THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR VIVITRA 150 (TRASTUZUMAB 150 MG) LYOPHILIZED POWDER FOR CONCENTRATE FOR INTRAVENOUS INFUSION

Version number 1.0
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1. Introduction

Vivitra 150 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. Vivitra 150 is approved in Tanzania for use in adults' population (only).

1.1 Product details

Registration number	TAN 23 H 0243
Brand name	Vivitra 150
Generic name, strength, and form	Each multiple use vial contains Trastuzumab 150 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	Vivitra 440
Marketing Authorization Holder	Cadila Healthcare Limited, Zydus Corporate Park, Scheme No. 63, Survey No. 536, Khoraj (Gandhinagar), NR Vaishnodevi Circle, Sarkhej – Gandhinagar – Highway, Ahmedabad – 382 481 India
Local Technical Representative	Pyramid Pharma Limited P.O. Box 16215, Dar es Salaam

1.2 Assessment procedure

The application for registration of Vivitra 150 was submitted on 21/05/2020. The product underwent full assessment. Assessment was completed in 2 (two) rounds of evaluation and the product was registered on 01/06/2023.

1.3 Information for users

Visual description of the finished product	Pale intact or slightly powdered lyophilized cake
Primary packing material	20 mL USP Type I clear tubular glass vial with slotted rubberstopper (grey bromo butyl) and pink flip-off seal
Secondary packing materials	A printed carton box
Shelf-life and storage condition	36 months, Store in 2°C – 8°C. Use within 28 days after reconstitution

	Store in 2°C – 8°C. Do not freeze the reconstituted solution
Route of administration	Intravenous Infusion
Therapeutic indications	**Metastatic Breast Cancer:** Vivitra is indicated for the treatment of patients with HER2 overexpressing metastatic breast cancer.Vivitra is also indicated in combination with aromatase inhibitor for the treatment ofpatients with HER2 overexpressing and hormone receptor-positive metastatic breast cancer. **Early Breast Cancer (EBC):** Vivitra is indicated for the treatment of patients with HER2 overexpressing early breastcancer following surgery, chemotherapy (neo adjuvant or adjuvant) and radiotherapy (ifapplicable). Vivitra is also indicated for adjuvant treatment of patients with HER2 overexpressing no depositive or node negative breast cancer i) as part of treatment regimen comprising doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel ii) with docetaxel and carboplatin. **Metastatic Gastric Cancer (MGC):** Vivitra is indicated for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma in combination with capecitabine or5-fluorouracil and cisplatin who have not received prior anti-cancer treatment 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: Vivitra 150

Composition: Each multiple use vial contains Trastuzumab 150 mg
Pack size: 1 bottle

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

Storage conditions: Store the lyophilized powder between 2°C – 8°C.

Use within 28 days after reconstitution

Store in 2°C – 8°C. Do not freeze the reconstituted solution

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/physician experienced in the treatment of cancer patients.

The details of the primary pack include:

Brand name and strength: Vivitra 150

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Cadila Healthcare 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

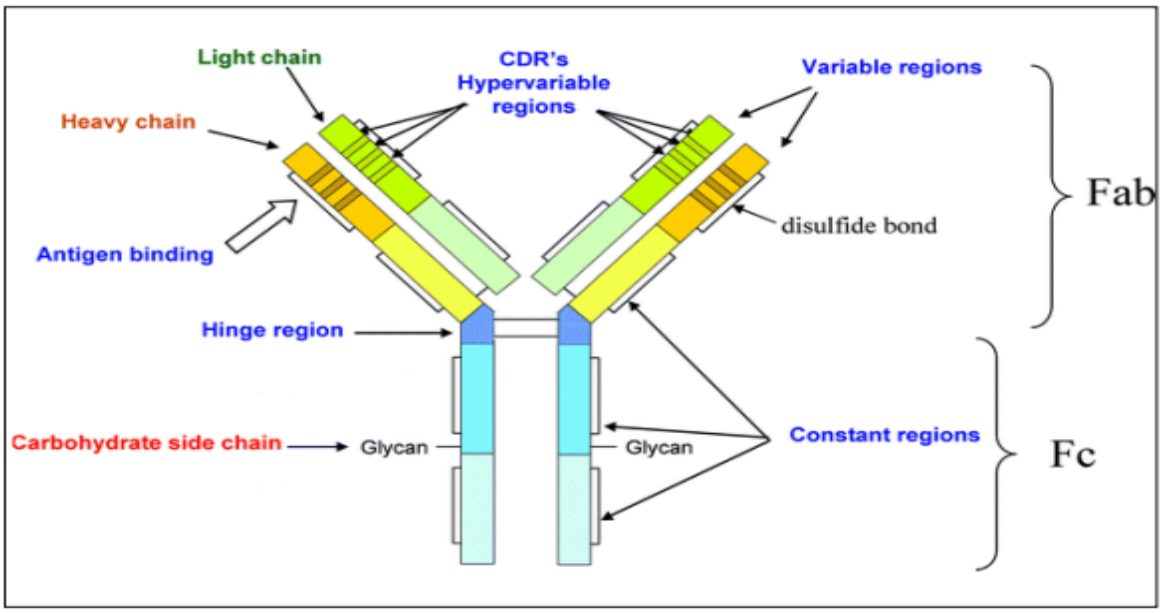
General Information

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 Cadila Healthcare Ltd., Plot Survey No. 23, 25/P, 37, 40/P, 42 to 47, Sarkhej-Bavla N.H.No.8A, Opp. Ramdev Masala, Village - Changodar, Tal - Sanand, Dist: Ahmedabad – 382213. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by Food and Drug Control Department-india. Trastuzumab active substance 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 active substance specifications were set as per in-house standards and ICHQ6B. The parameters monitored during quality control are: Appearance (clarity and colour), pH, protein concentration, polypeptide profile, polypeptide profile, purity, glycan structure, distribution of charged species variants, peptide mapping, anti-proliferation activity, host cell-derived contaminating protein, host cell derived contaminating DNA, bacterial endotoxins, osmolarity, bioburden and residual protein – A leachates. 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 36 months when packed in Celcius Pak Bag at -25°C ± 5°C

Quality of the Drug Product

Formulation

Vivitra 150 is a pale intact or slightly powdered lyophilized cake

Vivitra 150 contains the Trastuzumab, and other ingredients listed here after: L-Histidine Hydrochloride monohydrate, L-Histidine, α, α-Trehalosedihydrate, Polysorbate 20. 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.

Diluent: Bacteriostatic water for injection contains 1.1% benzyl alcohol as a preservative (20 mL)

Manufacture

The finished product manufacturer is Cadila Healthcare Ltd., Plot Survey No. 23, 25/P, 37, 40/P, 42 to 47, Sarkhej-Bavla N.H.No.8A, Opp. Ramdev Masala, Village - Changodar, Tal - Sanand, Dist: Ahmedabad - 382213 Gujarat state, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on DD/MM/YYYY.

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: appearance, pH, protein concentration, residual moisture content, polypeptide profile, purity, distribution of charged species variants, in-vitro apoptosis assay, bacterial endotoxins, osmolality, particulate matter for small volume injections, uniformity of mass, sterility, abnormal toxicity, glycan structure analysis. 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 20 mL USP Type I clear tubular glass vial with slotted rubberstopper (grey bromo butyl) and pink flip-off seal 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.

Safety and efficacy information

Overview of Efficacy

The Indian phase III clinical trial was conducted for approval of CHL's Trastuzumab in India and was designed to compare the efficacy and safety of CHL's Trastuzumab with Herclon (Reference Product, Roche/Genentech) in 102 patients with metastatic breast cancer.

A summary of the clinical trial including an overview of efficacy is provided below.

Investigational Product: CHL's Trastuzumab drug product 150 mg **Reference product**: Herclon (Reference Product, Roche/Genentech) **Phase of development:** Comparative Phase III Study.

Title of study: A prospective, randomized, multi-centric clinical study to compare Trastuzumab (Test Product, Zydus) with Trastuzumab (Reference Product, Roche/Genentech) in patients with metastatic breast cancer.

Objectives

The purpose of this study was to determine the pharmacokinetics, safety, tolerability and efficacy of Trastuzumab (Test, Zydus) as compared to Herclon (Reference Product, Roche/Genentech), both in combination with Paclitaxel in patients with Metastatic Breast Cancer.

Primary Objective:

Primary objective was to compare the single dose truncated pharmacokinetics (Cmax, AUC0-168hrs) of Trastuzumab (Zydus) as compared to Herclon (Reference) up to Day 7, both in combination with Paclitaxel in patients with Metastatic Breast Cancer.

Secondary Objectives:

Secondary objective was to evaluate the safety, tolerability efficacy, pharmacokinetics and immunogenicity of Trastuzumab (Zydus) in combination with Paclitaxel in patients with Metastatic breast cancer given for 3months.

It was administered in combination with paclitaxel, at an initial dose of 8 mg/kg as a 90-minute intravenous infusion during first chemotherapy cycle; followed by (second cycle onwards) subsequent dose of 6 mg/kg i.v 30-90-minute intravenous infusion once every three weeks, for four cycles.

Paclitaxel: Paclitaxel was administered at a dose of 175 mg/m^2 intravenous infusion every 3 weekly in both treatment groups (i.e. Test and Reference group) for four cycles.

Number of subjects:

A total of 102 patients were randomized to receive Test (N= 67) and Reference (N= 35) drug. The safety population consisted of all 102 patients receiving the study drug. Of the 102 patients randomized, 100 patients were included in the ITT population; 65 patients in Test group and 35 patients in Reference group. Total 93 subjects (62 subjects in test group and 31 subjects in reference group) completed the entire study

treatment as per protocol and were included in PP population.

Results:

Pharmacokinetic Results:

Table 1: Summary of Pharmacokinetic Data for Trastuzumab (Test Product: Trastuzumab Injection 150mg) (n=32) *

Pharmacokineticparameter	N	Arithmetic mean	Standarddeviation	Coeff ofVariation (%)
C_{max}(µg/ mL)	32	198.009	39.204	19.799
AUC_{0-168} (µg.hr/mL)	30**	19719.501	4192.343	21.260

Notes:
(*) Subject#36 and Subject#37 had pre-dose concentration greater than 5% of the C_{max} in Test treatment. Hence, as per protocol these subjects are excluded from the final pharmacokinetic and statistical analysis.

(**) For Test Product, Subject#12 and Subject#19 were not considered for calculation of$AUC_{0-168hrs}$ due to insufficient sampling time point in elimination phase. Hence, n=30 instead of 32 for $AUC_{0-168hrs}$.

(Reference product: Trastuzumab Injection 150MG) (N=34)

Pharmacokinetic parameter	N	Arithmetic mean	Standard deviation	Coeff of Variation (%)
C_{max}(µg/ mL)	34	208.582	52.196	25.024
AUC_{0-168} (µg.hr/ mL)	32***	20031.544	6018.152	30.043

Note: -
(***) For Reference Product, Subject#11 and Subject#95 were not considered for calculation of $AUC_{0-168hrs}$ due to insufficient sampling time point in elimination phase. Hence, n=32 instead of 34 for $AUC_{0-168hrs}$.

Table 2: Test & Reference geometric mean, ratio, 90% confidence intervals, inter- subject cv (%) and power based on log-transformed data for Trastuzumab

Pharmacokinetic parameter	Geometric mean				Ratio (%)
	N	Test	N	Reference	
C_{max}(µg/ mL)	32	192.275	34	204.543	94.00
AUC_{0-168} (µg.hr/ mL)	30	18922.276	32	19488.876	97.09
Pharmacokineticparameter	**90% ConfidenceIntervals**		**Inter Subject CV(%)**		**Power**
C_{max}(µg/ mL)	(86.48%;102.18%)		20.359		0.9966
AUC_{0-168} (µg.hr/ mL)	(87.50%;107.74%)		24.554		0.9697

Summary of Pharmacokinetics Results: For the log transformed Trastuzumab data, the 90% confidence intervals about the ratio of the Test geometric mean to Reference.

geometric mean is within the 80% to 125% limits for C_{max} (86.48%;102.18%) and $AUC_{0\text{-}168hrs}$ (87.50%;107.74%).

Conclusion (Pharmacokinetics): Based on these results, Trastuzumab Injection 150mg manufactured by Cadila Healthcare Ltd., India and Herclon Trastuzumab Injection 150mg, manufactured by Genentech Inc., USA, Imported and marketed by Roche Products (India) Pvt. Ltd., India, are bioequivalent.

Efficacy result:

Objective Response Rate (ORR) (21 days after last dose i.e. Cycle 4): Patients were evaluated for Objective Response Rate based on Recist 1.1 criteria. Response rate was based on sum of complete response (CR) and partial response (PR) at the end of study.

The Objective Response Rate (ORR) at end of study (21 days after last dose i.e. Cycle 4) was 71.0% (44 out of 62 patients) in Test group and 64.5% (11 out of 31 patients). There was no statistically significant difference (p>0.05) observed between test group and reference group based on ORR.Overall response rate at the end of study in both the group is described below:

Table 3: Analysis of overall response rate (ORR) on visit 7 (day 85) by treatment groups by population

Response Rate	Test (N = 62) n (%)	Reference (N = 31) n (%)	90% Confidence Interval	p-value *
Yes	44 (71.0%)	20 (64.5%)	(-12.99, 25.89)	0.5266
No	18 (29.0%)	11 (35.5%)		.

Abbreviations: N = number of subjects in specified treatment; n = number of subjects at specified category.
Test: Trastuzumab of Cadila Healthcare Ltd.; Reference: Herclon (Trastuzumab) of Roche/Genentech.
*p - values are calculated from Chi-square test.
Note: ORR is calculated as the sum of complete responses and partial responses (CR + PR).

No. of subjects with Complete response (CR), Partial response (PR), Stable disease (SD) and Progressive disease (PD) was described in below table:

Table 2-5: Summary of tumor overall response by treatment groups at visit 7 (day 85) by population

Responses	Test (N =62) n (%)	Reference (N = 31) n (%)	Total (N =93) n (%)
CR (Complete Response)	1 (1.6%)	0 (0.0%)	1 (1.1%)
PR (Partial Response)	43 (69.4%)	20 (64.5%)	63 (67.7%)

PD (Progressive Disease)	8 (12.9%)	5 (16.1%)	13 (14.0%)
SD (Stable Disease)	10 (16.1%)	6 (19.4%)	16 (17.2%)
Abbreviations: N = number of subjects in specified treatment; n = number of subjects at specified category. Test: Trastuzumab of Cadila Healthcare Ltd.; Reference: Herclon (Trastuzumab) of Roche /Genentech.			

Immunogenicity Results:

Immunogenicity was also compared between test and reference arms. Among 102 patients with metastatic breast cancer, two patients in test arm (one patient on Visit 4: Day22and one patient on Visit 7:Day84) and one patient in reference arm(onVisit4:

Day 22) tested positive for human anti-human antibody (HAHA) based on enzyme-linked immunosorbent assay (ELISA) method. These positive samples were analyzed for their neutralizing ability using a neutralization ADA assay and were found to be negative in terms of drug neutralization ability. Therefore, all the patients in both arms were negative for neutralizing anti-drug antibody. Overall, the occurrence of human anti Human antibody (HAHA) in both the treatment groups was similar both in terms of prevalence and its drug neutralizing ability.

Overview of Safety

The Indian phase III clinical trial was conducted for approval of CHL's Trastuzumab in India and was designed to compare the efficacy and safety of CHL's Trastuzumab with Herclon(Reference Product, Roche/Genentech)in 102 patients with metastatic breast cancer.

A summary of the clinical trial including an overview of safety is provided below.
Investigational Product: CHL's Trastuzumab drug product 150 mg **Reference product**: Herclon (Reference Product, Roche/Genentech) **Phase of development:**Comparative Phase III Study

Title of study: A prospective, randomized, multi-centric clinical study to compare Trastuzumab (Test Product, Zydus) with Trastuzumab (Reference Product, Roche/Genentech) in patients with metastatic breast cancer.

Objectives

The purpose of this study was to determine the pharmacokinetics, safety, tolerability and efficacy of Trastuzumab (Test, Zydus) as compared to Herclon (Reference Product, Roche/Genentech), both in combination with Paclitaxel in patients with Metastatic Breast Cancer.

It was administered in combination with paclitaxel, at an initial dose of 8 mg/kg as a 90-minute intravenous infusion during first chemotherapy cycle; followed by (second cycle onwards) subsequent dose of 6 mg/kg i.v 30-90-minute intravenous infusion once everythree weeks, for four cycles.Paclitaxel: Paclitaxel was administered at a dose of 175 mg/m^2 intravenous infusion every 3 weekly in both treatment groups (i.e. Test and Reference group) for four cycles. √✔

Safety conclusion:

A total of 329 AES was reported. Out of these, 160 AEs were reported with test group and 169

AEs were reported with reference group. Total 70 patients (42 patients in test group and 28 patients in reference group) reported at least one adverse event.Sixteen patients experienced serious adverse events during the study.

Eight patients in Test group had SAEs (total 09 SAEs including 3 deaths). Eight patients in Reference group had SAEs (total 11 SAEs). Out of these, one patient had ongoing SAE at the end of study with final outcome of death (death occurred after the end ofstudy).

TEST GROUP:

Eight of patients treated with test group had serious adverse event(s) including death in three patients. Any of the death was not related to the study drug.Total 160 AEs were reported in patients on Test group. There were 97 (60.6%) AEs with mild severity, 46 (28.8%) AEs with moderate severity and 17 (10.6%) AEs with severe severity.6 (3.8%) AEs were definitely related, 13 (8.1%) AEs were probably related, 9 (5.6%) AEswerepossiblyrelated,4(2.5%) AEs withdoubtfulcausalityand128(80.0%) AEs
were unrelated/not related to Trastuzumab. No patients were discontinued due to adverse events.Total 20 AEs are ongoing and they were under follow up.

Reference group:

Total 08 patients treated with reference group had serious adverse event(s). Out of these, one patient had ongoing SAE at the end of study with final outcome of death (death occurred after the end of study).Total 169 AEs were reported in patients on Reference group.There were 85 (50.3%) AEs with mild severity, 59 (34.9%) AEs with moderate severity and 25 (14.8%) AEs with severe severity. 9 (5.3%) AEs were definitely related, 7 (4.1%) AEs were probably related,16 (9.5%) AEs were possibly related, 9 (5.3%) AEs with doubtful causality and 128 (75.7%) AEs were unrelated/not related to Trastuzumab.Total 8 AEs are ongoing and they were under follow up.

Overall conclusion:

Efficacy of Trastuzumab (Test Product, Zydus) is comparable with that of Trastuzumab (Reference Product, Roche/Genentech) in patients with HER2+ metastatic breast cancer. Immunogenicity results are also comparable between both the groups. Both the treatments showed comparable safety profile based on the safety data. Overall, Trastuzumab injection of Zydus is effective and safe in patients with metastatic breast cancer.

Benefits and risks conclusions

Trastuzumab is a glycosylated protein produced by genetically engineered Chinese Hamster Ovary (CHO) cells as a secreted protein. Glycosylation occurs on the F_c portion of heavy-chains.

The pharmacotherapeutic group of Trastuzumab is Antineoplastic agents. Trastuzumab is a recombinant humanized monoclonal antibody that binds selectively to an antigen called human epidermal growth factor 2 (HER2).

CHL has conducted a highly comprehensive characterization of the physicochemical and biological properties of its Trastuzumab product in comparison with the commercial product Herceptin to establish biosimilarity. These analyses revealed the CHL product to be a close to

fingerprint match of the product to originator's product, Herceptin. After establishing quality biosimilarity to a very high degree, CHL's Trastuzumab was subjected to a panel of animal toxicity studies. These studies confirmed that the drug was well tolerated and comparable to Herceptin in its toxicity profile complementing the findings of Quality biosimilarity.

The final assessment of biosimilarity rests on the demonstration of safety and efficacy in a clinical setting. CHL has conducted a Phase 3 clinical trial in India. The study is titled, "A prospective, randomized, multi-centric clinical study to compare Trastuzumab (Test Product, Zydus) with Trastuzumab (Reference Product, Roche/Genentech) in patients with metastatic breast cancer". The clinical trial results indicate that CHL's product is safe, well tolerated and efficacious drug. The adverse events reported in Phase III clinical trial of CHL's Trastuzumab drug product were same as that reported for Herceptin. Based on the Quality, Non-clinical and Clinical biosimilarity as well as CHL's extensive market experience, several patients are using the Trastuzumab therapy and are benefitting from its use.

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. Vivitra 150 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>.

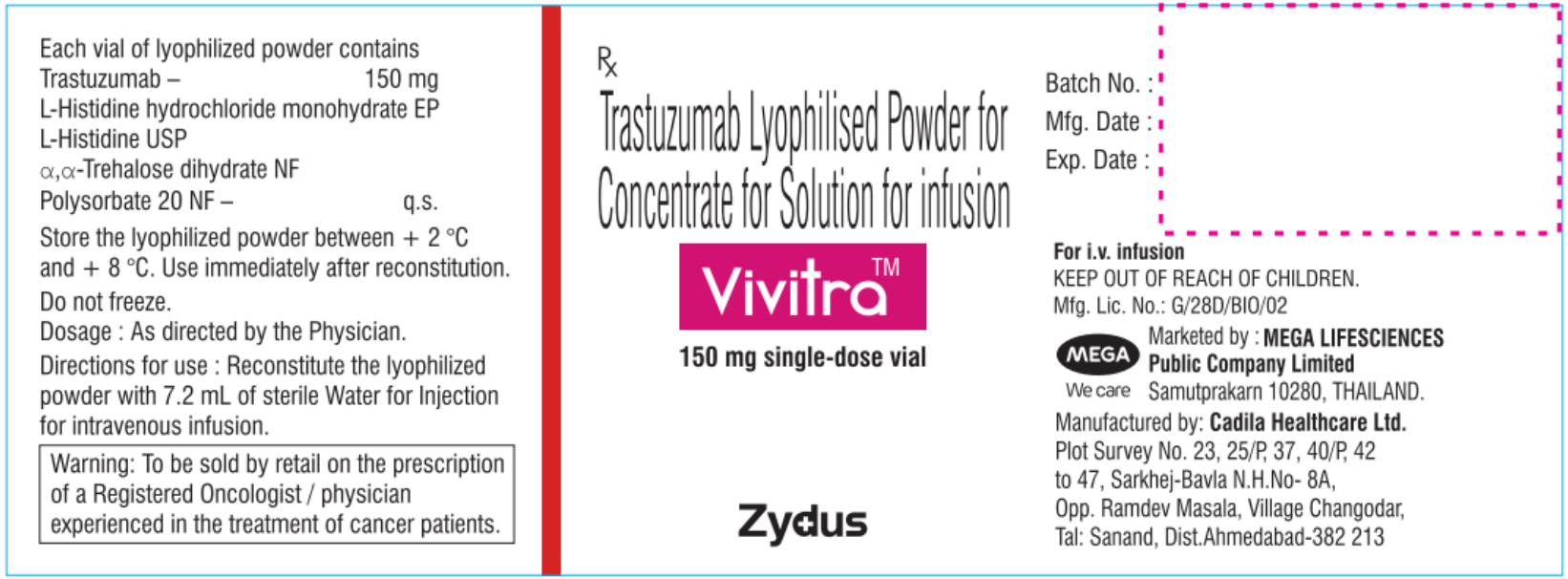
PART 5: CHANGE HISTORY

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

Annex I: Mock up labels;

Primary pack label;

A. Trastuzumab



B. Bacteriostatic Water for Injection

Secondary pack label;