TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR PERJETA (PERTUZUMAB 420 MG/ 14 ML) CONCENTRATE FOR SOLUTION FOR INFUSION

Version number 1.0

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1. Introduction

Perjeta is an Anticancer medicine belonging to antineoplastic agents, monoclonal antibodies group. Pertuzumab is a recombinant humanised monoclonal antibody that specifically targets the extracellular dimerization domain (subdomain II) of the human epidermal growth factor receptor 2 protein (HER2), and thereby, blocks ligand-dependent heterodimerisation of HER2 with other HER family members, including EGFR, HER3 and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signalling through two major signal pathways, mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Inhibition of these signalling pathways can result in cell growth arrest and apoptosis, respectively. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC). While pertuzumab alone inhibited the proliferation of human tumour cells, the combination of pertuzumab and trastuzumab significantly augmented antitumour activity in HER2-overexpressing xenograft models.

Brand name is approved in Tanzania for use in adults

1.1 Product details

Registration number	TAN 21 HM 0223
Brand name	Perjeta
Generic name, strength and form	Pertuzumab, 420 mg/ 14 mL concentrate for solution for injection
ATC classification	L01XC13 Antineoplastic agents, monoclonal antibodies
Distribution category	POM
Country of origin	Switzerland
Associated product	NA
Marketing Authorization Holder	F. Hoffmann- La Roche Ltd Grenzacherstrasse 124, 4070 Basel Switzerland
Local Technical Representative	Okinawa Pharmacy Ltd, Plot No. 2319/9 Makunganya Street Illala P.O. Box 45728, **DAR ES SALAAM.**

1.2 Assessment procedure

The application for registration of Perjeta was submitted on 15th January, 2019. The product underwent abridged, joint EAC assessment. Assessment was completed in 2 rounds of evaluation. Perjeta was registered on June 03, 2021.

1.3 Information for users

Visual description of the finished product	Clear to slightly opalescent, colourless to pale yellow, solution
Primary packing material	USP Type I Glass Vial

Secondary packing materials	
Shelf-life and storage condition	24 months, 2-8°C
Route of administration	Intravenous use
Therapeutic indications	Early breast cancer Perjeta is indicated for use in combination with trastuzumab and chemotherapy in: • the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence (see section 5.1) • the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence (see section 5.1) Metastatic breast cancer Perjeta is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

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: Perjeta

Composition: Pertuzumab, 420 mg/ 14 mL

Pack size: 1 vial of 20 mL

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Store at 2°C-8°C, do not freeze; keep vial in the outer carton in order to protect from light

Manufacturer address: Roche Diagnostics GmbH, Sandhoferstrasse 116, 68305 Mannheim

Unique identifier: NA

Special warnings/precautions or instructions for use: NA

The details of the primary pack include:
Brand name and strength: Perjeta, 420 mg/ 14 mL

Manufacturing details: batch number, manufacturing date, expiry date

Name of manufacturer: Roche Diagnostics GmbH

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.

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

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

General Information
Pertuzumab API is non-compendia
Molecular formula: NA
Chemical name: Immunoglobulin G1, anti-(human neu (receptor)), (human-mouse monoclonal 2C4 heavy chain), disulfide with human-mouse monoclonal 2C4 κ-chain, dimer

Critical physico-chemical properties of the API

Table S.1.3-1 Pertuzumab General Properties

Property	Molecule Details
Structure	Pertuzumab is a recombinant humanized monoclonal antibody based upon the human IgG1(κ) framework sequence.
Amino Acid Composition	Refer to Figure 1 and Figure 2 in section *S.1.2 Structure* for the amino acid sequences of the light chain and heavy chain, respectively.
Binding Site	Refer to Figure 1 and Figure 2 in section *S.1.2 Structure* for the complementarity-determining regions.
Molecular Weight	The molecular mass of intact pertuzumab is approximately 148,088 Daltons for the antibody form with each heavy chain terminating at glycine residue 448 and containing a G0 oligosaccharide.
Extinction Coefficient	1.50 mL mg^{-1} cm g^{-1} at 278 nm.
Isoelectric Point	8.7
Glycosylation	An N-linked glycosylation site is found at Asn299 in the Fc domain with complex biantennary fucosylated structures containing zero (G0), one (G1), or two (G2) terminal galactose residues. The G0 structure is the predominant glycoform.
Biological Activity	Pertuzumab acts by blocking the association of HER2 with the other HER family members, including HER1 (EGFR), HER3, and HER4. Pertuzumab can also prevent formation of HER2 homodimerization. As a result, pertuzumab inhibits ligand-initiated intracellular signaling pathways, mitogen-activated protein (MAP) kinase, and phosphoinositide 3 (PI3) kinase. Inhibition of these signaling pathways can result in growth arrest and apoptosis.
Potency Assay	Potency by Bioassay measures the ability of pertuzumab to inhibit proliferation of a human breast carcinoma cell line. The specific activity of the pertuzumab Reference Standard Batch anti2C4907-2 (*Section S.5 Reference Standards or Materials*) is defined as 1.00×10^4 Units/mg.
Clinical Experience	Clinical experience with pertuzumab in patients with metastatic breast cancer has shown that it is well tolerated and effective.

Manufacture

The API manufacturing site is Genentech, Inc., 1000 New Horizons Way, Vacaville, CA 95688, 9431, USA was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by competent Authority of Switzerland (Swissmedic). Pertuzumab API is manufactured by fermentation 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 (peptide map), purity (BET, CE-SDS, SE-HPLC, bioburden), potency (bioassay), quantity (content of protein), pH, content of

polysorbate 20 and osmolality. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system
The re-test period of Pertuzumab API is 36 months when packed in tri-clamp ferrule with an attached dip-tube and standard manual diaphragm valve made of stainless steel and ethylene propylene diene monomer rubber (EPDM), respectively and stored at –20°C

Quality of the Finished Pharmaceutical Product

Formulation
Perjeta is a clear to slightly opalescent, colorless to pale yellow, liquid. Perjeta contains Pertuzumab and other ingredients listed here after: L-Histidine, glacial acetic acid, sucrose, polysorbate 20 and water for injection. 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 Roche Diagnostics GmbH, Sandhoferstrasse 116, 68305 Mannheim, 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, visible particles, identity (CZE), sterility (Ph. Eur/USP/JP), BET, purity (SE-HPLC), potency (bioassay), extractable volume (Ph. Eur./USP/JP), pH, osmolality. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system
Stability studies were conducted on 3 batches of the finished product stored at 2 - 8°C for 24 months and 25°C/60% for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in USP type I glass vial sealed with fluoro-resin laminated liquid type rubber stopper at 2 - 8°C.

Safety and efficacy information

Safety and efficacy of Perjeta was established through full clinical studies. The summary of all studies performed to support the indication are listed in below

Study	Phase	Indication	Dose [a]/Regimens	Patients Treated	Status [b]
Single-agent studies					
Phase I, dose escalation					
TOC2297g	Ia	Advanced solid tumors	0.5, 2.0, 5.0, 10.0, and 15.0 mg/kg qw3k	21	Completed

JO17076 [c,]	I	Advanced solid tumors	5.0, 10.0, 15.0, 20.0 and 25.0 mg/kg q3wk	18	Completed
Phase II					
TOC2689g	II	Advanced ovarian cancer	Cohort 1: 420 mg qw3k[a] Cohort 2: 1050 mg qw3k[a]	61 62	Completed
BO16934	II	MBC with low HER2 expression	Arm A: 420 mg qw3k[a] Arm B: 1050 mg qw3k	41 37	Completed
BO17004	II	HRPC, chemotherapy naive	Cohort 1: 420 mg qw3k[a] Cohort 2: 1050 mg qw3k[a]	35 33	Completed
TOC2682g	II	CRPC pretreated withdocetaxel	420 mg qw3k[a]	41	Completed
TOC2572g	II	Advanced, recurrentNSCLC	420 mg qw3k[a]	43	Completed
Combination Therapy Studies					
Phase I studies					
BO17003	Ib	Advanced solid tumors	Cohort 1: pertuzumab: 1050 mg q3wk capecitabine: 825, 1000, 1250 mg/m^2	18	Completed
BO17021	Ib	Advanced solid tumors	pertuzumab: 1050 mg docetaxel: 60,75 mg/m2or pertuzumab: 420 mg (840 mgloading dose) Docetaxel 75, 100 mg/m2 q3w	19	Completed
WO20024	Ib	Advanced NSCLC	pertuzumab: 420 mg q3wk Cohort 1: erlotinib: 100 mg/day Cohort 2: erlotinib 150 mg/day	15	Completed
Phase II/III randomized studies					
TOC3258g	II	Platinum-resistant ovarian,	gemcitabine: 800 mg/m2 ± pertuzumab: 420 mg q3wk	Gemcitabine+ Pertuzumab	Completed

		peritoneal, orfallopian tube cancer		: 65 Gemcitabine: 65	
WO20697 (NEOSPHERE)	II	HER2+, locally advanced, inflammatory or early stage breast cancer (EBC)	Pertuzumab: 840 mg loading dose IV, then 420 mg IV every 3 weeks for 4 cycles. Trastuzumab: 8 mg/kg loading dose IV, then 6 mg/kg every 3 weeks for 4 neoadjuvant cycles and up to 1 year total post-surgery. Docetaxel: 75 mg/m2 escalating, if tolerated, to 100 mg/m2 IV every 3 weeks for 4 cycles. T+D (Regimen A), PtZ+T+D (Regimen B), Ptz+T (Regimen C) Ptz+D (Regimen D).	417	Completed
BO17929	II	HER2-positive MBC	Pertuzumab: loading dose of 840 mg given i.v. over 60± 10 minutes, followed by a maintenance dose of 420 mg given i.v. over 30± 10 minutes if well tolerated. Cohort 1 (Ptz+T) Cohort 2 (Ptz +T) Cohort 3 (Ptz)	24 42 29	Completed
Pivotal Phase III, randomized study					
WO20698/TOC4129g (CLEOPATRA)	III	HER2-positive MBC (first-line treatment)	Placebo + docetaxel + trastuzumab Pertuzumab + docetaxel + trastuzumab pertuzumab: 420 mg q3w (840 mg loading dose) trastuzumab: 6 mg/kg q3w (8 mg/kg loading dose) docetaxel: 75 mg/m2 escalating to 100 mg/m2 q3w	402[d] 402	Completed

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. Perjeta 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

TMDA Tanzania Medicines & Medical Devices Authority	**TANZANIA PUBLIC ASSESSMENT REPORT**	***TMDA/DMC/MRE/F/016*** ***Rev #:***