954 mm

310 mm

To be sold by retail on prescription of a registered oncologist only

Trastuzumab Lyophilized Powder for Concentrate for Solution for Infusion

Eleftha®

1 NAME OF THE MEDICINAL PRODUCT
Trastuzumab lyophilized powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each single use vial contains…………Trastuzumab 150 mg
Each multiple use vial contains……….Trastuzumab 440 mg

Each ml of vial contains:

Name of ingredient	Quantity (mg/ml)	Function
Trastuzumab (INH)	21	API
Histidine hydrochloride (Ph .Eur.,USP)	0.47	Buffering Agent
L-Histidine (Ph .Eur.,USP)	0.30	Buffering Agent
Trehalsoe Dihydrate (Ph .Eur.,USP)	19.1	Maintain Isotonicity
Polysorbate 20 (Ph .Eur.,USP)	0.09	Stabilizer
Water for injection (IP, Ph .Eur.,USP)	q.s. to 1.0 ml	Vehicle

The reconstitution of lyophilized trastuzumab is prepared by using 7.2 ml of Sterile Water for Injection (SWFI) and 20 ml of Bacteriostatic Water for Injection (BWFI) (containing 1.1% w/v benzyl alcohol) for 150 mg and 440 mg vial, respectively, each ml of concentrate contains 21 mg of trastuzumab.

3 PHARMACEUTICAL FORM
Lyophilized powder for concentrate for solution for infusion
Solution for reconstitution

4 CLINICAL PARTICULARS

4.1 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.

4.2 Posology and method of administration
During a phase III clinical study in patients with HER2-positive metastatic breast cancer, Trastuzumab (manufactured by Intas Pharmaceuticals Limited) was administered as intravenous (IV) infusion with loading dose of 8 mg/kg body weight followed by maintenance dose of 6 mg/kg body weight, beginning three weeks after the loading dose. Patients received trastuzumab for total 6 cycles along with IV infusion of paclitaxel 175 mg/m^2 per cycle.

Information provided below is based on the innovator data.
HER2 testing is mandatory prior to initiation of therapy. Trastuzumab treatment should be administered by a qualified healthcare professional.

Trastuzumab should be administered via an IV infusion only. Do not administer as an IV push or bolus.

In order to prevent medication errors it is important to check the vial labels to ensure that the drug being prepared and administered is trastuzumab and not trastuzumab emtansine.

Posology

Metastatic breast cancer
Three-weekly schedule
The recommended initial loading dose is 8 mg/kg body weight. The recommended maintenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.

Weekly schedule
The recommended initial loading dose of trastuzumab is 4 mg/kg body weight. The recommended weekly maintenance dose of trastuzumab is 2 mg/kg body weight, beginning one week after the loading dose.

Administration in combination with paclitaxel or docetaxel
In the pivotal trials, paclitaxel or docetaxel was administered the day following the first dose of trastuzumab and immediately after the subsequent doses of trastuzumab if the preceding dose of trastuzumab was well tolerated.

Administration in combination with an aromatase inhibitor
In the pivotal trial trastuzumab and anastrozole were administered from day 1. There were no restrictions on the relative timing of trastuzumab and anastrozole at administration.

Early breast cancer

Three-weekly and weekly schedule
As a three-weekly regimen the recommended initial loading dose of trastuzumab is 8 mg/kg body weight. The recommended maintenance dose of trastuzumab at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.
As a weekly regimen (initial loading dose of 4 mg/kg followed by 2 mg/kg every week) concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide.

Metastatic gastric cancer

Three-weekly schedule
The recommended initial loading dose is 8 mg/kg body weight. The recommended maintenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.

Breast cancer and gastric cancer

Duration of treatment
Patients with metastatic breast cancer or metastatic gastric cancer should be treated with trastuzumab until progression of disease.

Patients with early breast cancer should be treated with trastuzumab for 1 year or until disease recurrence, whichever occurs first; extending treatment in early breast cancer beyond one year is not recommended.

Dose reduction
No reductions in the dose of trastuzumab were made during clinical trials. Patients may continue therapy during periods of reversible, chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time. Refer to the labeling documents for paclitaxel, docetaxel or aromatase inhibitor for information on dose reduction or delays.

If left ventricular ejection fraction (LVEF) percentage drops ≥10 points from baseline AND to below 50%, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further, or if symptomatic congestive heart failure (CHF) has developed, discontinuation of trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.

Missed doses
If the patient has missed a dose of trastuzumab by one week or less, then the usual maintenance dose (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent maintenance doses should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

If the patient has missed a dose of trastuzumab by more than one week, a re-loading dose of trastuzumab should be administered over approximately 90 minutes (weekly regimen: 4 mg/kg; three-weekly regimen: 8 mg/kg) as soon as possible. Subsequent trastuzumab maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen 6 mg/kg respectively) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules respectively.

Special populations
Dedicated pharmacokinetic (PK) studies in the elderly and those with renal or hepatic impairment have not been carried out. In a population PK analysis, age and renal impairment were not shown to affect trastuzumab disposition.

Paediatric population
There is no relevant use of trastuzumab in the paediatric population.

Method of administration
Trastuzumab loading dose should be administered as a 90-minute IV infusion. Do not administer as an IV push or bolus. Trastuzumab IV infusion should be administered by a healthcare provider prepared to manage anaphylaxis and an emergency kit should be available. Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Interruption or slowing the rate of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion.

For instructions on reconstitution of trastuzumab IV formulation before administration, see section 6.6.

4.3 Contraindications
Information provided in this section is based on the innovator data.
Hypersensitivity to trastuzumab, murine proteins, or to any of the excipients listed in "List of excipients".
Severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

4.4 Special warnings and precautions for use
Information provided in this section is based on the innovator data.
In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.
HER2 testing must be performed in a specialized laboratory which can ensure adequate validation of the testing procedures.
Currently no data from clinical trials are available on re-treatment of patients with previous exposure to trastuzumab in the adjuvant setting.

Cardiac dysfunction
General considerations
Patients treated with trastuzumab are at increased risk for developing CHF (New York Heart Association [NYHA] Class II-IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving trastuzumab therapy alone or in combination with paclitaxel or docetaxel, particularly following anthracycline (doxorubicin or epirubicin) containing chemotherapy. These may be moderate to severe and have been associated with death. In addition, caution should be exercised in treating patients with increased cardiac risk, e.g. hypertension, documented coronary artery disease, CHF, LVEF of <55%, older age.

All candidates for treatment with trastuzumab, but especially those with prior anthracycline and cyclophosphamide (AC) exposure, should undergo baseline cardiac assessment including history and physical examination, electrocardiogram (ECG), echocardiogram, and/or multigated acquisition (MUGA) scan or magnetic resonance imaging. Monitoring may help to identify patients who develop 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. A careful risk-benefit assessment should be made before deciding to treat with trastuzumab.

Trastuzumab may persist in the circulation for up to 7 months after stopping trastuzumab treatment based on population PK analysis of all available data. Patients who receive anthracyclines after stopping trastuzumab may possibly be at increased risk of cardiac dysfunction. If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Formal cardiological assessment should be considered in patients in whom there are cardiovascular concerns following baseline screening. In all patients cardiac function should be monitored during treatment (e.g. every 12 weeks). Monitoring may help to identify patients who develop cardiac dysfunction. Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g. every 6 - 8 weeks). If patients have a continued decrease in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of trastuzumab therapy has been seen.

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

If symptomatic cardiac failure develops during trastuzumab therapy, it should be treated with standard medicinal products for CHF. Most patients who developed CHF or asymptomatic cardiac dysfunction in pivotal trials improved with standard CHF treatment consisting of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a beta-blocker. The majority of patients with cardiac symptoms and evidence of a clinical benefit of trastuzumab treatment continued on therapy without additional clinical cardiac events.

Metastatic breast cancer
Trastuzumab and anthracyclines should not be given concurrently in combination in the metastatic breast cancer setting.
Patients with metastatic breast cancer who have previously received anthracyclines are also at risk of cardiac dysfunction with trastuzumab treatment, although the risk is lower than with concurrent use of trastuzumab and anthracyclines.

Early breast cancer
For patients with early breast cancer, 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. In patients who receive anthracycline-containing chemotherapy further monitoring is recommended, and should occur yearly up to 5 years from the last administration of trastuzumab, or longer if a continuous decrease of LVEF is observed.

Patients with history of myocardial infarction (MI), angina pectoris requiring medical treatment, history of or existing CHF (NYHA Class II –IV), LVEF of <55%, other cardiomyopathy, cardiac arrhythmia requiring medical treatment, clinically significant cardiac valvular disease, poorly controlled hypertension (hypertension controlled by standard medical treatment eligible), and hemodynamic effective pericardial effusion were excluded from adjuvant and neoadjuvant early breast cancer pivotal trials with trastuzumab and therefore treatment cannot be recommended in such patients.

Adjuvant treatment
Trastuzumab and anthracyclines should not be given concurrently in combination in the adjuvant treatment setting.

In patients with early breast cancer an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when trastuzumab was administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin and was more marked when trastuzumab was administered concurrently with taxanes than when administered sequentially to taxanes. Regardless of the regimen used, most symptomatic cardiac events occurred within the first 18 months. In one of the 3 pivotal studies conducted in which a median follow-up of 5.5 years was available a continuous increase in the cumulative rate of symptomatic cardiac or LVEF events was observed in patients who were administered trastuzumab concurrently with a taxane following anthracycline therapy up to 2.37% compared to approximately 1% in the two comparator arms (anthracycline plus cyclophosphamide followed by taxane and taxane, carboplatin and trastuzumab).

Risk factors for a cardiac event identified in four large adjuvant studies included advanced age (> 50 years), low LVEF (<55%) at baseline, prior to or following the initiation of paclitaxel treatment, decline in LVEF by 10-15 points, and prior or concurrent use of anti-hypertensive medicinal products.

In patients receiving trastuzumab after completion of adjuvant chemotherapy, the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracycline given prior to initiation of trastuzumab and a body mass index (BMI) >25 kg/m^2.

Neoadjuvant-adjuvant treatment
In patients with early breast cancer eligible for neoadjuvant-adjuvant treatment, trastuzumab should be used concurrently with anthracyclines only in chemotherapy-naive patients and only with low-dose anthracycline regimens i.e. maximum cumulative doses of doxorubicin 180 mg/m^2 or epirubicin 360 mg/m^2.

If patients have been treated concurrently with a full course of low-dose anthracyclines and trastuzumab in the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after surgery. In other situations, the decision on the need for additional cytotoxic chemotherapy is determined based on individual factors.

Experience of concurrent administration of trastuzumab with low dose anthracycline regimens is currently limited to two trials.

In the pivotal trial, trastuzumab was administered concurrently with neoadjuvant chemotherapy containing three cycles of doxorubicin (cumulative dose 180 mg/m^2).

The incidence of symptomatic cardiac dysfunction was 1.7% in the trastuzumab arm.
Other pivotal trial was designed to demonstrate non-inferiority of treatment with trastuzumab subcutaneous formulation versus treatment with trastuzumab IV formulation based on coprimary PK and efficacy endpoints (trastuzumab C_{trough} at pre-dose Cycle 8, and pCR rate at definitive surgery, respectively). In the trial, trastuzumab was administered concurrently with neoadjuvant chemotherapy that contained four cycles of epirubicin (cumulative dose 300 mg/m^2); at a median follow-up of 40 months, the incidence of congestive cardiac failure was 0.0% in the trastuzumab IV arm.
Clinical experience is limited in patients above 65 years of age.

Infusion-related reactions (IRRs) and hypersensitivity
Serious IRRs to trastuzumab infusion including dyspnoea, hypotension, wheezing, hypertension, bronchospasm, supraventricular tachyarrhythmia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria and angioedema have been reported. Pre-medication may be used to reduce risk of occurrence of these events. The majority of these events occur during or within 2.5 hours of the start of the first infusion. Should an infusion reaction occur the infusion should be discontinued or the rate of infusion slowed and the patient should be monitored until resolution of all observed symptoms. These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. The majority of patients experienced resolution of symptoms and subsequently received further infusions of trastuzumab. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and co-morbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with trastuzumab.

Initial improvement followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported. Fatalities have occurred within hours and up to one week following infusion.

On very rare occasions, patients have experienced the onset of infusion symptoms and pulmonary symptoms more than six hours after the start of the trastuzumab infusion. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur.

Pulmonary events
Severe pulmonary events have been reported with the use of trastuzumab in the post-marketing setting. These events have occasionally been fatal. In addition, cases of interstitial lung disease including lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported. Risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy. These events may occur as part of an infusion-related reaction or with a delayed onset. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and co-morbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with trastuzumab. Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

Benzyl alcohol
Benzyl alcohol, used as a preservative in bacteriostatic water for injection in 440 mg multiple-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 hypersensitivity to benzyl alcohol, trastuzumab should be reconstituted with water for injection, and only one dose per trastuzumab vial should be used. Any unused portion must be discarded. Sterile water for injection, used to reconstitute 150 mg single use vials, does not contain benzyl alcohol.

4.5 Interactions with other medicinal products and other forms of interaction
Information provided in this section is based on the innovator data.

No formal drug interaction studies have been performed. Clinically significant interactions between trastuzumab and the concomitant medicinal products used in clinical trials have not been observed.

Effect of trastuzumab on the pharmacokinetics of other antineoplastic agents
Pharmacokinetic data from two studies in women with HER2-positive metastatic breast cancer suggested that exposure to paclitaxel and doxorubicin (and their major metabolites 6-α hydroxylpaclitaxel, POH, and doxorubicinol, DOL) was not altered in the presence of trastuzumab (8 mg/kg or 4 mg/kg IV loading dose followed by 6 mg/kg q3w or 2 mg/kg q1w IV, respectively). However, trastuzumab may elevate the overall exposure of one doxorubicin metabolite, (7-deoxy-13 dihydro-doxorubicinone, D7D). The bioactivity of D7D and the clinical impact of the elevation of this metabolite was unclear.

Data from a single-arm study of trastuzumab (4 mg/kg IV loading dose and 2 mg/kg IV weekly) and docetaxel (60 mg/m^2 IV) in Japanese women with HER2-positive metastatic breast cancer, suggested that concomitant administration of trastuzumab had no effect on the single dose PK of docetaxel.

The results of a substudy performed in male and female Japanese patients with advanced gastric cancer suggested that the exposure to the bioactive metabolites (e.g. 5-FU) of capecitabine was not affected by concurrent use of cisplatin or by concurrent use of cisplatin plus trastuzumab.

However, capecitabine itself showed higher concentrations and a longer half-life when combined with trastuzumab. The data also suggested that the PK of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus trastuzumab.

Pharmacokinetic data from a study in patients with metastatic or locally advanced inoperable HER2-positive cancer suggested that trastuzumab had no impact on the PK of carboplatin.

Effect of antineoplastic agents on trastuzumab pharmacokinetics
By comparison of simulated serum trastuzumab concentrations after trastuzumab monotherapy (4 mg/kg loading/2 mg/kg q1w IV) and observed serum concentrations in Japanese women with HER2-positive metastatic breast cancer no evidence of a PK effect of concurrent administration of docetaxel on the PK of trastuzumab was found.

Comparison of PK results from two Phase II studies and one Phase III study in which patients were treated concomitantly with trastuzumab and paclitaxel and two Phase II studies in which trastuzumab was administered as monotherapy, in women with HER2-positive metastatic breast cancer indicates that individual and mean trastuzumab trough serum concentrations varied within and across studies but there was no clear effect of the concomitant administration of paclitaxel on the PK of trastuzumab. Comparison of trastuzumab PK data from study in which women with HER2-positive metastatic breast cancer were treated concomitantly with trastuzumab, paclitaxel and doxorubicin to trastuzumab PK data in studies where trastuzumab was administered as monotherapy or in combination with anthracycline plus cyclophosphamide or paclitaxel, suggested no effect of doxorubicin and paclitaxel on the PK of trastuzumab.

Pharmacokinetic data from study suggested that carboplatin had no impact on the PK of trastuzumab.

The administration of concomitant anastrozole did not appear to influence the PK of trastuzumab.

4.6 Fertility, pregnancy and lactation
Information provided in this section is based on the innovator data.

Fertility
There is no fertility data available.

Women with childbearing potential
Women of childbearing potential should be advised to use effective contraception during treatment with trastuzumab and for 7 months after treatment has concluded.

Pregnancy
Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg trastuzumab IV formulation and have revealed no evidence of impaired fertility or harm to the foetus.

Placental transfer of trastuzumab during the early (days 20–50 of gestation) and late (days 120–150 of gestation) foetal development period was observed. It is not known whether trastuzumab can affect reproductive capacity. As animal reproduction studies are not always predictive of human response, 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 foetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving trastuzumab. Women who become pregnant should be advised of the possibility of harm to the foetus.

If a pregnant woman is treated with trastuzumab or if a patient becomes pregnant while receiving trastuzumab or within 7 months following the last dose of trastuzumab, close monitoring by a multidisciplinary team is desirable.

Breast feeding
A study conducted in lactating cynomolgus monkeys at doses 25 times that of the weekly human maintenance dose of 2 mg/kg trastuzumab IV formulation demonstrated that trastuzumab is secreted in the milk. The presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 1 month of age. It is not known whether trastuzumab is secreted in human milk. As human IgG1 is secreted into human milk, and the potential for harm to the infant is unknown, women should not breast-feed during trastuzumab therapy and for 7 months after the last dose.

4.7 Effects on ability to drive and use machines
Information provided in this section is based on the innovator data.

Trastuzumab has no or 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 abate.

4.8 Undesirable effects
Information provided below is based on the study conducted with Intas Trastuzumab.

In a prospective, multicentric, randomized, open-label, parallel-group, phase III study in women with HER2-overexpressing metastatic breast cancer, 120 patients were randomized to receive Trastuzumab (manufactured by Intas Pharmaceuticals Limited; n=82) or Herclon™ (marketed by Roche; n=38) at IV loading dose of 8 mg/kg (for 1st cycle) and maintenance dose of 6 mg/kg for subsequent cycles on day 1 of each chemotherapy cycle of 21 days, for up to 6 cycles. Patients were also administered with paclitaxel 175 mg/m^2 per cycle during the study. All 120 patients were included in safety population.

Total 441 adverse events (AEs) were reported in 79 patients during the study: 327 AEs in 54 patients from Intas Trastuzumab group and 114 AEs in 25 patients from Herclon™ group. The most commonly reported AEs with Intas Trastuzumab (incidence in ≥5% patients) during the study were alopecia (25.6%), pain (22%), nausea (19.5%), peripheral neuropathy (14.6%), pyrexia (9.8%), anaemia (9.8%), diarrhoea (9.8%), vomiting (9.8%), pain in extremity (8.5%), headache (8.5%), abdominal pain (8.5%), cough (7.3%), constipation (6.1%), gastritis (6.1%), and asthenia (6.1%). Two deaths were reported in Intas Trastuzumab group during the study; both deaths were due to cardio-pulmonary arrest and unrelated to the drug. Total 7 other serious AEs (SAEs) were reported by 5 patients during the study: 2 in Herclon group and 5 in Intas Trastuzumab group. All the SAEs recovered without sequelae.

The causality assessment was judged as unrelated for 5 SAEs and as related for 2 SAEs (both were hospitalization following AE with Intas Trastuzumab).

Table 1: Adverse Events Reported in Women with HER2-overexpressing Metastatic Breast Cancer Treated with Intas Trastuzumab or Herclon™ (Safety Population)

System organ class Preferred term	No. of AEs (% of patients) Intas Trastuzumab (n=82)	 Herclon™ (n=38)
Blood and lymphatic system disorders		
Anaemia	14 (9.8)	7 (7.9)
Febrile neutropenia	1 (1.2)	0 (0.0)
Leukocytosis	2 (1.2)	1 (2.6)
Neutropenia	4 (3.7)	0 (0.0)
Cardiac disorders		
Bundle branch block right	0 (0.0)	1 (2.6)
Cardio-respiratory arrest	2 (2.4)	0 (0.0)
Tachycardia	1 (1.2)	0 (0.0)
Ventricular extrasystoles	1 (1.2)	0 (0.0)
Ear and labyrinth disorders		
Vertigo	1 (1.2)	0 (0.0)
Vestibular disorder	1 (1.2)	0 (0.0)
Gastrointestinal disorders		
Abdominal discomfort	2 (2.4)	0 (0.0)
Abdominal pain	8 (8.5)	1 (2.6)
Abdominal pain upper	1 (1.2)	0 (0.0)
Constipation	5 (6.1)	2 (5.3)
Diarrhoea	9 (9.8)	3 (7.9)
Gastritis	23 (6.1)	8 (5.3)
Hyperchlorhydria	3 (3.7)	0 (0.0)
Mouth haemorrhage	1 (1.2)	0 (0.0)
Nausea	33 (19.5)	10 (13.2)
Vomiting	9 (9.8)	3 (7.9)
General disorders and administration site conditions		
Asthenia	5 (6.1)	1 (2.6)
Chest pain	4 (3.7)	1 (2.6)
Chills	1 (1.2)	0 (0.0)
Local swelling	1 (1.2)	0 (0.0)
Oedema peripheral	1 (1.2)	1 (2.6)
Pain	64 (22.0)	18 (13.2)
Peripheral swelling	1 (1.2)	1 (2.6)
Pyrexia	8 (9.8)	7 (13.2)
Immune system disorders		
Hypersensitivity	1 (1.2)	0 (0.0)
Infections and infestations		
Nasopharyngitis	0 (0.0)	1 (2.6)
Upper respiratory tract infection	0 (0.0)	1 (2.6)
Viral upper respiratory tract infection	0 (0.0)	1 (2.6)
Injury, poisoning and procedural complications		
Wound secretion	1 (1.2)	1 (2.6)
Investigations		
Alanine aminotransferase increased	2 (2.4)	0 (0.0)
Aspartate aminotransferase increased	2 (2.4)	0 (0.0)
Blood glucose increased	1 (1.2)	0 (0.0)
Ejection fraction decreased	1 (1.2)	0 (0.0)
Neutrophil count increased	2 (2.4)	1 (2.6)
Weight decreased	3 (3.7)	0 (0.0)
White blood cell count decreased	1 (1.2)	0 (0.0)
White blood cell count increased	0 (0.0)	1 (2.6)
Metabolism and nutrition disorders		
Decreased appetite	1 (1.2)	0 (0.0)
Dehydration	0 (0.0)	1 (2.6)
Hyperglycaemia	1 (1.2)	1 (2.6)
Iron deficiency	1 (1.2)	0 (0.0)
Musculoskeletal and connective tissue disorders		
Arthralgia	2 (2.4)	0 (0.0)
Back pain	2 (2.4)	3 (7.9)
Bone pain	1 (1.2)	0 (0.0)
Neck pain	3 (3.7)	1 (2.6)
Pain in extremity	22 (8.5)	9 (7.9)
Nervous system disorders		
Burning sensation	2 (2.4)	0 (0.0)
Headache	9 (8.5)	3 (7.9)
Hypoaesthesia	3 (3.7)	3 (5.3)
Neuropathy peripheral	13 (14.6)	4 (10.5)
Paraesthesia	2 (2.4)	0 (0.0)
Renal and urinary disorders		
Oliguria	0 (0.0)	1 (2.6)
Respiratory, thoracic and mediastinal disorders		
Cough	6 (7.3)	3 (7.9)
Dyspnoea	3 (3.7)	1 (2.6)
Haemoptysis	1 (1.2)	0 (0.0)
Tachypnoea	1 (1.2)	0 (0.0)
Skin and subcutaneous tissue disorders		
Alopecia	21 (25.6)	12 (28.9)
Erythema	1 (1.2)	0 (0.0)
Hyperhidrosis	1 (1.2)	0 (0.0)
Pruritus	2 (2.4)	1 (2.6)
Pruritus generalised	1 (1.2)	0 (0.0)
Rash	2 (2.4)	0 (0.0)
Urticaria	1 (1.2)	0 (0.0)
Vascular disorders		
Hypertension	1 (1.2)	0 (0.0)
Hypotension	1 (1.2)	0 (0.0)

Immunogenicity
In a multicentric, randomized, open-label, parallel-group, phase III study in 120 women with HER2-overexpressing metastatic breast cancer, incidence of anti-drug antibody against Intas Trastuzumab and Herclon™ was evaluated. Blood samples were collected at baseline, end of cycle 3 and end of cycle 6. All samples were negative for anti-drug antibodies against trastuzumab.

Information provided below is based on the innovator data.

Summary of the safety profile
Amongst the most serious and/or common adverse reactions reported in trastuzumab usage (IV and subcutaneous formulations) to date are cardiac dysfunction, infusion-related reactions, haematotoxicity (in particular neutropenia), infections and pulmonary adverse reactions.

Tabulated list of adverse reactions

In this section, the following categories of frequency have been used: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Presented in Table 2 are adverse reactions that have been reported in association with the use of IV trastuzumab alone or in combination with chemotherapy in pivotal clinical trials and in the post-marketing setting.

All the terms included are based on the highest percentage seen in pivotal clinical trials.

Table 2: Undesirable Effects Reported with IV Trastuzumab Monotherapy or in Combination with Chemotherapy in Pivotal Clinical Trials (N=8386) and in Post-Marketing

System organ class	Adverse reaction	Frequency
Infections and infestations	Infection	Very common
	Nasopharyngitis	Very common
	Neutropenic sepsis	Common
	Cystitis	Common
	Herpes zoster	Common
	Influenza	Common
	Sinusitis	Common
	Skin infection	Common
	Rhinitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
	Erysipelas	Common
	Cellulitis	Common
	Pharyngitis	Common
	Sepsis	Uncommon
Neoplasms benign, malignant and unspecified (incl. Cysts and polyps)	Malignant neoplasm progression	Not known
	Neoplasm progression	Not known
Blood and lymphatic system disorders	Febrile neutropenia	Very common
	Anaemia	Very common
	Neutropenia	Very common
	White clood cell count decreased/ leucopenia	Very common
	Thrombocytopenia	Very common
	Hypoprothrombinaemia	Not known
	Immune thrombocytopenia	Not known
Immune system disorders	Hypersensitivity	Common
	Anaphylactic reaction[+]	Not known
	Anaphylactic shock[+]	Not known
Metabolism and nutrition disorders	Weight decreased/Weight loss	Very common
	Anorexia	Very common
	Hyperkalaemia	Not known
Psychiatric disorders	Insomnia	Very common
	Anxiety	Common
	Depression	Common
	Thinking abnormal	Common
Nervous system disorders	Tremor[1]	Very common
	Dizziness	Very common
	Headache	Very common
	Paraesthesia	Very common
	Dysgeusia	Very common
	Peripheral neuropathy	Common
	Hypertonia	Common
	Somnolence	Common
	Ataxia	Common
	Paresis	Rare
	Brain oedema	Not known
Eye disorders	Conjunctivitis	Very common
	Lacrimation increased	Very common
	Dry eye	Common
	Papilloedema	Not known
	Retinal haemorrhage	Not known
Ear and labyrinth disorders	Deafness	Uncommon
Cardiac disorders	Blood pressure decreased[1]	Very common
	Blood pressure increased[1]	Very common
	Heart beat irregular[1]	Very common
	Palpitation[1]	Very common
	Cardiac flutter[1]	Very common
	Ejection fraction decreased*	Very common
	Cardiac failure (congestive)[+]	Common
	Supraventricular[+1] tachyarrhythmia	Common
	Cardiomyopathy	Common
	Pericardial effusion	Uncommon
	Cardiogenic shock	Not known
	Pericarditis	Not known
	Bradycardia	Not known
	Gallop rhythm present	Not known
Vascular disorders	Hot flush	Very common
	Hypotension[+1]	Common
	Vasodilatation	Common
Respiratory, thoracic and mediastinal disorders	Wheezing[+1]	Very common
	Dyspnea[+]	Very common
	Cough	Very common
	Epistaxis	Very common
	Rhinorrhea	Very common
	Pneumonia[+]	Common
	Asthma	Common
	Lung disorder	Common
	Pleural effusion[+]	Common
	Pneumonitis	Rare
	Pulmonary fibrosis[+]	Not known
	Respiratory distress[+]	Not known
	Respiratory failure[+]	Not known
	Lung infiltration[+]	Not known
	Acute pulmonary oedema[+]	Not known
	Acute respiratory distress syndrome[+]	Not known
	Bronchospasm[+]	Not known
	Hypoxia[+]	Not known
	Oxygen saturation decreased[+]	Not known
	Laryngeal oedema	Not known
	Orthopnoea	Not known
	Pulmonary oedema	Not known
	Interstitial lung disease	Not known
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting	Very common
	Nausea	Very common
	Lip swelling[1]	Very common
	Abdominal pain	Very common
	Dyspepsia	Very common
	Constipation	Very common
	Stomatitis	Very common
	Pancreatitis	Common
	Haemorrhoids	Common
	Dry mouth	Common
Hepatobiliary disorders	Hepatocellular injury	Common
	Hepatitis	Common
	Liver tenderness	Common
	Jaundice	Rare
	Hepatic failure	Not known
Skin and subcutaneous tissue disorders	Erythema	Very common
	Rash	Very common
	Swelling face[1]	Very common
	Alopecia	Very common
	Nail disorder	Very common
	Palmar-plantar erythrodysaesthesia syndrome	Very common
	Acne	Common
	Dry skin	Common
	Ecchymosis	Common
	Hyperhydrosis	Common
	Maculopapular rash	Common
	Pruritus	Common
	Onychoclasis	Common
	Dermatitis	Common
	Urticaria	Uncommon
	Angioedema	Not known
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	Muscle tightness[1]	Very common
	Myalgia	Very common
	Arthritis	Common
	Back pain	Common
	Bone pain	Common
	Muscle spasma	Common
	Neck pain	Common
	Pain in extremity	Common
Renal and urinary disorders	Renal disorder	Common
	Glomerulonephritis membranous	Not known
	Glomerulonephropathy	Not known
	Renal failure	Not known
Pregnancy, puerperium and perinatal conditions	Oligohydramnios	Not known
	Renal hypoplasia	Not known
	Pulmonary hypoplasia	Not known
Reproductive system and breast disorders	Breast inflammation/mastitis	Common
General disorders and administration site conditions	Asthenia	Very common
	Chest pain	Very common
	Chills	Very common
	Fatigue	Very common
	Influenza-like symptoms	Very common
	Infusion related reaction	Very common
	Pain	Very common
	Pyrexia	Very common
	Mucosal inflammation	Very common
	Peripheral oedema	Very common
	Malaise	Common
	Oedema	Common
Injury, poisoning and procedural complications	Contusion	Common

[+] Denotes adverse reactions that have been reported in association with a fatal outcome.
[1] Denotes adverse reactions that are reported largely in association with Infusion-related reactions. Specific percentages for these are not available.
* Observed with combination therapy following anthracyclines and combined with taxanes

Description of selected adverse reactions

Cardiac dysfunction
Congestive heart failure (NYHA Class II – IV) is a common adverse reaction associated with the use of trastuzumab and has been associated with a fatal outcome. Signs and symptoms of cardiac dysfunction such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S3 gallop, or reduced ventricular ejection fraction, have been observed

Eleftha

Eleftha

Front Side

Reason For Revision: New Artwork					**Artwork No. :** AW-QA-1863-00	
Supersedes No.: NA						
Reason For Replacement : NA						
	Prepared by	**Approved by**				**Authorized By**
Department	**APD**	**Packing (FP)**	**Regulatory**	**Medical**	**QA**	**QA**
Signature						
Date						
Name						
Designation						

Product Name : ELEFTHA Vial-Insert
Size : 954 x 310 mm
No. of Colour : 1 (Black)
No. of fold : ~106 x ~31 mm
Nos. of fold : 12
Finishing of insert : "Tear Here" tape for closing
Type of paper : Bible Paper
GSM of paper : 40± 10gsm
040119

in patients treated with trastuzumab.

In 3 pivotal clinical trials of adjuvant trastuzumab given in combination with chemotherapy, the incidence of grade 3/4 cardiac dysfunction (specifically symptomatic Congestive Heart Failure) was similar in patients who were administered chemotherapy alone (i.e. did not receive trastuzumab) and in patients who were administered trastuzumab sequentially after a taxane (0.3-0.4%). The rate was highest in patients who were administered trastuzumab concurrently with a taxane (2.0%). In the neoadjuvant setting, the experience of concurrent administration of trastuzumab and low dose anthracycline regimen is limited.

When trastuzumab was administered after completion of adjuvant chemotherapy NYHA Class III-IV heart failure was observed in 0.6% of patients in the one-year arm after a median follow-up of 12 months. In study BO16348, after a median follow-up of 8 years the incidence of severe CHF (NYHA Class III & IV) in the trastuzumab 1 year treatment arm was 0.8%, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6%.

Reversibility of severe CHF (defined as a sequence of at least two consecutive LVEF values ≥50 % after the event) was evident for 71.4% of trastuzumab-treated patients. Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 79.5% of patients. Approximately 17 % of cardiac dysfunction related events occurred after completion of trastuzumab.

In the pivotal metastatic trials of IV trastuzumab, the incidence of cardiac dysfunction varied between 9% and 12% when it was combined with paclitaxel compared with 1% – 4% for paclitaxel alone. For monotherapy, the rate was 6% – 9%. The highest rate of cardiac dysfunction was seen in patients receiving trastuzumab concurrently with anthracycline/cyclophosphamide (27%), and was significantly higher than for anthracycline/cyclophosphamide alone (7% – 10%). In a subsequent trial with prospective monitoring of cardiac function, the incidence of symptomatic CHF was 2.2% in patients receiving trastuzumab and docetaxel, compared with 0% in patients receiving docetaxel alone.

Most of the patients (79%) who developed cardiac dysfunction in these trials experienced an improvement after receiving standard treatment for CHF.

Infusion reactions, allergic-like reactions and hypersensitivity
It is estimated that approximately 40% of patients who are treated with trastuzumab will experience some form of infusion-related reaction. However, the majority of infusion-related reactions are mild to moderate in intensity (NCI-CTC grading system) and tend to occur earlier in treatment, i.e. during infusions one, two and three and lessen in frequency in subsequent infusions.

Reactions include chills, fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, respiratory distress, rash, nausea, vomiting and headache. The rate of infusion-related reactions of all grades varied between studies depending on the indication, the data collection methodology, and whether trastuzumab was given concurrently with chemotherapy or as monotherapy.

Severe anaphylactic reactions requiring immediate additional intervention can occur usually during either the first or second infusion of trastuzumab and have been associated with a fatal outcome.

Anaphylactoid reactions have been observed in isolated cases.

Haematotoxicity
Febrile neutropenia, leukopenia, anaemia, thrombocytopenia and neutropenia occurred very commonly. The frequency of occurrence of hypoprothrombinemia is not known. The risk of neutropenia may be slightly increased when trastuzumab is administered with docetaxel following anthracycline therapy.

Pulmonary events
Severe pulmonary adverse reactions occur in association with the use of trastuzumab and have been associated with a fatal outcome. These include, but are not limited to, pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency.

Immunogenicity
In the neoadjuvant-adjuvant early breast cancer treatment setting, 8.1% (24/296) of patients treated with trastuzumab IV developed antibodies against trastuzumab (regardless of antibody presence at baseline). Neutralizing anti-trastuzumab antibodies were detected in post-baseline samples in 2 of 24 trastuzumab IV patients.

The clinical relevance of these antibodies is not known; nevertheless the PK, efficacy (determined by pathological Complete Response [pCR]) and safety determined by occurrence of administration related reactions (ARRs) of trastuzumab IV did not appear to be adversely affected by these antibodies.

There are no immunogenicity data available for trastuzumab in gastric cancer.

4.9 Overdose
Information provided in this section is based on the innovator data.

There is no experience with overdose in human clinical trials. Single doses of trastuzumab alone greater than 10 mg/kg have not been administered in the clinical trials; a maintenance dose of 10 mg/kg q3w following a loading dose of 8 mg/kg has been studied in a clinical trial with metastatic gastric cancer patients. Doses up to this level were well tolerated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC03

Trastuzumab is a recombinant humanized IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2). Overexpression of HER2 is observed in 20%-30% of primary breast cancers. Studies of HER2-positivity rates in gastric cancer (GC) using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization (CISH) have shown that there is a broad variation of HER2-positivity ranging from 6.8% to 34.0% for IHC and 7.1% to 42.6% for FISH. Studies indicate that breast cancer patients whose tumours overexpress HER2 have a shortened disease-free survival compared to patients whose tumours do not overexpress HER2. The extracellular domain of the receptor (ECD, p105) can be shed into the blood stream and measured in serum samples.

Mechanism of action
Trastuzumab binds with high affinity and specificity to sub-domain IV, a juxta-membrane region of HER2's extracellular domain. Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. As a result, trastuzumab has been shown, in both in vitro assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2. Additionally, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC). In vitro, trastuzumab-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Clinical efficacy
Information provided below is based on the study conducted with Intas Trastuzumab.

Metastatic breast cancer
Efficacy and safety profile of trastuzumab (manufactured by Intas Pharmaceuticals Limited) and Herclon™ (marketed by Roche) was evaluated in a prospective, multicentric, randomized, open-label, parallel-group, phase III study in patients with HER2-overexpressing metastatic breast cancer. Female patients aged between 18 and 65 years (both inclusive) who had documented evidence of HER2-overexpressing metastatic breast cancer histologically or cytologically, had not previously received any chemotherapy for metastatic disease, had at least one measurable lesion as per RECIST 1.1 and eligible for taxanes as well as trastuzumab were included in the study.

Total 120 patients were randomized to receive Intas Trastuzumab (n=82) or Herclon™ (n=38) at IV loading dose of 8 mg/kg (for 1st cycle) and maintenance dose of 6 mg/kg for subsequent cycles on day 1 of each chemotherapy cycle of 21 days for up to 6 cycles. Patients were also administered with paclitaxel 175 mg/m^2 per cycle during the study. The primary efficacy endpoint was overall response rate (complete response [CR] + partial response [PR]) using RECIST 1.1 criteria at the end of chemotherapy cycle 3 and cycle 6. Additional efficacy endpoints included best overall response (CR+PR) and disease control rate (CR+PR+stable disease [SD]).

Out of 120 patients randomized, 102 patients were included in per-protocol (PP) population (69 from Intas Trastuzumab group and 33 from Herclon™ group) and 114 patients were included in intent-to-treat (ITT) population (78 from Intas Trastuzumab group and 36 from Herclon™ group). Results of the primary and secondary efficacy endpoints from the PP population are summarized in Table 3. Intas Trastuzumab was non-inferior to Herclon™ regarding the primary efficacy endpoint. Similar conclusions were reported for the ITT population.

Table 3: Efficacy Results of Intas Trastuzumab and Herclon™ in Treatment of HER2-overexpressing Metastatic Breast Cancer (Per-protocol Population)

Endpoint	Number of patients (%)		Treatment difference (95% CI)
	Intas Trastuzumab (n=69)	Herclon™ (n=33)	
Overall response rate – Cycle 4	48 (69.57%)	13 (39.39%)	30.17% (10.28%, 50.07%)
Overall response rate – Cycle 6	33 (47.83%)	9 (27.27%)	20.55% (1.32%, 39.78%)
Best overall response rate	33 (47.83%)	9 (27.27%)	20.55% (1.32%, 39.78%)
Disease control rate	64 (92.75%)	27 (81.82%)	10.94% (-3.58%, 25.45%)

5.2 Pharmacokinetic properties
Information provided below is based on study conducted with Intas Trastuzumab.

Pharmacokinetic (PK) profile of Intas Trastuzumab and Herclon™ were evaluated in a subset of female patients with HER2-overexpressing metastatic breast cancer as a part of the multicentric, randomized, open-label, parallel-group, phase III study. Patients were administered with a loading dose of 8 mg/kg of Intas Trastuzumab or Herclon™ as an IV infusion. Serum samples were collected from 20 patients (14 from Intas Trastuzumab and 6 from Herclon™ group) for up to 22 days during chemotherapy cycle 1. Of these 20 patients, only 19 patients were analyzed; 1 patient was excluded from the analysis due to three consecutive missing samples. Descriptive statistics of PK parameters of Intas Trastuzumab and Herclon™ is provided in Table 4.

Table 4: Pharmacokinetic Parameters of Intas Trastuzumab and Herclon in Women with HER2-overexpressing Metastatic Breast Cancer (Cycle 1)

Parameter (Unit)	Mean ± SD (untransformed data)	
	Intas Trastuzumab (n=13)	Herclon (n=6)
AUC_{0-22d} (µg.h/ml)	24958.030 ± 7754.1302	25253.903 ± 7636.2143
C_{max} (µg/ml)	199.144 ± 37.3145	244.827 ± 99.3967
T_{max} (h)[1]	2.500 (1.500 - 8.000)	2.009 (1.000 - 4.000)

AUC: area under the serum concentration versus time curve; C_{max}: maximum serum concentration; T_{max}: time corresponding to Cmax
[1] Median (minimum-maximum) value reported for T_{max}

Information provided below is based on the innovator data.

The PK of trastuzumab were evaluated in a population PK model analysis using pooled data from 1,582 subjects, including patients with HER2 positive metastatic breast cancer, early breast cancer, advanced gastric cancer or other tumor types, and healthy volunteers, in 18 Phase I, II and III trials receiving trastuzumab IV. A two-compartment model with parallel linear and non-linear elimination from the central compartment described the trastuzumab concentration-time profile. Due to non-linear elimination, total clearance increased with decreasing concentration. Therefore, no constant value for half-life of trastuzumab can be deduced. The $t_{1/2}$ decreases with decreasing concentrations within a dosing interval (Table 4). metastatic breast cancer and early breast cancer patients had similar PK parameters (e.g. clearance (CL), the central compartment volume (V_c)) and population-predicted steady-state exposures (C_{min}, C_{max} and AUC). Linear clearance was 0.136 L/day for metastatic breast cancer, 0.112 L/day for early breast cancer and 0.176 L/day for advanced gastric cancer. The non-linear elimination parameter values were 8.81 mg/day for the maximum elimination rate (V_{max}) and 8.92 µg/ml for the Michaelis-Menten constant (K_m) for the metastatic breast cancer, early breast cancer, and advanced gastric cancer patients. The central compartment volume was 2.62 L for patients with metastatic breast cancer and early breast cancer and 3.63 L for patients with advanced gastric cancer. In the final population PK model, in addition to primary tumor type, body-weight, serum aspartate aminotransferase and albumin were identified as a statistically significant covariates affecting the exposure of trastuzumab.

However, the magnitude of effect of these covariates on trastuzumab exposure suggests that these covariates are unlikely to have a clinically meaningful effect on trastuzumab concentrations.

The population predicted PK exposure values (median with 5th - 95th Percentiles) and PK parameter values at clinically relevant concentrations (C_{max} and C_{min}) for metastatic breast cancer, early breast cancer and advanced gastric cancer patients treated with the approved q1w and q3w dosing regimens are shown in Table 5 (Cycle 1), Table 6 (steady state) and Table 7 (PK parameters).

Table 5: Population Predicted Cycle 1 PK Exposure Values (median with 5th - 95th Percentiles) for Trastuzumab IV Dosing Regimens in Metastatic Breast Cancer, Early Breast Cancer and Advanced Gastric Cancer Patients

Regimen	Primary tumor type	N	C_{min} (µg/ml)	C_{max} (µg/ml)	$AUC_{0-21days}$ (µg.day/ml)
8 mg/kg + 6 mg/kg q3w	MBC	805	28.7 (2.9 - 46.3)	182 (134 - 280)	1376 (728 - 1998)
	EBC	390	30.9 (18.7 - 45.5)	176 (127 - 227)	1390 (1039 - 1895)
	AGC	274	23.1 (6.1 - 50.3)	132 (84.2 – 225)	1109 (588 – 1938)
4 mg/kg + 2 mg/kg qw	MBC	805	37.4 (8.7 - 58.9)	76.5 (49.4 - 114)	1073 (597 – 1584)
	EBC	390	38.9 (25.3 - 58.8)	76.0 (54.7 - 104)	1074 (783 - 1502)

AGC: advanced gastric cancer; EBC: early breast cancer; MBC: metastatic breast cancer

Table 6: Population Predicted Steady State PK Exposure Values (median with 5th - 95th Percentiles) for Trastuzumab IV Dosing Regimens in Metastatic Breast Cancer, Early Breast Cancer and Advanced Gastric Cancer Patients

Regimen	Primary tumor type	N	$C_{min,ss}$ (µg/ml)	$C_{max,ss}$ (µg/ml)	$AUC_{ss,0-21days}$ (µg.day/ml)	Time to steady-state* (week)
8 mg/kg + 6 mg/kg q3w	MBC	805	44.2 (1.8 – 85.4)	179 (123 - 266)	1736 (618 - 2756)	12
	EBC	390	53.8 (28.7 - 85.8)	184 (134 - 247)	1927 (1332 -2771)	15
	AGC	274	32.9 (6.1 – 88.9)	131 (72.5 – 251)	1338 (557 - 2875)	9
4 mg/kg + 2 mg/kg qw	MBC	805	63.1 (11.7 - 107)	107 (54.2 - 164)	1710 (581 - 2715)	12
	EBC	390	72.6 (46 - 109)	115 (82.6 - 160)	1893 (1309 -2734)	14

AGC: advanced gastric cancer; EBC: early breast cancer; $C_{min,ss}$: C_{min} at steady state; $C_{max,ss}$: C_{max} at steady state; MBC: metastatic breast cancer

*** time to 90% of steady-state

Table 7: Population Predicted PK Parameter Values at Steady State for Trastuzumab IV Dosing Regimens in Metastatic Breast Cancer, Early Breast Cancer and Advanced Gastric Cancer Patients

Regimen	Primary tumor type	N	Total CL range from $C_{max,ss}$ to $C_{min,ss}$ (L/day)	$t_{1/2}$ range from max,ss to $C_{min,ss}$ (day)
8 mg/kg + 6 mg/kg q3w	MBC	805	0.183 – 0.302	15.1 – 23.3
	EBC	390	0.158 – 0.253	17.5 – 26.6
	AGC	274	0.189 – 0.337	12.6 – 20.6
4 mg/kg + 2 mg/kg qw	MBC	805	0.213 – 0.259	17.2 – 20.4
	EBC	390	0.184 – 0.221	19.7 – 23.2

AGC: advanced gastric cancer; EBC: early breast cancer; MBC: metastatic breast cancer

Trastuzumab washout
Trastuzumab washout period was assessed following q1w or q3w IV administration using the population PK model. The results of these simulations indicate that at least 95% of patients will reach concentrations that are <1 µg/ml (approximately 3% of the population predicted $C_{min,ss}$, or about 97% washout) by 7 months.

Circulating shed HER2 ECD
The exploratory analyses of covariates with information in only a subset of patients suggested that patients with greater shed HER2-ECD level had faster nonlinear clearance (lower Km) (p<0.001). There was a correlation between shed antigen and SGOT/AST levels; part of the impact of shed antigen on clearance may have been explained by SGOT/AST levels.

Baseline levels of the shed HER2-ECD observed in metastatic gastric cancer patients were comparable to those in metastatic breast cancer and early breast cancer patients and no apparent impact on trastuzumab clearance was observed.

5.3 Preclinical safety data
Information provided below is based on studies conducted with Intas Trastuzumab.

In 28-day repeat-dose toxicity studies in Wistar rats and New Zealand white rabbits, no observed adverse effect level (NOAEL) of trastuzumab was 250 mg/kg and 125 mg/kg, respectively when administered as IV injection once week.
Information provided below is based on the innovator data.

There was no evidence of acute or multiple dose-related toxicity in studies of up to 6 months, or reproductive toxicity in teratology, female fertility or late gestational toxicity/placental transfer studies. Trastuzumab is not genotoxic. A study of trehalose, a major formulation excipient did not reveal any toxicities.

No long-term animal studies have been performed to establish the carcinogenic potential of trastuzumab, or to determine its effects on fertility in males.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Histidine Hydrochloride
L - Histidine
Trehalose dihydrate
Polysorbate 20
Water for injection

6.2 Incompatibilities
This medicinal product must not be mixed or diluted with other medicinal products except those mentioned under "Special precautions for disposal and other handling".

Do not dilute with glucose/dextrose solutions since these cause aggregation of the protein.

6.3 Shelf life
150 mg single use vial and 440 mg multiple use vial
36 months from date of manufacturing when stored at 2°C to 8°C.

Reconstituted solution from Trastuzumab 150 mg single use vial
150 mg vials are reconstituted with commercially available sterile water for injection (not supplied with this product) and are for single use only. The reconstituted product is stable for 48 hours when stored at 2°C to 8°C.

Reconstituted solution from Trastuzumab 440 mg multiple use vial
440 mg vials when reconstituted with, bacteriostatic water for injection which is supplied with Trastuzumab 440 mg vial, are stable for 28 days after reconstitution when stored at 2°C to 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.

Solution for infusion containing reconstituted product
The reconstituted solution should be further diluted immediately. The infusion solution (0.9% sodium chloride infusion solution in polyvinylchloride or non-polyvinylchloride bags or low density polyethylene bottles) containing reconstituted product is stable for 24 hours when stored at temperature not more than 25°C.

6.4 Special precautions for storage
Store in a refrigerator at 2°C to 8°C.
For storage conditions of the opened medicinal product, see "Shelf-life" and "Special precautions for disposal and other handling".

6.5 Nature and contents of container
150 mg single use vial
One 20 ml USP type I glass vial containing 150 mg of Trastuzumab.

440 mg multiple use vial
One 50 ml USP type I glass vial containing 440 mg of Trastuzumab and one 20 ml vial of bacteriostatic water for injection containing 1.1% benzyl alcohol.

6.6 Special precautions for disposal and other handling
150 mg single use vial

Reconstitution
The 150 mg vial is reconstituted with 7.2 ml sterile water for injection (not supplied with this product) to yield single use solution containing approximately 21 mg/ml trastuzumab, at pH of approximately 6.0. Use of other reconstitution solutions should be avoided.
Use appropriate aseptic technique when performing following reconstitution steps:
- Using a sterile syringe, slowly inject 7.2 ml of sterile water for injection (not supplied) in the vial containing the lyophilized trastuzumab, directing the stream into the lyophilized cake.
- Swirl the vial gently to aid reconstitution. DO NOT SHAKE.
- Slight foaming of the product upon reconstitution may be present; it is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes.
- The reconstituted solution results in a colourless to pale yellow transparent solution and should be essentially free of visible particulates.
- Use trastuzumab solution immediately following reconstitution with sterile water for injection, as it contains no preservative and is intended for single use only. If not used immediately, store the reconstituted trastuzumab solution for up to 48 hours at 2°C to 8°C; discard any unused trastuzumab after 48 hours. DO NOT FREEZE.

Dilution
- Determine the dose (mg) of trastuzumab.
- Determine the volume of 21 mg/ml reconstituted trastuzumab solution required (see below "Determine the volume of solution required").
- Withdraw this amount from the vial and add it to an infusion bag containing 250 ml of 0.9% sodium chloride injection. Do not use with glucose/dextrose containing solutions.
- Gently invert the bag to mix the solution.
- The trastuzumab solution for infusion should be administered immediately after preparation. If diluted aseptically, it is stable for 24 hours when stored at 2°C to 8°C. Discard after 24 hours. DO NOT FREEZE.

440 mg multiple use vial

Reconstitution
The 440 mg vial is reconstituted with 20 ml bacteriostatic water for injection (supplied with this product) containing 1.1% benzyl alcohol as a preservative to yield multiple-dose solution containing approximately 21 mg/ml trastuzumab, at pH of approximately 6.0. In patients with known hypersensitivity to benzyl alcohol, it is recommended to reconstitute vial with 20 ml sterile water for injection (without preservative) to yield single use solution and it can be used within 48 hours of reconstitution, it stored 2°C to 8°C.
Use appropriate aseptic technique when performing following reconstitution steps:
- Using a sterile syringe, slowly inject 20 ml of bacteriostatic water for injection (supplied with this product) in the vial containing the lyophilised trastuzumab, directing the stream into the lyophilised cake.
- Swirl the vial gently to aid reconstitution. DO NOT SHAKE.
- Slight foaming of the product upon reconstitution may be present; it is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes.
- The reconstituted solution results in a colourless to pale yellow transparent solution and should be essentially free of visible particulates.
- Reconstituted trastuzumab solution in bacteriostatic water for injection can be stored at 2°C to 8°C for 28 days; discard any unused trastuzumab after 28 days. If trastuzumab is reconstituted with sterile water for injection, use immediately or can be stored up to 48 hours at 2°C to 8°C and discard any unused portion. DO NOT FREEZE.

Dilution
- Determine the dose (mg) of trastuzumab.
- Determine the volume of 21 mg/ml reconstituted trastuzumab solution required (see below "Determine the volume of solution required").
- Withdraw this amount from the vial and add it to an infusion bag containing 250 ml of 0.9% sodium chloride Injection. Do not use with glucose/dextrose containing solutions.
- Gently invert the bag to mix the solution.
- The trastuzumab solution for infusion should be administered immediately after preparation. If diluted aseptically, solution can be stored at 2°C to 8°C for 24 hours. Discard after 24 hours. DO NOT FREEZE.

Determine the volume of the solution required (150 mg single use and 440 mg multiple use vial):

- Based on a loading dose of 4 mg trastuzumab/kg body weight, or a subsequent weekly dose of 2 mg trastuzumab/kg body weight:

$$\text{Volume (ml)} = \frac{\text{Body weight (kg) x dose (4 mg/kg for leading or 2 mg/kg for maintenance)}}{\text{21 (mg/ml, concentration for reconstituted solution)}}$$

- Based on a loading dose of 8 mg trastuzumab/kg body weight, or a subsequent 3-weekly dose of 6 mg trastuzumab/kg body weight:

$$\text{Volume (ml)} = \frac{\text{Body weight (kg) x dose (8 mg/kg for leading or 6 mg/kg for maintenance)}}{\text{21 (mg/ml, concentration for reconstituted solution)}}$$

Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration.

No incompatibilities between trastuzumab and polyvinylchloride, polyethylene or polypropylene bags or low density polyethylene bottles have been observed.

Any unused or waste material should be disposed in accordance with local requirements.

7 MARKETING AUTHORIZATION HOLDER
Intas Pharmaceuticals Limited
Plot No. 423/P/A, Sarkhej - Bavla Highway, Village: Moraiya,
Taluka: Sanand, District: Ahmedabad 382 213, Gujarat, India

8. MANUFACTURING SITE FOR BACTERIOSTATIC WATER FOR INJECTION
Intas Pharmaceuticals Limited
Plot No. 457 - 458, Village. Matoda, Bavla Road, Dist: Ahmedabad.

9. MANUFACTURING SITE FOR TRASTUZUMAB DRUG PRODUCT IN VIAL

INTAS PHARMACEUTICALS LTD.
Plot No. 423/P/A, Sarkhej - Bavla Highway,
Village - Moraiya, Taluka - Sanand,
District - Ahmedabad-382 213, Gujarat, INDIA.

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