THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR TRASTMAB 440 (TRASTUZUMAB 440 MG) LYOPHILIZED POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION

Version number 1.0
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TMDA Headquarters, Plot No. 56/1, Block E, Kisasa B Centre, Hombolo Road, P. O. Box 1253, Dodoma – Tanzania, Telephone: +255 (26) 2961989/2061990/+255 (22) 2450512/2450751/2452108, Email: info@tmda.og.tz, Website: **www.tmda.go.tz**

Toll free: 0800110084

1. Introduction

TRASTMAB 440 is a potential biosimilar to the trastuzumab products marketed globally as Herceptin (reference product) for the same indications as the reference product, including HER2-positive early breast cancer (EBC), metastatic breast cancer (MBC) and metastatic gastric cancer (MGC). Trastuzumab is a recombinant humanised IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2). Trastuzumab selectively binds to the extracellular domain of HER2 and thereby preventing HER2 signalling. In addition, trastuzumab binds to fragment crystallizable (Fc) receptors on immune effector cells, facilitating immune destruction of HER2-expressing cancer cells. TRASTMAB 440 is approved in Tanzania for use in adults' population (only).

1.1 Product details

Registration number	TAN 23 H 0260
Brand name	TRASTMAB 440
Generic name, strength, and form	Each multiple use vial contains Trastuzumab 440 mg. Bacteriostatic Water for Injection USP 20 mL Vial After reconstitution, 1 mL concentrate contains: 21 mg of Trastuzumab
ATC classification	L01XC03 – Antineoplastic agents, monoclonal antibodies
Distribution category	POM
Country of origin	India
Associated product	N/A
Marketing Authorization Holder	Intas Pharmaceuticals Limited Plot No. 423/P/A, Sarkhej - Bavla Highway, Village: Moraiya, Taluka: Sanand Ahmedabad – 382 213, Gujarat, India
Local Technical Representative	Metro Pharmaceuticals Co Limited P.O. Box 2797, Dar es Salaam.

1.2 Assessment procedure

The application for registration of TRASTMAB 440 was submitted on 27/08/2021. The product underwent full assessment. Assessment was completed in 3 (three) rounds of evaluation and the product was registered on 01/06/2023.

1.3 Information for users

Visual description of the finished product	White to pale yellow lyophilized powder or cake
Primary packing material	50 mL USP type-I (lyo) glass vials, stoppered with 20 mm bromobutyl rubber stoppers and sealed with 20 mm aluminium flip-off seals

	Co-packed with Bacteriostatic Water for Injection packed in glass vial of 20 mL Vial
Secondary packing materials	A printed carton box
Shelf-life and storage condition	36 months, Store in 2°C – 8°C in a refrigerator. Do not freeze.
Route of administration	Intravenous Infusion
Therapeutic indications	Trastuzumab is indicated for: Breast cancer Metastatic breast cancer (a) the treatment of patients with metastatic breast cancer who have tumors that overexpress human epidermal growth factor receptor 2 (HER2). (b) in combination with an aromatase inhibitor for the treatment of patients with HER2- positive and hormone receptor-positive metastatic breast cancer. Early breast cancer Trastuzumab is indicated for the treatment of patients with HER2-positive early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable). Trastuzumab is indicated for adjuvant treatment of HER2 over-expressing node positive or node negative (ER/PR negative or with high risk feature) breast cancer: (a) as part of a treatment regimen consisting of doxorubicin, cyclophosphamide and either paclitaxel or docetaxel (b) with docetaxel and carboplatin Trastuzumab is indicated for the treatment of patients with HER2-positive early breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant trastuzumab therapy, for locally advanced (including inflammatory) disease or tumors >2 cm in diameter. Metastatic gastric cancer Trastuzumab in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of patients with

	HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received prior anti-cancer treatment for their metastatic disease. Trastuzumab should only be used in patients with metastatic gastric cancer whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory FISH+ result, or IHC3+, as determined by an accurate and validated assay.

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: TRASTMAB 440

Composition: Each multiple use vial contains Trastuzumab 440 mg
Pack size: 1 bottle

Manufacturing details: batch number, manufacturing date, and expiry date

Storage conditions: Store in 2°C – 8°C in a refrigerator. Do not freeze

Manufacturer address: physical address of release site

Unique identifier: Not applicable

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

The details of the primary pack include:

Brand name and strength: TRASTMAB 440

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 Substance

Information on the quality of the active substance was submitted in form of DMF.

Trastuzumab

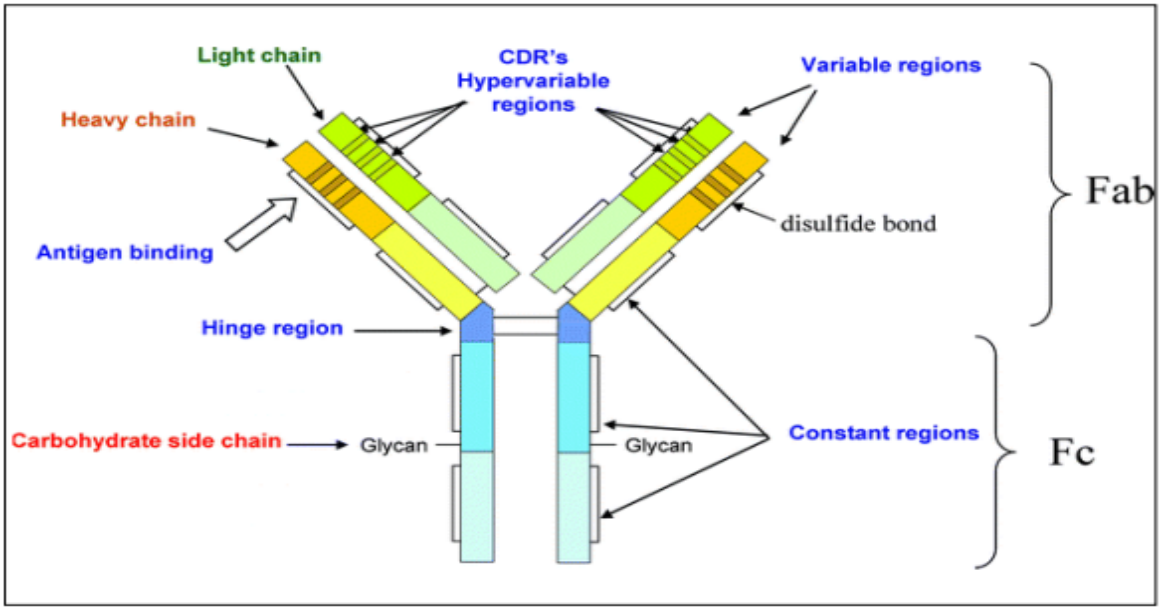
General Information

Trastuzumab active substance is non-compendia.

Chemical name: Immunoglobulin G1 (human-mouse monoclonal rHuMab HER2γ_1-chain antihuman p185c-erbB²receptor), disulfide with human-mouse monoclonal rHuMab HER2 light chain, dimer.

Molecular Formula : $C_{6460}H_{9972}N_{1724}O_{2014}S_{44}$

Structure:



General properties

Trastuzumab is a humanized monoclonal antibody of IgG1, consisting of two identical heavy chains and two identical light chains that are connected to each other by four disulfide bonds. It contains 1326 amino acids (as a mature antibody without signal sequence) and has an apparent molecular weight of ~145 kDa.

Trastuzumab contains a total of 16 cysteine residues, which are involved in both intra chain and inter-chain disulfide bonds. Twelve (12) disulfide bonds are intra-chain linkages (four in the light chain and eight in heavy chain). Also, there are four inter-chain disulfide bonds (two links each light chain and heavy chain; and two disulfide bonds in the hinge region link the two heavy chains). The most common glycan structures for IgG possess zero, one or two terminal galactose (G) residues with or without a fuse (F) and are defined as G0, G0F, G1F and G2F.

Manufacture

Trastuzumab active substance manufacturer is Intas Pharmaceuticals Limited, Plot No. 423 / P / A, Sarkhej - Bavla Highway, Village Moraiya, Taluka Sanand, Ahmedabad - 382213, Gujarat, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the TMDA. Trastuzumab is derived through fermentation process. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The active substance specifications were set as per in-house standards and ICHQ6B. The parameters monitored during quality control are: Visual (physical) appearance, pH, protein concentration by OD280 nm, relative potency by cell-based bioassay, purity tests by CE-HPLC (charge related impurities), SE-HPLC (HMW Impurities), SE-HPLC (LMW Impurities), residual protein A, host cell derived protein, residual DNA, bioburden, and bacterial endotoxins. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The shelf-life period of Trastuzumab active substance is 12 months when packed in Sterile Celsius FFT Bag (3T, TPE) or Flexboy® Bioprocessing bag at -20°C ± 5°C

Quality of the Drug Product

Formulation

TRASTMAB 440 is a white to pale yellow lyophilized powder or cake.

TRASTMAB 440 contains the Trastuzumab, and other ingredients listed here after: histidine hydrochloride L – histidine, trehalose dihydrate, polysorbate 20, 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 sites to TMDA GMP standards was confirmed through site inspection on 09/05/2019.

Specifications

The finished product is non-compendia. The manufacturer controls the quality of the finished product as per in-house and ICH requirements. The parameters monitored during quality control are: physical appearance, moisture content, reconstitution time, osmolality, pH, particulate matter, protein concentration by OD280 nm, relative potency by cell-based bioassay, purity tests by CE-HPLC (charge related impurities), SE-HPLC (HMW Impurities), SE-HPLC (LMW Impurities), bacterial endotoxins and sterility. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on three (3) batches of the finished product stored at 5°C ± 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 USP Type-I glass vials (50 mL), stoppered with 20 mm bromobutyl rubber stopper and sealed using 20 mm aluminium flip-off seal when stored at 2°C – 8°C.

After reconstitution with bacteriostatic water for injection the reconstituted solution is physically and chemically stable for 28 days at 2°C – 8°C. The reconstituted solution contains preservative and is therefore suitable for multiple use. If sterile water for injection is used to reconstitute 440 mg vial, the solution is stable for only 48 hours and must be discarded thereafter.

Safety and efficacy information

Summary of Clinical studies of Immunogenicity
Immunogenicity Endpoints and Assessments

Serum samples of 115 patients (79 in Intas Trastuzumab arm and 36 in Herclon arm) were analysed for immunogenicity from the safety population of 120 patients; 3 patients did not have any immunogenicity data and 2 patients had only visit 1 pre-dose data. Immunogenicity was evaluated by assessing serum samples for the presence of anti-trastuzumab antibody in both the groups at baseline. The serum samples of patients were analyzed for the detection of anti-trastuzumab antibody using bridging ELISA method. None of the sample at different visits was positive for anti-trastuzumab antibodies.

Summary of Clinical Studies of Efficacy

Efficacy Endpoints and Assessments

The primary efficacy endpoint was overall response rate (ORR) as per Response Evaluation Criteria for Solid Tumours 1.1 (RECIST 1.1) at the end of cycle 3 and cycle 6. ORR was defined

as proportions of patients whose overall response is complete response (CR) or partial response (PR). Patients without a confirmed CR or PR were considered as failure in computing the ORR. CR and PR were evaluated by measuring tumour size. ORR was assessed by an independent reviewer and by the principal investigator. The review done by the independent reviewer was blinded and the review done by the principal investigator was not blinded.

Additional efficacy endpoints were:

- Disease control rate (DCR), defined as the proportion of patients whose BOR is CR, PR, or stable disease (SD).
- Best overall response (BOR) rate, defined as the proportion of patients whose BOR is CR or PR.

ORR and BOR were assessed by the blinded independent medical imaging department of Lambda Therapeutic Research Limited, India.

A point estimate and a two-sided 95% confidence interval (CI) were computed for response rates (CR+PR) from overall response of the two treatment groups and their difference at the end of cycle 3 and cycle 6. To prove non-inferiority, lower limit of 95% CI for difference of proportions of ORR between Intas Trastuzumab and Herclon at cycle 6 should not be less than -20%. For the additional efficacy endpoints, a point estimate and a two-sided 95% CI were computed for DCR and BOR of the two treatment groups and their difference.

Results

Study Subjects

Total 163 patients were screened, of which 43 failed during screening: 36 did not meet inclusion/exclusion criteria, 1 lost to follow-up, and 6 withdrew the informed consent. Total 120 patients were randomized and dosed: 82 patients received Intas Trastuzumab and 38 patients received Herclon.

For DCR, no statistically significant difference was observed between Test Product-T and Reference Product-R for both, PP population (P=0.0958) and ITT population (P=0.2586).

BOR response did not differ from ORR, as CR and PR were similar for both the endpoints.

Efficacy conclusions

The efficacy results of Study 625-14 demonstrate that Intas Trastuzumab is non-inferior to Herclon, as the primary endpoint (ORR) met the predefined acceptance criteria of non-inferiority.

Summary of Clinical studies of Safety

Safety Assessment

Safety was evaluated by adverse events (AE) monitoring, medical history, vital signs, physical examination, laboratory testing (haematology, biochemistry, urine analysis) pregnancy test, ECG, ECHO, and CT/MRI/bone scan.

With respect to causality assessment, 128 AEs (97 AEs in Intas Trastuzumab group vs. 31 AEs in Herclon group) were judged as probable/likely related to the IMPs, 57 AEs (38 AEs vs. 19 AEs) as possible, 249 AEs (187 AEs vs. 62 AEs) as unlikely, and 6 AEs (5 AEs vs. 1 AE) as unassessable/unclassifiable. One AE was judged as conditional/unclassified in Herclon group.

Common Adverse Events

For the safety population (n=120), the most common AE was pain (64 AEs for Test vs. 18 AEs for Reference), followed by nausea (33 AEs vs. 10 AEs), alopecia (21 AEs vs. 12AEs), pain in extremities (22 AEs vs. 9 AEs), gastritis (23 AEs vs. 8 AEs), and anaemia (14 AEs vs. 7 AEs). In both the groups, i.e. Test Product-T and Reference Product-R, common AEs were similar. The most common AEs, those occurring in at least 5% of patients receiving either study drug.

Death

Total 2 patients receiving Test Product-T died during the study period due to cardio-pulmonary arrest. Causal relationship was unassessable for one death and unlikely for the other death.

Adverse Events of Special Interest

None of the patients discontinued the study due to AEs.

Safety conclusion

The study did not have any major safety concerns Most of the AEs noted in the study were mild or moderate and unlikely or probably related to the study drugs. Two deaths occurred in the Intas Trastuzumab arm: one was unassessable and the other was unlikely related to the study drug. Total 7 SAEs were reported, of which only 2 SAEs were possibly related to the study drugs. Overall, Intas Trastuzumab and Herclon were well tolerated and had similar safety profiles.

Summary of Clinical Studies of Pharmacokinetics

Pharmacokinetics Endpoints and Assessments

A 20-patient subgroup (14 in Test Product-T group and 6 in Reference Product-R group) was assessed for pharmacokinetic (PK). The following PK endpoints were assessed:

PK Parameter	Definition	Unit
$AUC_{0\text{-}22d}$	Area under the serum concentration-time curve from time 0 to the truncated time of 22 days	µg. h/mL
C_{max}	The maximum measured serum concentration following each treatment	µg/mL
T_{max}	The time to reach C_{max}	hour

PK analysis was performed on patients identified suitable as the PK population. The serum samples of patients were analyzed using a validated LC-MS/MS method for trastuzumab. PK parameters were calculated from the serum concentration vs. time profile using non-compartmental model of Phoenix® WinNonlin® Version 6.4 (Certara L.P.). Actual time points of the sample collection were used for the calculation of PK parameters. Actual infusion duration was considered for the PK analysis. All concentration values below the lower limit of quantification were set to zero for the PK and statistical calculations. Descriptive statistics were computed and reported for concentration data and PK parameters of trastuzumab. Wilcoxon rank-sum test was performed for the comparison of T_{max} and two-sample t-test was performed for the comparison of C_{max} and $AUC_{0\text{-}22d}$.

The table below summarizes the PK parameters of trastuzumab for Test Product-T and Reference Product-R. The PK analysis was planned for 20 patients; however, only 19 patients were considered for the statistical analysis as 1 patient was excluded due to 3 consecutive missing samples (the last 3 samples).

Pharmacokinetic Parameters of Trastuzumab (N = 19)

Parameters (Units)	Mean ± SD (untransformed data)		P-value
	Test Product-T (N=13)	Reference Product-R (N=6)	
$AUC_{0\text{-}22d}$ (µg. h/mL)	24958.030 ± 7754.1302	25253.903 ± 7636.2143	0.9390
C_{max} (µg/mL)	199.144 ± 37.3145	244.827 ± 99.3967	0.3196
T_{max} (h)*	2.500 (1.500 - 8.000)	2.009 (1.000 - 4.000)	0.4018

Parameters (Units)	Mean ± SD (untransformed data)		P-value
	Test Product-T (N=13)	Reference Product-R (N=6)	

*T_{max} is represented in median (min-max) value.

P-values are calculated using Wilcoxon rank-sum test for T_{max} and using two-sample t-test for C_{max} and AUC_{0-22d}. P-value is statistically significant if it is < 0.05.

PK Conclusion

Intas Trastuzumab and Herclon had similar PK profile following 8 mg/kg Trastuzumab as an intravenous infusion in patients with HER2-overexpressing metastatic breast cancer.

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. TRASTMAB 440 lyophilized powder for concentrate for solution for infusion 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

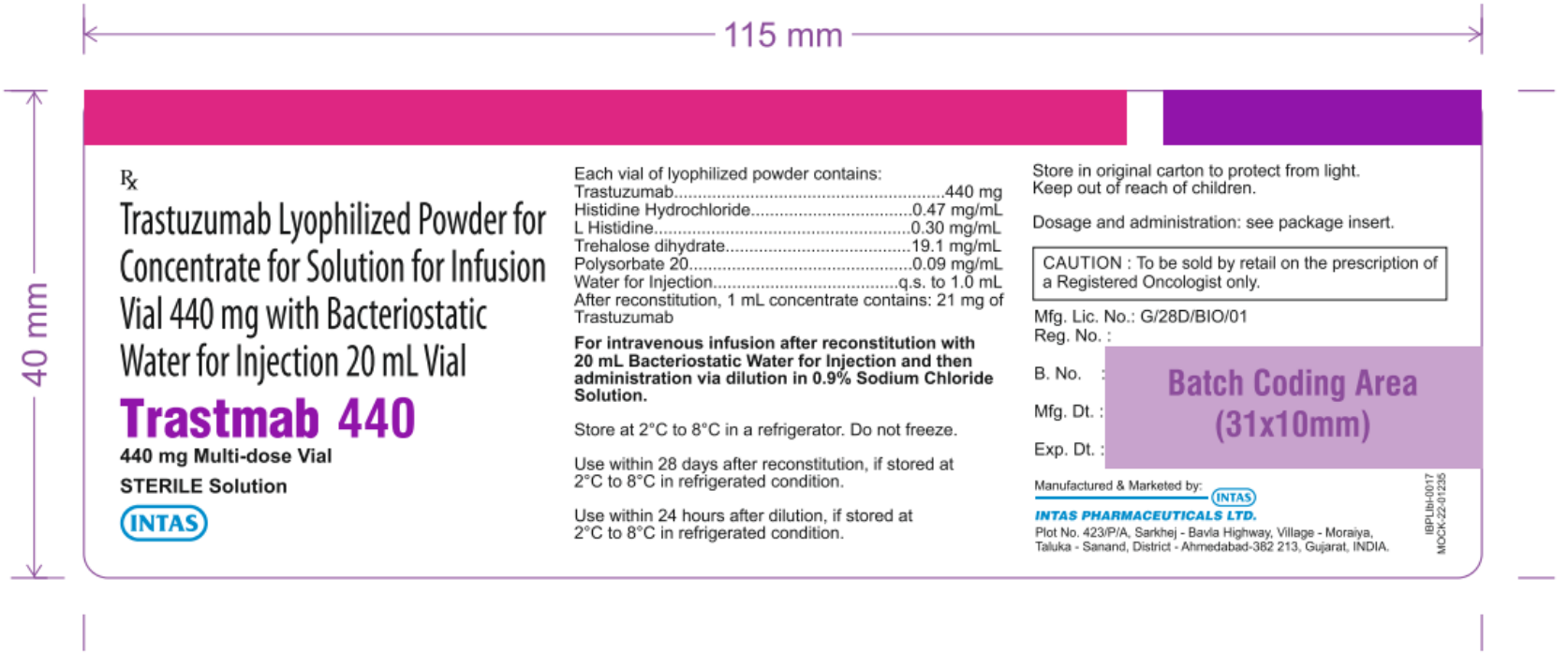
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

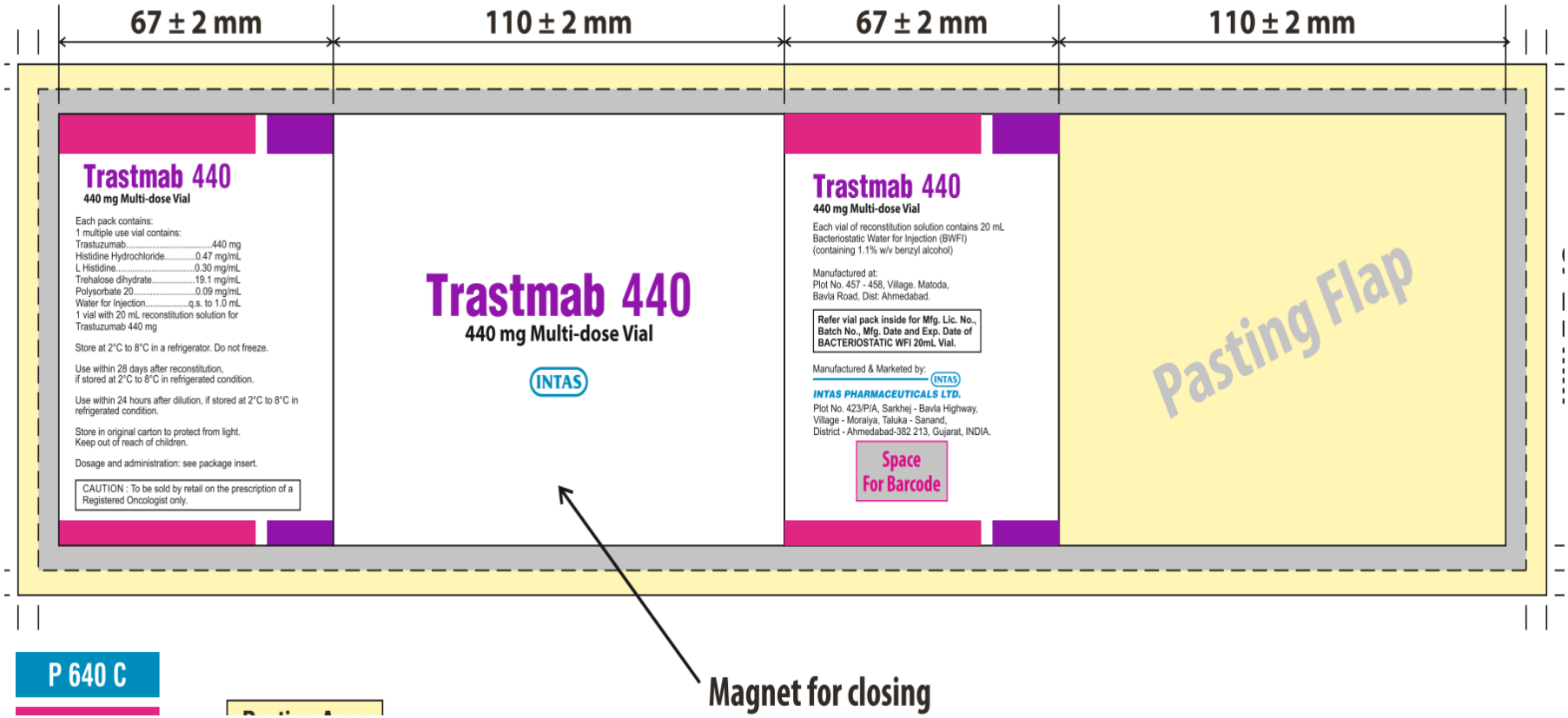
Version number	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up labels;

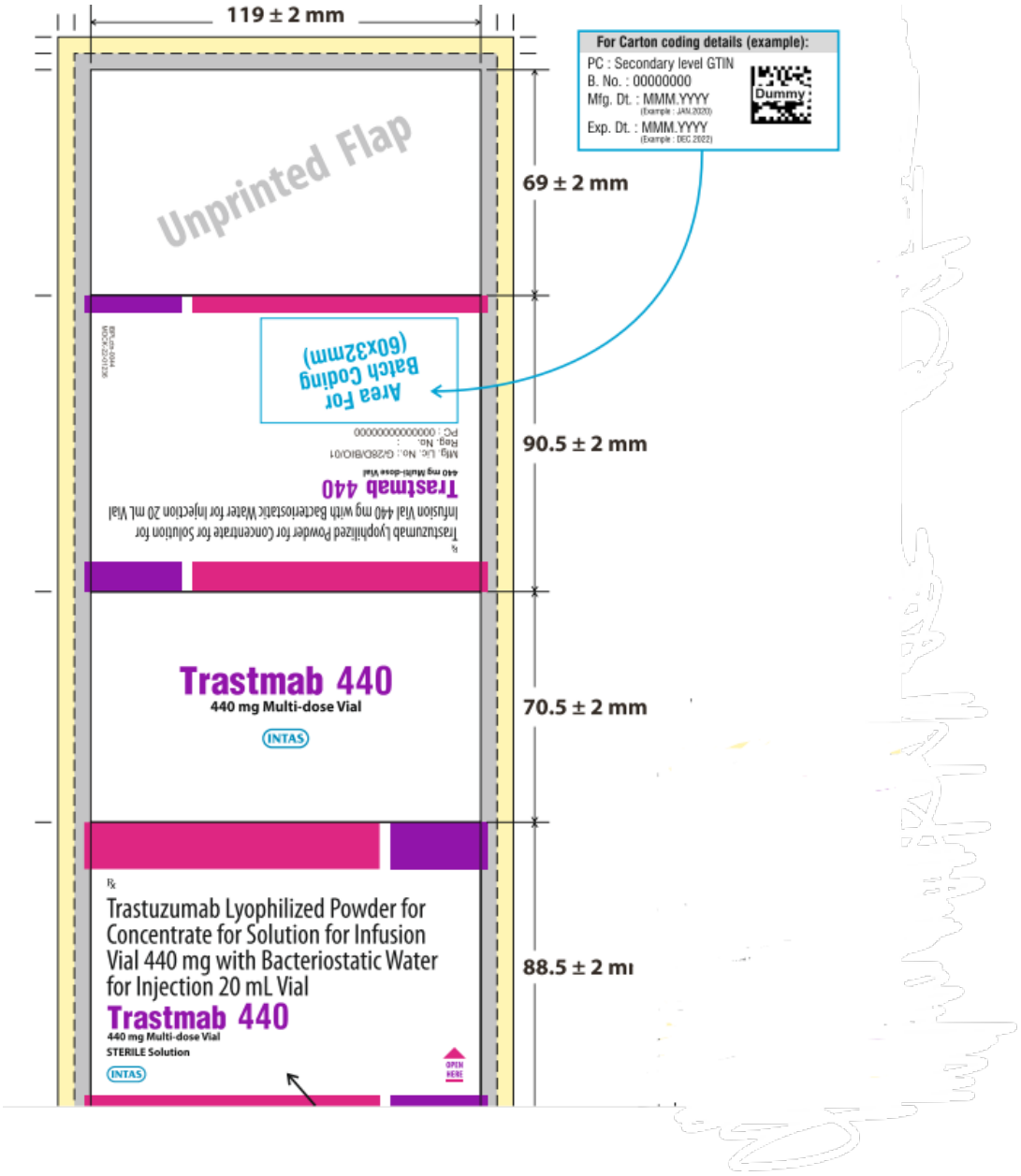
Primary pack label;



Secondary pack label;



Effective date: 03/10/2022



Effective date: 03/10/2022