EDA Assessment Report for human medicinal product

(Scientific Discussion)

Novistoric Plus 10/10 mg Film Coated Tablets

Novistoric Plus 10/5 mg Film Coated Tablets

Ezetimibe 10 mg & Rosuvastatin 10 mg (as Calcium)

Ezetimibe 10 mg & Rosuvastatin 5 mg (as Calcium)

Date: December, 2024

I. Introduction

-Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Novistoric Plus Film Coated Tablets from Future Pharmaceutical Industries, Egypt.

-The product is a combination of rosuvastatin, an HMG CoA-reductase inhibitor (statin), and ezetimibe, a dietary cholesterol absorption inhibitor, indicated in adults:

*As an adjunct to diet in patients with primary non-familial hyperlipidemia to reduce low-density lipoprotein cholesterol (LDLC).

*Alone or as an adjunct to other LDL-C lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDLC.

II. Quality Aspect

Drug Substance (Ezetimibe)

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is white powder, freely soluble in alcohol, soluble in acetonitrile, insoluble in aqueous solvents and non-polar solvents like hexane. Ezetimibe has three chiral centers. Ezetimibe exhibits polymorphism and the crystalline form resulting from the manufacturing process is Form A.
- The synthesis of drug substance includes 4 steps with the formation of 4 intermediates was revised and found to comply with ICH Q11 (Development and Manufacture of Drug Substances)
- The drug substance is elucidated via IR, H^1 NMR, C^{13} NMR Mass spectrometry, elemental analysis, X-ray powder diffraction (XRPD) and UV.
- The drug substance specifications are description, solubility, identification, water determination, specific optical rotation, residue on ignition, organic impurities, assay and residual solvents.
- Analytical methods were adequately described and validated. They were revised and found to be suitable for the required testing.
- The applicant provided batch analysis results of 3 batches. The results of all tests were well within the specification limits and batch data was found acceptable.
- The drug substance is packed in inner clear polythene bag placed under nitrogen and outer black Polythene bag followed by triple laminated Aluminum bag in HDPE drum
- Stability of API is is submitted in accelerated 40°C±2°C / 75%±5% RH and long-term storage conditions 25°C±2°C / 60% ±5% RH and conclude the conformity of specifications during the shelf life and storage conditions. The stability of the API is confirmed when stored in a tightly closed container, protected from moisture at room temperature.

Drug Substance (Rosuvastatin "As Calcium")

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is off-white to creamish white powder, soluble in acetonitrile and acetone. Rosuvastatin calcium has two chiral centers having configuration as 3(R) and 5(S). Also known to have two geometrical isomers (E) and (Z). The supplier manufactures (E) form of Rosuvastatin calcium.
- The synthesis of drug substance includes 3 steps with the formation of 2 in situ intermediates was revised and found to comply with ICH Q11 (Development and Manufacture of Drug Substances).
- The drug substance is elucidated via IR, H^1 NMR, C^{13} NMR Mass spectrometry, elemental analysis, XRPD & UV.
- The drug substance specifications are Identification by IR, organic impurities (HPLC), assay (HPLC), calcium content, specific optical rotation, water determination, enantiomeric purity and residual solvents
- Analytical methods were adequately described and validated. They were revised and found to be suitable for the required testing.
- The applicant provided batch analysis results of 3 batches. The results of all tests were well within the specification limits and batch data was found acceptable.
- The drug substance is packed in inner clear polythene bag under nitrogen and outer black polythene bag followed by triple laminated aluminum bag placed in the HDPE drum.
- Stability of API is submitted in accelerated 40°C±2°C /75% ± 5% RH and long-term storage conditions 25°C±2°C / 60% ±5% RH and conclude the conformity of specifications during the shelf life and storage conditions. The stability of the API is confirmed when stored in a tightly closed container, protected from moisture at room temperature.

Medicinal Product

Product Description

- **For both strengths:** Pale red to red, round, biconvex film coated tablet, plain from both sides.
- The product is packed in OPA/ALU/PVC/ALU blister contain 10 tablets in each.
- **For both strengths:** The excipients are Dibasic Calcium Phosphate Anhydrous, Lactose monohydrate (DC) spray dried, Crospovidone XL-10, Microcrystalline cellulose (PH 102), Sodium lauryl sulfate, Colloidal silicon dioxide (Aerosil 200), Magnesium stearate, Lactose monohydrate fine powder, Povidone K30, Microcrystalline cellulose (PH 102), Croscarmellose sodium, Red iron oxide (C.I No: 77491), Sodium lauryl sulfate and Opadry II Pink.

- **Pharmaceutical development**, the development of the product has been described, the choice of excipients is justified and their functions explained. It was aimed to develop a product equivalent to the reference product.
- Overall, the choices of the packaging, manufacturing process, compatibility, overage physicochemical properties and microbiological attributes are justified.
- **Manufacturing process**, the manufacturing process consists of Preparation of Rosuvastatin layer, Preparation of Ezetimibe layer, Compression, Coating and Packaging.
- The applicant submitted the process validation protocol of the manufacturing process in line with relevant guidelines and committed to provide the process validation report for the first three production batches
- **Control of excipients**, all excipients comply with USP except Opadry II Pink which is controlled according to in house specifications.
- **Product specification** includes Description, Water content, Identification of Rosuvastatin & Ezetimibe, Assay Rosuvastatin & Ezetimibe, Dissolution of Rosuvastatin & Ezetimibe, organic impurities, Uniformity of mass, Disintegration time, Uniformity of dosage units of Rosuvastatin & Ezetimibe and microbial limits
- **The Analytical methods** used in testing the finished pharmaceutical product were presented in the dossier. They were reviewed and found to be suitable for the required testing
- **Batch Analysis** from the proposed production site were provided for 3 batches of each strength. The results of all tests were well within specification limits and batch data was found acceptable.
- **Container closure system** is OPA/ALU/PVC/ALU blister contains 10 film coated tablets in each then placed in Carton box and insert.
- **Stability** of finished pharmaceutical products are submitted in accelerated (40°C/75% RH) and long-term (30°C/65% RH) storage conditions. Detailed review was carried out for all stability indicating parameters and all found in line with their acceptance criteria throughout all time intervals. The provided stability study supports the proposed shelf life of 2 years when stored at a temperature not exceeding 30̊C in dry place.
- Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies. A declaration/certificate of TSE/BSE free is submitted for Lactose monohydrate.

Summary basis of opinion:
From Chemistry, Manufacture and Control perspective, the main concerns found during the evaluation process were as follow:

For the Drug substance (Ezetimibe):
-Results of XRPD for three batches should be submitted to confirm the polymorphic form of Ezetimibe resulting from the manufacturing process.
-The control strategy for triethyl amine and dimethyl formamide as residual solvents should be clarified.
-The chemical names of potential genotoxic impurities should be clarified as well as their control strategy according to ICH M7.

For the Drug substance (Rosuvastatin):
-Risk assessment of benzene as a contaminant of the solvents used in the manufacture of Rosuvastatin should be submitted.
-The process related impurities and degradation products that can be carried over to the final API should be discussed clarifying their control strategy.
-Risk assessment of Genotoxic impurities according to ICH M7 guideline should be submitted.

For the Drug product:
-The precautions taken during the manufacturing process to protect the product from light and moisture should be clarified.

-The specification limit for dissolution test should be revised based on the dissolution results of biobatch in development section which support more restricted limit according to *"EMA Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action"*.

-The high specification limit of water content should be revised taking into consideration the results in stability data which support more restricted limit.

The Quality of the drug product has been found satisfactory after:
- The supplier of Ezetimibe submitted XRPD for 3 batches and the 2Θ angles were found match with those of the crystalline form A in the available scientific literature.
- The supplier of Ezetimibe submitted results of triethyl amine and dimethyl formamide in three consecutive commercial batches and all results were found below the detection limits of these solvents.
- The supplier of Ezetimibe provided risk assessment of genotoxic impurities as well as carryover study of potential genotoxic impurities and their results were found below their detection limits.
- The supplier of Rosuvastatin provided the results of benzene in three commercial batches of the API and all results were found below the detection limit of benzene (i.e; less than 30% of the benzene limit according to ICH Q3C guideline)
- The supplier of Rosuvastatin provided discussion on the process related impurities and degradation products according to USP monograph of Rosuvastatin Calcium.
- The supplier of Rosuvastatin performed the risk assessment as per ICH M7 using the two (Q) SAR

prediction methodologies, which concluded that there's no potential risk of genotoxic impurities being carried over to the final API.
- The manufacturer clarified that the product is protected from light and moisture by using Na lamp and storing the bulk product in tight container with silica gel, respectively.
- The specification limit of dissolution test has been tightened based on the dissolution results of biobatch in line with *"EMA Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action"*.
-The specification limit of water content has been tightened based on the stability results of water content test.

III. Non-Clinical

No new preclinical data have been submitted with this application. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application. An Environmental Risk Assessment has not been performed as this product is intended for generic substitution and therefore will not result in an increase of risk to the environment during use, storage and disposal.

IV. Clinical Aspects

Introduction

Ezetimibe/Rosuvastatin are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.

Mechanism of Action

-Ezetimibe
The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. Ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.

-Rosuvastatin
Rosuvastatin is an inhibitor of HMG CoA-reductase, the rate-limiting enzyme that converts 3-hydroxy3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. In in vivo and in vitro studies, rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

Indications

1- As an adjunct to diet in patients with primary non-familial hyperlipidemia to reduce low-density lipoprotein cholesterol (LDL-C).

2- Alone or as an adjunct to other LDL-C-lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C.

Pharmacokinetics

Absorption

-Ezetimibe

After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). After a single 10-mg dose of ezetimibe to fasted adults, mean ezetimibe peak plasma concentrations (Cmax) of 3.4 to 5.5 ng/mL were attained within 4 to 12 hours (Tmax). Ezetimibe-glucuronide mean Cmax values of 45 to 71 ng/mL were achieved between 1 and 2 hours (Tmax). There was no substantial deviation from dose proportionality between 5 and 20 mg. The absolute bioavailability of ezetimibe cannot be determined, as the compound is virtually insoluble in aqueous media suitable for injection. Concomitant food administration (high-fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as ezetimibe 10-mg tablets. The Cmax value of ezetimibe was increased by 38% with consumption of high-fat meals.

-Rosuvastatin

In clinical pharmacology studies in man, peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral dosing. Both Cmax and AUC increased in approximate proportion to rosuvastatin dose. The absolute bioavailability of rosuvastatin is approximately 20%. The AUC of rosuvastatin does not differ following evening or morning drug administration. Administration of rosuvastatin with food did not affect the AUC of rosuvastatin.

Distribution

-Ezetimibe

Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.

-Rosuvastatin

Mean volume of distribution at steady-state of rosuvastatin is approximately 134 liters. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.

Excretion

-Ezetimibe

Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation with subsequent biliary and renal excretion. Minimal oxidative metabolism has been observed in all species evaluated. In humans, ezetimibe is rapidly metabolized to ezetimibe-glucuronide. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are eliminated from plasma with a half-life of approximately 22 hours for both ezetimibe and ezetimibe-glucuronide. Plasma concentration-time profiles exhibit multiple peaks, suggesting enterohepatic recycling. Following oral administration of 14C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) accounted for approximately 93% of the total radioactivity in plasma. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10day collection period. Ezetimibe was the major component in feces and accounted for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.

-Rosuvastatin

Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450\2C9, and in vitro studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of the parent compound. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by the parent compound.

Following oral administration, rosuvastatin and its metabolites are primarily excreted in the feces (90%). The elimination half-life (t½) of rosuvastatin is approximately 19 hours. After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route.

Bioequivalence Study

The bioequivalence study of Novistoric plus 10/10mg film coated tablets Manufactured by Future Pharmaceutical Industries was done relative to Ezetrol 10mg film coated tablets (MSD) & Crestor 10mg (AstraZeneca) administered to healthy participants.

Biowaiver

The EDA was granted a biowaiver for the lower strength Novistoric Plus 10/5mg film coated tablets based on the following arguments:

- The qualitative and quantitative composition of the different strengths is the same.
- All strengths of Novistoric Plus are manufactured by the same process.
- Ezitimibe/Rosuvastatin has linear pharmacokinetics over the therapeutic dose range.
- All tablets strengths have comparable dissolution profiles according to the provided in vitro dissolution data.

Design

This study was comparative, open-label, single-dose, randomized, two-treatment, three-period, three-sequence, fasting, crossover bioequivalence study, the dosing periods will be separated by a washout period of two weeks that will be left between periods.

Biological Samples Collection;

Pre-dose, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00,4.50, 5.00,5.50, 6.00,6.50, 7.00,8.00, 10.00, 12.00, 24.00, 48.00 and 72.00 hrs post dose administration.

Sample Collection & Sample Processing

-Twenty-Six (26) Blood samples were collected though indwelling cannula placed forearm vein with a suitable disposable syringe.

-On Labeled poly propylene tubes containing heparin as anti-coagulant five milliliters (5 ml) were collected from subjects as blood sampling interval schedule
-After blood sampling for all subjects at each sampling points, the tubes were centrifuged.
- After centrifugation plasma was separated from each sample and transferred into tubes.
- The polyethylene tubes containing plasma separated are stored at -70°C (±15°C) until analysis.
- The total volume of blood drawn for the purpose of this study was approximately (277 mL) from each subject.

Analytical Methods

All procedures used to perform the bio-analyses of Ezetimibe/Rosuvastatin in subject samples were executed according to international guidelines and official publications. CRO developed validated method to ensure data integrity, Accuracy and Precision of data generated during sampling, sample treatment and bioanalyses.

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of **Rosuvastatin** 10mg under **fasting conditions**.

Treatment N=33	**AUC0-t ng.h/ml**		**AUC0-∞ ng.h/ml**		**Cmax ng/ml**		**tmax h**	
Test	**129.594 (50.130 -453.163)**		**133.282 (51.245- 494.870)**		**11.535 (3.170- 35.019)**		**2.500**	
Reference	**Ref.1 121.665 (49.264 - 468.614)**	**Ref.2 110.044 (39.801- 462.415)**	**Ref.1 123.871 (50.185 - 480.779)**	**Ref.2 112.327 (41.004 - 474.477)**	**Ref.1 10.483 (3.452 - 38.965)**	**Ref.2 9.619 (2.921 - 39.927)**	**Ref.1 2.500**	**Ref.2 4.000**
***Ratio (90%) CI**	**107.32 (100.04-115.13)**		**107.72 (100.04-115.59)**		**110 (100.75-120.37)**		------	
CV (%)	---		-------		------		------	

*ln-transformed values

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of **Total Ezetimibe** 10mg under **fasting conditions**.

Treatment N=33	**AUC0-t ng.h/ml**		**AUC0-∞ ng.h/ml**		**Cmax ng/ml**		**tmax h**	
Test	**1501.978 (546.185+3214.542)**		**1654.696 (546.881-4426.881)**		**158.146 (55.538-344.484)**		**1.25**	
Reference 1&2	**Ref.1 1444.884 (530.083 - 3543.266)**	**Ref.2 1435.314 (719.868 - 3067.832)**	**Ref.1 1521.233 (531.113- 3680.472)**	**Ref.2 1557.508 (787.340- 3377.998)**	**Ref.1 173.963 (47.786 – 411.765)**	**Ref.2 173.700 (39.706- 363.889)**	**Ref.1 1.250**	**Ref.2 1.250**
***Ratio (90%) CI**	**104.22 (98.15-110.66)**		**105.18 (98.48-112.32)**		**92.42 (85.95-99.39)**		------	
CV (%)	---		-------		------		------	

*ln-transformed values

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of **Free Ezetimibe** 10mg under **fasting conditions**.

Treatment N=33	**AUC0-t ng.h/ml**		**AUC0-∞ ng.h/ml**		**Cmax ng/ml**		**tmax h**	
Test	**82. 874 (31.923-177.258)**		**94.667 (33.128- 260.312)**		**3.513 (1.295-7.313)**		10	
Reference	**Ref.1 77.078 (32.354 - 163.869)**	**Ref.2 78.663 (30.066- 170.750)**	**Ref.1 85.782 (33.687- 242.571)**	**Ref.2 96.572 (30.812 - 366.855)**	**Ref.1 3.724 (1.136 - 7.764)**	**Ref.2 3.515 (1.394 - 7.036)**	**Ref.1 6**	**Ref.2 6**
***Ratio (90%) CI**	**105.92 (98.70-113.66)**		**108.43 (98.79-119.02)**		**95.40 (86.59-105.10)**		------	
CV (%)	---		-------		------		------	

*ln-transformed values

Conclusion

-The 90% confidence intervals calculated for AUC $_{0-t,}$ $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 80-125%.

-Based on this study demonstrated that the active pharmaceutical ingredients Ezetimibe/Rosuvastatin in Novistoric plus 10/10mg film coated tablets manufactured by Future Pharmaceutical Industries versus Ezetrol 10mg film coated tablets (MSD) & Crestor 10mg (AstraZeneca) are Bioequivalent after a single oral dose of test and reference administration under fasting conditions on 33 participants