TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR BEVAMAB 400 (BEVACIZUMAB 400 MG/16 ML) CONCENTRATE FOR SOLUTION FOR INTRAVENOUS INFUSION

Version number 1.0

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1. Introduction

Bevamab 400 has been developed by Intas as a proposed biosimilar product to the reference medicinal product Avastin of Genentech/Roche having bevacizumab as the active substance. Bevamab 400 is antineoplastic medicine belongs to the pharmacotherapeutic group "monoclonal antibodies" (ATC code: L01XC07). Bevacizumab (Avastin, Genentech/Roche) is a recombinant humanised monoclonal antibody of the immunoglobulin (Ig) G1 class that selectively binds to Vascular endothelial growth factor (VEGF). The binding of bevacizumab to VEGF inhibits the binding of VEGF to its receptors on the surface of endothelial cells, Flt-1 (also known as VEGF receptor-1 [VEGFR-1]) and kinase insert domain receptor (also known as VEGF receptor-2 [VEGFR-2]). Neutralizing the biological activity of VEGF inhibits the formation of new tumour vasculature, causes regression in newly-formed tumour vasculature, and normalises the remaining tumour vasculature, thereby inhibiting tumour growth. Bevamab 400 is approved in Tanzania for use only in adult patients.

1.1 Product details

Registration number	TAN 20 HM 0411
Brand name	Bevamab 400
Generic name, strength and form	Each vial contains; 400mg/16mL (25mg/mL)
ATC classification	ATC code L01FG01 - antineoplastic agents, other antineoplastic agents, monoclonal antibodies
Distribution category	POM
Country of origin	India
Associated product	Bevamab 100
Marketing Authorization Holder	Intas Pharmaceuticals Limited, Plot No. 423/P/A. Sarkhej – Bavla, Highway, Village: Moraiya, Taluka: Sanand Ahmedabad – 382 213, Gujarat, India E-mail: Balaji_Sunkara@intaspharma.com
Local Technical Representative	Metro Pharmaceuticals CO. Limited, Indira Gandhi Street, P.O. Box 2797, Dar es Salaam, Tanzania E-mail: metropharma@ctvsatcom.net

1.2 Assessment procedure

The application for registration of Bevamab 400 was submitted on 29 November, 2019. The product underwent full assessment. Assessment was completed in 2 (two) rounds of evaluation and the product was registered on 25 September, 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 coated chlorobutyl rubber stopper and aluminium flip off seal
Secondary packing materials	A printed carton box

Shelf-life and storage condition	Unopened Vial: 24 months with storage conditions 'Store between 2°C to 8 °C. Do not freeze' Diluted Solution: Within 24 hours after dilution when stored at temperature 25ºC
Route of administration	Intravenous
Therapeutic indications	Bevacizumab is indicated for the treatment of: 1. In addition to platinum-based chemotherapy, indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology. 2. Metastatic carcinoma of the colon or rectum in adult patients in combination with fluoropyrimidine-based chemotherapy. 3. Advanced and/or metastatic renal cell cancer in adult patients as first line treatment in combination with Interferon alfa-2a. 4. Advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer in adult patients as the front-line treatment in combination with carboplatin and paclitaxel. For treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer and naïve to VEGF receptor-targeted agents including bevacizumab. 5. Platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in adult patients in combination with paclitaxel, topotecan or pegylated doxorubicin who received only up to two prior chemotherapy regimens and naïve to VEGF receptor-targeted agents including bevacizumab. 6. Persistent, recurrent, or metastatic carcinoma of the cervix in adult patients in combination with paclitaxel and cisplatin/topotecan who cannot receive platinum therapy. 7. Glioblastoma with progressive disease in adult patients following prior therapy as a single agent.

	8. Metastatic breast cancer as first line treatment in combination with capecitabine in adult patients in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Metastatic breast cancer as first line treatment in adult patients in combination with paclitaxel.

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: Bevamab 400

Composition: Bevacizumab 400 mg in 16 mL (25mg/mL), trehalose dihydrate, mono-sodium dihygrogen phosphate monohydrate, di-sodium hydrogen phosphate anhydrous, polysorbate 20, and water for injection

Pack size: 1vial

Manufacturing details: batch number, manufacturing date and expiry date

Storage conditions: Unopened Vial: 24 months with storage conditions 'Store between 2^{o}C to 8 ^{o}C. Do not freeze'

Diluted Solution: Within 24 hours after dilution when stored at temperature 25^{o}C

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

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: To be sold by retail only on the prescription of an Oncologist only, read the package insert before use

The details of the primary pack include:

Brand name and strength: Bevamab 400

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Intas Pharmaceuticals Limited
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.

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 DMF.

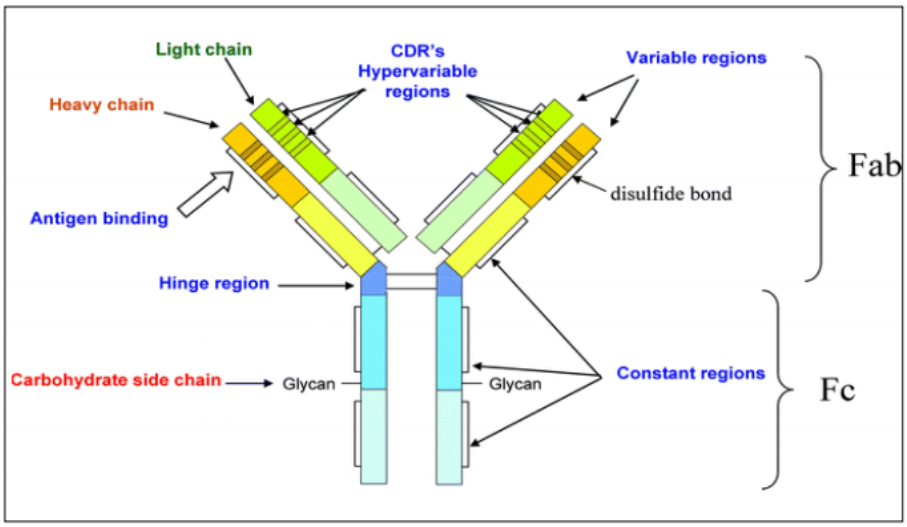
General Information

Bevacizumab API is non-compendia.

Molecular formula: C6638H10160N1720O2108S44

Chemical name: humanized IgG1k type of monoclonal antibody

Structure:



Bevacizumab is a humanized IgG1k type of monoclonal antibody. It corresponds to approximately 93% human sequence consisting of constant regions and 7% mouse sequence that forms CDR part. Each of the two light chains is composed of 214 amino acids while each of the heavy chains has 453 amino acid residues. The total molecular weight is approximately 149 kDa. The light and heavy chains are covalently linked by an intra chain disulfide bond; whereas the two heavy chains are linked through two inter chain disulfide bonds. As commonly observed with monoclonal antibodies, bevacizumab also exhibits C- terminal lysine heterogeneity. At asparagine 303 one N-linked glycosylation site is present. The oligosaccharides structures are biantennary with a core

fucose and two branches that mainly have terminal zero, one or two galactose (G0, G1 or G2) residues. The predominant glycoform is G0F.

Manufacture

Bevacizumab API manufacturer is Intas Pharmaceuticals Limited, Plot No. 423/P/A, Sarkhej - Bavla Highway, Village, Moraiya, Taluka: Sanand, Ahmedabad – 382 213, Gujarat, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by Gujarat Food and Drug Control Administration-India. Bevacizumab 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 ICH guidelines. The parameters monitored during quality control are: appearance, pH, assay, assay and identity, purity and impurities, process-related impurities, bioburden, bacterial endotoxin. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The shelf-life period of Bevacizumab API is 18 months respectively when packed in 12 L Celsius® FFT bag or 10L Flexboy® bag internally coated with Ethyl Vinyl Acetate (EVA) contact layer at the intended storage condition of -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 the API Bevacizumab and other ingredients listed here after: trehalose dihydrate, 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, 8th Edition in terms of function and quantities.

Manufacture

The finished product manufacturer is 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 09/05/2019.

Specifications

The FPP is non-compendia. The manufacturer controls the quality of the finished product as per in-house standards and ICH requirements. The parameters monitored during quality control are: appearance, pH, osmolality, extractable volume, particulate matter, assay, assay and identity,

purity, bioburden, and bacterial endotoxin. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on 3 (three) batches of the finished product stored at 5±3°C for 36 months and 25°C±2°C for 6 months. Based on the stability data presented, the approved shelf-life is 36 months when stored in 20 mL USP type I glass vial with fluroresin coated chlorobutyl rubber stopper and aluminium flip off seal with storage conditions 'Store between 2ºC to 8 ºC. Do not freeze'.

In additional, stability data have been provided demonstrating that the reconstituted solution remains stable for 24 hours when stored at temperature 25ºC.

Safety and efficacy information

Detailed Discussion of Product Development

Intas bevacizumab have been developed as a biosimilar to Avastin™ which is manufactured & marketed by F. Hoffmann-La Roche Limited, Switzerland. As a part of the development of biosimilar bevacizumab, Intas has performed various studies comparing physicochemical properties and also preclinical toxicology studies in rats, rabbits, mice & Guinea pigs. All these studies showed similar profiles for both the drugs; the details of which have been provided in the complete common technical document.

Overview of Efficacy

The results of the current study indicate that the proportion of patients with best overall response rate (CR + PR) were 40.58% in Intas Bevacizumab arm as compared to 42.42% in Avastin arm in the ITT population (p value – 0.8594). This shows that the response rate obtained with the test drug is comparable to the response obtained with reference drug. None of the patient had CR (complete response), while PR (partial response) was seen among 40.58% and 42.42% of patients in test and reference arm respectively.

Disease control rate (DCR), is a summative measurement of Complete Response (CR) or Partial Response (PR) or Stable disease (SD). In the present study the DCR was 95.65% in test arm, while it was 90.91% in reference arm (p value – 0.3409). These results suggest that the disease control rate was similar in both the groups. Overall response rate (ORR) is defined as the proportion of patients who achieved a complete response or a partial response at the end of study. The reported ORR in the current study was 36.23% with test drug and 36.36% with the reference drug (36.36%). Thus, the ORR achieved in both the groups was nearly similar. The above calculated parameters prove that the clinical efficacy of the test product, that is, Intas Bevacizumab is comparable to reference medicinal product, that is, Avastin manufactured by F. Hoffmann-La Roche limited.

Overview of Safety

The safety profile of bevacizumab used in combination with gemcitabine and cisplatin is as follows. Data from 102 patients who received at least one dose of bevacizumab was included for safety analysis. Against the background of a relatively toxic chemotherapy regimen (cisplatin plus

gemcitabine), treatment with bevacizumab, in general, did add to toxicity. There was a total of 351 treatment emergent adverse events (TEAEs) reported by 84 patients during the conduct of study. Of the 351 adverse events, 223 AEs were mild, 101 AEs were moderate and 27 AEs were serious in nature. Two hundred fifty-three (255) TEAEs were reported after receipt of Test Product and Ninety-six (96) TEAEs were reported after receipt of Reference Product. Most of the adverse events were not related to the study drug. Out of 351 TEAEs, majority of the AEs, 341, recovered completely, however, 10 AEs resulted in death. Of these 10 deaths reported, six were seen in patients receiving reference drug, while four were reported in patients receiving test drug. Death was related to the study drug only in one patient, this patient was randomized in test arm, while in all the other cases death was not related to the study drug. The toxicities in general were easily manageable except for a few rare cases. No major safety concern was reported during the conduct of the study.

The most frequently reported AEs were nausea, vomiting, hypertension, asthenia, anaemia, neutropenia, proteinuria, bleeding, tachycardia, constipation, diarrhoea, abdominal discomfort, pyrexia, mouth ulcers, pain, chest pain, dizziness, alopecia, dyspnoea & cough. These were the expected adverse events reported with the use of bevacizumab and other chemotherapy agents used during the conduct of the study.

When the safety data of the current study was compared with the safety data of similar studies done in the past in the patients of NSCLC, it was seen that the safe data was comparable. In the study done by Mok TSk et al., the most frequently reported or observed serious adverse drug reactions were nausea, hypertension, bleeding, proteinuria, thrombotic events and wound-healing complications. In a study by Johnson DH et al, the commonly reported adverse events were nausea and/or vomiting, renal toxicity, peripheral neuropathy, leucopenia, diarrhea, and minor systemic events such as fever, headache, rash, and chills. Study by Herbst RS et al, also reported similar adverse events.

Overall, the safety and tolerability of Bevacizumab developed by the Intas Pharmaceuticals Ltd., is comparable with that of reference medicinal product- Avastin™ developed by F. Hoffmann-La Roche limited. No clinically significant differences observed between both the groups. Results of the study demonstrated that similar biologic product- Bevacizumab manufactured by Intas Pharmaceuticals Ltd. has comparable efficacy profile to that of reference medicinal product- Bevacizumab - F. Hoffmann-La Roche limited. No major safety concerns were reported during the clinical trial with the use of similar biologic product- Bevacizumab manufactured by Intas Pharmaceuticals Ltd., India in comparison with reference medicinal product- Avastin™ developed by F. Hoffmann-La Roche limited. In conclusion, similar biologic product- Bevacizumab manufactured by Intas Pharmaceuticals Ltd., India, is therapeutically equivalent to the reference medicinal product- Bevacizumab of F. Hoffmann-La Roche limited, in patients of Unresectable or Metastatic Non-Squamous Non-Small Cell Lung Carcinoma (NSCLC).

Conclusions

Applicant had already conducted non-clinical studies of test product to prove safety profile of test product at human intended dose. The clinical study was conducted with intention to prospectively collect the data on patients that are randomly assigned to either Bevacizumab of Intas Pharmaceuticals Ltd or Avastin™ of F. Hoffmann-La Roche Limited. Dose & frequency of administration of drug product was also as per standard line of therapy. No additional tests or diagnostic procedures were conducted in this study other than those are scheduled in this study protocol, except certain procedures require by Investigator in favour of patient safety concern. Hence, the conduct of the clinical study was not put any additional risk/burden to the patient.

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. 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

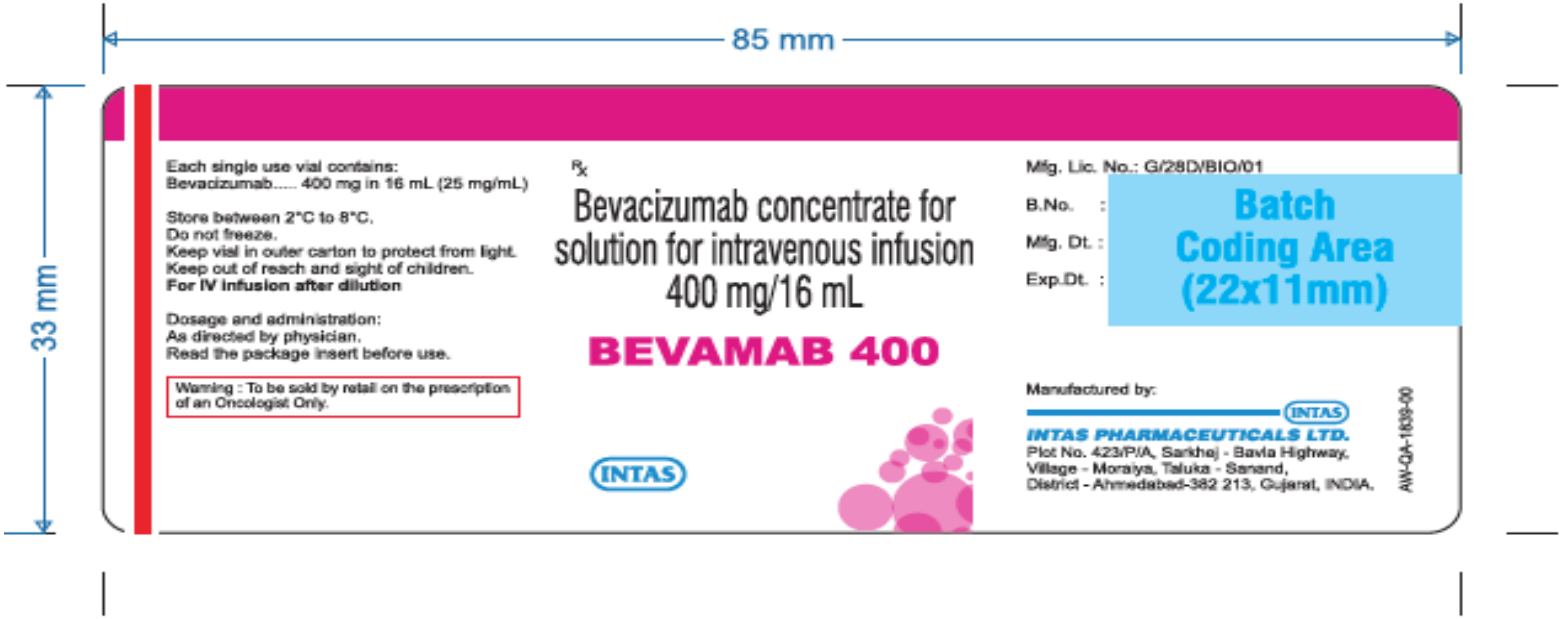
NA

PART 5: CHANGE HISTORY

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

Annex I: Mock up labels;

Primary pack label;



Secondary pack label;