Public assessment summary report

Name of the Finished Pharmaceutical Product	CELMANTIN 10 mg film-coated tablets CELMANTIN 20 mg film-coated tablets
Manufacturer	Medochemie limited cyprus 1-10 constantinoupoleos street 3011 limassol cyprus
Active Pharmaceutical Ingredient	Rosuvastatin, as rosuvastatin calcium

1. Introduction

Celmantin belongs to a group of medicines called statins. Celmantin is used to correct the levels of fatty substances in the blood called lipids, the most common of which is cholesterol.

2. Assessment of quality

Active pharmaceutical Ingredient (API)

Rosuvastatin calcium is a white or almost white, hygroscopic powder. It is slightly soluble in water, freely soluble in methylene chloride, practically insoluble in anhydrous ethanol.

Solubility of Rosuvastatin calcium was tested in 5 different media covering a pH range from 1.0 to 6.6. The results showed that the solubility of Rosuvastatin calcium was directly proportional to the pH.

Rosuvastatin calcium is known to exist in several polymorphic forms. Literature investigation revealed that for the Canadian innovator Crestor film coated tablet tablets, the amorphous form of rosuvastatin calcium was used, which was confirmed by X-Ray diffraction crystallography. Data with respect to particle size of API batches included in the bio-batches and overall pharmaceutical development were provided and acceptance criteria were concluded.
Rosuvastatin Calcium has two chiral centers, therefore theoretically four stereo isomers are possible with absolute stereo chemical configurations (3*R*, 5*S*), (3*R*, 5*R*), (3*S*, 5*S*) and (3*S*, 5*R*). Rosuvastatin calcium manufactured by MSN Laboratories Private Limited has the 3R, 5S configuration.

Batch results for three representative batches manufactured in commercial scale were provided. All batches were manufactured using the process described in the product dossier. And tested using the methods described in the dossier. All results comply with the specification and demonstrate consistent quality of the batches produced.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture:

The drug products considered in this dossier "Rosuvastatin 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets", fulfill the criteria for essential similarity with the reference medicinal products Crestor 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets manufactured and marketed by AstraZeneca in various EU and other countries.

All the excipients used in the formulation of Rosuvastatin 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets were well known and widely used in the pharmaceutical industry.

Medochemie was based on Pharmascience formulation development studies and final conclusions to manufacture confirmatory scale-up batches of Rosuvastatin 5mg, 10mg, 20mg and 40mg and evaluate physicochemical characteristics of the tablets, dissolution profiles and stability. One scale-up batch was manufactured for Rosuvastatin 5mg and 40mg and two scale-up batches for Rosuvastatin 10mg and 20mg, to the final formulation composition and pilot lots.
Comparative dissolution profiles between the reference Crestor film coated tablets, the pilot batches of Rosuvastatin film coated tablet tablets manufactured by Pharmascience and the production batches of Rosuvastatin film coated tablet tablets manufactured by Medochemie were performed using the dissolution method described in the product dossier. Comparative dissolution studies have been performed in three dissolution media covering a pH range from pH 3 to pH 6.6. In all three dissolution media studied, the batches of test product Rosuvastatin 5mg, 10mg, 20mg & 40mg and innovator Crestor 5mg, 10mg, 20mg & 40mg had similar dissolution profiles with more than 85% of rosuvastatin dissolved within 15 minutes.

Manufacture of the product

The process validation schemes for the manufacturing process of Rosuvastatin film coated tablets at the Medochemie site were presented in module 3.2.R of the dossier. For the batch size of 100,000 tablets three validation runs per dosage strength of the product have been currently executed according to the process described in the protocols. The *process validation reports were* presented in section 3.2.P.3.5. The final conclus*ion of the validation wa*s that 'the manufacturing process of Rosuvastatin 5mg, 10mg, 20mg & 40mg *film coated tablet tablets wa*s consistent & robust'.

Specifications:

The critical HPLC methods for the determination of the stability indicating Assay, Content Uniformity, Dissolution and Related Substances have been developed and validated at Pharmascience R&D laboratory. The analytical methodology has been transferred to Medochemie and an inter laboratory qualification was performed to demonstrate that both control laboratories were producing equivalent results. A forced degradation study on the finished product has been also performed by Pharmascience and included in the dossier. All the appropriate parameters have been validated and the results were found within the validation acceptance criteria.

Batch analyses were provided for ten batches manufactured at Medochemie. Tabulated analytical results for each strength of Rosuvastatin film coated tablet were presented. The respective Medochemie's certificates of analysis were included in the documentation.

The impurities controlled in the finished product were those impurities specified in the Ph.Eur monograph for Rosuvastatin calcium, which were also declared by the API manufacturer to be potential impurities in the active substance either arising from the route of synthesis or resulting as degradation products.

For the standardization of the Rosuvastatin calcium working standard (WS), water content and assay were determined. The assay was determined by two analysts, on the same day, using the same analytical instrument, in replicate, each analyst performing 6 replicate testing. The mean potency of the assay result and an internal batch number (MCB) was assigned to the working standard which was then split into suitable aliquots, placed in vials, labeled, and stored under appropriate conditions.

The Rosuvastatin calcium WS currently used by Medochemie for routine analyses is from MSN (Batch no.: RV1861015, MCB: A21002). Standardization of the working standard was done against the primary reference standard Rosuvastatin calcium EP CRS (batch no. 1), using the HPLC assay method of the Ph.Eur monograph for Rosuvastatin calcium.

Other ingredients:

Typical certificates of analysis from the manufacturers of the excipients and the corresponding certificates of analysis from the finished product manufacturer were presented in the documentation and result found to be acceptable.

The excipients are cellulose, microcrystalline PH-101, cellulose, microcrystalline PH-102, crospovidone Type A, magnesium Stearate, silica colloidal anhydrous and water, Purified. Opadry II Yellow 33K12488 is used for the film coating of Rosuvastatin 5 mg tablets, Opadry II Pink 33K94423 is used for the film coating of Rosuvastatin 10 mg and 20 mg tablets, and Opadry II Pink 33K94424 is used for the film coating of Rosuvastatin 40 mg tablets.

The analytical procedures used for the excipients described in a pharmacopoeia were those of the corresponding pharmacopoeial monographs. The tests for identification and sulphated ash performed by the finished product manufacturer on the Opadry coating agents.

Stability testing:

The following stability indicating parameters have been monitored on the stability batches manufactured by Medochemie: physical appearance, average weight, hardness, disintegration, water content, dissolution, related substances and assay of the active ingredient. Microbiological control and identification of the active ingredient and colorants were performed at the beginning and end of shelf life. The frequency and storage condition used during the stability study were as per the requirements indicated on the medicine registration guideline.

3. Bioequivalence study Data

Two bioequivalence studies have been conducted for Rosuvastatin film coated tablets:
One bioequivalence study was conducted between Rosuvastatin 10 mg (Lot No: E5G055, Mfg. site: Medochemie-Central Factory, Mfg. date: 7/2011) and Crestor 10mg (Lot No: HX759, AstraZeneca, Exp. Date: 4/2014), and another one bioequivalence study was conducted between Rosuvastatin 40 mg (Lot No: E5G054, Mfg. site: Medochemie-Central Factory, Mfg. Date: 7/2011) and Crestor 40mg (Lot No: HX903, AstraZeneca, Exp. Date: 3/2014).

The test product batches used in the BE studies were commercial scale batches of 100,000 tablets batch size, representative of the product to be marketed. For the selection of the reference products used in the BE studies dissolution studies were performed on various innovator products Crestor 5 mg, 10 mg, 20 mg and 40 mg film coated tablet tablets sourced from several EU markets.

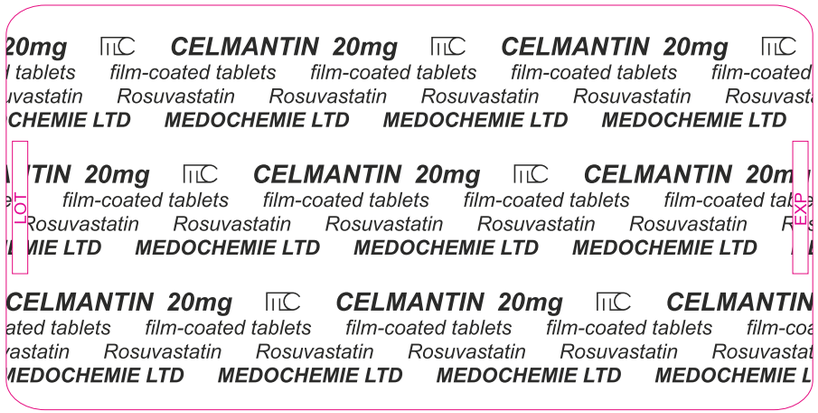
For all the reference products studied in a pH range of pH 3 to pH 6.6, the dissolution profiles have been found similar. In all batches and dissolution media, the active was rapidly released with more than 85% of rosuvastatin dissolved within 15 minutes. The same was observed for the dissolution profiles of the products under evaluation, Rosuvastatin 5 mg, 10 mg, 20 mg and 40 mg film coated tablet tablets. Crestor 10 mg and 40 mg marketed in Cyprus were selected to be used as the reference products in the bioequivalence studies. The assay content and the impurity content were also evaluated for the selected batches of the reference products. The assay of the reference products does not differ by more than 5% compared to the assay of the test products, and impurities have been found in low levels.

The certificates of analysis for the test batches E5G055 & E5G054, and reference batches HX759 & HX903 were presented

4. Conclusion

Based on assessment of data on quality, safety and efficacy the assessors considered that the benefit–risk profile of Celmantin was acceptable for the following indication: treatment of hypercholesterolaemia Adults, adolescents and children aged 6 years or older with primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) and for prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event , as an adjunct to correction of other risk factors.

Size: 59,2x118mm



SIZE: 253 mm


CELMANTIN 20mg
film-coated tablets
Rosuvastatin
MEDOCHEMIE LTD

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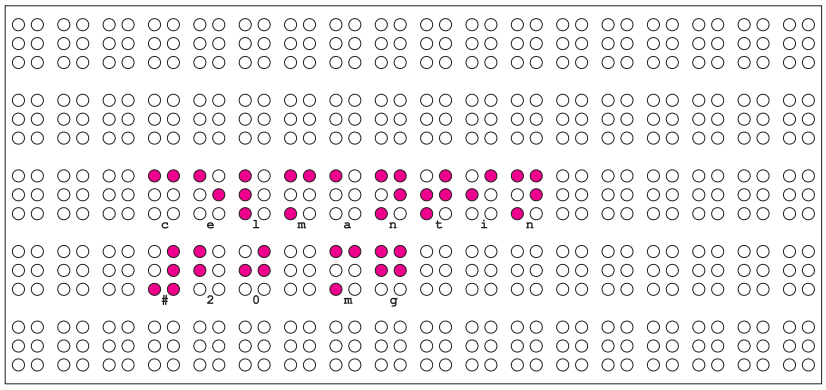

VARNISH FREE AREA

CELMANTIN 20mg

30 film-coated tablets

Each film-coated tablet contains 20mg Rosuvastatin as Rosuvastatin Calcium.
Lactose and Titanium dioxide (E171) are included among the excipients.
For further information see enclosed leaflet.
Store below 30°C in the original package, in order to be protected from light.
Keep out of the sight and reach of children.
Prescription only medicine.For Oral Use.
Manufacturer: Medochemie Ltd - Central Factory,
1-10 Constantinoupoleos Street, 3011 Limassol, Cyprus (EU)
Medochemie Ltd - Factory AZ,
2 Michael Erakleous Street, Agios Athanasios Industrial Area,
4101 Limassol, Cyprus (EU)
M.A. Holder: Medochemie Ltd, Cyprus (EU)

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PHARMACODE

LOT:
MF:
EX:

CODE/.....

CELMANTIN 20mg
30 film-coated tablets

PHARMACODE

CELMANTIN 20mg
Rosuvastatin

30 film-coated tablets

MEDOCHEMIE

MEDOCHEMIE

SIZE: 63 x 24 x 125mm

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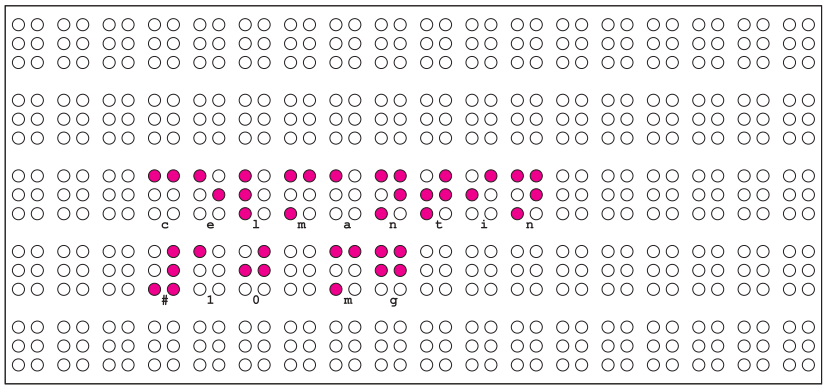
PANTONE 342 C
PANTONE 336 C
BLACK

BRAILLE



VARNISH FREE AREA

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Keep out of the sight and reach of children.
Prescription only medicine.For Oral Use.
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Medochemie Ltd - Factory AZ,
2 Michael Erakleous Street, Agios Athanasios Industrial Area,
4101 Limassol, Cyprus (EU)
M.A. Holder: Medochemie Ltd, Cyprus (EU)

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PHARMACODE

LOT:
MF:
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CODE/.....

CELMANTIN 10mg

30 film-coated tablets

PHARMACODE

CELMANTIN 10mg
Rosuvastatin

30 film-coated tablets

MEDOCHEMIE

MEDOCHEMIE

SIZE: 63 x 24 x 125mm

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PANTONE 342 C
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