CMDh/223/2005
February 2014

Public Assessment Report

Scientific discussion

Zenon Neo
10 mg/10 mg film-coated tablets
20 mg/10 mg film-coated tablets
40 mg/10 mg film-coated tablets
rosuvastatin (as rosuvastatin calcium)/ezetimibe

CZ/H/0696/001-003/DC

Date: 11. 9. 2019

This module reflects the scientific discussion for the approval of Zenon Neo. The procedure was finalised on 3.2.2019.

I. INTRODUCTION

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

Zenon Neo is fixed combination product consisting of two well-known active substances rosuvastatin and ezetimibe, two lipid-lowering compounds with complementary mechanisms of action. Zenon Neo reduces elevated total cholesterol (total-C), LDL-C, apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C), and increases high-density lipoprotein cholesterol (HDL-C) through dual inhibition of cholesterol absorption and synthesis. This medicinal product belongs to the pharmacotherapeutic group HMG-CoA reductase inhibitors in combination with other lipid modifying agents (ATC code: C10BA06).

The product is indicated for*:*

Primary Hypercholesterolaemia/Homozygous Familial Hypercholesterolaemia (HoFH)
<Invented name> is indicated for substitution therapy in patients who are adequately controlled with rosuvastatin and ezetimibe given concurrently at the same dose level as in the fixed combination, but as separate products, as adjunct to diet for treatment of primary hypercholesterolaemia (heterozygous familial and non-familial) or homozygous familial hypercholesterolaemia.

Prevention of Cardiovascular Events
<Invented name> is indicated as substitution therapy in adult patients who are adequately controlled with rosuvastatin and ezetimibe given concurrently, at the same dose level as in the fixed dose combination, but as separate products to reduce the risk of cardiovascular events with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS).

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

The marketing authorisation has been granted pursuant to Article 10b of Directive 2001/83/EC (i.e. a fixed combination application). The concerned member states (CMSs) involved in procedure were: BE, BG, CR, CY, DK, FI, EL, IE, IT, NO, PL, PT, RO, SK, SI and SE.

This application claimed substitution indications only, and thus to fulfil the currently valid requirements of CHMP/EWP/191583/05, CHMP/EMEA/CHMP/SWP/258498/2005, and EMA/CHMP/158268/2017 guidelines, the Applicant provided the justification on clinical and pharmacological rationale, development rationale, pharmacodynamics, efficacy and safety of the combination based on bibliographic data and supported by a wide clinical use.
Furthermore, the following studies were conducted by the Applicant to document lack of PK interaction and demonstrate the bioequivalence with reference monocomponent formulations (Crestor 40 mg, tablets for rosuvastatin and Ezetrol 10 mg, tablets for ezetimibe): an interaction study and bioequivalence study under fasting condition. In addition, the Applicant requested a biowaiver for 10 mg/10 mg and 20 mg/10 mg presentations.

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

No Paediatric Investigation Plan (PIP) was submitted.
Scientific advice regarding procedural-regulatory issues was given by the RMS CZ before submission of the application.

II. QUALITY ASPECTS

II.1 Introduction

Zenon Neo 10 mg/10 mg are white to off-white, round, biconvex, film-coated tablets with a diameter about 9.1 mm.
Zenon Neo 20 mg /10 mg are yellow to light yellow, round, biconvex, film-coated tablets with a diameter about 9.9 mm.
Zenon Neo 40 mg /10 mg are pink, round, biconvex, film-coated tablets with a diameter about 11.1 mm.

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, microcrystalline cellulose, sodium laurilsulfate, povidone, colloidal silicon dioxide, crosscarmellose sodium, 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 Drug Substance

Active substance Ezetimibe

The active substance Ezetimibe is not mentioned in European Pharmacopoeia. The documentation on the active substance was presented in form of ASMF by the 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 was described in Restricted parts ASMF in detail. The manufacturer produces ezetimibe in seven stages. Appropriate description of process and in-process controls was presented.
A detailed discussion of organic impurities, inorganic impurities and residual solvents was presented. A discussion on possible genotoxic impurities was included.
Active substance specification is acceptable; methods used were appropriately described and validated with exception of some simple methods. Batch analysis results were provided. All results were within the limits of the specification. The reference standards were adequately described and characterised.
For the primary packaging materials specifications (including identification by IR), method description and a certificates of analysis were provided. The material complies with directive 2002/72/EC (incl. amendments).

Stability tests were performed according to corresponding ICH/CHMP guidelines.

Active substance Rosuvastatin calcium

The active substance rosuvastatin calcium is described in monograph no. 2631 on European Pharmacopoeia. The documentation on the active substance rosuvastatin calcium was presented in form of CEP by two manufacturers.

Active substance specification followed by drug product manufacturer is acceptable. Methods used were appropriately described and validated. Batch analysis results were provided. All results were within the limits of the specification. The reference standards were adequately described and characterised.

Re-test period of the rosuvastatin calcium from the first manufacturer is 36 months according to CEP. Stability tests of rosuvastatin calcium from the second manufacturer were performed according to corresponding ICH/CHMP guidelines. This manufacturer provided stability data of production to support the proposed retest period of 36 months.

II.3 Medicinal Product

The pharmaceutical dosage form of the product is film-coated tablet (each strength has different colour and size). The tablets are a new formulation and the advantage of this new formulation is separation of active ingredients, Rosuvastatin calcium and Ezetimibe. The new product Ezetimibe/Rosuvastatin contains the same excipients as generic monocomponent products already produced by Zentiva. This was the main reason to change excipient composition, when compared to composition of innovator products Crestor (rosuvastatin) and Ezetrol (ezetimibe).

Apart from the information as stated above 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.

The formulation development of the product was described, the choice of excipients was justified and their functions were explained. Comparative dissolution profiles were submitted. The dissolution profiles of the finished product showed equivalence to the reference products.

The manufacturing process was 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 were adequately described and validated. Analysis data of three commercial scale batches were provided. All results were well within the specification limits.

The used reference standards were described.

The suppliers confirmed that the packaging materials (OPA/Al/PVC//Al foils) comply with the EU and Ph. Eur. requirements.

Stability data for three batches per strength were carried out under long term, intermediate and accelerated conditions. The approved shelf-life is 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 Neo 10 mg/10 mg, 20 mg/10 mg, 40 mg/10 mg film-coated tablets have a proven chemical-pharmaceutical quality. Sufficient controls were done for the active substances and finished products.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of rosuvastatin and ezetimibe are well known. As ezetimibe and rosuvastatin are a widely used, well-known active substances, the Applicant did not provided additional studies and further studies were not required.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology was adequate and there were no objections to approval of Zenon Neo from a non-clinical point of view.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Zenon Neo is intended for substitution indication, this would not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

The Applicant presented a sufficient clinical overview and conducted a pharmacokinetic interaction study and bioequivalence study under fasting condition to document the lack of PK interaction and demonstrate the bioequivalence with reference monocomponent formulations. In addition, the provided co-prescription data confirmed that ezetimibe and rosuvastatin are commonly prescribed together and therefore the substitutional therapy is reasonable.

IV.2 Pharmacokinetics

To compare the bioavailability of rosuvastatin and ezetimibe fixed dose combination with the co-administration of reference monocomponent formulations, the bioequivalence study under fasting conditions with the highest strength 40 mg/10 mg was conducted. Additionally, the drug interaction study was performed to assess the potential of pharmacokinetic interaction between rosuvastatin and ezetimibe.

Bioequivalence study: ZNV-P5-545

The study was designed as a single centre, randomized, single dose, laboratory-blinded, two-way, crossover comparative and was conducted under fasting conditions on 58 healthy male subjects.

Results

Table I. Pharmacokinetic parameters for rosuvastatin (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	c_{max} ng/ml	t_{max} h
Trt-1 (N=58)	193457.24 ± 85999.75	199159.71 ± 89709.89	22351.50 ± 12934.99	4.50 (1.50 – 5.00)

		(considered N=53)		
Trt-2 (N=58)	191390.44 ± 82822.34	197006.38 ± 86126.04 *(considered N=53)*	21113.94 ± 10494.80	4.50 (1.50 – 5.00)
***Ratio (90% CI)**	100.43% (95.05%, 106.12%)	*not considered*	103.52% (95.71%, 111.96%)	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.

AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products

$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.

$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}

c_{max} Maximum plasma concentration

t_{max} Time until c_{max} is reached

****ln-transformed values***

Table II. Pharmacokinetic parameters for free ezetimibe (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	c_{max} ng/ml	t_{max} h
Trt-1 (N=58)	65743.41 ± 25051.88	*not considered*	2913.91 ± 1442.26	5.00 (0.50 – 12.00)
Trt-2 (N=58)	65871.19 ± 25179.74	*not considered*	3078.87 ± 1494.27	5.00 (0.50 – 24.00)
***Ratio (90% CI)**	99.92% (95.69%, 104.35%)	*not considered*	93.54% (87.26%, 100.27%)	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.

AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products

$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.

$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}

c_{max} Maximum plasma concentration

t_{max} Time until c_{max} is reached

****ln-transformed values***

Table III. Pharmacokinetic parameters for total ezetimibe (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	c_{max} ng/ml	t_{max} h
Trt-1 (N=58)	649.17	*not considered*	60.02	0.75 (0.50 – 5.03)
Trt-2 (N=58)	667.38	*not considered*	61.07	1.00 (0.50 – 10.00)
***Ratio (90% CI)**	98.72% (95.11%, 102.47%)	*not considered*	99.56% (92.14%, 107.58%)	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.

AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products

$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.

$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}

c_{max}	Maximum plasma concentration
t_{max}	Time until c_{max} is reached

ln-transformed values

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence study Zenon Neo 40 mg/10 mg, film-coated tablets is considered bioequivalent with both reference formulations given concomitantly Crestor (rosuvastatin) 40 mg film-coated tablet and Ezetrol (ezetimibe) 10 mg tablet.

The results of this study with 40 mg/10 mg formulation can be extrapolated to other strengths 10 mg/10 mg and 20 mg/10 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

Drug-drug interaction study EEI-P3-683

The Applicant conducted an interaction study to assess the potential of pharmacokinetic interaction between rosuvastatin and ezetimibe.

Results of this study demonstrated that the pharmacokinetic profiles of rosuvastatin, free ezetimibe and total ezetimibe were not impacted by the concomitant administration of the two reference products, when compared to administration of the reference formulations alone, thus suggesting that there is no drug interaction between rosuvastatin and ezetimibe.

IV.3 Pharmacodynamics

The Applicant provided an adequate review of bibliographic data relating to mechanism of action of rosuvastatin and ezetimibe and their pharmacodynamic effects.

IV.4 Clinical efficacy

The clinical overview is based on the scientific literature evaluating the efficacy of co-administration of ezetimibe and rosuvastatin in the claimed indications. The number of appropriate clinical trials was cited and comprehensively discussed by the Applicant. To further support the co-administration of both monocomponents, the co-prescription data confirming that they are commonly prescribed together was submitted. In overall, the Applicant has provided sufficient clinical efficacy data on co-administration of rosuvastatin and ezetimibe for treatment of primary hypercholesterolemia and prevention of cardiovascular events both in terms of substitution therapy.

IV.5 Clinical safety

The safety profile of both monocomponents, ezetimibe and rosuvastatin, is well known and was adequately described in the provided Clinical overview. The safety data from presented clinical studies (bibliographic data) with combined use of rosuvastatin and ezetimibe did not reveal any additional safety concerns and thereby demonstrated the acceptable safety profile of this fixed dose combination. In accordance, the results obtained from bioequivalence and pharmacokinetic studies did not indicate any new safety risks.

IV.6 Risk Management Plan

The Applicant submitted a Risk Management Plan (RMP) in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to its rosuvastatin/ezetimibe products Zenon Neo 10 mg/10 mg, 20 mg/10 mg, 40 mg/10 mg film-coated tablets.

Summary table of safety concerns as approved in the RMP:

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

No pharmacovigilance activities were planned besides routine ones.
Only routine risk minimization measures were proposed.
The safety concerns and the proposed activities and measures were endorsed.

IV.7 Discussion on the clinical aspects

The efficacy and safety of this rosuvastatin/ezetimibe fixed dose combination intended for the substitution indication were demonstrated through the literature data, co-prescription data and an interaction study and bioequivalence study.

The bioequivalence between the medicinal product Zenon Neo 40 mg/10 mg, film-coated tablets and both reference formulations given concomitantly Crestor (rosuvastatin) 40 mg, film-coated tablet and Ezetrol (ezetimibe) 10 mg, tablets was shown. These results could be extrapolated, based on the biowaiver, to the additional intended strengths 10 mg/10 mg and 20 mg/10 mg.

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 results showed 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

Based on the review of the data on quality, safety and efficacy, the risk-benefit ratio for the applications for Zenon Neo 10 mg/10 mg, 20 mg/10 mg and 40 mg/10 mg, film-coated tablets were considered positive.

The SmPC, PIL and labelling are satisfactory.

Agreement between Member States was reached during the procedure. There was no discussion in the CMDh. The decentralised procedure was finalised with a positive outcome on 3.2.2019.

No conditions pursuant to Article 21a or 22 of Directive 2001/83/EC have been made during the procedure.