For the use of a Registered Medical Oncologist / Practitioner or a Hospital or a Laboratory only

HERHOPE™
(Trastuzumab Lyophilized Powder for Concentrate for Solution for infusion)

PHARMACEUTICAL FORM AND COMPOSITION

Lyophilized powder for concentrate for solution for infusion

- **440 mg Multi dose lyophilized powder for infusion**
- **150 mg Multi-use lyophilized powder for infusion**

Herhope™ is white to pale intact or slightly powdered lyophilized cake for reconstitution. The reconstitution of the lyophilized cake yields, a clear, colourless to pale yellow liquid solution. Herhope™ is available in two different presentations viz multi-use vial containing 150 mg and multi-dose vial containing 440 mg of trastuzumab in the form of lyophilized powder for solution for intravenous infusion

Table 1: Composition of Herhope™ Drug Product – **150 mg** Multi-use vial and **440 mg** multi-dose vial.

Sr. No.	Ingredients	Multi-use vial (150 mg strength)	Multi-dose vial (440 mg strength)
Active ingredient			
1	Trastuzumab	150 mg	440 mg
Inactive ingredients			
2	L-Histidine hydrochloride monohydrate EP	3.36 mg	9.9 mg
3	L-Histidine USP	2.16 mg	6.4 mg
4	α,α-Trehalose dihydrate NF	136.2 mg	400 mg
5	Polysorbate 20 NF	0.6 mg	1.8 mg
6	pH	6.0	6.0

Reconstitution

Multi-use lyophilized product in vial: Each vial containing 150 mg of Herhope™ Drug Product is reconstituted with 7.2 mL of Sterile Bacteriostatic Water for Injection (BWFI) containing 1.1% benzyl alcohol as a preservative to yield a solution at a concentration of 21 mg / mL.

Multi-dose lyophilized product in vial: Each vial containing 440 mg of Herhope™ Drug Product is reconstituted with 20 mL of sterile bacteriostatic water containing 1.1% benzyl alcohol as a preservative to yield a solution at a concentration of 21 mg / mL.

WARNING: **CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY**

Cardiomyopathy: Herhope™ can result in sub-clinical and clinical cardiac failure manifesting as Congestive heart failure (CHF) and decreased Left ventricular ejection fraction (LVEF) with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue Herhope™ for cardiomyopathy.

Infusion reactions, Pulmonary toxicity: Discontinue Herhope™ for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.

Embryo-Fetal Toxicity: Exposure to Herhope™ during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death.

DESCRIPTION

Trastuzumab is a recombinant humanized monoclonal IgG1 antibody (containing 1328 amino acids) produced in Chinese Hamster Ovary (CHO) cell line. It is directed against an antigen called human epidermal growth factor receptor 2 (HER2). HER2 is found in large amounts on the surface of some cancer cells where it stimulates their growth. When trastuzumab binds to HER2 it stops the growth of such cells leading to cell death.

THERAPEUTIC INDICATION

Metastatic Breast Cancer (MBC):

Trastuzumab is indicated for the treatment of patients with HER2 overexpressing metastatic breast cancer. Trastuzumab is also indicated in combination with aromatase inhibitor for the treatment of patients with HER2 overexpressing and hormone receptor-positive metastatic breast cancer.

Early Breast Cancer (EBC):

Trastuzumab is indicated for the treatment of patients with HER2 overexpressing early breast cancer following surgery, chemotherapy (neo adjuvant or adjuvant) and radiotherapy (if applicable).

Trastuzumab is also indicated for adjuvant treatment of patients with HER2 overexpressing node positive 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):

Trastuzumab is indicated for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma in combination with Capecitabine or 5-fluorouracil and cisplatin who have not received prior anti-cancer treatment for their metastatic disease.

POSOLOGY AND METHOD OF ADMINISTRATION [1]

Prior to initiation of Trastuzumab therapy HER2 testing is compulsory. Trastuzumab should be administrated as an intravenous infusion.

Do not administer Herhope™ as an intravenous push or bolus.

Weekly schedule:
Loading dose: The recommended initial loading dose is 4 mg per kg of body weight administered as a 90-minute intravenous infusion.
Patients should be observed for fever and chills or other symptoms related to infusion, because the stopping of infusion may help control such symptoms. The infusion may be restarted when symptoms subside.
Subsequent doses: The recommended weekly dose is 2 mg per kg of body weight. If the previous dose was well tolerated, the dose can be administered as a 30-minute infusion. Patients should be observed for fever and chills or other symptoms related to infusion.
Alternative 3-weekly schedule: First loading dose of 8 mg per kg of body weight administered as infusions over approximately 90 minutes, followed by 6 mg per kg of body weight repeated at 3 weekly intervals. If the initial dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion.

If patient misses a dose of Trastuzumab by one week or less, then the usual dose of Herhope^{TM} (6 mg per kg of body weight) should be administered as soon as possible without waiting until the next planned cycle. Subsequent maintenance doses of 6 mg per kg of body weight should then be given every 3 weeks, according to the previous schedule.
If the patient misses a dose of Herhope^{TM} by more than one week, a re-loading dose of Herhope^{TM} of 8 mg per kg of body weight should be administered over approximately 90 minutes. Subsequent maintenance doses of 6 mg per kg of body weight should then be given every 3 weeks from that point.

Dose Modifications:
• *Infusion reaction:*
o Reduce the rate of infusion for mild to moderate infusion reactions
o Interrupt the infusion in patients with dyspnoea or significant hypotension
o Discontinue Herhope^{TM} for severe and or life threatening infusion reactions

• *Cardiomyopathy*
o Examine the patient for LVEF prior to Herhope^{TM} therapy and subsequently at regular interval after the treatment.

• *Withhold* Herhope^{TM} *treatment for atleast four weeks in case of following*
o ≥ 16% absolute reduction in LVEF from the pretreatment value
o LVEF below the standard of care defined by the institute of the normal and 10% of absolute decrease in LVEF from pretreatment values.

Herhope^{TM} treatment may be resumed if within 4 to 8 weeks LVEF returns to normal limits and the absolute reduction from baseline is ≤ 15%. Permanently discontinue the treatment if there is a persistent (more than 8 weeks) LVEF decline or for suspension of Herhope^{TM} dosing on more than 3 occasions for cardiomyopathy.

Dose reduction
During the clinical study carried out with Herhope^{TM} reduction of dose was not required.

Patients may continue Herhope^{TM} therapy during periods of reversible, chemotherapy-induced myelosuppression, but they should be monitored carefully for complications of neutropenia during that time.

CONTRAINDICATIONS [1]

Herhope™ (Trastuzumab) is contraindicated in patients with known hypersensitivity to trastuzumab or to any other component of the drug product (Herhope™).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE [1]

HER2 testing either by immunohistochemistry (IHC) or fluorescence immunosorbent hybridization (FISH) must be performed in a specialized laboratory prior to initiation of Herhope™ treatment. Herhope™ treatment should only be initiated under supervision of an oncologist/ physician experienced in the treatment of cancer patients.

Infusion-related reactions (IRRs) and hypersensitivity [1-3]

Serious infusion related reactions reported infrequently to trastuzumab infusion include dyspnoea, hypotension, bronchospasm, respiratory distress, wheezing, anaphylaxis, urticaria, angioedema reduced oxygen saturation, hypertension and supraventricular tachyarrhythmia. To reduce risk of occurrence of these events, pre-medication may be used. The majority of these events are reported during or within 2.5 hours of the start of the first infusion. It is recommended that the infusion should be discontinued or the rate of infusion slowed, if any infusion reaction occurs. The patient should be monitored until resolution of all observed symptoms. These symptoms can be treated with an analgesic/antipyretic, or an antihistamine. The majority of patients who experienced resolution of symptoms have subsequently received further trastuzumab infusions. In rare cases, infusion reactions have resulted in a fatal outcome.

Patients at increased risk of a fatal infusion reaction include those who are experiencing dyspnoea at rest due to complications of advanced malignancy/ comorbidities. Therefore, such patients should not be treated with trastuzumab. Delayed reactions with rapid clinical deterioration have also been reported with trastuzumab with fatalities within hours and up to one week following infusion. Rarely, infusion reaction and pulmonary symptoms were reported more than six hours after the start of trastuzumab infusion. Patients should be warned of the possibility of such delayed onset symptoms and should be instructed to contact their doctor when these symptoms occur.

Pulmonary events

Reported pulmonary events include: acute respiratory distress syndrome, pneumonia, interstitial lung disease, pneumonitis, pleural effusion, acute pulmonary edema, respiratory distress, and respiratory insufficiency. Severe pulmonary events with occasional fatalities have also been reported. Prior or concomitant anticancer therapy such as gemcitabine, taxanes, vinorelbine and radiation therapy are associated with increased risk of interstitial lung disease. Patients experiencing dyspnoea at rest due to complications of advanced malignancy/ comorbidities are at increased risk of a fatal infusion reaction. Therefore, such patients should not be treated with trastuzumab. Trastuzumab should be cautiously used in pneumonitis, especially in patients being treated with taxanes concomitantly.

Cardiac dysfunction

Trastuzumab therapy is associated with increased risk of developing congestive heart failure (NYHA class II-IV) or asymptomatic cardiac dysfunction. These cases may be moderate to severe and have been associated with death. These events have been reported in patients receiving trastuzumab therapy alone or in combination with docetaxel or paclitaxel, especially following anthracycline (doxorubicin or epirubicin) based chemotherapy.

Trastuzumab should be cautiously used in patients with increased cardiac risk, e.g. hypertension, coronary artery disease, congestive heart failure, LVEF <55% and older age. Baseline cardiac assessment including history, physical examination, electrocardiogram (ECG), echocardiogram, and/or multigated acquisition (MUGA) scan or magnetic resonance imaging (MRI) should be performed in all patients prior to start of trastuzumab treatment, especially those with prior anthracycline and cyclophosphamide (AC) exposure. A careful risk-benefit assessment should be made before deciding to treat with trastuzumab. Patients should be monitored to detect the development of cardiac dysfunction. Cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of trastuzumab.

Patients who receive anthracyclines after stopping trastuzumab may possibly be at increased risk of cardiac dysfunction, as trastuzumab persists in the circulation for up to 7 months after stopping trastuzumab treatment. Therefore, if possible, anthracycline-based therapy should be avoided for up to 7 months after stopping trastuzumab.

Cardiac function should be monitored during treatment (e.g. every 12 weeks) in all patients to identify patients who develop cardiac dysfunction. More frequent monitoring (e.g. every 6 - 8 weeks) may be performed in patients who develop asymptomatic cardiac dysfunction. Discontinuation of trastuzumab therapy should be considered if the patients have a continued decrease in left ventricular function, but remain asymptomatic, if no clinical benefit of trastuzumab therapy is evident.

The safety of continuation or resumption of trastuzumab has not been reported in patients who experience cardiac dysfunction. If LVEF drops ≥10 ejection fraction points from baseline and to below 50%, trastuzumab treatment should be suspended and repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, or symptomatic CHF has developed, discontinuation of trastuzumab therapy should be strongly considered, unless the benefits of treatment outweigh the risks for the individual patient. All such patients should be referred to cardiologist for assessment and followed up.

Symptomatic cardiac failure developed during trastuzumab therapy should be treated with standard therapy for CHF. In the Metastatic breast cancer (MBC) setting, trastuzumab and anthracyclines should not be given concurrently in combination. Benzyl alcohol, used as a preservative in BWFI in the 440 mg multi-dose vial, has been associated with toxicity in neonates and children up to 3 years old. When administering trastuzumab to a patient with a known sensitivity to benzyl alcohol, trastuzumab should be reconstituted with sterile bacteriostatic water for injection, and only one dose per trastuzumab vial should be used. Any unused portion must be discarded. Sterile Bacteriostatic Water for Injection, used to reconstitute the 150 mg multi-use vial, contain benzyl alcohol.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

There have been no formal drug interaction studies performed with trastuzumab in humans. Clinically significant interactions with the concomitant medication used in clinical trials have not been observed with respect to Trastuzumab.

PREGNANCY
Trastuzumab should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus. In the post marketing setting, cases of oligohydramnios have been reported in pregnant women receiving trastuzumab. It is not known whether trastuzumab can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. Reported animal reproduction studies revealed no evidence of impaired fertility or harm to the foetus.

NURSING MOTHERS
It is not known whether trastuzumab is secreted in human milk. As human IgG is secreted into human milk, and the potential for harm to the infant is unknown, breast-feeding should be avoided during trastuzumab therapy.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Trastuzumab has negligible influence on the ability to drive or use machines. However, patients experiencing infusion-related symptoms should be advised not to drive and use machines until symptoms disappear.

ADVERSE EVENTS OBSERVED IN THE CLINICAL TRIAL WERE:
Table 2: Adverse events observed in the clinical trial
ADVERSE EVENTS REPORTED WITH THE USE OF TRASTUZUMAB [3]

System Organ Class term	Preferred term	Total (N=102) (n%)
Blood and lymphatic system disorders	Anaemia	4 (3.9%)
	Leukocytosis	1 (1.0%)
	Neutropenia	2 (2.0%)
	Thrombocytopenia	1 (1.0%)
Cardiac disorders	Atrial fibrillation	1 (1.0%)
	Cardiac failure congestive	1 (1.0%)
	Left ventricular dysfunction	1 (1.0%)
	Palpitations	1 (1.0%)
	Pericardial effusion	1 (1.0%)
	Tachycardia	1 (1.0%)
Gastrointestinal disorders	Abdominal pain	1 (1.0%)
	Aphthous stomatitis	1 (1.0%)
	Constipation	1 (1.0%)
	Diarrhoea	1 (1.0%)
	Nausea	1 (1.0%)
	Stomatitis	2 (2.0%)
	Vomiting	4 (3.9%)
General disorders and administration site conditions	Asthenia	1 (1.0%)
	Chest pain	1 (1.0%)
	Chills	4 (3.9%)
	Generalised oedema	1 (1.0%)
	Pyrexia	1 (1.0%)
Infections and infestations Investigations	Gastroenteritis	1 (1.0%)
	Echocardiogram abnormal	1 (1.0%)
	Ejection fraction decreased	1 (1.0%)

	Electrocardiogram abnormal	1 (1.0%)
Musculoskeletal and connective tissue disorders	Arthralgia	2 (2.0%)
	Myalgia	1 (1.0%)
Nervous system disorders	Dizziness	1 (1.0%)
	Dysaesthesia	1 (1.0%)
	Hypoaesthesia	1 (1.0%)
	Neuropathy peripheral	3 (2.9%)
Psychiatric disorders	Insomnia	1 (1.0%)
Renal and urinary disorders	Acute kidney injury	1 (1.0%)
	Oliguria	1 (1.0%)
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1 (1.0%)
	Dyspnoea exertional	1 (1.0%)
Skin and subcutaneous tissue disorders	Alopecia	4 (3.9%)
	Rash pruritic	1 (1.0%)

Following adverse events reported with the use of intravenous Trastuzumab alone or in combination with chemotherapy:

General disorders and administration site conditions: Asthenia, Influenza-like symptoms, Infusion related reaction, Chest pain, Chills, Pain, Fatigue, Mucosal inflammation, Pyrexia, Peripheral oedema, Oedema, Malaise

Blood and lymphatic system disorders: Anaemia, Neutropenia, Febrile neutropenia, Thrombocytopenia, White blood cell count decreased/leukopenia, Hypoprothrombinaemia

Infections and infestations: Infection, Neutropenic sepsis, Nasopharyngitis, Herpes zoster, Sinusitis, Influenza, Cystitis, Cellulitis, Upper respiratory tract infection, Urinary tract infection, Rhinitis, Sepsis, Pharyngitis, Erysipelas, Skin infection

Cardiac disorders: Palpitation, Cardiac flutter, Heart beat irregular, Ejection fraction decreased, Blood pressure decreased, Blood pressure increased, Cardiac failure (congestive), Supraventricular tachyarrhythmia, Pericardial effusion, Cardiomyopathy, Cardiogenic shock, Pericarditis, Bradycardia, Gallop rhythm present

Vascular disorders: Hot flush, Vasodilatation, Hypotension

Respiratory, thoracic and mediastinal disorders: Cough, Wheezing, Epistaxis, Dyspnoea, Rhinorrhoea, Pneumonia, Pleural effusion, Asthma, Lung disorder, Pneumonitis, Pulmonary fibrosis, Respiratory failure, Respiratory distress, Lung infiltration, Acute pulmonary oedema, Bronchospasm, Acute respiratory distress syndrome, Hypoxia, Interstitial lung disease, Orthopnoea, Pulmonary oedema, Laryngeal oedema, Oxygen saturation decreased

Gastrointestinal disorders: Nausea, Diarrhoea, Vomiting, Lip swelling, Abdominal pain, Dyspepsia, Stomatitis, Constipation, Pancreatitis, Dry mouth, Haemorrhoids

Hepatobiliary disorders: Liver tenderness, Hepatocellular injury, Hepatitis, Jaundice, Hepatic failure

Metabolism and nutrition disorders: Anorexia, Weight decreased/Weight loss, Hyperkalaemia *Immune system disorders:* Hypersensitivity, Anaphylactic shock, Anaphylactic reaction *Psychiatric disorders:* Insomnia, Depression, Thinking abnormal, Anxiety

Nervous system disorders: Tremor, Paraesthesia, Dysgeusia, Dizziness, Headache, Ataxia, Peripheral neuropathy, Hypertonia, Somnolence, Paresis, Brain oedema

Ear and labyrinth disorders: Deafness

Eye disorders: Lacrimation increased, Conjunctivitis, Dry eye, Retinal haemorrhage, Papilloedema

Musculoskeletal and connective tissue disorders: Muscle tightness, Myalgia, Arthralgia, Arthritis, Bone pain, Back pain, Pain in extremity, Neck Pain, Muscle spasms *Skin and subcutaneous tissue disorders:* Erythema, Alopecia, Rash, Swelling face, Palmar-plantar erythrodysaesthesia syndrome, Nail disorder, Acne, Ecchymosis, Dry skin, Dermatitis, Onychoclasis, Maculopapular rash, Hyperhydrosis, Pruritus, Urticaria, Angioedema
Renal and urinary disorders: Renal disorder, Renal failure, Glomerulonephritis membranous, Glomerulonephropathy
Reproductive system and breast disorders: Breast inflammation/mastitis
Pregnancy, puerperium and perinatal conditions: Pulmonary hypoplasia, Oligohydramnios, Renal hypoplasia Injury, poisoning and procedural complications: Contusion
Neoplasms benign, malignant and unspecified (incl. Cysts and polyps): Neoplasm progression, malignant neoplasm progression

OVERDOSE
There is no experience with over dosage of trastuzumab in clinical trials.

PHARMACOLOGICAL PROPERTIES
PHARMACODYNAMIC PROPERTIES [1-2]
Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies
ATC code: L01XC03

Mechanism of action:
Trastuzumab binds with high affinity and specificity to an epitope located in the extracellular sub-domain IV of HER2 present juxtaposed to the cell membrane region. Binding of trastuzumab to HER2 inhibits HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, leading to an inhibition of proliferation of HER2 overexpressing human tumor cells both *in-vitro* and *in-vivo*. Trastuzumab is also known to carry out its function *in-vitro* via an immune effector mechanism, ADCC (antibody-dependent cell-mediated cytotoxicity), by binding to HER2 overexpressing cancer cells in the presence of NK cells.

CLINICAL EFFICACY AND SAFETY [5]
Clinical Trial in Indian Patients
In a clinical trial conducted in 102 female patients with HER2+ metastatic breast cancer, received four cycles of trastuzumab (loading dose 8 mg/kg intravenous infusion on day 1 and subsequently 6 mg/kg intravenous infusion every three weekly) and paclitaxel (175 mg/m^2 intravenous infusion every three weekly). Sixty seven patients received CHL's Trastuzumab and thirty five patients received Reference Trastuzumab. The pharmacokinetics, efficacy, safety and immunogenicity were evaluated in Test and Reference groups.

Efficacy conclusions Objective Response Rate (ORR): 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 the 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% (20 out of 31 patients) in Reference group. There was no statistical significant difference ($p>0.05$) observed between test group and reference group based on ORR.

Table 3: Overall response rate at the end of study in both the groups: Analysis of overall response rate (ORR) on visit 7 (Day 85) by treatment groups by population

Table 4: No. of subjects with Complete response (CR), Partial response (PR), Stable disease (SD) and Progressive disease

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 Manufacturer;
Reference: Trastuzumab of Originator.
*p - values are calculated from Chi-square test.
Note: ORR is calculated as the sum of complete responses and partial responses (CR + PR).

(PD): Summary of tumor overall response by treatment groups at visit 7 (Day 85) by PP 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 Manufacturer.
Reference: Trastuzumab of Originator.

With respect to immunogenicity, Among 102 patients with metastatic breast cancer, only two patients in test group and one patient in reference group tested positive for human anti-human antibody (HAHA) based on enzyme-linked immunosorbent assay (ELISA) method. These three samples were found to be negative in drug neutralization. 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.

Safety conclusions

Most of the reported AEs were of mild to moderate category in both the treatment groups. Overall, test product and reference product were well tolerated and safety profile of the test product and reference product were comparable during the study.

Pharmacokinetic study conclusion
Pharmacokinetics of CHL's Trastuzumab was determined in patients of metastatic breast cancer in a comparative study. Summary of key pharmacokinetic parameters (primary endpoints) of CHL's Trastuzumab and reference product observed during the study is described in Table 5 below:

Table 5: Test & Reference Geometric mean, Ratio, 90% Confidence Intervals, Intra-Patient 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
$_{0\text{-}18}$ (µg.hr/ mL)	30	18922.276	32	19488.876	97.09
Pharmacokinetic Parameter	90% Confidence Intervals		Inter Subject CV (%)		Power
C_{max} (µg/ mL)	(86.48%;102.18%)		20.359		0.9966
$AUC_{0\text{-}168}$ (µg.hr/ mL)	(87.50%;107.74%)		24.554		0.9697

Abbreviations: N = number of subjects in specified treatment.
Test: Trastuzumab of Manufacturer
Reference: Trastuzumab of Originator.

For the log transformed trastuzumab data, the 90% confidence intervals about the ratio of the Test geometric mean to Reference geometric mean are within the 80% to 125% limits for Cmax (86.48%; 102.18%) and AUC0-168hrs (87.50%; 107.74%). Based on these results CHL's Trastuzumab (Manufacturer's) and Reference product are bioequivalent in pharmacokinetics.

Additionally AUC_t (µg.hr/ mL), T_{max} (hours) and $t_{1/2}$ (hours) were also evaluated for the test and reference products and found to be comparable.

PRECLINICAL SAFETY DATA OF CHL's TRASTUZUMAB
Preclinical studies for CHL's Trastuzumab (Manufacturer's) were performed as per GLP standards. The rationale for dose selection was based on human therapeutic dose of 4 mg/kg and all doses were calculated to animal doses based on body surface area. Toxicological studies included independent acute toxicity studies in mice and rats by intravenous route of administration as well as Repeated dose toxicity studies (comparative) by intravenous route comprising weekly dosing schedule over a period of four weeks was performed in rats and rabbits. Local tolerance evaluation was a part of repeated dose toxicity studies.

In acute studies, CHL's Trastuzumab revealed a good safety margin in terms of mortality over the acute dose of 400 mg/kg in mice & 200 mg/kg in rats by intravenous and were approximately 8x of the human equivalent dose. No mortality, apparent signs of toxicity, adverse changes in body weights and gross pathological lesions were noticed in both mice and rats when compared to vehicle control groups.

Comparative study comprising of repeated weekly intravenous administration of CHL's Trastuzumab (Manufacturer) and reference product was conducted over a period of four weeks at dose levels of 25, 62.5 & 125 mg/kg in rats and 12.5, 31.25 & 62.5 mg/kg in rabbits. The selected dose levels were 1x, 2.5x & 5x of the human equivalent dose. A recovery group was maintained for a period of two weeks at 5x of the human equivalent dose. Vehicle control groups were maintained with main study & recovery groups. An approved reference (originator) product was used at 1x of the human equivalent dose. No mortality occurred in both rats and rabbits. No adverse changes were noticed during detailed clinical examination, body weight and feed intake determinations, hematological, biochemical, organ weight estimations, bone marrow examination and gross or histopathological evaluation. No any differences were noticed in these studies from reference (originator) product in both rats and rabbits. No any delayed toxicity was noticed during treatment free recovery period of two weeks. The immunogenic response in CHL's trastuzumab (Manufacturer) treated groups were comparable to that of reference (originator) product treated group. NOAEL was considered to be more than 5x of human equivalent dose (125 mg/kg in rats and 62.5 mg/kg in rabbits) by weekly intravenous administration over a period of four weeks.

Thus, the overall pre-clinical profile of CHL's Trastuzumab is found to be comparable to reference originator product and considered to be safe at the recommended dose in humans.

PHARMACEUTICAL PARTICULARS

Active Ingredients- Trastuzumab

List of excipients-L-Histidine hydrochloride monohydrate EP, L-Histidine USP, α,α-Trehalose dihydrate NF, Polysorbate 20 NF.

INCOMPATIBILITIES

No incompatibilities between trastuzumab and polyvinylchloride, polyethylene or polypropylene bags have been observed. Dextrose (5%) solution should not be used since it causes aggregation of the protein. It should not be mixed or diluted with other drugs.

SHELF LIFE

36 months

STORAGE

Store between 2°C and 8°C.

Shelf-life of the reconstituted solution

440 mg vials (for Multi-dose use)

Reconstitute the lyophilized powder (*440 mg strength)* with 20 ml of sterile bacteriostatic water for injection. Reconstituted solution should be used within 28 days of reconstitution when stored refrigerated between 2°C and 8°C. The reconstituted solution contains preservative and is therefore suitable for multiple uses. Any remaining reconstituted solution should be discarded after 28 days.

150 mg vials (for Multi-use only)

Reconstitute the lyophilized powder 150 mg strength with 7.2 mL sterile bacteriostatic water for injection. Reconstituted solution should be used within 28 days of reconstitution when stored refrigerated between 2°C and 8°C. The reconstituted solution contains preservative and is therefore suitable for multiple uses. Any remaining reconstituted solution should be discarded after 28 days.

If sterile water for injection is used to reconstitute the lyophilized powder (150 mg strength) should be used immediately, If not further diluted immediately, in-use storage times and conditions prior to dilution are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C; unless reconstitution has taken place in controlled and validated aseptic conditions.
Do not freeze the reconstituted solution.

Shelf-life of the solution for infusion containing the reconstituted solution
The infusion solution (0.9% sodium chloride infusion solution) containing the reconstituted solution is, physically and chemically stable for 24 hours (do not store above 30°C).

Special Instruction for Use, Handling and Disposal
Appropriate aseptic technique should be used.

The 440 mg vial of (Herhope™) is reconstituted with 20 mL Sterile Bacteriostatic Water for Injection, containing 1.1% benzyl alcohol, as supplied. This yields a solution for multiple use containing 21 mg/ml Trastuzumab. Use of other reconstitution solvents should be avoided.

The 150 mg vial of (Herhope™) is reconstituted with 7.2 mL of sterile bacteriostatic water for injection, containing 1.1% benzyl alcohol, as supplied.

Medicine: Keep out of reach of children

Herhope™ should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted Herhope™ may result in problems with the amount of trastuzumab that can be withdrawn from the vial.

Instructions for Reconstitution - 440 mg vial:
1. Using a sterile syringe, slowly inject 20 ml of Sterile Bacteriostatic water into the Herhope™ 440 mg vial containing the lyophilized trastuzumab, directing the stream into the lyophilized cake.

2. Swirl vial gently to aid reconstitution. DO NOT SHAKE!

Instructions/or Reconstitution -150 mg vial:
1. Using a sterile syringe, slowly inject 7.2 mL of Sterile Bacteriostatic water into the Herhope™ 150 mg vial containing the lyophilized trastuzumab, directing the stream into the lyophilized cake.
2. Swirl vial gently to aid reconstitution. DO NOT SHAKE! Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The reconstituted Herhope™ results in a colourless to pale yellow transparent solution and should be essentially free of visible particles.

Instruction for dilution:
Determine the volume of the solution required
•For loading dose (4 mg/kg body weight) or maintenance dose (2 mg/kg body weight):

Volume (mL) =	Body weight (kg) x dose (4 mg / kg for loading or 2 mg / kg for maintenance)
	21 (mg / ml, concentration of reconstitution solution)

•For loading dose (8 mg /kg body weight) or a subsequent 3 weekly dose (6 mg/kg body weight):

Volume (mL) =	Body weight (kg) x dose (8 mg / kg for loading or 6 mg / kg for maintenance
	21 (mg / ml, concentration of reconstitution solution)

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 ml of 0.9% sodium chloride. Dextrose (5%) solution should not be used (see Incompatibilities). The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration. Once the infusion is prepared it should be administered immediately.

NATURE AND CONTENTS OF CONTAINER

Container closure of CHL's Trastuzumab (Herhope™) lyophilized powder for Injection: Glass Vials (Borosilicate USP Type I glass) with slotted rubber stopper and flip-off seals. Container closure of Solution for Reconstitution: Glass Vials (Borosilicate USP Type I glass) with rubber stopper and flip-off seals / Glass Ampoules (Borosilicate USP Type I glass).

SPECIAL PRECAUTIONS FOR DISPOSAL

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via waste water and disposal through household waste should be avoided.

MANUFACTURED BY

Cadila Healthcare Ltd.
Ahmedabad

MARKETED BY

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

REFERENCES:

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