TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR TECENTRIQ (ATEXOLIZUMAB 1200 MG/20 ML) CONCENTRATE FOR SOLUTION FOR INFUSION

Version number 1.0

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1. Introduction

Tecentriq is an anticancer is a medicine belonging to antineoplastic agents, monoclonal antibodies. Tecentriq exerts is activity by binding to Programmed death-ligand 1 (PD-L1) may be expressed on tumour cells and/or tumour-infiltrating immune cells, and can contribute to the inhibition of the antitumour immune response in the tumour microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T-cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production. Tecentriq is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to PD-L1 and provides a dual blockade of the PD-1 and B7.1 receptors, releasing PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the antitumour immune response without inducing antibody-dependent cellular cytotoxicity. Atezolizumab spares the PD-L2/PD-1 interaction allowing PD-L2/PD-1 mediated inhibitory signals to persist.
Tecentriq is approved in Tanzania for use in adults only

1.1 Product details

Registration number	TAN 21 HM 0228
Brand name	Tecentriq
Generic name, strength and form	Atexolizumab 1200 Mg/20 mL, Concentrate for Solution for Infusion
ATC classification	ATC code: L01XC32 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 Tecentriq was submitted on 28th June 2019. The product underwent abridged joint EAC assessment. Assessment was completed in 2 rounds of evaluation. Tecentriq was registered on 03rd June 03, 2021

1.3 Information for users

Visual description of the finished product	Clear, colourless to slightly yellowish liquid
Primary packing material	USP type 1 glass vial with fluororesin butyl rubber stopper and sealed with flip off aluminium cap
Secondary packing materials	Carboard carton box

Shelf-life and storage condition	36 months, 2-8°C
Route of administration	Intravenous
Therapeutic indications	Urothelial carcinoma Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC): • after prior platinum-containing chemotherapy, or • who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5% Early-stage non-small cell lung cancer Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection for adult patients with Stage II to IIIA (7th edition of the UICC/AJCC-staging system) non-small cell lung cancer (NSCLC) whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and whose disease has not progressed following platinum-based adjuvant chemotherapy Metastatic non-small cell lung cancer Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC. In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies Tecentriq, in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% TC or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving Tecentriq Small cell lung cancer Tecentriq, in combination with carboplatin and etoposide, is indicated for the first-line treatment of

	adult patients with extensive-stage small cell lung cancer (ES-SCLC) Triple-negative breast cancer Tecentriq in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease. Hepatocellular carcinoma Tecentriq, in combination with bevacizumab, is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therap

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/both 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: Tecentriq

Composition: Atexolizumab 1200 Mg/20 mL, L-histidine, Glacial acetic acid, Sucrose, Polysorbate 20 and Water for injections

Pack size: 1 x 20 mL vial

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Store in a refrigerator (2 °C – 8 °C), DO NOT FREEZE
Manufacturer address: F. Hoffmann-La Roche Ltd., Wurmisweg, 4303 Kaiseraugst, Switzerland

Unique identifier: NA

Special warnings/precautions or instructions for use: NA

The details of the primary pack include:

Brand name and strength: Tecentriq
Manufacturing details: batch number, manufacturing date, expiry date
Name of manufacturer: F. Hoffmann-La Roche Ltd

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 DMF, Full details

General Information
Atezolizumab API is non-compendia.
Molecular formula: NA
Chemical name: human immunoglobulin G1 (IgG1) monoclonal MPDL3280A heavy chain, disulfide linked with humanized monoclonal MPDL3280A k-chai, dimer

Structure:

Atezolizumab is a humanized monoclonal antibody based on an immunoglobulin G1 (IgG1) framework that contains heavy chain VHIII and light chain VκI subgroup sequences. The recombinant antibody is produced in Chinese hamster ovary (CHO) cells and consists of two heavy chains (448 amino acid residues each) and two light chains (214 amino acid residues each).

Light chain amino acid sequence	Heavy chain amino acid sequence
Figure 2.3.S-1 Light Chain Amino Acid Sequence 1 DIQMTQSPSSLSASVGDRVTITC**RASQDVSTAVA**WYQQKPGKAPKLLIY**S** 51 **ASFLYS**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQYLYHPAT**FGQ 101 GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV 151 DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG 201 LSSPVTKSFNRGEC 214 Note 1: The calculated molecular mass of the light chain is 23,365 Da (cysteine residues are in the reduced form). Note 2: Complementarity-determining regions are shown in **bold**.	**Figure S.1.2-2 Amino Acid Sequence of Heavy Chain** 1 EVQLVESGGGLVQPGGSLRLSCAAS**GFTFSDSWIH**WVRQAPGKGLEWV**AW** 51 **ISPYGGSTYYADSVKG**RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR**RH** 101 **WPGGFDY**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY 151 FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI 201 CNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD 251 TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASST 301 YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY 351 TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD 401 SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK 448 Note 1: The calculated molecular mass of the heavy chain without C-terminal lysine is 48,829 Da (cysteine residues are in the reduced form). Note 2: Complementarity-determining regions are shown in **bold**. Note 3: Position 298 indicates an amino acid substitution (asparagine to alanine) in the CH2 domain of each heavy chain.

Physico-chemical properties of the API

Table S.1.3-1 Atezolizumab General Properties

Property	Molecule Details
Molecular Composition	Refer to Figure S.1.2-1 and Figure S.1.2-2 in *Structure* for the amino acid sequences of the light chain and heavy chain, respectively
Molecular Formula	$C_{6434}H_{9878}O_{1996}N_{1702}S_{42}$ (peptide chains only, without heavy chain C-terminal lysine residues)
Molecular Mass	Approximately 144,356 Da (peptide chains only, without heavy chain C-terminal lysine residues)
Extinction Coefficient	1.62 mL mg^{-1} cm^{-1} at 278 nm
Isoelectric Point	8.8
Immunoglobulin Subclass	IgG1 with V_HIII and Vκ I variable region subgroups
Glycosylation	Nonglycosylated: the conserved N-glycosylation site (heavy chain Asn 298) is substituted with Ala 298 by design
Biological Activity	Inhibits PD-L1/PD-1 and PD-L1/B7.1 interactions leading to the reactivation of PD-1-expressing T cells
Binding Region	Complementarity-determining regions as shown in Figure S.1.2-1 and Figure S.1.2-2 in *Structure*
Binding Affinity	*In vitro* binding affinity to the recombinant human PD-L1: K_d = 0.433 nM by equilibrium binding assay

IgG1 = immunoglobulin G1; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1.

Manufacture

The API manufacturing site, F. Hoffmann-La Roche Ltd., Grenzachestrasse 124, CH-4070 Basel, Switzerland was noted to comply with GMP requirements as evidenced by the GMP certificate issued by Swissmedic. Atezolizumab 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 and description, pH, osmolality, polysorbate content, identification (peptide mapping), purity (SE-HPLC, IE-HPLC), bacterial endotoxins, quantity (protein concentration by UV), potency (cell-based assay). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The shelf-life period of Atezolizumab API is 24 months when packed in stainless steel and stored at 2°C-8°C.

Quality of the Finished Pharmaceutical Product

Formulation

Tecentriq is provided as a sterile, single-use, colorless to slightly yellow solution. Tecentriq contains Atezolizumab 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 F. Hoffmann-La Roche Ltd., Wurmisweg, 4303 Kaiseraugst, Switzerland. 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 (peptide mapping), sterility (Ph. Eur/USP/JP), BET, purity (SE-HPLC, IE-HPLC, NR-CE-SDS), 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 5ºC ± 3ºC for 36 months and 25ºC ±2ºC, 60% for 6 months. Based on the stability data presented, the approved shelf-life is 36 months when stored in USP type I glass vial sealed with fluoro-resin laminated liquid at 2 - 8°C.

Safety and efficacy information

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

Overview of clinical studies performed to establish the clinical efficacy of Atezolizumab

Protocol No.	Location of Synopsis/Location of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.3 Human PK Studies								
GO27831 (PCD4989g)	**Interim CSR** Report No. 1064914 Synopsis and Interim CSR Data cutoff: 2 December 2014	To evaluate safety, tolerability, and PK	Multicenter, first-in-human, dose-escalation, open-label study	atezolizumab Phase I formulation: 0.01 mg/kg to 20 mg/kg IV q3w Phase III formulation	All solid tumor types n = 483 NSCLC Cohort n = 88 UC Cohort n = 92	Patients with locally advanced or metastatic solid tumors (including NSCLC) and hematologic malignancies	Up to 1 year or until loss of clinical benefit	Ongoing Interim CSR: Full report Supplemental Results

	Supplemental Results Report Report No. 1068014 Data cutoff: 7 August 2015			: 1200 mg IV q3w				Report: Abbreviated report
JO28944	**Primary CSR** Report No. 1067192 Synopsis and Primary CSR Data cutoff: 15 November 2014	To evaluate safety, tolerability, and pharmacokinetics (PK)	Multicenter, dose-escalation, open-label study	atezolizumab 10 mg/kg IV every 3 weeks (q3w) atezolizumab 20 mg/kg IV q3w	n = 6	Patients with advanced or metastatic solid tumors	Two treatment cycles, and then until withdrawal criteria were met	Ongoing Primary CSR Full report
5.3.5 Efficacy and Safety Studies (UC)								
5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication								
GO29294 (IMvigor211)	**Results Report** Report No. 11076559 Data cutoff: 13 March 2017	To evaluate the efficacy and safety of atezolizumab compared with chemotherapy in patients with locally advanced or metastatic UC who have progressed during or following a platinum-containing regimen	Global, multicenter, open-label, randomized, controlled study	atezolizumab 1200 mg IV q3w vinflunine 320 mg/m2 q3w or paclitaxel 175 mg/m2 q3w, or docetaxel 75 mg/m2 q3w	Total randomized n = 931 atezolizumab arm n =467 chemotherapy arm n=464 (vinflunine n=250 paclitaxel or docetaxel n =214)	Patients with locally advanced or metastatic urothelial carcinoma who have progressed during or following a platinum-containing regimen	Atezolizumab arm: Until loss of clinical benefit or unacceptable toxicity Chemotherapy arm: Until disease progression or unacceptable toxicity	Ongoing Results report
5.3.5.2 Study Reports of Uncontrolled Clinical Studies								
Protocol No.	**Location of Synopsis**	**Location of Report**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage regimen; Route of Admin.**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**	**StudyStatus; Type of Report**
GO29293 (IMvigor210)	**Primary CSR** Report No. 1065272: Synopsis and Primary CSR Data cutoff: 5 May 2015 **Update CSR** Report No. 1067870 Synopsis and Update CSR Data cutoff: 14 September 2015	To evaluate IRF-assessed ORR per RECIST 1.1, INV-assessed ORR per modified RECIST (primary efficacy endpoints), PFS, DOR, OS, 1-year OS (secondary efficacy endpoints), safety and tolerability, PK	Global, multicenter, monotherapy, single arm trial	atezolizumab 1200 mg IV q 3 weeks	Cohort 1 (1L) = 118 Cohort 2 (2L+) = 311	Patients with locally advanced or 1L metastatic (ineligible for cisplatin-based chemotherapy) and 2L+ UC patients (patients who failed a prior platinum-based therapy or progressed within 12 months of a platinum-containing treatment	Cohort 1: Until disease progression Cohort 2: Until loss of clinical benefit	Ongoing Primary and update CSRs: Full reports Supplemental Results Reports Abbreviated reports

	Supplemental Results Report Report No. 1067871. Data cutoff: 27 November 2015 Supplemental Results Report Report No. 1073475. Data cutoff: 4 July 2016					administered in the neoadjuvant or adjuvant setting). Approximately 30% of the patient population in each cohort was required to be PD-L1-selected (IC2/3).		
5.3.5 Efficacy and Safety Studies (NSCLC)								
5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication								
GO28915 (OAK)	**Primary CSR** Report No. 1070445 Synopsis and Primary CSR Data cutoff: 7 July 2016	To evaluate the efficacy and safety of atezolizumab compared with docetaxel in patients with previously treated locally advanced or metastatic NSCLC, in an all- comer population, as well as in subgroups defined by PD-L1 expression.	Global, multicenter, open-label, randomized, controlled study	atezolizumab 1200 mg IV q3w docetaxel 75 mg/m^2 IV q3w	Total randomized n = 1225 atezolizumab arm n = 612 docetaxel arm n = 613 First 850 randomized intent-to-treat patients n = 850 atezolizumab arm n = 425 docetaxel arm n = 425	Patients with locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen	Atezolizumab arm: Until loss of clinical benefit or unacceptable toxicity Docetaxel arm: Until disease progression or unacceptable toxicity	Ongoing Primary CSR Full report
GO28753 (POPLAR)	**Primary CSR** Report No. 1065672 Synopsis and Primary CSR Data cutoff: Primary analysis: 8 May 2015 Third interim analysis: 30 January 2015	To evaluate the efficacy of atezolizumab compared with docetaxel as measured by overall survival (OS) (primary efficacy endpoint), overall response rate (ORR), duration of	Global, multicenter, open-label, randomized, controlled study	atezolizumab 1200 mg IV q3w docetaxel 75 mg/m^2 IV q3w	Total randomized n = 287 atezolizumab arm n = 144 docetaxel arm n = 143	Patients with locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen	Atezolizumab arm: Until loss of clinical benefit or unacceptable toxicity Docetaxel arm: Until disease progression	Ongoing Primary CSR Full report

Protocol No.	**Location of Synopsis**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage regimen; Route of Admin.**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**	**Study Status; Type of Report**
	Supplemental Results Report	response (DOR),					or unacceptable toxicity	Supplemental Results Report

	Report No. 1069440 Data cutoff: 1 December 2015	progression free survival (PFS) (secondary efficacy endpoints), as well as safety and tolerability, and PK						Abbreviated report
5.3.5.2 Study Reports of Uncontrolled Clinical Studies								
GO28754 (BIRCH)	**Primary CSR** Report No. 1066811 Synopsis and Primary CSR Data cutoff: 28 May 2015 Supplemental Results Report Report No. 1068549 Data cutoff 1 October 2015	To evaluate efficacy of atezolizumab as measured by independent review facility (IRF)-assessed ORR per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, (primary efficacy endpoint), PFS, DOR, time in response (TIR), OS, 1-year OS (secondary efficacy endpoints), as well as safety and tolerability, and PK	Global, multicenter, single arm study	atezolizumab 1200 mg IV q3w	Total enrolled n = 667 Cohort 1 (1L) n = 142 Cohort 2 (2L) n = 271 Cohort 3 (3L+) n = 254	PD-L1-selected (TC2/3 or IC2/3) patients with locally advanced or metastatic NSCLC who were either treatment-naive in the metastatic setting (1L) or who had experienced disease progression during or following treatment with one platinum-based regimen (2L) or more than 2 regimens (3L+), one of which had to have been a platinum-containing regimen for advanced disease	Cohort 1: Until disease progression or unacceptable toxicity Cohort 2: Until loss of clinical benefit or unacceptable toxicity Cohort 3: Until loss of clinical benefit or unacceptable toxicity	Ongoing Primary CSR Full report Supplemental Results Report Abbreviated report
GO28625 (FIR).	**Primary CSR** Report No. 1064438 Synopsis and Primary CSR Data cutoff: 7 January 2015	To evaluate the efficacy of atezolizumab as measured by investigator-assessed ORR per modified RECIST (primary efficacy endpoint), PFS, DOR, OS (secondary efficacy endpoints), as well as safety and tolerability, and PK	Global, multicenter, single-arm study	atezolizumab 1200 mg IV q3w	Total enrolled n = 138 Cohort 1 (1L) n = 31 Cohort 2 (2L+) n = 94 Cohort 3 (2L+ w/ previously treated brain metastases) n = 13	PD-L1-selected (TC2/3 or IC2/3) patients with locally advanced or metastatic NSCLC who had not received prior chemotherapy (Cohort 1), who had progressed during or following a prior platinum-based chemotherapy	Cohort 1: Until disease progression or unacceptable toxicity Cohort 2: Until loss of clinical benefit or unacceptable toxicity Cohort 3: Until loss of clinical benefit or unacceptable toxicity	Ongoing Primary CSR Full report

						regimen without restriction to the maximum number of prior therapies (Cohort 2), and 2L+ patients with previously treated brain metastases (Cohort 3)		

1L=first-line treatment; 2L=second-line treatment; 2L+=second-line treatment and beyond; 3L=third-line treatment; 3L+=third- line treatment and beyond; CSR=clinical study report; DOR=duration of response; IC=tumor-infiltrating immune cell; INV=investigator; IRF=independent review facility; IV=intravenous; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PD-L1=programmed death - ligand 1; PFS=progression-free survival; PK=pharmacokinetics; q3w=every 3 weeks; RECIST=response Evaluation criteria in solid tumors; TC=tumor cells; TIR=time in response; UC=urothelial carcinoma

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. Tecentriq 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