TMDA/DMC/MRE/F/016

Revision#

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR VIZIMPRO (DACOMITINIB MONOHYDRATE 45 MG) IMMEDIATE RELEASE FILM COATED TABLETS

Version number 1.0

11th April, 2022

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1. Introduction

Vizimpro 45 Mg Tablets is an anticancer medicine belonging to Antineoplastic and Immunomodulating Agents group. Dacomitinib is a pan-human epidermal growth factor receptor (HER) (EGFR/HER1, HER2, and HER4) inhibitor, with activity against mutated EGFR with deletions in exon 19 or the L858R substitution in exon 21. Dacomitinib binds selectively and irreversibly to its HER family targets thereby providing prolonged inhibition. Vizimpro 45 mg Tablets is approved in Tanzania for use in adults

1.1 Product details

Registration number	TAN 22 HM 0143
Brand name	Vizimpro 45 mg Tablets
Generic name, strength and form	Dacomitinib Monohydrate, 45 mg film coated tablets
ATC classification	ATC Code: L01EB07 Antineoplastic and Immunomodulating Agents
Distribution category	POM
Country of origin	Germany
Associated product	Vizimpro 15 mg Tablets and Vizimpro 30 mg Tablets
Marketing Authorization Holder	Pfizer Laboratories Limited 1st Floor Vienna Court, State House Crescent Road, Kenya
Local Technical Representative	Macnaughton Limited Mek one Plaza, Plot no 4/1 & 8/1, P.O. Box 79400, Dar es Salaam, Tanzania

1.2 Assessment procedure

The application for registration of Vizimpro 45 Mg Tablets was submitted on 28th October, 2021. The product underwent joint EAC assessment. Assessment was completed in 1 rounds of evaluation. Vizimpro 45 Mg Tablets was registered on 11th April, 2022

1.3 Information for users

Visual description of the finished product	Blue, round biconvex tablet, debossed with Pfizer on one side and DCB45 on the other
Primary packing material	high-density polyethylene (HDPE) bottles with polypropylene (PP) cap Aluminum foil blisters with aluminum foil backing
Secondary packing materials	Cardboard box
Shelf-life and storage condition	60 months

Route of administration	Store below 30ºC
Therapeutic indications	Vizimpro, as monotherapy, is indicated for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations.

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: Vizimpro (Dacomitinib Monohydrate 45 mg) film coated tablets

Composition: Dacomitinib Monohydrate 45 mg

Pack size: 7, 28 and 100 for HPDE and 3 x10's for Alu-Alu blisters

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Store below 30ºC

Manufacturer address: Pfizer Manufacturing Deutschland, Betriebsstatte Freiburg, Mooswaldallee, 1-D 79090 Freiburg, Germany

Unique identifier: NA

Special warnings/precautions or instructions for use: The product contains lactose

The details of the primary pack include:
Brand name and strength: Vizimpro (Dacomitinib Monohydrate 45 mg) film coated tablets
Manufacturing details: batch number, manufacturing date, expiry date
Name of manufacturer: Pfizer Manufacturing Deutschland

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.
Describe any approved deviation to the requirements and the justification for the deviation.

Mock labels are appended as annex I

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

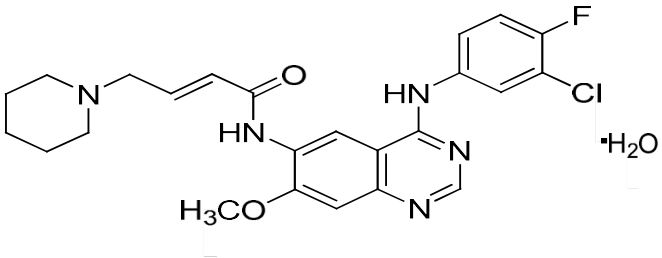
Information on quality of the API was submitted in form of Full details

General Information
Dacomitinib Monohydrate API is non-compendia

Molecular formula: C24H27ClFN5O3

Chemical name: (2E)-N-{4-[(3-Chloro-4-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}-4-(piperidin-1-yl)but-2-enamide monohydrate

Structure:



Physico-chemical properties of the API

Dacomitinib is a non-hygroscopic, white to pale yellow powder that is practically insoluble in water, slightly soluble in acetone and acetonitrile and sparingly soluble in acetic acid. It is classified as BCS Class II (low solubility and high permeability) based on the Biopharmaceutical Classification System. The active substance does not exhibit chirality. The active substance shows polymorphism. Three relevant forms of dacomitinib have been identified: monohydrate Form A, monohydrate Form B and anhydrous Form C. Dacomitinib monohydrate Form A is the solid state form selected for development and commercialization. This is the thermodynamically favoured and predominant solid state form which was identified from extensive form screening experiments and crystallization studies. The manufacturing process has been designed to ensure monohydrate Form A is produced.

Manufacture

The API manufacturing site is Pfizer Ireland Pharmaceuticals Ringaskiddy API Plant Ringaskiddy, County Cork, Ireland complies with GMP requirements as evidenced by the GMP certificate issued by Health Products Regulatory Authority of Ireland (HPRA). Dacomitinib 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, identification (by IR), assay (by HPLC), related substances, water content, residual solvents and particle size distribution. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Dacomitinib Monohydrate API is 60 months when packed in double low-density polyethylene (LDPE) anti-static liners within a high-density polyethylene (HDPE) drum and stored at 25ºC.

Quality of the Finished Pharmaceutical Product

Formulation

Vizimpro is a Blue, round biconvex tablet, debossed with Pfizer on one side and DCB45 on the other Vizimpro contains Dacomitinib monohydrate and other ingredients listed here after
Microcrystalline Cellulose
Lactose Monohydrate
Sodium Starch Glycolate
Magnesium Stearate
Purified Water
Opadry® II Blue 85F30716 (Polyvinyl Alcohol – part hydrolyzed, Talc, Titanium Dioxide Macrogol, FD&C Blue # 2/Indigo Carmine Aluminium Lake)
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. Ingredient, Lactose Monohydrate is of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product was manufactured at Pfizer Manufacturing Deutschland GmbH, Betriebsstätte Freiburg, Mooswaldallee 1, 79090 Freiburg, 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 and ICHQ3B requirements. The parameters monitored during quality control are: Appearance, identification (by UV and HPLC), Assay (by HPLC), related substances (by HPLC), dissolution, uniformity of dosage units (by content uniformity), water content, microbial enumeration test and test for specified organism. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on three batches of the finished product stored at 30°C/75 %RH for 60 months and 40ºC/75%RH for 6 months. Based on the stability data presented, the approved shelf-life is 60 months when stored in HDPE bottles with PP cap or in Aluminium foil blisters and stored at 30°C.

Safety and efficacy information

Safety and efficacy of Vizimpro was established through full clinical studies. The summary of all studies performed are listed in below tables.

Summary of included studies

Protocol	Phase	Subjects	N	PK Sampling
A7471001	1	Patients with solid tumors	121	Serial and Sparse
A7471002	2	Patients with advanced NSCLC	66	Serial and Sparse
A7471003	1/2	Patients with advanced NSCLC	55	Serial and Sparse
A7471005	1	Patients with solid tumors	13	Serial and Sparse
A7471009	3	Patients with NSCLC	878 Total (439 dacomitinib Arm)	Sparse
A7471014	1	Patients with solid tumors	16	Serial
A7471015	1	HVs	24	Serial
A7471017	2	Patients with NSCLC	89	Sparse
A7471018	1	HVs with or without normal hepatic function	8	Serial
A7471020	1	HVs	6	Serial
A7471021	1	HVs	14	Serial
A7471022	1	HVs	32	Serial
A7471027	2	Patients with metastatic squamous cell cancer of the head and neck	69	Serial and Sparse
A7471028	2	Patients with NSCLC	188 Total (94 dacomitinib Arm)	Sparse
A7471031	1b	Patients with NSCLC	22	Sparse
A7471039	1	HVs	14	Serial
A7471042	2	Patients with NSCLC	236	Serial and Sparse
A7471046	1	HVs	14	Serial
A7471047	2	Patients with NSCLC	41	Serial and Sparse
A7471050	3	Patients with NSCLC	452 Total (227 dacomitinib Arm)	Serial and Sparse
A7471051	1	HVs	14	Serial

HVs=healthy volunteers; N=number of subjects enrolled; NSCLC=non-small cell lung cancer; PK=pharmacokinetic.

Summary of dacomitinib studies to support the proposed indication

Study methods	Pivotal Study	Key Supportive Study	Supportive Studies		
	A7471050	A7471017 Cohort A[a]	A7471009	A7471028	A7471011
Development Phase	Phase 3	Phase 2	Phase 3	Phase 2	Phase 3
Design	Open-label, randomized active-controlled	Open-label, single-arm	Double-blind, randomized active-controlled	Open-label, randomized active-controlled	Double-blind, randomized placebo-controlled

Characteristics of advanced NSCLC (including prior treatment, if applicable)	• Newly Diagnosed Stage IIIB/IV or recurrent disease
	• EGFR-activating mutations
	• No prior systemic chemo-therapy for advanced disease
		• Stage IIIB-IV
		• EGFR-activating mutations, or patients who were pheno-typically likely to have tumours with
		  • EGFR-activating mutations
		  • No prior systemic chemo-therapy for advanced disease
			• Locally advanced or metastatic (Stage III-IV)
			• At least 1 prior chemo-therapy
				• Stage IIIB-IV
				• 1 or 2 prior chemo-therapy regimens
					• Stage IIIB-IV
					• Up to 3 prior chemo-therapy regimens and at least 1 therapy with erlotinib or gefitinib

Dacomitinib Starting Dose QD	45 mg	45 mg or 30 mg[b]	45 mg	45 mg	45 mg
Comparator Dose QD	Gefitinib 250 mg	None	Erlotinib 150 mg	Erlotinib 150 mg	Placebo
Study Dates (FPFV-LPLV)	09 May 2013- Not reached yet[c]	11 March 2009-30 April 2015	16 June 2011-14 September 2015	10 November 2008-15 August 2014	23 December 2009-18 June 2015
Number of Patients in ITT population[d]	Dacomitinib 227 Gefitinib 225	Dacomitinib 89[b]	Dacomitinib 439 Erlotinib 439	Dacomitinib 94 Erlotinib 94	Dacomitinib 480 Placebo 240
Number of patients with NSCLC with EGFR-activatin g mutations in ITT population	Dacomitinib 227 Gefitinib 225	Dacomitinib 45[e]	Dacomitinib 37 Erlotinib 39	Dacomitinib 16 Erlotinib 9	Dacomitinib 83 Placebo 52

Abbreviations: CSR=clinical study report; EGFR=epidermal growth factor receptor; FPFV=date of first patient first visit; HER=human epidermal growth factor receptor; ITT=intent-to-treat; LPLV=date of last patient last visit; NSCLC=non-small cell lung cancer; QD=once daily; sCSR=supplemental clinical study report.

a. Cohort B explored the utility of dacomitinib in HER2-amplified or HER2-mutated NSCLC in any line of therapy, and thus the results for this cohort are not summarized in this SCE, as they are not relevant to the proposed indication.

b. Study 1017 Cohort A had two dose groups: (1) dacomitinib at a starting dose of 45 mg (N=59) and (2) dacomitinib at a starting dose of 30 mg, increased to 45 mg after 2 cycles if the 30-mg dose was tolerated (N=30). Numbers of patients shown in this table are for both dose groups combined.

c. Study 1050 is completed, ie, the final analysis of the primary endpoint has been completed and a CSRs is available. At the time of this submission, it is anticipated that some patients in pivotal Study 1050 will still be receiving treatment and/or be in follow-up for secondary endpoints including overall survival (OS) or safety.

d. Number enrolled or randomized.

e. Of the 45 patients with NSCLC with EGFR-activating mutations in Study 1017 Cohort A, 16 were in the 30-mg starting dose group and 29 were in the 45-mg starting dose group.

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. Vizimpro 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

NA

PART 5: CHANGE HISTORY

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

Annex I: Mock up label

Blister label