron oxide and red iron oxide, meet the specifications in Commission regulation (EU) 231/2012 and USP/NF.

Quality control of drug product
Adequate specifications are applied for the hard capsule drug product with tests on appearance of capsule, appearance of capsule filling, average mass/uniformity of mass of capsule filling, uniformity of dosage units, drug substances identification, water content, dissolution for both drug substances, related substances for both drug substances, and microbiological quality.
Batch analytical data of two batches per strength have been provided, demonstrating compliance with the specification.

Stability of drug product
For each capsule strength four batches have been tested at 25°C/60% RH and 40°C/75% RH, for up to 18 respectively 12 months. Significant changes were not found either in the physical or in the chemical test characteristics of the product. Based on the stability data provided the claimed shelf-life of 24 months in the proposed blister packaging can be accepted. The restriction of the storage condition to *Not above 30°C* is justified in view of the requirement in the Ph. Eur. monograph on capsules. The additional storage labeling is acceptable in view of the forced degradation results, including photostability testing: *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
Valid TSE CEP versions are applicable for magnesium stearate from animal origin (only ezetimibe tablets) and all gelatin sources.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

The following post-approval commitment was made:
- The MAH committed to re-evaluate the shelf-life specifications for impurities and assay.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacokinetics and toxicology

For this full-mixed application, the MAH provided an overview summarising the relevant literature on the pharmacology of rosuvastatin and ezetimibe. The pharmacokinetics and toxicology were also

reviewed. No new studies have been performed. This is acceptable, as both active substances are well known.
The current product concerns rosuvastatin as a zinc salt, whereas the reference product contains a calcium salt. The change in salt form from calcium to zinc could in theory have an effect on the kinetics of the product. However, bioequivalence has been shown *in vivo* and therefore a difference is not expected.

With regard to safety, the toxicity profile of rosuvastatin remains unchanged. The MAH provided some toxicity data on zinc. Since the potential dose of zinc due to the intake of Ridutrin is lower than the recommended intake from the diet, there is no safety concern regarding the zinc component of the product.

As the concentrations of one specific impurity are above the qualification limit, a toxicological qualification has been provided by the MAH. This impurity is also a metabolite, in both monkeys and humans. Although the exact exposures are not known, it is clear that the degree of exposure in monkeys to the metabolite/impurity at the No Observed Adverse Effect Level (NOEAL) was in excess of the potential exposure in humans. The impurity has therefore been qualified at the specification limits proposed.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Ridutrin is intended for substitution of both active ingredients used in separate tablets, its use will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

This medicinal product contains two established active substances, which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. The Member States agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Rosuvastatin and ezetimibe are well-known active substances with established efficacy and tolerability.

The clinical development program was designed to evaluate the comparative bioavailability between Ridutrin hard capsules and tablets containing the separate active substances taken concomitantly. For this application, the MAH submitted a bioequivalence study, which is discussed below. The pharmacological rationale for the use of rosuvastatin and ezetimibe in combination is adequately justified in the published literature. A bibliographical data analysis regarding efficacy and safety has been presented in this application. No further studies have been performed and none are considered necessary.

IV.2 Pharmacokinetics

The pharmacokinetic properties of both active substances are well known. The clinical overview provides an elaborate overview of pharmacokinetic data on rosuvastatin, zinc, and ezetimibe. Additionally the MAH provided information on the potential of pharmacokinetic interaction of rosuvastatin and ezetimibe, including an article of Kosoglou et al. (2004[1]) in which no evidence could be found for a clinically relevant pharmacokinetic interaction between the two substances. Additionally, this is confirmed by the innovator SmPC of both separate compounds.

To support the application, the MAH has submitted the report of a single dose, randomised, two-way crossover bioequivalence study comparing the test product Ridutrin 40 mg/10 mg hard capsules (Egis

[1] Kosoglou T, Statkevich P, Yang B, Suresh R, Zhu Y, Boutros T, Maxwell SE, Tiessen R, Cutler DL. Pharmacodynamic interaction between ezetimibe and rosuvastatin. Curr Med Res Opin. 2004 Aug;20(8):1185-95.

Pharmaceuticals Plc., Hungary) with the reference products Crestor® 40 mg film-coated tablets (AstraZeneca Ltd, UK) and Ezetrol® 10 mg tablets (MSD-SP Limited, UK) taken concomitantly under fasting conditions.

The choice of the reference product in the bioequivalence study has been justified by comparison of compositions of reference products in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
A biowaiver was requested for the 10/10 mg and 20/10 mg strengths. The results of the bioequivalence study apply to the Ridutrin 10/10 mg and 20/10 mg strengths as well, because:

- Rosuvastatin has linear pharmacokinetics in the therapeutic dose range (not applicable for ezetimibe)
- All strengths were manufactured by the same manufacturer and process.
- The qualitative composition of the different strengths is the same.
- The dissolution profiles for the 10/10 mg and 20/10 mg strengths were demonstrated to be similar to the 40/10 mg strengths.
- The ratio between amounts of each active ingredient and excipients is the same in all strengths.

The biowaiver is therefore acceptable.

Bioequivalence study

Design
Bioequivalence was investigated with a single centre, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover study in 56 healthy white male subjects. Treatment 1 was a single Ridutrin 40 mg/10 mg capsule (Test), and treatment 2 consisted of a Crestor® 40 mg film-coated tablet (Reference-1) and a tablet of Ezetrol® 10 mg (Reference-2) taken concomitantly. After a supervised overnight fast, a single dose of the assigned formulations was orally administered in the morning. There were 2 dosing periods, separated by a washout period of 14 days.

For analysis of rosuvastatin blood samples were collected pre-dose and at 0.75, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 12, 16, 24, 48 and 72 hours after drug administration.
For ezetimibe and ezetimibe phenyl glucuronide blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 20, 24, 48 and 72 hours after drug administration.

The design of the study is acceptable. The washout period (more than 10 elimination half-lives) was long enough to prevent from carry-over effect. The sampling schedule was adequate to characterize the pharmacokinetic profile of rosuvastatin, ezetimibe and total ezetimibe. The two active substances may be taken without reference to food intake. The bioequivalence study under fasting conditions is in accordance with the CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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
Fifty-three (53) from the 56 enrolled subjects completed the crossover design and received a single oral dose of the assigned treatment on day 1 and day 15. Two subjects withdrew consent from the study after dosing of period 1 for personal reasons. A third subject was withdrawn from the study after dosing of period 2 due to a gastrointestinal adverse event (vomiting).

Handling of withdrawals was adequate and the withdrawals were in line with the protocol. C_{max} and AUC_{0-72} for unconjugated ezetimibe and AUC_t for rosuvastatin were not calculated for one subject, and the AUC_{0-72} of unconjugated ezetimibe was not calculated for another subject. This was adequately justified, as these subjects did not complete the blood sampling schedule.

In summary, for rosuvastatin, 53 subjects were included in the pharmacokinetic and statistical analysis. One subject was included for the C_{max} and T_{max} parameters only. For ezetimibe, 52 subjects were included in the pharmacokinetic and statistical analysis. One subject was included for the C_{max} and T_{max} parameters only.

Table 1: Pharmacokinetic data for unconjugated ezetimibe

Pharmacokinetic parameter	Arithmetic Means (±SD)	
	Test product	Reference product
$AUC_{(0-72)}$ (pg.h/mL)	74761.2 (±39865.5)	73420.2 (±31991.9)
$AUC_{(0-\infty)}$(pg.h/mL)	84972.4 (±41753.4)	84364.8 (±40469.5)
C_{max}(pg/mL)	3326.2 (±1786.4)	3630.3 (±2072.4)
t_{max} (h)[1]	6.00 (1.00 – 12.00)	5.77 (1.00 – 16.00)

[1] Median (Min, Max)

Table 2: Bioequivalence evaluation of unconjugated ezetimibe

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%
$AUC_{(0-72)}$	97.80	91.65 – 104.36	19.7
C_{max}	92.14	85.11 – 99.76	24.5

Table 3: Pharmacokinetic data for rosuvastatin

Pharmacokinetic parameter	Arithmetic Means (±SD)	
	Test product	Reference product
AUC_T (ng.h/mL)	215.857 (±135.784)	224.827 (±136.249)
$AUC_{(0-\infty)}$(ng.h/mL)	223.866 (±137.119)	233.188 (±136.160)
C_{max}(ng/mL)	22.971 (±17.978)	24.126 (±16.192)
t_{max} (h)[1]	4.50 (1.50 – 6.00)	4.50 (1.50 – 6.00)

[1] Median (Min, Max)

Table 4: Bioequivalence evaluation of rosuvastatin

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%
AUC_T	96.92	92.52 - 101.53	14.2
C_{max}	93.51	87.85 - 99.54	19.4

Conclusion on bioequivalence study

No pre-dose levels were detected. Bioequivalence is shown appropriately based on unconjugated ezetimibe and rosuvastatin. The 90% CI for the test/reference ratios of geometric means for $AUC_{(0-72)}$ (91.65 – 104.36%) and C_{max} (85.11 - 99.76%) of unconjugated ezetimibe, and AUC_T (92.52 - 101.53%) and C_{max} (87.85 - 99.54%) of rosuvastatin are completely contained within the acceptance range of 80.00-125.00%. Bioequivalence is established for the parent compound unconjugated ezetimibe, in accordance with the current bioequivalence guideline. The formulations were well tolerated, with no major side effects.

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 Clinical efficacy

The Ridutrin combination capsule is intended for a substitution indication. The MAH has provided an overview to support the combined use of the monocomponents rosuvastatin and ezetimibe based on lipid lowering studies and an overview of drug utilization data from a number of countries in Europe. Specific studies such as EXPLORER[2] and ACTE[3] indicate additional lipid lowering efficacy of the combination in comparison to monotherapy of rosuvastatin. Current guidelines, such as the ESC/EAS guideline, recommend combinations of statins with other lipid lowering drugs for combination therapy, including the combination of a statin and ezetimibe. This is a treatment option for adults with primary hypercholesterolaemia who have been initiated on statin therapy when serum total or low-density lipoprotein (LDL) cholesterol concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy and consideration is being given to changing from initial statin therapy to an alternative statin.

Overall, in line with the CHMP/EWP/191583/05 entitled "Questions and answers on the clinical development of fixed combinations of drugs belonging to different therapeutic classes in the field of cardio-vascular treatment and prevention" the use of the monoproducts can be considered widespread, well known, and the rationale of their combined use is supported by pharmacological principles. Also the arguments of simplifying therapy as justification of a fixed dose combination can be considered valid.

IV.4 Clinical safety

Both components are well known with respect to their safety profile. The MAH provided data on the adverse events reported with the combination of rosuvastatin and ezetimibe. Although the data obtained in the ACTE and EXPLORER studies may be limited as only comparison of adding ezetimibe to rosuvastatin has been investigated and the time span is limited, the safety information of the combination does not indicate that additional safety risks exist.

IV.5 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 Ridutrin 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg capsules, hard.

- **Summary table of safety concerns as approved in RMP**

Important identified risks	• Sceletal muscle effects: myalgia, myopathy, myositis, increased CK-levels, rhabdomyolysis (with or without acute renal failure), immune-mediated necrotising myopathy, myoglobinuria and myoglobinaemia (in the setting of rhabdomyolysis and myopathy) • Hypersensitivity reactions including angioedema • Abnormal liver function: Increased transaminases, hepatitis, jaundice • Urinary effects (proteinuria) • Pancreatitis • Diabetes mellitus • Stevens-Johnson syndrome and toxic

[2] EXPLORER: EXamination of Potential Lipidmodifying effects Of Rosuvastatin in combination with Ezetimibe versus Rosuvastatin alone

[3] ACTE: EfficACy and SafeTy of Ezetimibe Added On to Rosuvastatin Versus Up Titration of Rosuvastatin in Hypercholesterolemic Patients at Risk for Coronary Heart Disease

	epidermal necrolysis • Drug-drug interactions (including: ciclosporin, various protease inhibitor combinations with ritonavir, gemfibrozil, eltrombopag, dronedarone, itraconazole, warfarin, other vitamin K antagonists and ezetimibe). • Tendon rupture and rotator cuff syndrome • Thrombocytopenia/decreased platelet count • Memory loss • Depression • Sleep disorders (including insomnia and nightmares)
Important potential risks	• Hepatic failure: including hepatic necrosis and fulminant hepatitis • Interstitial lung disease • Renal failure (including acute and chronic renal failure) and renal impairment • Peripheral neuropathy • Amyotrophic lateral sclerosis • Cholecystitis/Cholelithiasis • Drug-drug interaction with fibrates (other than gemfibrozil) • Off-label use (including paediatric off-label use)
Missing information	• Product use in children • Elderly • Pregnancy and lactation • Product use in patients with severe hepatic impairment • Product use in patients with severe renal impairment • Asian population: increased plasma exposure • Product use in patients with very low low-density lipoprotein cholesterol (LDL-C) levels • Genetic polymorphisms: increased plasma exposure

The safety specification has been brought in line with the RMP for the innovator products of the individual components. For the brand leader product of rosuvastatin, Crestor, additional risk minimisation measures regarding off-label use are in place. Since the risks of rosuvastatin fully apply to the combination product Ridutrin, evidence of off-label use will be actively reviewed with appropriate follow-up action. This has been included as an important potential risk and a targeted questionnaire will be used to obtain specific information on this issue. The member states considered this RMP acceptable.

IV.6 Discussion on the clinical aspects

The combined use of rosuvastatin and ezetimibe is well established. The literature data submitted by the MAH support the use of the fixed dose combination. The bioequivalence study shows satisfactory results: a single capsule of Ridutrin 40 mg/10 mg can be used instead of co-administration of the separate products Crestor 40 mg and Ezetrol 10 mg tablets. A biowaiver was granted for the two lower

strengths. Risk management is adequately addressed.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of a preliminary round of testing with 4 participants, followed by two rounds of testing with 10 participants each. Fifteen questions were prepared to test for traceability, comprehensibility and applicability.
The results of the first round of testing met the study objectives. Therefore, no amendments to the PL were considered necessary. Also the results of the second round of testing met the study objectives.
In addition to the questionnaire, there were five questions at the end of the test in order to gain an opinion/feedback of the subject's interpretation of the full package leaflet. From the subject's answers to these questions and general comments, no adaptation of the PL was deemed necessary.
There were sufficient questions about the critical sections. 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. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ridutrin 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg capsules, hard have a proven chemical-pharmaceutical quality and are considered an acceptable new formulation. Both rosuvastatin and ezetimibe are well known, established 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 reference products Crestor and Ezetrol. The efficacy and safety profile is considered the same as for the monocomponents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC closely resembles the approved SmPCs for Crestor and Ezetrol. The SmPC, package leaflet and labelling are in the agreed templates.

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 this fixed dose combination is approvable, since bioequivalence has been demonstrated with the innovator products of the individual components. The decentralised procedure was finalised with a positive outcome on 30 June 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached

Summary Public Assessment Report

non-generics

Ridutrin 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg capsules, hard

(rosuvastatin and ezetimibe)

NL/H/3017/001-003/DC

Date: 14 October 2014

Summary Public Assessment Report

non-generics

Ridutrin 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg capsules, hard

Active substances: rosuvastatin and ezetimibe

This is a summary of the public assessment report (PAR) for Ridutrin 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg capsules, hard. It explains how this medicine was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Ridutrin capsules.

For practical information about using this medicine, patients should read the package leaflet or contact their doctor or pharmacist.

What is Ridutrin and what is it used for?
This medicine contains two active substances: rosuvastatin and ezetimibe. These substances are also available as separate tablets marketed under several trade names such as Crestor® (rosuvastatin) and Ezetrol® (ezetimibe).

Ridutrin is used to lower levels of total cholesterol, “bad” cholesterol (LDL cholesterol) and fatty substances called triglycerides in the blood. In addition, it also raises levels of “good” cholesterol (HDL cholesterol). This medicine can be used by patients whose cholesterol levels cannot be controlled by a cholesterol lowering diet alone. The patient should stay on a cholesterol lowering diet while taking this medicine.
This medicine may be prescribed to adult patients who are already taking both rosuvastatin and ezetimibe as separate tablets.

How does this medicine work?
Ridutrin contains two different active substances in one capsule. One of the active substances is rosuvastatin, belonging to the group of so called statins, the other active substance is ezetimibe. This medicine works to reduce cholesterol in two ways: it reduces the cholesterol absorbed in the digestive tract, as well as the cholesterol the body makes by itself. For most people, high cholesterol does not affect the way they feel because it does not produce any symptoms. However, if it is left untreated, fatty deposits can build up in the walls of the blood vessels causing them to narrow.
Sometimes, these narrowed blood vessels can get blocked which can cut off the blood supply to the heart or brain leading to a heart attack or a stroke. By lowering a patient’s cholesterol levels, the risk of having a heart attack, a stroke or related health problems can be reduced.

How is this medicine used?
The pharmaceutical form of Ridutrin is a hard capsule, and the route of administration is oral. The medicine can only be obtained with a prescription.

Please read section 3 of the PL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

How has this medicine been studied?
Because Ridutrin is intended for substitution of separate tablets containing rosuvastatin and ezetimibe, studies in patients have been limited to tests to determine that the capsule is bioequivalent to the individual tablets taken at the same time. Medicines are bioequivalent when they produce the same levels of the active substance in the body.
The studies have shown that the same amount of rosuvastatin and ezetimibe is produced in the blood after administration of the combination capsule or the two separate tablets.

What are the possible side effects from this medicine?
The most common side effects with Ridutrin (which may affect up to 1 in 10 people) are headache, constipation, feeling sick, muscle pain, feeling weak, dizziness, stomach ache, diarrhoea, flatulence (excess gas in the intestinal tract), feeling tired and elevations in some laboratory blood tests of liver function (transaminases). Also, an increase in the amount of protein in the urine may occur and cases

of diabetes have been reported. This is more likely to occur in patients who have high levels of sugars and fats in their blood, are overweight and have high blood pressure.

For the full list of all side effects reported with Ridutrin, see section 4 of the package leaflet.

Why is this medicine approved?
The Medicines Evaluation Board of the Netherlands decided that Ridutrin's benefits are greater than its risks and recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of this medicine?
A risk management plan has been developed to ensure that this medicine is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Ridutrin capsules, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about this medicine
In the Netherlands, the marketing authorisation for Ridutrin 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg capsules, hard was granted on 11 August 2014.

The full PAR for this medicine can be found on the website http://mri.medagencies.org/Human.
For more information about treatment with Ridutrin, read the package leaflet (for the 10/10 mg and 20/10 mg strengths - http://mri.medagencies.org/download/NL_H_3017_001_FinalPL.pdf; and for the 40/10 mg strength - http://mri.medagencies.org/download/NL_H_3017_003_FinalPL.pdf) or contact your doctor or pharmacist.

This summary was last updated in October 2014.