Public Assessment Report

Scientific discussion

Zenon 10 mg/10 mg, film-coated tablets
Zenon 10 mg/20 mg, film-coated tablets
Zenon 10 mg/40 mg, film-coated tablets
Ezetimibe / Rosuvastatin

CZ/H/455/01-03/DC

Date: 11.5.2015

This module reflects the scientific discussion for the approval of Zenon. The procedure was finalised on July 29, 2014.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Zenon 10 mg/10 mg (10 mg/20 mg; 10 mg/40 mg) film-coated tablets, from Zentiva, k.s., Praha, U Kabelovny 130, Praha 10, Czech Republic.

The product is indicated: as adjunctive therapy to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) for use in adult patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or homozygous familial hypercholesterolaemia, which are already treated and adequately controlled on the combination of ezetimibe and rosuvastatin.

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

Both active substances are already approved as monotherapy in the management of hypercholesterolaemia (different types). The original ezetimibe medicinal product is Ezetrol 10 mg Tablets (in the Czech Republic authorised since 2003 via DC procedure DE/H/396/001/DC) and the MA holder is Merck Sharp & Dohme. The original product for rosuvastatin is Crestor 10, 20 and 40 mg Tablets (in the Czech Republic authorised since 2003 via national procedure) and the MA holder is AstraZeneca.

According to the SmPC of the ezetimibe originator (Ezetrol), ezetimibe should be co-administered with an HMG-CoA reductase inhibitor (statin) to patients who are not appropriately controlled with a statin alone. Ezetimibe monotherapy is indicated in patients in whom a statin is considered inappropriate or is not tolerated.
Based on this information it can be concluded that ezetimibe and statins are widely prescribed to patients for a concomitant use and therefore the FDC formulation is a rational solution for these patients.

Both ezetimibe and rosuvastatin are hence well known substances in the treatment of the proposed indications and administration of these two components concomitantly has shown higher efficacy in comparison with the monotherapy and above that recently published meta-analysis has shown that the more pronounced reductions in LDL cholesterol safety produce definite further reductions in the incidence of heart attack, of revascularisation, and of ischemic stroke.

During the assessment of this procedure, there were no other fixed dose combination products containing ezetimibe and rosuvastatin authorised in the EU.

The concerned member states (CMS) involved in this procedure were Bulgaria, Estonia, Latvia, Lithuania, Poland, and Slovak Republic.

The marketing authorisation has been granted pursuant to Article 10b of Directive 2001/83/EC (fixed combination application).

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.

No new studies in the target population have been performed by the applicant which is acceptable taking into account the substitution indication.

The submission includes two bioequivalence studies comparing Zenon 10 mg/10 mg and Zenon 10 mg/40 mg with the single component innovator products Crestor and Ezetrol (respective strengths), concomitantly dosed. A biowaiver for the strength 10 mg/20 mg based on "bracketing approach" has been granted. Furthermore, the applicant has conducted his own PK interaction study comparing the concomitant administration of rosuvastatin and ezetimibe vs. ezetimibe and rosuvastatin alone.
Further clinical evaluation (efficacy and safety) of Zenon 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 (EMEA-001344-PIP01-12, waiver decision number P/0131/2013 – 5th October 2012) for the treatment of hypercholesterolemia in all subsets of the paediatric population.

Ezetimibe and Rosuvastatin are not mentioned in Ph. Eur. and for both ASs manufacturers the procedures of ASMF have been provided.

II. QUALITY ASPECTS

II.1 Introduction

Zenon 10 mg / 10 mg are white to off-white oblong film-coated tablets.
Zenon 10 mg / 20 mg are yellow to light yellow oblong film-coated tablets.
Zenon 10 mg / 40 mg are pink oblong film-coated tablets.

The tablets contain 10 mg, 20 mg or 40 mg rosuvastatin (as calcium) and 10 mg of ezetimibe.
The tablets are packed in OPA/Al/PVC//Al blisters.

The excipients are:
Core: lactose monohydrate, cellulose microcrystalline, sodium lauryl sulphate, povidone 25, croscarmellose sodium, silica colloidal anhydrous, magnesium stearate.
Coating layer: hypromellose 2910/5, macrogol 6000, titanium dioxide (E171), talc, iron oxide yellow (E172) – for 10/20 mg strength, iron oxide red (E172) – for 10 / 40 mg strength.

II.2 Active Substances

Active substance Ezetimibe
The active substance Ezetimibe is not mentioned in European Pharmacopoeia. The documentation on the active substance is presented in form of ASMF by ezetimibe manufacturer.
The general information given for the active substance comprises nomenclature, structure and general properties including polymorphism and chirality. Ezetimibe has three chiral centres in the molecule and exhibits optical isomerism. Isomer R, S, S is consistently produced. The anhydrous crystalline polymorphic form is used. Substance is hygroscopic and freely soluble in methanol and acetone, insoluble in water.
Manufacture is described in Restricted parts ASMF in detail. The manufacturer produces ezetimibe in seven stages. Appropriate description of process and in-process controls has been presented.
A detailed discussion of organic impurities, inorganic impurities and residual solvents is presented. A discussion on possible genotoxic impurities is included.

Active substance specification is acceptable; methods used are appropriately described and validated with exception of some simple methods. Batch analysis results have been provided. All results are within the limits of the specification. The reference standards are adequately described and characterised.
For the primary packaging materials specifications (including identification by IR), method description and a certificates of analysis are provided. The material complies with directive 2002/72/EC (incl. amendments).
Stability tests are performed according to corresponding ICH/CHMP guidelines.

Active substance Rosuvastatin calcium
The active substance Rosuvastatin calcium is not mentioned in European Pharmacopoeia. The documentation on the active substance Rosuvastatin calcium is presented in form of ASMF by its manufacturer.
The general information given for the active substance comprises nomenclature, structure and general properties including polymorphism and chirality. Rosuvastatin calcium has two chiral centres, four diastereosimers - active substance has 3R, 5S geometry. Rosuvastatin calcium is slightly hygroscopic, soluble in acetone and acetonitrile, insoluble in water.
Manufacture is described in Restricted parts ASMF in detail.
A detailed discussion of organic impurities, inorganic impurities and residual solvents is presented. A discussion on possible genotoxic impurities is included however deeper discussion on potential genotoxicity of some impurities is awaited.
Active substance specification is acceptable. Methods used are appropriately described and validated. Batch analysis results have been provided. All results are within the limits of the specification. The reference standards are adequately described and characterised.
For the primary packaging materials specifications (including identification by IR), method description and a certificates of analysis are provided. The material complies with directive 2002/72/EC (incl. amendments).
Stability tests are performed according to corresponding ICH/CHMP guidelines.

II.3 Finished Product
The pharmaceutical dosage form of the product is film-coated tablet (each strength has different colour). Qualitative composition of strengths is similar with exception of colorants in the coating layer.
The aim of the pharmaceutical development work was to develop a stable formulation containing 10 mg of Ezetimibe and 10, 20, 40 mg of Rosuvastatin calcium that would be pharmaceutically equivalent to the originators Crestor and Ezetrol.
The formulation development of the product has been described, the choice of excipients is justified and their functions are explained. Comparative dissolution profiles have been submitted. The dissolution profiles of the finished product show equivalence to the reference products.
The manufacturing process is well described and validated. The manufacturing process is considered to be a standard one.
All used excipients are widely used and comply with the requirements of the Ph. Eur. or USP.
For the control of the finished product specifications for release and shelf-life are used.
The analytical methods have been adequately described and validated. Analysis data of three commercial scale batches are provided. All results are well within the specification limits.
The used reference standards were described.
The suppliers confirm that the packaging materials (OPA/Al/PVC//Al foils) comply with the EU and Ph. Eur. requirements.
Stability data for three batches per strength are carried out under long term, intermediate and accelerated conditions. Stability data of on-going long-term and intermediate studies should

be provided. The manufacturer proposes shelf-life of 2 years with the storage condition "Store at temperature below 30°C in the original package in order to protect from moisture and light "

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier and appropriate supplements provided during the procedure, the member states consider that Zenon film-coated tablets, three strengths, have a proven chemical-pharmaceutical quality. Sufficient controls have been done for the active substances and finished products.

Follow-up measures:

Once the actual overage for active substance and coating suspension is fixed based on the first production bathes and is verified by validation process, the results will be provided.

III. NON-CLINICAL ASPECTS

For this fixed dose application, the MAH provided an overview summarising the relevant literature on the pharmacology, pharmacokinetics and toxicology of rosuvastatin and ezetimibe. No new studies have been performed which is acceptable, as both active substances are well known.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Zenon 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.2 Discussion on the non-clinical aspects

This product is a fixed-dose formulation of well-known 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. For this application, the MAH has submitted two bioequivalence studies, these are discussed below. Furthermore, the applicant has conducted PK interaction study which compares the concomitant administration of rosuvastatin and ezetimibe vs. ezetimibe and rosuvastatin alone.

No new studies in the target population have been performed by the applicant which is acceptable taking into account the substitution indication.
Clinical evaluation of efficacy and safety of Zenon was hence 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.

IV.2 Pharmacokinetics

The pharmacokinetic properties of both active substances are well known. The clinical overview provides a review of pharmacokinetic data on rosuvastatin and ezetimibe obtained from publicly available literature.

Additionally the MAH has submitted his own PK interaction study which compares the concomitant administration of rosuvastatin and ezetimibe vs. ezetimibe and rosuvastatin alone. This study did not show any relevant PK interactions between these two substances. This is also confirmed by the innovator SmPC of both separate compounds.

To support the application, the MAH has submitted reports of two bioequivalence studies comparing Zenon 10 mg/10 mg and Zenon 10 mg/40 mg with the single component innovator products Crestor and Ezetrol (respective strengths), concomitantly dosed.

Biowaiver

A biowaiver was requested for the strength 10/20 mg strength based on the "bracketing approach". As the conditions for this approach, set in the EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr), have been fulfilled, the biowaiver for this strength has been granted.

Bioequivalence studies

Study with Zenon 10mg/40 mg

Design

Bioequivalence was single centre, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover study in 44 healthy subjects conducted in fasting state. Treatment 1 was a single Ezetimibe/Rosuvastatin 10 mg/40 mg film-coated tablets (Test), and treatment 2 consisted of a tablets of Ezetrol 10 mg (Reference-1) and Crestor 40 mg film-coated tablets (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, 19 blood samples were collected from pre-dose to 72 hours after drug administration.
For ezetimibe and ezetimibe phenolic glucuronide 21 blood samples were collected from pre-dose to 72 hours after drug administration.

The design of the study is acceptable. The washout period 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 EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr).

Analytical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples.

Statistical methods

The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Forty-one (41) subjects were included in the pharmacokinetic and statistical analysis for ezetimibe and 42 subjects were included in the pharmacokinetic and statistical analysis for rosuvastatin.

One subject was withdrawn before dosing of period 2 for safety reasons (sunburn, eye redness and out of range pre-dose haematology values for period 2).

Two subjects were excluded from the pharmacokinetic and statistical analysis for ezetimibe due to a missing sample. These 2 subjects missed the 72-hour blood draw in period 1 that could have impacted their ezetimibe pharmacokinetic profile. Samples for ezetimibe were not collected in period 2 for these subjects. They were included in the pharmacokinetic and statistical analysis for rosuvastatin.

One subject was excluded from the pharmacokinetic and statistical analysis for rosuvastatin due to missing samples. This subject missed the 36- and 48-hour blood draws in period 1 that could have impacted his rosuvastatin pharmacokinetic profile. Samples for rosuvastatin were not collected in period 2 for this subject. He was included in the pharmacokinetic and statistical analysis for ezetimibe. This is acceptable, as the decision has been made before the bioanalysis and is in line with the study protocol.

Table 1. Summary of main Study Results – Free Ezetimibe

PARAMETER	TREATMENT-1 (TEST)		TREATMENT-2 (REFERENCE)	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (pg/mL)	3311.7	45.5	3385.4	42.4
ln (C_{max})	8.0136	5.4	8.0402	5.3
T_{max} (hours) [§]	10.00	46.9	6.00	58.9
AUC_{0-72} (pg·h/mL)	72618.2	35.2	68445.5	34.2
ln (AUC_{0-72})	11.1328	3.2	11.0749	3.2

[§] For T_{max}, the median is presented

Table 2. Comparison of Results with Standards for Bioequivalence – Free Ezetimibe

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TREATMENT-1 (TEST)	TREATMENT-2 (REFERENCE)		LOWER	UPPER
C_{max}	21.0	3009.2	3100.3	97.06	89.82	104.89
AUC_{0-72}	12.8	68042.0	64277.8	105.86	100.92	111.03

* units are ng/mL for C_{max} and ng·h/mL for AUC_{0-72}

Table 3. Summary of Main Study Results – Rosuvastatin

PARAMETER	TREATMENT-1 (TEST)		TREATMENT-2 (REFERENCE)	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	23.393	71.6	24.155	74.9
ln (C_{max})	2.9766	19.3	3.0003	19.4
T_{max} (hours) [§]	4.50	22.4	4.50	24.5
AUC_T (ng·h/mL)	205.312	61.0	221.013	61.9
ln (AUC_T)	5.1915	9.7	5.2578	9.8
AUC_∞ (ng·h/mL)	214.091	59.1	231.832	60.7
ln (AUC_∞)	5.2396	9.4	5.3080	9.6
$AUC_{T/\infty}$ (%)	96.71	3.4	96.04	3.5
K_{el} ($hours^{-1}$)	0.0490	27.2	0.0473	32.0
$T_{½el}$ (hours)	15.55	41.2	16.70	44.0

[§] For T_{max}, the median is presented

Table 4. Comparison of Results with Standards for Bioequivalence – Rosuvastatin

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TREATMENT-1 (TEST)	TREATMENT-2 (REFERENCE)		LOWER	UPPER
C_{max}	28.3	19.622	20.091	97.66	88.19	108.15
AUC_T	21.9	179.743	192.066	93.58	86.44	101.32

* units are ng/mL for C_{max} and ng·h/mL for AUC_T

Study with Zenon 10mg/10 mg

Design

Bioequivalence was investigated with a single centre, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover study in 44 healthy subjects/fasting state. Treatment 1 was a single Ezetimibe/Rosuvastatin 10 mg/10 mg film-coated tablets (Test), and treatment 2 consisted of a tablet of Ezetrol 10 mg (Reference-1) and Crestor 10 mg film-coated tablet (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, 19 blood samples were collected from pre-dose to 72 hours after drug administration.

For ezetimibe and ezetimibe phenolic glucuronide 21 blood samples were collected from pre-dose to 72 hours after drug administration.

The design of the study is acceptable. The washout period 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 EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr).

Analytical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples.

Statistical methods
The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Of the 44 who were included in the study, 42 subjects completed the crossover design and received a single oral dose of the assigned formulation on day 1 and day 15.

One subject withdrew consent from the study after dosing of period 1 for personal reasons. Another subject has been withdrawn prior to dosing of period 2 due to a positive drug abuse test.

Table 5. Summary of main Study Results – Free Ezetimibe and Comparison of Results with Standards for Bioequivalence – Free Ezetimibe

Free Ezetimibe

PARAMETER	TREATMENT-1 (TEST)		TREATMENT-2 (REFERENCE)	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (pg/mL)	3443.4	46.3	3497.0	40.3
ln (C_{max})	8.0458	5.5	8.0757	5.3
T_{max} (hours) *	5.00	51.8	5.00	64.9
AUC_{0-72} (pg·h/mL)	84226.0	43.3	82533.6	34.5
ln (AUC_{0-72})	11.2564	3.7	11.2619	3.1

* median is presented

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TREATMENT-1 (TEST)	TREATMENT-2 (REFERENCE)		LOWER	UPPER
C_{max}	25.7	3120.6	3215.3	97.06	88.44	106.51
AUC_{0-72}	19.5	77372.6	77797.5	99.45	92.64	106.77

* units are pg/mL for C_{max} and pg·h/mL for AUC_{0-72}

Table 6. Summary of main Study Results – Rosuvastatin and Comparison of Results with Standards for Bioequivalence – Rosuvastatin

Rosuvastatin

PARAMETER	TREATMENT-1 (TEST)		TREATMENT-2 (REFERENCE)	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	6.271	75.0	6.850	69.0
ln (C_{max})	1.6194	40.5	1.7357	35.6
T_{max} (hours) *	4.50	26.2	4.50	26.5
AUC_T (ng·h/mL)	53.584	54.5	57.912	51.0
ln (AUC_T)	3.8324	14.9	3.9335	13.2
AUC_∞ (ng·h/mL)	57.652	53.8	62.571	49.5
$AUC_{T/\infty}$ (%)	92.20	5.5	94.11	3.4
K_{el} ($hours^{-1}$)	0.0588	48.1	0.0540	39.4
$T_{½el}$ (hours)	15.00	54.5	15.44	49.4

* median is presented

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TREATMENT-1 (TEST)	TREATMENT-2 (REFERENCE)		LOWER	UPPER
C_{max}	26.0	5.050	5.673	89.02	81.03	97.81
AUC_T	20.3	46.134	50.952	90.54	83.93	97.68

* units are ng/mL for C_{max} and ng·h/mL for AUC_T

Conclusion on bioequivalence studies:

Bioequivalence between ezetimibe/rosuvastatin 10 mg/40 mg film-coated tablets, Ezetrol 10 mg tablets and Crestor 40 mg film-coated tablets as well as between ezetimibe/rosuvastatin 10 mg/10 mg film-coated tablets, Ezetrol 10 mg tablets and Crestor 10 mg film-coated tablets was demonstrated.

The formulations were well tolerated, with no major side effects observed.

Assurance 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) has been provided.

IV.3 Clinical efficacy

The fixed dose combination product Zenon is intended for a substitution indication. The MAH has provided clinical overview which argues that the insufficient efficacy of statin monotherapy and the usefulness of co-administering ezetimibe is supported by published evidence (3 publications).

The applicant states that rosuvastatin has been clearly shown to decrease LDL-C and also cites two studies which are showing that ezetimibe alone or in the presence of statin, lowers LDL-cholesterol more than statin alone.

The short term effect of rosuvastatin+ezetimibe therapy has been according to the applicant further demonstrated in EXPLORER study and ACTE study.

For the support of long term effects of the combination (ezetimibe+rosuvastatin) one additional publication was submitted by the applicant.

Overall, in line with the CHMP/EWP/191583/05 entitled "Questions and answers document 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 applicant supports the safety of the FDC formulation by the same data used for the purpose of demonstration of efficacy.

IV.5 Risk Management Plan

The MAH has submitted a EU risk management plan version 1.0 dated 28th November 2012, 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 Zenon 10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg film-coated tablets.

Summary of the safety concerns provided for the product as proposed by MAH:

Table 21: Summary of safety concerns and planned pharmacovigilance actions

Safety concern	Planned action
Important identified risks	
Rhabdomyolysis	Routine pharmacovigilance
Liver disorder	
New onset diabetes	
Important potential risks	
-	
Important missing information	
Safety and efficacy in children	Routine pharmacovigilance
Safety in patients with moderate or severe hepatic impairment (Child-Pugh score above 7)	

Summary of the risk minimisation measures by safety concern as proposed by MAH:

Table 26: Summary of the Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Rhabdomyolysis	Proposed text in SPC: Contraindication of the highest dose (10mg/40mg) in patients with myopathy in Section 4.3. Warning and recommendation for monitoring of CK levels in Section 4.4. Information on interaction with gemfibrozil and other lipid-lowering producst which can increase the risk of rhabdomyolysis in Section 4.8.	NA

	Listed in Section 4.8. Prescription only medicine.	
Liver disorder	Recommendation for posology in patients with liver disease in Section 4.2. Contraindication in Section 4.3. Warning in Section 4.4. Listed in Section 4.8. Prescription only medicine	NA
New onset diabetes	Warning in Section 4.4. Listed in Section 4.8. Prescription only medicine.	NA

Summary of the identified risks and missing information are endorsed by the RMS and CMSs. Also member states considered routine pharmacovigilance acceptable and no additional risk minimisation measures are proposed.

IV.6 Discussion on the clinical aspects

The combined use of rosuvastatin and ezetimibe is well known. The literature data submitted by the MAH support the use of the fixed dose combination. The bioequivalence studies show satisfactory results: a single film-coated tablet of Zenon (10 mg/40 mg and 10 mg/10 mg) can be used instead of co-administration of the separate products Crestor and Ezetrol tablets (respective strengths). A biowaiver was granted for the strength 10 mg/20 mg of the fixed dose combination. Risk management is adequately addressed.

V. USER CONSULTATION

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

Zenon 10 mg / 10 mg, 10 mg / 20 mg and 10 mg / 40 mg film-coated tablets have a proven chemical – pharmaceutical quality and are considered as acceptable fixed dose combination product. Both ezetimibe and rosuvastatin calcium are well known, established substances.

The proposed combination product was demonstrated to be bioequivalent with co-administration of the separate reference products Crestor and Ezetrol. Furthermore, the applicant has submitted PK interaction study which demonstrates that there are no PK interactions between ezetimibe and rosuvastatin. 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.

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 based on the submitted data. The decentralised procedure was finalised with a positive outcome on 29.7.2014.

Follow-up measures:

- Once the actual overage for active substance and coating suspension is fixed based on the first production batches and is verified by validation process, the results will be provided.