THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR XARELTO (RIVAROXABAN 2.5 MG) FILM COATED TABLETS

Version number 1.0
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1. Introduction

Xarelto 2.5 is an innovator medicine. Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrate. Xarelto is approved in Tanzania for use only in adult patients.

1.1.Product details

Registration number	TAN 21 H 0487
Brand name	Xarelto 2.5
Generic name, strength, and form	Each film-coated tablet contains 2.5 mg rivaroxaban
ATC classification	ATC Code- B01AF01–Direct factor Xa Inhibitors
Distribution category	POM
Country of origin	Germany
Associated product	Xarelto 10, Xarelto 15, Xarelto 20
Marketing Authorization Holder	E-mail:ra.middleafrica@bayer.com ;
Local Technical Representative	JD Pharmacy Limited, P.O. Box 1899, Dar es Salaam.

1.2.Assessment procedure

The application for registration of Xarelto was submitted on 25 June 2020. The product underwent abridge assessment. Assessment was completed in 2 (two) rounds of evaluation and the product was registered on 26 November 2021.

1.3.Information for users

Visual description of the finished product	Light yellow, round biconvex tablets (6 mm diameter radius, 9 mm radius of curvature) marked with the BAYER-cross on one side and ‘’2.5’’ and a triangle on the other side
Primary packing material	Polypropylene/Alu Blister
Secondary packing materials	A printed carton box
Shelf-life and storage condition	36 months, Do not store above 30°C
Route of administration	Oral

Therapeutic indications	Xarelto, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothromboticevents in adult patients after an acute coronarysyndrome (ACS) with elevated cardiac biomarkers. Xarelto, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischemic events.

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, the package insert contains full prescribing information as per SmPC.

Container labels
The product label information is presented in English. Details in the secondary pack label include:
Brand name: Xarelto

Composition: Each film-coated tablet contains 2.5 mg Rivaroxaban

Pack size: 28 film-coated tablets

Manufacturing details: batch number, manufacturing date, and expiry date

Storage conditions: Do not store above 30°C

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Contains lactose. See package insert for detailed directions for use and complete information on dosage

The details of the primary pack include:

Brand name and strength: Xarelto (2.5 mg)

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Bayer

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 Ingredients

Information on the quality of the API was submitted in form of DMF.

General Information

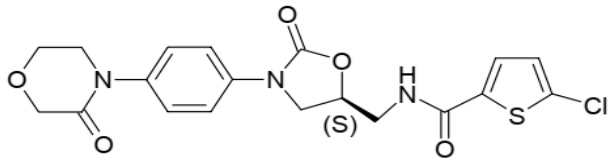
Rivaroxaban API is compendia in Ph.Eur. and BP.

Molecular formula: $C_{19}H_{18}ClN_3O_5S$

Chemical name:

5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl) phenyl]-1,3-oxazolidin-5-yl} methyl)-2-thiophenecarboxamide

Structure:



General properties

The active substance is a non-hygroscopic, crystalline white to yellowish solid, soluble in dimethylsulphoxide and insoluble in water. Rivaroxaban exhibits stereoisomerism due to the presence of one chiral centre. The S-isomer is the desired form. Enantiomeric purity is controlled routinely in the specifications.

Polymorphism has been observed for Rivaroxaban; Rivaroxaban crystallizes in three polymorphs;
thermodynamically stable form is used to manufacture the finished product. The same polymorphic form is manufactured by the API-DMF holder and it is routinely controlled in the active substance specification by XRPD.

Rivaroxaban is a class II substance in the BCS classification system. It has a low aqueous solubility, which is overcome by reducing the particle size with micronization. Appropriate limits have been included in the active substance specifications to monitor the particle size and size distribution.

Manufacture

Rivaroxaban API manufacturer is Bayer AG The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the <state the issuing

authorities>. Rivaroxaban 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 Ph.Eur. and BP standards and ICHQ3A. The parameters monitored during quality control are: Color, identity (IR, UV, and HPLC, Raman spectroscopy), particle size (laser diffraction), enantiomeric purity (HPLC), appearance of solution color (Ph. Eur), heavy metals (Ph. Eur), palladium (Ph. Eur), residual solvent (GC), assay (HPLC), related impurities (HPLC), water content (KF), sulphated ash (Ph. Eur), and microbial purity (Ph. Eur. / USP / Ph. Jap). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Rivaroxaban API is 36 months when packed in polypropylene foil bag 100 µm PP colorless transparent (1030) packed in tight closed containers for mechanical protection with storage condition 'Do not store above 25°C'.

Quality of the Finished Pharmaceutical Product

Formulation

Xarelto 2.5 is a light yellow, round, biconvex, film-coated tablet of a diameter of 6 mm and a radius of curvature of 9 mm. The tablet weight is 87.5 mg. The tablet markings are a triangle over "2.5" on one side and a Bayer cross on the other side.

Xarelto 2.5 contains the Rivaroxaban and other ingredients listed here after: Microcrystalline cellulose, Croscarmellose sodium, Lactose monohydrate, Hypromellose 2910, Sodium laurilsulphate, Magnesium stearate, Macrogol 3350, Hypromellose 2910, Titanium dioxide (E 171), Iron oxide yellow (E 172). The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, 8th Edition in terms of function and quantities.

Manufacture

The finished product manufacturers are Bayer AG, Kaiser-Wilhelm-Allee, 51368 Leverkusen, Germany, Bayer HealthCare Manufacturing S.r.l. Via delle Groane, 126, 20024 Garbagnate Milanese, Italy, and Stegemann Lohnverpackung &Logistischer Service e.K. Up'n Nien Esch 14, 48268 Greven, Germany. The compliance of the sites to TMDA GMP standards was confirmed through <site inspection/desk-review> on <date of GMP compliance>.

Specifications

The FPP is compendia in BP. 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 (TLC, NIR and HPLC), assay (HPLC), dissolution (HPLC), uniformity of dosage units (Ph. Eur), impurities (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 a 3(three) batches of the finished product stored at 30 ± 2°C & RH: 75 ± 5% RH for 36 months and 40± 2°C & RH: 75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 36 months when stored in Polypropylene/Alu blister with storage condition 'Do not store above 30°C'.

Safety and efficacy information

The product underwent abridge assessment hence this section was not reviewed.

4. Benefit-Risk Assessment and Conclusion

On basis of the 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. Xarelto 2.5 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

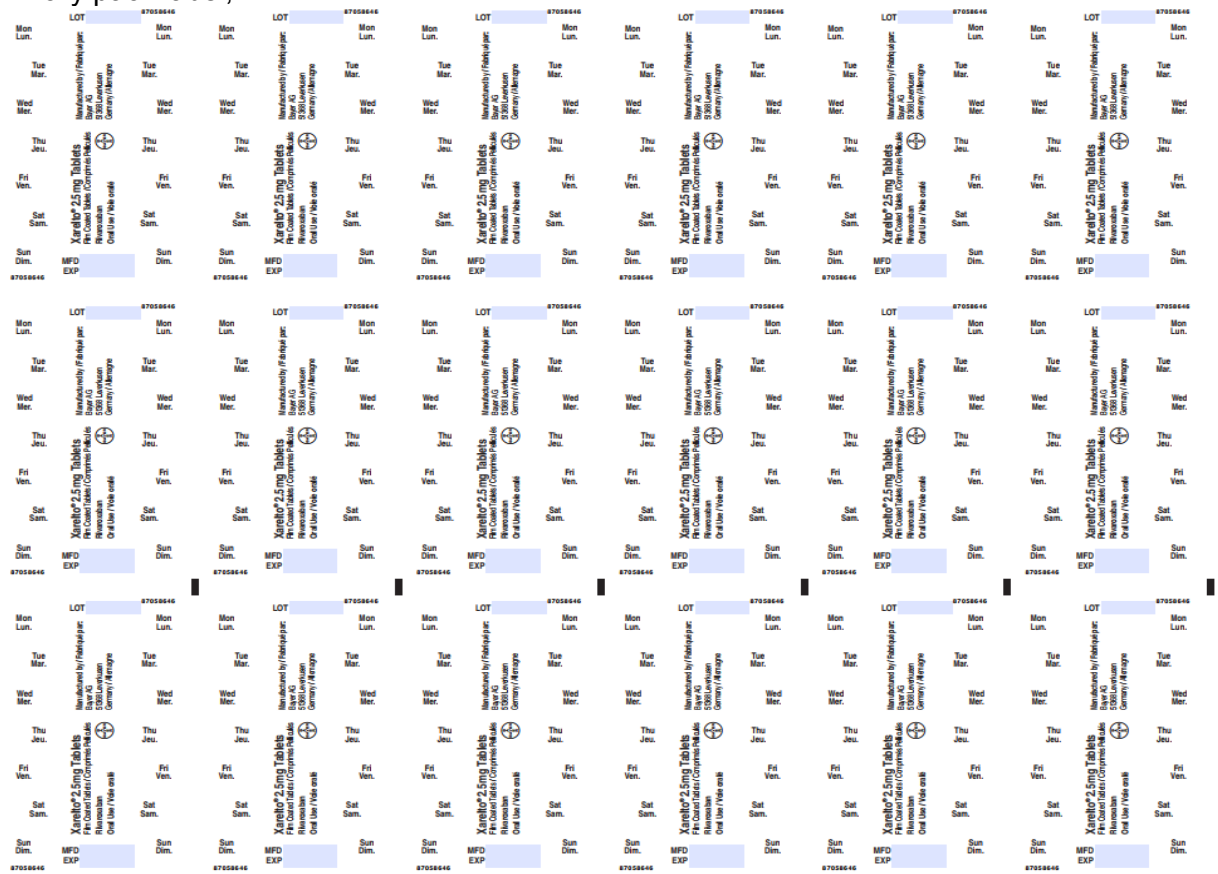
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

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

Annex I: Mock up labels;

Primary pack label;



Secondary pack label;

Effective date: 03/10/2022