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MINISTRYOFHEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR UPERIO 200 (97 MG SACUBITRIL AND 103 MG VALSARTAN (AS SACUBITRIL VALSARTAN SODIUM SALT COMPLEX) FILM COATED TABLETS

Version number 01, 06/01/2023

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1. Introduction

Uperio 200 is a fixed-dose combination product presented as film-coated tablets containing of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5 respectively.

Uperio is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. Clinical judgment should be used in deciding whom to treat as LVEF is a variable measure. Uperio is administered in place of an ACE inhibitor or ARB.

1.1 Product details

Registration number	TAN 22 HM 0398
Brand name	Uperio 200 mg film-coated tablets
Generic name, strength and form	Sacubitril and Valsartan Sodium
ATC classification	Agents acting on the renin-angiotensin system; angiotensin II receptor blockers (ARBs), other combinations, ATC code: C09DX04
Distribution category	POM
Country of origin	Italy
Associated product	The finished product is presented as a film-coated tablet containing 50 mg and 100 mg of Sacubitril and Valsartan Sodium as active substances
Marketing Authorization Holder	NVS Kenya Limited-on behalf of MAH-Novartis Overseas Investment Address: Britam Tower, 27th Floor, Hospital Road, Upper Hill P.O. Box 46057 00100 Nairobi Kenya
Local Technical Representative	JD Pharmacy Ltd Nyerere Road 10 Vigunguti, P.O Box 1899 Dar es Salaam

1.2 Assessment procedure

The application for registration of Uperio 200 was submitted on 08/07/2021. The product underwent abridged assessment. Assessment was completed in one round of evaluation. Sacubitril and Valsartan Sodium was registered on 21/09/2022.

1.3 Information for users

Visual description of the finished product	Light pink ovaloid biconvex film-coated tablet with bevelled edges, unscored, debossed with “NVR” on one side and “L11” on the other side. Approximate tablet dimensions 15.1 mm x 6.0 mm
Primary packing material	Pack of 4 x 7’s film coated tablets in PA/AL/PVC (Alu-Alu) blister pack
Secondary packing materials	Carton box alongside with a package insert
Shelf-life and storage condition	36 months Do not store above 30°C.Protect from moisture, store in original pack
Route of administration	Oral
Therapeutic indications	Uperio is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. Clinical judgment should be used in deciding whom to treat as LVEF is a variable measure. Uperio is administered in place of an ACE inhibitor or ARB.

2. Labelling and product information

Summary of product characteristics

The SmPC included all the relevant information to ensure correct and safe use of the medicine by healthcare providers. The complete SmPC can be accessed here.

Package insert/leaflet

The package insert is confirmed to be derived from the SmPC and contains sufficient data for the end user. Since the product is POM that is intended for long term use, the package insert contains both full prescribing information as per SmPC and simplified information for patients.

Container labels

The product label information is presented in English. Details in the secondary pack label include:
Brand name: Uperio 200 mg film-coated tablets
Composition: . This is a single dose of 226.206 mg sacubitril valsartan sodium hydrate) equivalent to 200mg film-coated tablets
Pack size: 4 x 7's tablets
Manufacturing details: batch number, manufacturing date, expiry date
Storage conditions: Do not store above 30°C. Protect from moisture, store in original pack
Manufacturer address: Novatis Farms S.P.A, Via Provincials Schito 131, 80058 Torre Annunziata (NA) Italy

Unique identifier: N/A
Special warnings/precautions or instructions for use: N/A

The details of the primary pack include:
Brand name and strength: Uperio 200 mg film-coated tablets
Manufacturing details: batch number, manufacturing date, expiry date
Name of manufacturer: Novatis Farms S.P.A, Via Provincials Schito 131, 80058 Torre Annunziata (NA) Italy.

The content of the primary and secondary labels was aligned to the requirements of the Part V of the Compendium: Guidelines on Format and Content of Product Labels for Medicinal products. The label contains sufficient information for proper identification of the medicine and post marketing follow up of the product.

Mock labels are appended as annex I. (Requested)

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

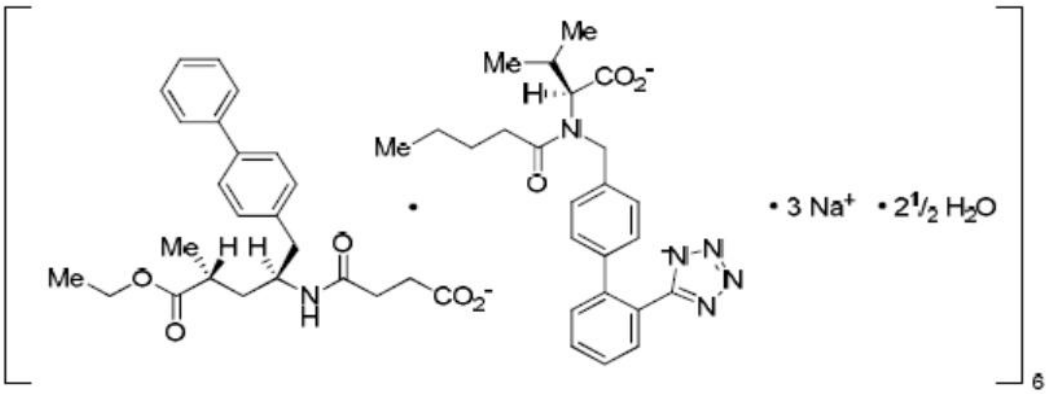
Information on quality of the API was submitted in form of full details.

General properties
Sacubitril and Valsartan Sodium API is non-compendia.

Molecular formula: $C_{288}H_{330}N_{36}O_{48}Na_{18}.15H_2O$

Chemical names:
octadecasodium hexakis-(4-{[(1S,3R)-1-([1,1'-biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4 oxobutyl] amino}-4-oxobutanoate) hexakis-(N-pentanoyl-N-{[2'-(1H-tetrazol-1-id-5-yl) [1,1'-biphenyl]-4-yl] methyl}-L-valinate) pentadecahydrate

Structure:



Critical physico-chemical properties are:

The sacubitril-valsartan complex is a white to almost white crystalline powder and is hygroscopic above 60% RH so needs to be protected from water. Solubility was measured for the individual active substances since the complex dissociates on dissolution which allows the active moieties to act independently in vivo. Both active substances exhibit pH dependent solubility in aqueous media, being freely soluble at neutral pH but much less soluble at lower pH. Both are soluble in alcoholic solvents but less so in aprotic organic media.

Sacubitril contains two chiral centres, one of which originates in a starting material, the other being created during the synthetic process and controlled in the subsequent intermediate specification. The single stereocentre in valsartan originates in a starting material. The active substance specification sets limits for all possible stereoisomers of the individual active substances.

Polymorphism has not been observed for the co-crystal complex. The sacubitril-valsartan complex was shown to be stable with respect to changes in polymorphic form in several studies.

Manufacture

The API manufacturing site; Zhejiang Jiuzhou Pharmaceutical Co, Limited No. 99, Waisha RD Jiaojiang, District Taizhou City,Zhejiang Province, 318 000 P. R. China, Zhejiang Raybow Pharmaceutical Co Limited No. 18, Nanyangsan RD, Linhai Taizhou

City, Zhejiang Province317 016 P.R. China and Raybow (Suzhou) Pharmaceutical Co, limited #18 Touglian Road Bix Sub district, Changshu City, JiangsuProvince, 215 537 P.R. China. Novartis Grimsby Ltd., Pyewipe, Grimsby, North East Lincolnshire, DN31 2SR, England, Novartis Pharma Stein AG, Schaffhauserstrasse, 4332 Stein,Switzerland.
The manufacturing facilities were noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by__ZHEJIANG FDA,MHRA_Swissmedic_respectively. Sacubitril and Valsartan Sodium API is manufactured by chemical synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The API specifications were set as per in-house standards and ICHQ3A. The parameters monitored during quality control are: appearance, identity (IR, UV, XRPD), assay (HPLC – individual components and co-crystal), sodium content (flame AAS), related substances (HPLC), stereoisomers (chiral HPLC), residual solvents (GC), water content (KF), heavy metals (ICP-MS), calcium (flame AAS), chloride (argentometry), microbial quality (Ph. Eur.) and particle size (laser diffraction). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The stability results indicate that the active substance made by the proposed manufacturers is sufficiently stable. The stability results justify the proposed retest period of 36 months in the proposed container which has been demonstrated to provide sufficient protection from moisture.

Quality of the Finished Pharmaceutical Product

Formulation

Uperio 200 mg film-coated tablets; Light pink ovaloid biconvex film-coated tablet with bevelled edges, unscored, debossed with “NVR” on one side and “L11” on the other side. Approximate tablet dimensions 15.1 mm x 6.0 mm.

Uperio 200 mg film-coated tablets contains sacubitril-valsartan complex and other ingredients listed here after: Microcrystalline cellulose, low-substituted hydroxypropylcellulose, crospovidone, magnesium stearate, talc and colloidal anhydrous silica. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 8th in terms of function and quantities.

Film coating: Hypromellose, titanium dioxide (E171), macrogol 4000, talc, iron oxide red (E172), iron oxide black (E172, low and high strength tablets) and iron oxide yellow (E172, middle strength tablets).

Manufacture

The finished product was manufactured at Novatis Farms S.P.A, Via Provincials Schito 131, 80058 Torre Annunziata (NA) Italy. The compliance of the site to TMDA GMP standards was confirmed through desk review on < >.

Specifications

The FPP is non-compendia. The manufacturer controls the quality of the finished product as per in-house standards and ICH requirements. The parameters monitored during quality control are: appearance, identification (IR, HPLC), identity of colorants (colour reaction, skip testing), mean mass, dissolution (Ph. Eur.), degradation products (HPLC), chiral purity (chiral HPLC), assay (HPLC), uniformity of dosage units (Ph. Eur.) and microbial enumeration (Ph. Eur., skip testing). The absence of a test for water content has been adequately justified as the slightly increased water content observed during stability studies had no impact on product performance. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on three (3) batches of the finished product stored at 30 ± 2°C & 75% ± 5% RH for 36 months and 40 ± 2°C & 75% ± 5% RH for 6 months. Based on available stability data, the proposed shelf-life of 36 months without specific storage conditions as stated in the SmPC (section 6.3) is acceptable.

Safety and efficacy information

TMDA has not assessed the primary data relating to preclinical and clinical aspects of this application and is taking over the results of the assessment of the foreign reference authority of EMA. The current TMDAPAR relating to preclinical and clinical aspects refers to the publicly available Assessment Report for Uperio 200 mg film-coated tablets/ Entresto issued by the EMA through Procedure No. EMEA/H/C/004062/0000.

4. Benefit-Risk Assessment and Conclusion

On basis ofthe data submitted, the current state of knowledge and compliance to Good Manufacturing Practice, the benefit of the product outweighs the risks associated with

its use when used in accordance to the summary of product characteristics Uperio 200 mg film-coated tablets is recommended for registration.

5. Post-approval updates

Variation applications

Reference number	Date submitted	Change requested	Recommendation	Granting date

Feedback from pharmacovigilance, post marketing surveillance and enforcement activities

Type of feedback	Impact	Response

Re-registration applications

Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

Version number	**Date**	**Description of update**	**Section(s) Modified**	**Approval date**

Annex I: Mock up label