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MINISTRYOFHEALTH

TANZANIAMEDICINES ANDMEDICALDEVICESAUTHORITY

PUBLIC ASSESSMENT REPORT FOR VERQUVO (VERICIGUAT 10 MG) FILM COATED TABLETS

Version number 01, 04/01/2023

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1. Introduction

Vericiguat is a stimulator of soluble guanylate cyclase (sGC). Heart failure is associated with impaired synthesis of nitric oxide (NO) and decreased activity of its receptor, sGC. Deficiency in sGC-derived cyclic guanosine monophosphate (cGMP) contributes to myocardial and vascular dysfunction. Vericiguat restores the relative deficiency in the NO-sGC-cGMP signalling pathway by directly stimulating sGC, independently of and synergistically with NO, to augment the levels of intracellular cGMP, which may improve both myocardial and vascular function. Medicine belonging to cardiac therapy, other vasodilators used in cardiac diseases, ATC code: C01DX22.

Vericiguat is approved in Tanzania for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction who are stabilized after a recent decompensation event requiring IV therapy.

1.1.Product details

Registration number	TAN 22 HM 0310
Brand name	Verquvo 10 mg film-coated tablets
Generic name, strength and form	Vericiguat
ATC classification	C01DX22, Cardiac therapy, other vasodilators used in cardiac diseases
Distribution category	POM
Country of origin	Germany
Associated product	The finished product is presented as a film-coated tablet containing 2.5 mg, 5 mg or 10 mg of Vericiguat as active substance
Marketing Authorization Holder	Bayer AG, 51368 Leverkusen Germany
Local Technical Representative	JD Pharmacy Limited, Dar Es Salaam, Tanzania

1.2.Assessment procedure

The application for registration of Vericiguat was submitted on19/10/2021. The product underwent abridged EAC joint assessment. Assessment was completed in one round of evaluation. Vericiguat was registered on 04/08/2022.

1.3.Information for users

Visual description of the finished product	Round biconvex, yellowish-orange film-coated tablet, with a diameter of 9 mm, marked with “10” on one side and “VC” on the other side
Primary packing material	The product is available in PVC/PVDC/ Aluminium foil or PP/Aluminium foil blisters, packed in a blister pack of 1x14 tablets
Secondary packing materials	Carton box alongside with a package insert
Shelf-life and storage condition	36 months Do not store above 30°C
Route of administration	Oral
Therapeutic indications	Verquvo is indicated for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction who are stabilized after a recent decompensation event requiring IV therapy

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: Verquvo 10 mg film-coated tablets
Composition: Vericiguat 10 mg film-coated tablets
Pack size:14's tablets
Manufacturing details: batch number, manufacturing date, expiry date
Storage conditions: Do not store above 30°C
Manufacturer address: Bayer AG, Kaiser-Wilhelm-Allee 51368 Leverkusen Germany.
Unique identifier: N/A
Special warnings/precautions or instructions for use: This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

The details of the primary pack include:
Brand name and strength: Verquvo 10 mg film-coated tablets
Manufacturing details: batch number, manufacturing date, expiry date
Name of manufacturer: Bayer AG Kaiser-Wilhelm-Allee 51368 Leverkusen Germany.

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.

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

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

General properties
Vericiguat API is non-compendia.

Molecular formula: $C_{19}H_{16}F_2N_8O_2$

Chemical names:
Methyl{4,6-diamino-2-[5-fluoro-1-(2-fluorobenzyl)-1Hpyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5 yl}carbamate

Structure:

Critical physico-chemical properties are:

The active substance is a white to yellowish non-hygroscopic crystalline powder. It is practically insoluble between pH 3-7 and is very slightly soluble at more acidic pH. The active substance is micronized to improve solubility. Five polymorphic forms were identified during development, along with several solvated and hydrated forms and amorphous material. The chosen commercial polymorphic form (modification I) is routinely produced by the manufacturing process and is the most thermodynamically stable between -20 and 80 °C. Vericiguat is achiral.

The solid-state properties of the active substance were further investigated by x-ray powder diffraction, differential scanning calorimetry, thermogravimetric analysis and moisture sorption.

Manufacture

The API manufacturing site,

Manufacturing site	Step
Bayer AG, Friedrich-Ebert-Straße 217 – 333, 42117 Wuppertal, Germany	Synthesis of Vericiguat intermediate Quality control testing
Bayer AG, Berlin Max-Dohrn-Straße 8, 10589 Berlin, Germany.	Micronization of Vericiguat micronized drug substance
Bayer AG, Bergkamen Ernst-Schering-Straße 14, 59192 Bergkamen, Germany	Quality control testing
Currenta GmbH & Co. OHG, Leverkusen, Analytik Chempark, Gebäude Q18 51368 Leverkusen,Germany	Quality control testing

The manufacturing facilities were noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by____ Local administrative district (Bezirksregierung) of Düsseldorf , Germany _____. Vericiguat 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 (material, colour), identity (IR, HPLC), particle size (laser diffraction), palladium (ICP-MS), water content (KF), residual solvents (GC), impurities (HPLC) and assay (HPLC). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure syste

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 36 months in the proposed container.

Quality of the Finished Pharmaceutical Product

Formulation

Verquvo 10 mg film-coated tablets; Round biconvex, yellowish-orange film-coated tablet, with a diameter of 9 mm, marked with “10” on one side and “VC” on the other side.

Verquvo 10 mg film-coated tablets contains Vericiguat and other ingredients listed here after: microcrystalline cellulose, croscarmellose sodium, hypromellose 2910, lactose monohydrate, magnesium stearate and sodium laurilsulfate. 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. Ingredient, lactose is of safety concern therefore appropriate warnings were included in the product label.

Film coat: iron oxide yellow, hypromellose 2910, talc and titanium dioxide

Manufacture

The finished product was manufactured at Bayer AG Kaiser-Wilhelm-Allee 51368 Leverkusen Germany. The compliance of the site to TMDA GMP standards was confirmed through desk review .

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 (form, colour, markings), identity (HPLC, UV), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), degradation products (HPLC), assay (HPLC) and microbial purity (Ph. Eur.). 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 Verquvo 10 mg Film coated tablets issued by the EMA through Procedure No. EMEA/H/C/005319/0000.

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 Verquvo 10 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	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up label

Effective date: 03/10/2022