TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR TALZENNA (TALAZOPARIB 0.25 MG) CAPSULES

Version number 1.0
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1. Introduction

Talzenna is an anticancer medicine belonging to Antineoplastic and Immunomodulating Agents group. Talazoparib is an inhibitor of PARP enzymes, PARP1, and PARP2. PARP enzymes are involved in cellular DNA damage response signalling pathways such as DNA repair, gene transcription, and cell death. PARP inhibitors (PARPi) exert cytotoxic effects on cancer cells by 2 mechanisms, inhibition of PARP catalytic activity and by PARP trapping, whereby PARP protein bound to a PARPi does not readily dissociate from a DNA lesion, thus preventing DNA repair, replication, and transcription, thereby resulting in apoptosis and/or cell death. Treatment of cancer cell lines that are harbouring defects in DNA repair genes with talazoparib single agent leads to increased levels of γH2AX, a marker of double stranded DNA breaks, and results in decreased cell proliferation and increased apoptosis. Talazoparib anti-tumour activity was also observed in a patient-derived xenograft (PDX) BRCA mutant breast cancer model where the patient was previously treated with a platinum-based regimen. In this PDX model talazoparib decreased tumour growth and increased γH2AX level and apoptosis in the tumours
Talzenna is approved in Tanzania for use in adults.

1.1 Product details

Registration number	TAN 22 HM 0114
Brand name	Talzenna
Generic name, strength and form	Talazoparib, 0.25 mg Hard gelatin capsules
ATC classification	ATC code: L01XX60 other antineoplastic agents
Distribution category	POM
Country of origin	Germany
Associated product	Talzenna 1 mg capsules
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 Talzenna was submitted on 14th April, 2021. The product underwent abridged and joint EAC assessment. Assessment was completed in 2 rounds of evaluation. Talzenna was registered on 11th April 2022

1.3 Information for users

Visual description of the finished product	Hard capsule with light red cap printed Pfizer and a white body printed with TLZ

Primary packing material	High-density polyethylene (HDPE) bottle and polypropylene (PP) closure with heat induction seal
Secondary packing materials	Cardboard carton box
Shelf-life and storage condition	36 months, Store below 30^0C
Route of administration	Oral
Therapeutic indications	Talzenna is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments (see section 5.1). Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine-based therapy, or be considered unsuitable for endocrine-based 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, 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: Talzenna

Composition: Talazoparib, 0.25 mg

Pack size: 30 capsules per bottle

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Store below 30^0C

Manufacturer address: Excella GmBH & Co. KG, Nurnberger Strasse 12, 90537 Feucht, Germany

Unique identifier: NA

Special warnings/precautions or instructions for use: NA

The details of the primary pack include:
Brand name and strength: Talzenna, 0.25 mg

Manufacturing details: batch number, manufacturing date, expiry date

Name of manufacturer: Excella GmBH & Co. KG

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

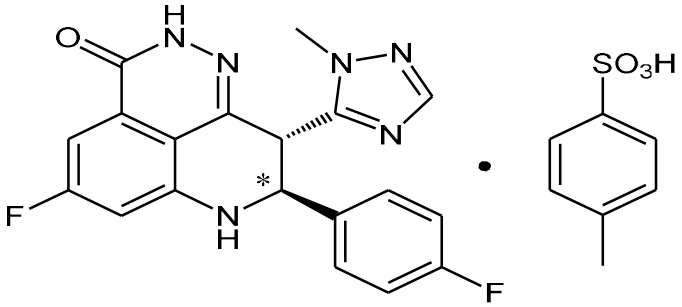
Quality of Active Pharmaceutical Ingredient(s)

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

General Information

Talazoparib API is non-compendia.
Molecular formula: C19H14F2N6O as free base or C26H22F2N6O4S as Tosylate salt
Chemical name: (8S,9R)-5-Fluoro-8-(4-fluorophenyl)-9- (1-methyl-1H-1, 2 ,4-triazol-5-yl) -2,7,8,9-tetrahydro-3H-pyrido (4,3,2-de) phthalazin-3-one mono (4-Methylbenzenesulfonate) (1:1)

Structure:



* Denotes ^{14}C-atom used in radiolabeled studies

Physico-chemical properties of the API

Talazoparib appears as white to yellow solid non-hygroscopic crystalline powder with low solubility. Talazoparib has two asymmetric centres, giving four possible stereoisomers. The absolute configuration at the 8-position is the S optical isomer. The absolute configuration at the 9-position is the R optical isomer. Talazoparib tosylate exists as a single crystal form.

Manufacture

The API manufacturing site, is Excella GmbH & Co. KG Nürnberger Strasse 12, 90537 Feucht, Germany. The site was noted to comply with GMP requirements as evidenced by the GMP certificate issued by competent Authority of Germany. Talazoparib 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 (visual), particle size distribution (laser diffraction), identification (IR, chiral identity), enantiomeric purity (chiral HPLC), assay (UPLC), residual solvents (GC), residue on ignition (Ph. Eur.), water content (KF) and organic impurities (UPLC, HPLC). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Talazoparib API is 48 months when packed in Double PE bag inside an aluminium pouch in a HDPE container and stored at 25ºC

Quality of the Finished Pharmaceutical Product

Formulation

Talzenna is a hard hypromellose (HPMC), opaque capsules (size #4, white body/ivory cap), body is printed with “TLZ 0.25” and the cap printed with “Pfizer” in black ink. Talzenna contains Talazoparib and other ingredients listed here after

Silicified Microcrystalline Cellulose and Silicon dioxide

HPMC Capsule Shell

Body

Hypromellose and Titanium Dioxide

Cap

Hypromellose, Yellow Iron Oxide and Titanium Dioxide

Print Ink
Shellac, Dehydrated Alcohol, Isopropyl Alcohol, Butyl Alcohol, Propylene Glycol, Strong Ammonia Solution, Black Iron Oxide, Potassium Hydroxide and Purified Water.

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.

Manufacture
The finished product was manufactured at Excella GmbH & Co. KG Nürnberger Strasse 12, 90537 Feucht, 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 (visual), identification (HPLC, UV), assay (HPLC), degradation products (HPLC), dissolution (Ph. Eur. - HPLC), uniformity of dosage units (Ph. Eur.), water content (Ph. Eur.) and microbial limits (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 batches of the finished product stored at 30°C/75 %RH for 36 months and 40ºC/75%RH for 6 months. Based on the stability data presented, the approved shelf-life is 36 months when stored in HDPE bottles with PP cap or in Alu/PVC/PVdC blisters and stored at 30°C.

Safety and efficacy information

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

Overview of Clinical Studies supporting clinical efficacy

Study Number	673-301 (C3441009)	673-201 (C3441008)	PRP-001 (C3441007)
Study Design	Phase 3 open-label; randomized 2:1 (talazoparib:PCT)	Phase 2 open-label, nonrandomized 2-stage, 2-cohort	Phase 1, first-in-human, open-label, dose-escalation and dose-expansion
Population	Locally advanced or metastatic breast cancer with gBRCA mutation; locally advanced HER2-negative breast cancer that is not amenable to curative radiation or surgical cure or metastatic disease appropriate for systemic single cytotoxic chemotherapy	Locally advanced or metastatic breast cancer with gBRCA mutation; received prior chemotherapy for metastatic disease	Advanced or recurrent solid tumours. Patients who had measureable disease in patients with gBRCA-mutated BC at baseline and received at least 1 dose of talazoparib 1 mg were included in the SCE (Evaluable BC Population)

Study Drug(s)	Talazoparib 1 mg/day PCT (capecitabine, eribulin, gemcitabine, vinorelbine)	Talazoparib 1 mg/day	Talazoparib 1 mg/day
Number of Study Sites	145 sites in 16 countries across North America, Europe, ROW randomized □1 patient	33 sites in the US and Europe	5 sites in the US, 1 sitein the UK
Number of Patients Enrolled / Treated	431 total enrolled / 412 treated Talazoparib: 287 enrolled /286 treated PCT: 144 enrolled / 126 treated	84 total enrolled / 83 treated, 48 in Cohort 1 (platinum pretreated) and 35 in Cohort 2 (□3 prior cytotoxic chemotherapies)	Patients with locally advanced or metastatic breast cancer with gBRCA mutations: • 14 patients treated with 1 mg/day
Data Cutoff Date for SCE	15 September 2017 (CSR)	01 September 2016 (CSR) 07 April 2017 (subsequent OS analysis	31 March 2015 (CSR)
		update)	
Primary Efficacy Endpoint	PFS by IRF (Sensitivity analyses: PFS by investigator, impact of poststudy antineoplastic therapy, and others)	ORR by IRF (Sensitivity analysis: impact of postbaseline [poststudy] antineoplastic therapy)	none
Secondary Efficacy Endpoints	ORR by investigator, OS	CBR24, DOR by IRF, PFS by investigator, OS	ORR by investigator, PFS, DOR, duration of stable disease, tumour burden
Exploratory Endpoints	DOR by investigator and QoL (EORTC QLQ-C30/QLQ-BR23)	QoL (EORTC QLQ-C30/QLQ-BR23); ORR, BOR, CBR24, and DOR by investigator; time to response and PFS by IRF; tumour burden; biomarkers	none

Source: 673-301 CSR, 673-201 CSR, PRP-001 CSR.
BOR=best overall response; CBR24=clinical benefit rate at 24 weeks; CSR=clinical study report; DOR=duration of response; EORTC=European Organization for Research and Treatment of Cancer; Evaluable BC=patients who had measureable BC at baseline and received at least 1 dose of talazoparib 1 mg; gBRCA=germline breast cancer susceptibility gene; HER2= human epidermal growth factor receptor 2; IRF=independent radiology facility; SCE=Summary of Clinical Efficacy; ORR=objective response rate; OS=overall survival; PCT=physician's choice treatment; PFS=progression-free survival; QLQ-BR23=Qualityof Life Questionnaire – Breast Cancer Module; QLQ-C30=Quality of Life Questionnaire – Core 30; QoL=quality of life; ROW=Rest of World; UK=United Kingdom; US=United States.
a. CBR24 was added as a secondary analysis in the SAP.

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. Talzenna 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