THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR BEVAMAB 400 (BEVACIZUMAB 400MG) SOLUTION FOR INJECTION

Version number 1.0
23 October 2023

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1. Introduction

BEVAMAB 400 is a generic medicine of Bevacizumab Solution for injection. BEVAMAB 400 is a an antioneoplastic medicine belonging to L01FG01- antineoplastic and immunomodulating agents, antineoplastic agents, monoclonal antibodies and antibody drug conjugates group. BEVAMAB 400 exerts is activity by binding to vascular endothelial growth factor (VEGF) thus regressing the vascularization of tumours, normalising remaining tumour vasculature, and inhibiting the formation of new tumour vasculature, thereby inhibiting tumour growth. BEVAMAB 400 is approved in Tanzania for use in adults.

1.1 Product details

Registration number	TAN 20 HM 0411
Brand name	BEVAMAB 400
Generic name, strength and form	Bevacizumab 400 mg Solution for injection
ATC classification	L01FG01- antineoplastic and immunomodulating agents, antineoplastic agents, monoclonal antibodies and antibody drug conjugates
Distribution category	POM
Country of origin	India
Associated product	State any other product of formulation, strength or site that is linked or associated with the product if applicable
Marketing Authorization Holder	Intas Pharmaceuticals Limited Plot No.423/P/A Sarkhej - BavlaHighway. Village:Moraiya,Taluka:Sanand Ahmedabad–382213 Gujarat,India.
Local Technical Representative	Metro Pharmaceuticals Co.Ltd. P.O.Box:2797, Indira Gandhi Street, Dar Es Salaam, Tanzania

1.2 Assessment procedure

The application for registration of BEVAMAB 400 was submitted on 29/11/2019. The product underwent full assessment. Assessment was completed in 2 rounds of evaluation. BEVAMAB 400 was registered on 25/09/2020.

1.3 Information for users

Visual description of the finished product	Clear to slightly opalescent, colorless to pale brown, sterile liquid
Primary packing material	20 mL USP type-1 glass vial with fluroresin

Effective date: 03/10/2022

	coated chlorobutyl rubber stopper and aluminium flip off seal
Secondary packing materials	
Shelf-life and storage condition	2 °C to 8 °C; do not freeze 24 months **Shelf life after reconstitution or dilution :**Upto 24 hours, Not more than 25°C ± 2°C , (unless dilution has taken place in controlled and validated aseptic conditions)
Route of administration	Intravenous (IV) Infusion
Therapeutic indications	For treatment of cancer ▪ Metastatic Colorectal Cancer (mCRC) ▪ Non-Squamous Non–Small Cell Lung Cancer (NSCLC) ▪ Glioblastoma ▪ Metastatic Renal Cell Carcinoma (mRCC) Persistent, Recurrent, or Metastatic Carcinoma of the Cervix Metastatic breast cancer (mBC)

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 that is intended for long term use, the package insert contains both full prescribing information as per SmPC and simplified information for patients.

Container labels

The product label information is presented in English. Details in the secondary pack label include:

Brand name: BEVAMAB 400

Composition: Bevacizumab concentrate for solution for intravenous infusion 400mg/16ml

Pack size: <primary & secondary pack>

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Store between 2 °C to 8 °C; do not freeze

Manufacturer address: Intas Pharmaceuticals Limited, Plot No. 423/P/A, Sarkhej - Bavla Highway. Village: Moraiya, Taluka: Sanand, Ahmedabad – 382 213, Gujarat, India.

Unique identifier: <state the unique identification used>

Special warnings/precautions or instructions for use: To be sold by retail on the prescription of an oncologist only.

The details of the primary pack include:
Brand name and strength: BEVAMAB 400(Bevacizumab concentrate for solution for intravenous infusion 400mg/16ml)
Manufacturing details: batch number, manufacturing date, expiry date
Name of manufacturer: Intas Pharmaceuticals Ltd

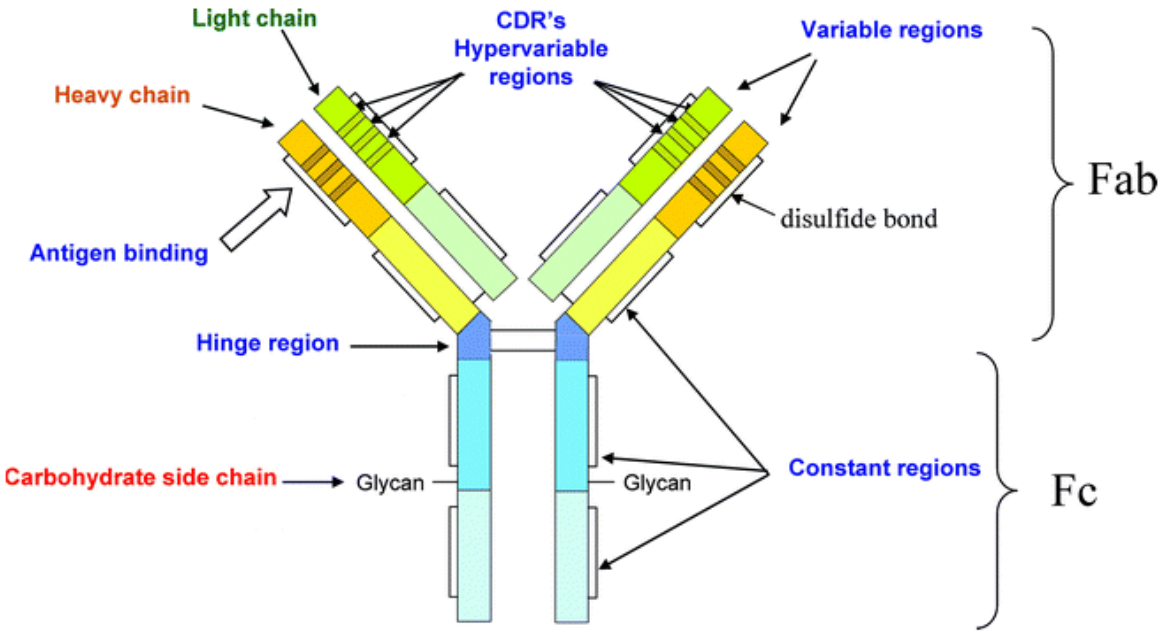
The content of the primary and secondary labels was aligned to the requirements of the Part V of the Compendium: Guidelines on Format and Content of Product Labels for Medicinal products. The label contains sufficient information for proper identification of the medicine and post marketing follow up of the product.
Describe any approved deviation to the requirements and the justification for the deviation.

3. Scientific discussion

Quality of drug substance (s)

Information on quality of the drug substance was submitted in form of full details.

General properties
Bevacizumab drug substance is non-compendia.
Molecular formula: $C_{6638}H_{10160}N_{1720}O_{2108}S_{44}$
Chemical name: Recombinant humanized monoclonal antibody to VEGF
Structure:



Critical physico-chemical properties of the API were <solubility, particle size, polymorphism>.

Manufacture

The API manufacturing site, Intas Pharmaceuticals Limited, Plot No. 423/P/A, Sarkhej - Bavla Highway, Village: Moraiya, Taluka: Sanand Ahmedabad – 382 213 Gujarat, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Food & Drug Control Administration, Gujarat State. Bevacizumab drug substance is manufactured by upstream and downstream processing using genetically engineered recombinant Chinese Hamster Ovary (CHO) suspension cell line. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The drug substance specifications were set as per in-house standards and ICHQ6B. The parameters monitored during quality control are: physical appearance, pH, protein concentration, relative potency (by cell based bioassay), CEX-HPLC, SE-HPLC (HMW impurities),SE-HPLC (LMW impurities), residual protein A, host cell derived protein, residual DNA and bacterial endotoxin. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Bevacizumab drug substance is 36 months when packed in Celsius® FFT Bag or 10L Flexboy® bag internally coated with Ethyl Vinyl Acetate (EVA) contact layer and stored at -20 °C ± 5 °C.

Quality of the Finished Pharmaceutical Product

Formulation

BEVAMAB 400 is a clear to slightly opalescent, colorless to pale brown, sterile liquid. BEVAMAB 400 contains Bevacizumab drug substance and other ingredients listed hereafter Trehalosedihydrate, Monosodium dihydrogen phosphate monohydrate, Disodium hydrogen phosphate anhydrous, 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 <number> in terms of function and quantities. Ingredient, <excipient> is of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product was manufactured at Intas Pharmaceuticals Limited, Plot No. 423/P/A, Sarkhej - Bavla Highway. Village: Moraiya, Taluka: Sanand, Ahmedabad – 382 213, Gujarat, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 01-02/04/2019.

Specifications

The FPP is non-compendia. The manufacturer controls the quality of the finished product as per in-house and ICHQ6B requirements. The parameters monitored during quality control are: physical appearance, pH, osmolality, extractable volume, particulate matter, protein concentration, relative potency (Cell based assay), CEX-HPLC, SE-HPLC (HMW impurities),SE-HPLC (LMW impurities), bacterial endotoxin and sterility testing.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 5 °C ± 3 °C for 24 months and 25 °C ± 2 °C for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in 20mL USP Type-I Clear Glass vial at 2 °C to 8 °C.

Safety and efficacy information

Safety and efficacy of BEVAMAB 400 was established through literature and clinical studies.

4. Benefit-Risk Assessment and Conclusion

On basis ofthe 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. BEVAMAB 400 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

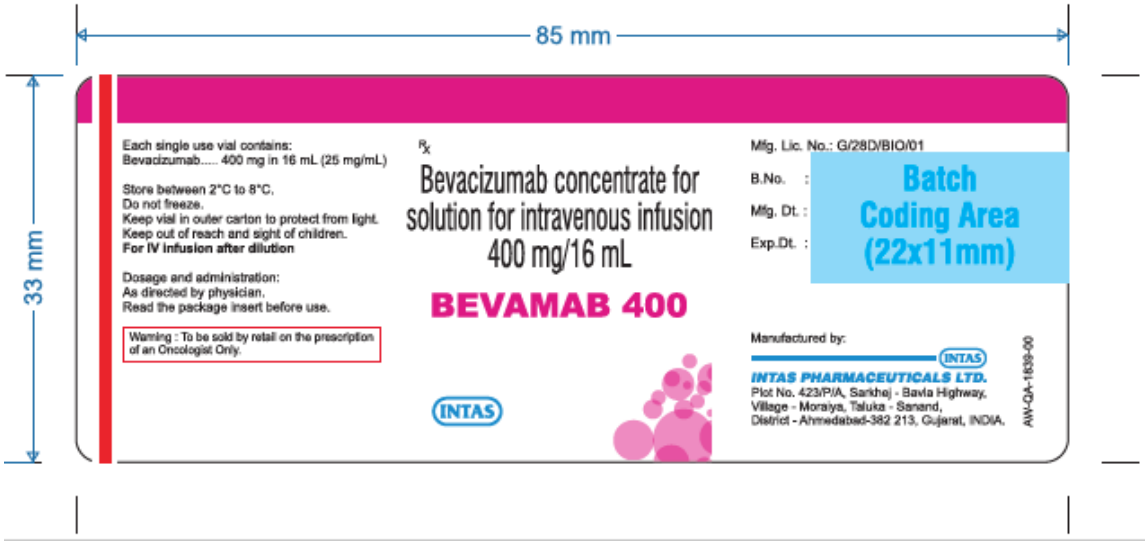
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to

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 label


85 mm
33 mm
Each single use vial contains:
Bevacizumab..... 400 mg in 16 mL (25 mg/mL)
Store between 2°C to 8°C.
Do not freeze.
Keep vial in outer carton to protect from light.
Keep out of reach and sight of children.
For IV infusion after dilution
Dosage and administration:
As directed by physician.
Read the package insert before use.
Warning : To be sold by retail on the prescription of an Oncologist Only.
℞
Bevacizumab concentrate for solution for intravenous infusion 400 mg/16 mL
BEVAMAB 400
INTAS
Mfg. Lic. No.: G/28D/BIO/01
B.No. :
Mfg. Dt. :
Exp.Dt. :
Batch Coding Area (22x11mm)
Manufactured by:
INTAS
INTAS PHARMACEUTICALS LTD.
Plot No. 423/P/A, Sarkhej - Bavla Highway,
Village - Moraiya, Taluka - Sanand,
District - Ahmedabad-382 213, Gujarat, INDIA.
AW-QA-1639-00