Summary Public Assessment Report

Generics

Rosuvastatin Galenicum 5mg, 10mg, 20mg and 40mg film-coated tablets
Rosuvastatin Calcium

MT/H/0202/001-004/DC

Date: June 2017

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This is a summary of the public assessment report (PAR) for Rosuvastatin Galenicum. It explains how Rosuvastatin Galenicum 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 Rosuvastatin Galenicum.

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

What is Rosuvastatin Galenicum and what is it used for?

Rosuvastatin Galenicum is a 'generic medicine'. This means that Rosuvastatin Galenicum is similar to a 'reference medicine' already authorised in the European Union (EU) called Crestor film coated tablets.

Rosuvastatin Galenicum is used in the treatment of high cholesterol levels. Rosuvastatin Galenicum can be used by patients who are adults, adolescents and children 6 years or older to treat high cholesterol or have other factors which can increase the risk of having a heart attack, stroke or related health problems.

How does Rosuvastatin Galenicum work?

Rosuvastatin Galenicum belongs to a group of medicines called statins.

Statins reduce high cholesterol levels in patients who are at a risk from a heart attack or stroke and diet or taking more exercise was not enough to lower these levels. These patients are still encouraged to carry on with a cholesterol-lowering diet and exercise whilst taking Rosuvastatin Galenicum.

Rosuvastatin Galenicum also decreases the risk of a heart attack, stroke or related health problems which can be caused by the disease atherosclerosis which is due to the build up of fatty deposits in the arteries. Rosuvastatin Galenicum can reduce the 'bad' cholesterol (LDL-C) and increase the 'good' cholesterol (HDL-C) found in the blood and also helps to block the production of 'bad' cholesterol. Rosuvastatin Galenicum also improves the body's ability to remove it from the blood

How is Rosuvastatin Galenicum used?

The pharmaceutical form of Rosuvastatin Galenicum is a film-coated tablet and the route of administration is oral.

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

Treatment with Rosuvastatin Galenicum for high cholesterol must start with the 5mg or 10mg dose and this depends on the cholesterol level, the level of risk of experiencing a heart attack or stroke and other factors that may make the patient more sensitive to possible side effects.

The doctor may decide to increase the starting dose and double it if necessary. There has to be a gap of four weeks between each dose adjustment.

The maximum daily dose is 40mg and only for patients with high cholesterol levels or with a high risk of heart attacks or stroke as the cholesterol levels are not lowered enough with 20mg.

The recommended daily dose for Rosuvastatin Galenicum to reduce the risk of heart attacks, stroke or related health problems is 20mg. However for children between 6 to17 years, the usual start dose is 5mg and the maximum daily dose is 10mg for children aged between 6 to 9 years and 20mg for those aged 10 to 17 years. The 40mg tablet should not be used by children.

Rosuvastatin Galenicum should be taken once a day, preferably at the same time every day with or without food. It should be swallowed whole with a drink of water.

It is important that the patient goes back to the doctor for regular checks to ensure that the cholesterol has reached and is maintained at the correct level. Treatment with Rosuvastatin Galenicum should not be stopped before talking to the doctor and any medical staff should be informed of the patient taking Rosuvastatin Galenicum when admitted to hospital or before starting any treatment.

The medicine can only be obtained with a prescription.

What benefits of Rosuvastatin Galenicum have been shown in studies?

Because Rosuvastatin Galenicum is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Crestor film coated tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

The company provided data from the published literature on Rosuvastatin Calcium.

What are the possible side effects of Rosuvastatin Galenicum?

Because Rosuvastatin Galenicum is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

Why is Rosuvastatin Galenicum approved?

It was concluded that, in accordance with EU requirements, Rosuvastatin Galenicum has been shown to have comparable quality and to be bioequivalent/be comparable to Crestor film-coated tablets. Therefore, the Medicines Authority decided that,as for Crestor film coated tablets, the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Rosuvastatin Galenicum?

A risk management plan has been developed to ensure that Rosuvastatin Galenicum 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 Rosuvastatin Galenicum, 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 Rosuvastatin Galenicum

The marketing authorisation for Rosuvastatin Galenicum was granted on 26th May, 2017.

The full PAR for Rosuvastatin Galenicum can be found on the website index http://mri.cts-mrp.eu/Human/

For more information about treatment with Rosuvastatin Galenicum, read the package leaflet http://www.medicinesauthority.gov.mt/advanced-search or contact your doctor or pharmacist.

This summary was last updated in 06-2017.

Public Assessment Report

Scientific discussion

Rosuvastatin Galenicum 5mg, 10mg, 20mg and 40mg film-coated tablets (Rosuvastatin Calcium)

MT/H/0202/001-004/DC

Date: 9th June, 2017

This module reflects the scientific discussion for the approval of *Rosuvastatin Galenicum 5mg, 10mg, 20mg and 40mg film-coated tablets*. The procedure was finalised at day 206. For information on changes after this date please refer to the module 'Update'.

I. Introduction

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Rosuvastatin Galenicum 5mg, 10mg, 20mg and 40mg film-coated tablets from Galenicum Health S.L.

The product is indicated for the treatment of hypercholesterolaemia and prevention of cardiovascular events.
A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

The reference product for this application is Crestor film coated tablets authorised by the Dutch NCA in 2004. The Marketing Authorisation Holder is Astra Zeneca B.V.

The CMSes involved in this procedure were DE,ES, FR and IT for the 5mg,10mg and 20mg strength and DE,ES,IT for the 40mg strength.

The product is subject to medical prescription.

II. Quality aspects

II.1 Introduction

Each tablet of Rosuvastatin Galenicum contains either 5mg, 10mg, 20mg or 40mg rosuvastatin as rosuvastatin calcium. The excipients are as follows:

Tablet core
Calcium citrate
Microcrystalline cellulose
Hydroxypropylcellulose
Mannitol
Lactose anhydrous
Crospovidone
Magnesium stearate

Tablet coat
Rosuvastatin 5 mg:
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc

Tartrazine (E102)
Sunset yellow FCF (E110)
Indigo carmine (E132)

Rosuvastatin 10 mg, 20 mg and 40 mg:
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc
Tartrazine (E102)
Allura red AC (E129)
Sunset yellow FCF (E110)
Indigo carmine (E132)

The medicinal product is packed in blisters of OPA/Aluminium/PVC/Aluminium foil. The following pack sizes are authorised:

- Blister packs 5 mg: 28, 30, 50, 60, 84, 90 and 100 film-coated tablets.
- Blister packs 10 mg: 20, 28, 30, 50, 60, 84, 90 and 100 film-coated tablets.
- Blister packs 20 mg: 20, 28, 30, 50, 60, 84, 90 and 100 film-coated tablets.
- Blister packs 40 mg: 28, 30, 50, 60, 84, 90 and 100 film-coated tablets.

II.2 2.2 Drug Substance

The active substance, Rosuvastatin Calcium is described in the European Pharmacopoeia (monograph 2631). The ASMF and CEP procedures are used for the active substance. There are three proposed manufacturers of the active substance, Rosuvastatin Calcium: an ASMF or CEP from each manufacturer is presented in support of the application for the drug product. Suitable letters of access/declarations of access from the respective ASMF/CEP holders have been submitted in respect of the procedure. The ASMF/CEP holders commit to ensure batch to batch consistency and to inform the applicant and the competent authority of any changes in the ASMF/CEP.

The control tests and specifications for the drug substance are adequately drawn up. The proposed retest periods for the drug substance from each respective ASM are acceptable.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained. The active ingredient and excipients used are well known and of pharmacopoeial quality.

The test biobatch is 10% of the proposed maximum batch size, and is the size of the minimum batch size proposed. Adequate dissolution results and comparative dissolution profiles have been provided complementary to the *in vivo* BE studies as well in support of the biowaiver of the strengths. The manufacturing process is adequately described and process validation has been adequately performed.

The control tests and specifications for the drug product are adequately drawn up. Validations of the analytical methods have been presented. Batch analysis has been performed on one pilot batch and two small production batches of both strengths. The batch analysis results show that the finished products meet the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The proposed shelf-life of 36 months with no special storage conditions for the drug product is considered acceptable.

III. Non-clinical aspects

III.1 Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which adequately summarises the information available to date on this topic. Rosuvastatin has been used extensively for approximately ten years and the overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data.

The RMS considers that the non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. The applicant also discusses the impurity profile of the medicinal product being applied for. No issue of concern is identified.

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Rosuvastatin Galenicum is intended for generic substitution, this 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

The application is made under reference to article 10(1) of Directive 2001/83/EC as amended. Abridged applications avoid the need for repetitive tests on animals and humans.

IV. Clinical aspects

IV.1 Introduction

The applicant has submitted one bioequivalence study under fasting conditions using the highest (40mg) strength in the range of strengths being applied for. This is line with the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev 01 which

states that the bioequivalence study should be conducted at the highest strength. This is considered adequate for this type of application.

IV.2 Pharmacokinetics

Biowaiver

The applicant requested a biowaiver for Rosuvastatin 5mg, 10mg and 20mg in Module 3. A detailed justification has been provided in Module 5 and discussed in the clinical overview (Module 2)

Bioequivalence studies

Study 224-10

This was a randomised, single centre, open-label, balanced, two-way, single dose, crossover comparative oral bioavailability study to establish comparative bioequivalence of Rosuvastatin 40mg film coated tablets (Test:manufactured by Biofarm Sp. Z.o.o) and Crestor 40mg film coated tablets (MAH: Astra Zeneca) in 36 healthy, adult, human subjects under fasting conditions. The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety and tolerability of a single dose of Rosuvastatin 40mg film coated tablets.

The study centre Lambda Therapeutic Research Sp. Z.o.o. Poland and the Clinical Investigator was Malgorzata Jonak MD. The studies were conducted between 11 March 2011 and 31 May 2011 (Period 1: 02 April 2011-08 April 2011 and Period II: 09 April 2011-12 April 2011).

Results

Table 5
Summary of Pharmacokinetic Parameters for Rosuvastatin 40mg under fasting conditions (n=36)

Parameters (Units)	Mean ± SD (Un-transformed data)	
	Reference Product -R	Test Product -T
T_{max} (h)*	4.500	4.500
C_{max} (ng / mL)	41.910 ± 22.8452	42.064 ± 20.2615
AUC_{0-t} (ng.h / mL)	356.749 ± 155.4124	350.252 ± 140.9206
$AUC_{0-\infty}$ (ng.h / mL)	382.616 ± 162.4484	375.927 ± 144.2641
λz (1 / h)	0.042 ± 0.0170	0.042 ± 0.0180
$t_{½}$ (h)	18.947 ± 6.6796	19.355 ± 7.6236
AUC_%Extrap_obs (%)	7.049 ± 4.0656	7.583 ± 4.8659

* T_{max} is represented as median value

Table 6
ANOVA 90% CI (Log transformed) and CV% for primary parameters of Rosuvastatin 40mg (test vs. reference) (Fasting, n=36).

Parameters (Units)	(Ln-transformed) Geometric least squares mean			90% Confidence Interval (Parametric)
	Test Product	Reference Product	Ratio (T / R)%	
C_{max} (ng / mL)	37.287	37.071	100.6	90.11 – 112.28%
AUC_{0-t} (ng.h / mL)	321.174	329.644	97.4	91.34 – 103.93%
$AUC_{0-\infty}$ (ng.h / mL)	348.028	354.991	98.0	92.33 – 104.10%

Conclusion on bioequivalence studies:

Based on the submitted bioequivalence study results, Rosuvastatin 40mg film coated tablets (Test: manufactured by Biofarm Sp. Z.o.o) and Crestor 40mg film coated tablets (MAH: Astra Zeneca) are considered bioequivalent in healthy, adult, human subjects under fasting conditions.

The results of study 224-10 with the 40mg film coated tablets can be extrapolated to Rosuvastatin 5mg, 10mg and 20mg, according to conditions in *Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01).*

IV.3 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 Rosuvastatin Galenicum.

Table VI-1 Summary of safety concerns

Important identified risks	Rhabdomyolysis
	Myopathy, myositis, myalgia, CK increases, myoglobinuria and myoglobinaemia (in the setting of rhabdomyolysis and myopathy)
	Increased transaminases, hepatitis, jaundice
	Pancreatitis
	Memory loss
	Proteinuria
	Diabetes mellitus
	Depression
	Sleep disorders (including insomnia and nightmares)
	IMNM
	Thrombocytopenia/decreased platelet count
	SJS/TEN
	Tendon disorders
	Peripheral neuropathy
	Drug-drug interactions including ciclosporin, various protease inhibitor combinations with ritonavir, simeprevir, clopidogrel, gemfibrozil, eltrombopag, dronedarone, warfarin, other vitamin K antagonists, fusidic acid, and ezetimibe.
Important potential risks	Renal failure (including acute and chronic renal failure) and renal impairment
	Hepatic failure (including hepatic necrosis and fulminant hepatitis)
	ALS
	ILD
	Drug-drug interactions with fibrates (other than gemfibrozil)
Missing information	Children <6 years of age
	DDI studies in the paediatric population

ALS Amyotrophic lateral sclerosis; CK Creatine kinase; DDI Drug-drug interaction; ILD Interstitial lung disease; IMNM Immune-mediated necrotising myopathy; LDL-C Low-density lipoprotein cholesterol; SJS Stevens-Johnson syndrome; TEN Toxic epidermal necrolysis.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed. Targeted follow up of adverse events in the following areas through questionnaires on rhabdomyolysis, renal failure, hepatic failure, interstitial lung disease, pregnancies with delivery dates and paediatric subjects will be undertaken. This will form part of routine pharmacovigilance.

This request is in line with other RMPs for other generic products containing the same substance for the same indication.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 05, signed and dated 27-Mar-2017 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

IV.4 Discussion on the clinical aspects

The application is made under reference to article 10(1) of Directive 2001/83/EC as amended. Abridged applications avoid the need for repetitive tests on animals and humans.

V. User consultation

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Crestor 5mg,10mg,20mg and 40mg film-coated tablets for scientific content, NL/H/0343/001-004/E/001 and Dexketoprofen Galenicum 25mg film-coated tablets for design and layout PT/H/1000/001-002/DC. The bridging report submitted by the applicant is acceptable.

VI. Overall conclusion, benefit/risk assessment and recommendation

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to Rosuvastatin 5mg, 10mg, 20mg and 40mg, film-coated tablets, are of sufficient quality in view of the present European regulatory requirements.

Based on the submitted bioequivalence study results, Rosuvastatin 40mg film coated tablets (Test:manufactured by Biofarm Sp. Z.o.o) and Crestor 40mg film coated tablets (MAH: Astra Zeneca) are considered bioequivalent in healthy, adult, human subjects under fasting conditions.

The results of study 224-10 with the 40mg film coated tablets can be extrapolated to Rosuvastatin 5mg, 10mg and 20mg, according to conditions in *Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01).*