To be sold by retail on prescription of a registered oncologist only Early breast cancer Three-weekly and weekly schedule rastuzumab Lyophilized Powder for Concentrate for Solution for Infusion 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 Eleftha 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 cyclophos-NAME OF THE MEDICINAL PRODUCT astuzumab lyophilized powder for concentrate for solution for infusion Metastatic gastric cancer 2 QUALITATIVE AND QUANTITATIVE COMPOSITION Three-weekly schedule Each single use vial contains.....Trastuzumab 150 mg The recommended initial loading dose is 8 mg/kg body weight. The recommended main Each multiple use vial contains......Trastuzumab 440 mg tenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose. Each ml of vial contains: Breast cancer and gastric cancer Name of ingredient Function Duration of treatment (mg/ml) Patients with metastatic breast cancer or metastatic gastric cancer should be treated with stidine hydrochloride (Ph .Eur.,USI uffering Age trastuzumab until progression of disease. istidine (Ph .Eur.,USF Patients with early breast cancer should be treated with trastuzumab for 1 year or until rehalsoe Dihvdrate (Ph.Eur., USP) 19.1 disease recurrence, whichever occurs first; extending treatment in early breast cancer beyond one year is not recommended. olvsorbate 20 (Ph .Eur..US Vater for injection (IP, Ph .Eur.,USP) q.s. to 1.0 ml Vehicle <u>Dose reductio</u> reconstitution of lyophilized trastuzumab is prepared by using 7.2 ml of Sterile Wa-No reductions in the dose of trastuzumab were made during clinical trials. Patients may ter for Injection (SWFI) and 20 ml of Bacteriostatic Water for Injection (BWFI) (containing continue therapy during periods of reversible, chemotherapy-induced myelosuppression 1.1% w/v benzyl alcohol) for 150 mg and 440 mg vial, respectively, each ml of concenbut they should be monitored carefully for complications of neutropenia during this time. trate contains 21 mg of trastuzumab. Refer to the labeling documents for paclitaxel, docetaxel or aromatase inhibitor for information on dose reduction or delays. **3 PHARMACEUTICAL FORM** Lyophilized powder for concentrate for solution for infusion If left ventricular ejection fraction (LVEF) percentage drops ≥10 points from baseline Solution for reconstitution 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 fur-4 CLINICAL PARTICULARS ther, or if symptomatic congestive heart failure (CHF) has developed, discontinuation of trastuzumab should be strongly considered, unless the benefits for the individual patient 4.1 Therapeutic Indications are deemed to outweigh the risks. All such patients should be referred for assessment by astuzumab is indicated for: a cardiologist and followed up. Breast cancer Metastatic breast cancer If the patient has missed a dose of trastuzumab by one week or less, then the usual (a) the treatment of patients with metastatic breast cancer who have tumors that overexmaintenance dose (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg) should be press human epidermal growth factor receptor 2 (HER2) administered as soon as possible. Do not wait until the next planned cycle. Subsequent (b) in combination with an aromatase inhibitor for the treatment of patients with maintenance doses should be administered 7 days or 21 days later according to the HER2-positive and hormone receptor-positive metastatic breast cancer. weekly or three-weekly schedules, respectivel Early breast cancer If the patient has missed a dose of trastuzumab by more than one week, a re-loading rastuzumab is indicated for the treatment of patients with HER2-positive early breast dose of trastuzumab should be administered over approximately 90 minutes (weekly cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if 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/ Trastuzumab is indicated for adjuvant treatment of HER2 over-expressing node positive kg respectively) should be administered 7 days or 21 days later according to the weekly or node negative (ER/PR negative or with high risk feature) breast cancer: or three-weekly schedules respectively. (a) as part of a treatment regimen consisting of doxorubicin, cyclophosphamide and ei-Special populations ther paclitaxel or docetaxel Dedicated pharmacokinetic (PK) studies in the elderly and those with renal or hepatic (b) with docetaxel and carboplatin impairment have not been carried out. In a population PK analysis, age and renal impair-Trastuzumab is indicated for the treatment of patients with HER2-positive early breast ment were not shown to affect trastuzumab disposition. cancer in combination with neoadiuvant chemotherapy followed by adjuvant trastuzumab therapy, for locally advanced (including inflammatory) disease or tumors >2 cm in Paediatric population There is no relevant use of trastuzumab in the paediatric population. Metastatic gastric cancer Method of administration rastuzumab in combination with capecitabine or 5-fluorouracil and cisplatin is indicated Trastuzumab loading dose should be administered as a 90-minute IV infusion. Do not for the treatment of patients with HER2-positive metastatic adenocarcinoma of the stomadminister as an IV push or bolus. Trastuzumab IV infusion should be administered by ach or gastroesophageal junction who have not received prior anti-cancer treatment for a healthcare provider prepared to manage anaphylaxis and an emergency kit should their metastatic disease be available. Patients should be observed for at least six hours after the start of the Trastuzumab should only be used in patients with metastatic gastric cancer whose tufirst infusion and for two hours after the start of the subsequent infusions for symptoms mours have HER2 overexpression as defined by IHC2+ and a confirmatory FISH+ result, like fever and chills or other infusion-related symptoms. Interruption or slowing the rate or IHC3+, as determined by an accurate and validated assay. of the infusion may help control such symptoms. The infusion may be resumed when Eleftha symptoms abate. 4.2 Posology and method of administration During a phase III clinical study in patients with HER2-positive metastatic breast can-If the initial loading dose was well tolerated, the subsequent doses can be administered cer, Trastuzumab (manufactured by Intas Pharmaceuticals Limited) was administered as a 30-minute infusion as intravenous (IV) infusion with loading dose of 8 mg/kg body weight followed by main-For instructions on reconstitution of trastuzumab IV formulation before administration, tenance dose of 6 mg/kg body weight, beginning three weeks after the loading dose. see section 6.6. atients received trastuzumab for total 6 cycles along with IV infusion of paclitaxel 175 mg/m<sup>2</sup> per cycle. 4.3 Contraindications Information provided in this section is based on the innovator data. Information provided below is based on the innovator data. Hypersensitivity to trastuzumab, murine proteins, or to any of the excipients listed in "List HER2 testing is mandatory prior to initiation of therapy. Trastuzumab treatment should be administered by a qualified healthcare professional. of excipients". Severe dvspnoea at rest due to complications of advanced malignancy or requiring sup-Trastuzumab should be administered via an IV infusion only. Do not administer as an IV plementary oxygen therapy. push or bolus. 4.4 Special warnings and precautions for us In order to prevent medication errors it is important to check the vial labels to ensure that Information provided in this section is based on the innovator data. the drug being prepared and administered is trastuzumab and not trastuzumab emtansine. 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 Metastatic breast cancer HER2 testing must be performed in a specialized laboratory which can ensure adequate Three-weekly schedule validation of the testing procedures. The recommended initial loading dose is 8 mg/kg body weight. The recommended main-Currently no data from clinical trials are available on re-treatment of patients with previtenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks ous exposure to trastuzumab in the adjuvant setting. after the loading dose. Weekly schedule Cardiac dysfunction The recommended initial loading dose of trastuzumab is 4 mg/kg body weight. The rec-General considerations ommended weekly maintenance dose of trastuzumab is 2 mg/kg body weight, beginning ents treated with trastuzumab are at increased risk for developing CHF (New York one week after the loading dose Heart Association [NYHA] Class II-IV) or asymptomatic cardiac dysfunction. These Administration in combination with paclitaxel or docetaxel events have been observed in patients receiving trastuzumab therapy alone or in com-In the pivotal trials, paclitaxel or docetaxel was administered the day following the first bination with paclitaxel or docetaxel, particularly following anthracycline (doxorubicin or dose of trastuzumab and immediately after the subsequent doses of trastuzumab if the epirubicin) containing chemotherapy. These may be moderate to severe and have been preceding dose of trastuzumab was well tolerated. associated with death. In addition, caution should be exercised in treating patients with Administration in combination with an aromatase inhibitor increased cardiac risk, e.g. hypertension, documented coronary artery disease, CHF In the pivotal trial trastuzumab and anastrozole were administered from day 1. There were LVEF of <55%, older age. no restrictions on the relative timing of trastuzumab and anastrozole at administration.

## **Reason For Revision:** New Artwork

NA

## Supersedes No.: NA

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Department	APD	Packing (FP)	Regulatory	Medica
Signature				
Date				
Name				
Designation				

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

Frastuzumab 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 cancel 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 valvula lisease, 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 treatmen 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<sup>2</sup>. 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<sup>2</sup> or epirubicin 360 mg/m<sup>2</sup>.

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<sup>2</sup>).

Artwork No. : AW-QA-1863-00 **Authorized By** QA QA

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<sub>trough</sub> at pre-dose Cycle 8, and pCR rate at definitive surgery, respectively). In the trial, trastuzumab was adminisered concurrently with neoadiuvant chemotherapy that contained four cycles of epirub cin (cumulative dose 300 mg/m<sup>2</sup>); 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.

#### nfusion-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 dysphoea 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 nonary 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.

#### ulmonary 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 nalignancy and co-morbidities may be at increased risk of pulmonary events. Therefore, hese patients should not be treated with trastuzumab. Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

#### Benzvl alcohol

Benzyl alcohol, used as a preservative in bacteriostatic water for injection in 440 mg nultiple-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 penzyl alcoho

#### 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 etween 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-a hydroxylpaclitaxel, POH, and doxorubicinol, DOL) was not altered in the pres ence of trastuzumab (8 mg/kg or 4 mg/kg IV loading dose followed by 6 mg/kg q3w or 2 ma/kg g1w 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<sup>2</sup> IV) in Japanese women with HER2-positive metasta 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 no 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 inop-

erable HER2-positive cancer suggested that trastuzumab had no impact on the PK of

#### 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 pa-

tients were treated concomitantly with trastuzumab and paclitaxel and two Phase II studies in which trastuzumab was administered as monotherapy, in women with HER2-pos itive metastatic breast cancer indicates that individual and mean trastuzumab troug

serum concentrations varied within and across studies but there was no clea the concomitant administration of paclitaxel on the PK of trastuzumab. Comp trastuzumab PK data from study in which women with HER2-positive metastat cancer were treated concomitantly with trastuzumab, paclitaxel and doxorubicin tuzumab PK data in studies where trastuzumab was administered as monothera ombination with anthracycline plus cyclophosphamide or paclitaxel, suggested

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

The administration of concomitant anastrozole did not appear to influence the

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

There is no fertility data available Women with childbearing potential

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

Reproduction studies have been conducted in cynomolgus monkeys at doses times that of the weekly human maintenance dose of 2 mg/kg trastuzumab IV for 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) a days 120-150 of gestation) foetal development period was observed. It is not

whether trastuzumab can affect reproductive capacity. As animal reproduction are not always predictive of human response, trastuzumab should be avoided pregnancy unless the potential benefit for the mother outweighs the potential ris In the post-marketing setting, cases of foetal renal growth and/or function impair

association with oligohydramnios, some associated with fatal pulmonary hypor the foetus, have been reported in pregnant women receiving trastuzumab. Won 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 pregna eceiving trastuzumab or within 7 months following the last dose of trastuzuma monitoring by a multidisciplinary team is desirable.

## Breast feeding

A study conducted in lactating cynomolgus monkeys at doses 25 times that of the ly human maintenance dose of 2 mg/kg trastuzumab IV formulation demonstr astuzumab is secreted in the milk. The presence of trastuzumab in the serum monkeys was not associated with any adverse effects on their growth or deve from birth to 1 month of age. It is not known whether trastuzumab is secreted i milk. As human IgG1 is secreted into human milk, and the potential for harm to the is unknown, women should not breast-feed during trastuzumab therapy and for 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 machine ver, patients experiencing infusion-related symptoms should be advised not to use machines until symptoms abate.

#### 4.8 Undesirable effects

Information provided below is based on the study conducted with Intas Trastuzur In a prospective, multicentric, randomized, open-label, parallel-group, phase III s women with HER2-overexpressing metastatic breast cancer, 120 patients were ra ized to receive Trastuzumab (manufactured by Intas Pharmaceuticals Limited: Herclon<sup>™</sup> (marketed by Roche; n=38) at IV loading dose of 8 mg/kg (for 1<sup>st</sup> cy maintenance dose of 6 mg/kg for subsequent cycles on day 1 of each chem cycle of 21 days, for up to 6 cycles. Patients were also administered with paclita mg/m<sup>2</sup> per cycle during the study. All 120 patients were included in safety populat otal 441 adverse events (AEs) were reported in 79 patients during the study in 54 patients from Intas Trastuzumab group and 114 AEs in 25 patients from H group. The most commonly reported AEs with Intas Trastuzumab (incidence in ents) during the study were alopecia (25.6%), pain (22%), nausea (19.5%), pe neuropathy (14.6%), pyrexia (9.8%), anaemia (9.8%), diarrhoea (9.8%), vomiting pain in extremity (8,5%), headache (8,5%), abdominal pain (8,5%), cough (7,3% pation (6.1%), gastritis (6.1%), and asthenia (6.1%). Two deaths were reported uzumab group during the study; both deaths were due to cardio-pulmo and unrelated to the drug. Total 7 other serious AEs (SAEs) were reported by uring the study: 2 in Herclon group and 5 in Intas Trastuzumab group. All th recovered without sequelae.

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

Table 1: Adverse Events Reported in Women with HER2-overexpr ic Breast Cancer Treated with Intas Trastuzumab or Herclon™ (Safety Po

	No. of AEs (% c	of patients)	
System organ class Preferred term	Intas Trastu- zumab (n=82)	Herclon™ (n=38)	
Blood and lymphatic syst	tem 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 disorde	ers		
Vertigo	1 (1.2)	0 (0.0)	
Vestibular disorder	1 (1.2)	0 (0.0)	

**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

fish of breast to tras- py or in or effect         System organ class Preferred term         Ints Trastu- zumab (n=82)         Herc zumab (n=82)           o effect         Gastrointestinal discorters         Construction Abdominal pain upper         1         0         0           a PK of         Gastrointestinal discorters         9         0         0         0           a PK of         Diarrhoea         9         0         3         0           Constipation         5         6         1         2         0           Mutring         Constipation         5         6         1         0           Constipation         5         6         1         1         0         0           Mutring         Constipation         5         6         1         1         0           Nausea         33         10         0         0         0         0         0           Induston         Peripheral disorders and aministration site cond Asteneia and infectations         1 </th <th>ffect of</th>	ffect of
Prefered term         Zumab (n=82)         (n= 2)           bo distas- py or in o effect         Gastrointestinal disorders         (n= Abdominal pain upper 1 (1.2)         (n           a before         Abdominal pain upper 1 (1.2)         0 (0)         (1)         (1)           a before         Abdominal pain upper 1 (1.2)         0 (0)         (1)         (1)           a before         Abdominal pain upper 1 (1.2)         0 (0)         (1)         (1)           a before         (1)         (1)         (1)         (1)         (1)           a before         (1)         (1)         (1)         (1)         (1)         (1)           a before         (1)         (	
Construction         Construction         Construction         Construction         Construction           a PK of         Construction         6 (B)         1 (2)         0 (0)           a PK of         Construction         5 (B)         2 (2,4)         0 (0)           a PK of         Construction         5 (B)         2 (C)         0 (0)           a PK of         Construction         5 (B)         3 (C)         0 (0)           Mouth namorrhage         1 (1,2)         0 (0)         0 (0)         0 (0)           Nausea         3 (19,5)         10 (0)         0	
Addominal disconfort         2 (2,4)         0 (0           Abdominal pain         8 (8,5)         1 (2           Abdominal pain         9 (8,5)         1 (2           Abdominal pain         9 (9,8)         3 (2           Abdominal gain upper         1 (1,2)         0 (1)           Multiple         1 (1,2)         0 (1)           Nausea         3 (19,5)         10 (1)           Nausea         3 (19,5)         10 (1)           Asthenia         5 (6,1)         1 (1,2)         0 (1)           Asthenia         6 (1,1)         1 (1,2)         0 (1)           Asthenia         6 (4,12,0)         18 (1,2)         1 (1,2)           Asthenia         1 (1,2)         1 (1,2)         0 (1)           Induiton         Peripheral swelling         1 (1,2)         0 (1)           Int while         Infections         1 (1,2)         0 (1)           I during         Upper respiratory tract         0 (0,0)         1 (1) <t< td=""><td></td></t<>	
Abdominal pain upper         1 (1.2)         0 (0.7)           a PK of         Diarrhoea         9 (9.8)         3 (1.2)           b PK of         Diarrhoea         9 (9.8)         3 (1.2)         0 (1.2)           constpandin         S (6.1)         2 (2.0)         1 (1.2)         0 (1.2)           constpandin         Gastrifis         2 (3.6)         8 (8.6)         1 (1.2)         0 (1.2)           of during         9 (9.8)         3 (3.7)         0 (1.2) <td< td=""><td></td></td<>	
the PK         Abdominal pain upper         1 (1.2)         0 (0)           a PK of         Constipation         5 (6 1)         2 (2)           Constipation         3 (3 7)         0 (0)           Multiple         5 (6 1)         1 (1 2)         0 (0)           Multiple         5 (6 1)         1 (1 2)         0 (0)           Multiple         1 (1 2)         0 (0)         1 (1 2)         0 (0)           Multiple         1 (1 2)         1 (1 2)         1 (1 2)         1 (1 2)           Multiple         1 (1 2)         1 (1 2)         1 (1 2)         1 (1 2)           Multiple         1 (1 2)         1 (1 2)         1 (1 2)         1 (1 2)           Multiple         1 (1 2)         1 (1 2)         1 (1 2)         1 (1 2)           Multiple         1 (1 2)         1 (1 2)         1 (1 2)         1 (1 2)           Multiple         Multiple         1 (1 2)         1 (1 2)         1 (1 2	) enect
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advisition         23 (0, 1)         0 (0)           Hyperchlorhydria         3 (3, 7)         0 (0)           Nausea         33 (19, 5)         10 (0)           Nausea         33 (19, 5)         10 (0)           Verticity         General disorders and administration site condination sine condination site condinating condinating site site s	PK of
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Druritus generalized $1(1,2)$	
	ation)
Urticaria 1 (1.2) 0 (I Vascular disorders	
Hypertension 1 (1.2) 0 (	
Hypotension 1 (1.2) 0 (	
Immunogenicity	
In a multicentric, randomized, open-label, parallel-group, phase III	
with HER2-overexpressing metastatic breast cancer, incidence o	

and in the post-marketing	•	
	I on the highest percentage seen in	
	ts Reported with IV Trastuzumab I otherapy in Pivotal Clinical Trials Post-Marketing	
System organ class	Adverse reaction	Frequency
	Infection Nasopharyngitis	Very common Very common
	Neutropenic sepsis	Common
	Cystitis	Common
	Herpes zoster	Common
	Influenza Sinusitis	Common Common
nfections and infestations	Skin infection	Common
	Rhinitis	Common
	Upper respiratory tract infection Urinary tract infection	Common Common
	Erysipelas	Common
	Cellulitis	Common
	Pharyngitis	Common
Neoplasms benign, malig-	Sepsis Malignant neoplasm progression	Uncommon Not known
nant and unspecified (incl.	Neoplasm progression	Not known
Cysts and polyps)	1 1 8	
	Febrile neutropenia Anaemia	Very common Very common
	Neutropenia	Very common
Blood and lymphatic system disorders	White clood cell count decreased/ leucopenia	Very common
	Thrombocytopenia Hypoprothrombinaemia	Very common Not known
	Immune thrombocytopenia	Not known
	Hypersensitivity	Common
Immune system disorders	Anaphylactic reaction* Anaphylactic shock*	Not known Not known
	Weight decreased/Weight loss	Very common
Metabolism and nutrition disorders	Anorexia	Very common
	Hyperkalaemia	Not known
	Insomnia Anxiety	Very common Common
Psychiatric disorders	Depression	Common
	Thinking abnormal	Common
	Tremor <sup>1</sup> Dizziness	Very common Very common
	Headache	Very common
	Paraesthesia	Very common
Nervous system disorders	Dysgeusia Peripheral neuropathy	Very common Common
Norvous system disorders	Hypertonia	Common
	Somnolence	Common
	Ataxia	Common
	Paresis Brain oedema	Rare Not known
	Conjunctivitis	Very common
	Lacrimation increased	Very common
Eye disorders	Dry eye Papilloedema	Common Not known
	Retinal haemorrhage	Not known
Ear and labyrinth disorders	Deafness	Uncommon
	Blood pressure decreased <sup>1</sup>	Very common
	Blood pressure increased <sup>1</sup> Heart beat irregular <sup>1</sup>	Very common Very common
	Palpitation <sup>1</sup>	Very common
	Cardiac flutter <sup>1</sup>	Very common
	Ejection fraction decreased* Cardiac failure (congestive)*	Very common Common
Cardiac disorders	Supraventricular <sup>+1</sup> tachyarrhythmia	Common
	Cardiomyopathy	Common
	Pericardial effusion	Uncommon
	Cardiogenic shock	Not known
	Pericarditis Bradycardia	Not known Not known
	Gallop rhythm present	Not known
	L lot fluch	Von common
Vascular disorders	Hot flush Hypotension <sup>+1</sup>	Very common Common

In this section, the following categories of frequency have been used: very commor

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 de-

(≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000

System organ class	Adverse reaction Wheezing <sup>+1</sup>
	Dyspnea⁺
	Cough
	Epistaxis
	Rhinorrhea
	Pneumonia⁺ Asthma
	Lung disorder
	Pleural effusion <sup>+</sup>
	Pneumonitis
Booniratory therapic and	Pulmonary fibrosis <sup>+</sup> Respiratory distress <sup>+</sup>
Respiratory, thoracic and mediastinal disorders	Respiratory failure <sup>+</sup>
	Lung infiltration*
	Acute pulmonary oedema*
	Acute respiratory distress s
	drome <sup>+</sup> Bronchospasm <sup>+</sup>
	Hypoxia⁺
	Oxygen saturation decrease
	Laryngeal oedema
	Orthopnoea
	Pulmonary oedema Interstitial lung disease
	Diarrhoea
	Vomiting
	Nausea
	Lip swelling <sup>1</sup>
Gastrointestinal disorders	Abdominal pain Dyspepsia
	Constipation
	Stomatitis
	Pancreatitis
	Haemorrhoids
	Dry mouth Hepatocellular injury
	Hepatitis
Hepatobiliary disorders	Liver tenderness
	Jaundice
	Hepatic failure
	Erythema
	Rash Swelling face <sup>1</sup>
	Alopecia
	Nail disorder
	Palmar-plantar erythrodysa
	sia syndrome
Skin and subcutaneous	Acne Dry skin
tissue disorders	Ecchymosis
	Hyperhydrosis
	Maculopapular rash
	Pruritus
	Onychoclasis
	Urticaria
	Angioedema
	Arthralgia
	Muscle tightness <sup>1</sup>
	Myalgia Arthritis
Musculoskeletal and con-	Back pain
nective tissue disorders	Bone pain
	Muscle spasma
	Neck pain
	Pain in extremity Renal disorder
Renal and urinary disor-	Glomerulonephritis membra
ders	Glomerulonephropathy
	Renal failure
Pregnancy, puerperium	Oligohydramnios
and perinatal conditions	Renal hypoplasia
Reproductive system and	Pulmonary hypoplasia
breast disorders	Breast inflammation/mastiti
	Asthenia
	Chest pain
	Chills Fatigue
	Influenza-like symptoms
General disorders and ad-	Infusion related reaction
ministration site conditions	Pain
	Pyrexia Musesel inflormation
	Mucosal inflammation
	Peripheral oedema Malaise
	Oedema
Injury, poisoning and pro-	Contusion
cedural complications	
- D - I	a that have been reported in
	s that have been reported in
Denotes adverse reactions outcome. Denotes adverse reactions	s that are reported largely in

sion-related reactions. Specific percentages for these are n Observed with combination therapy following anthracycline with taxanes

Description of selected adverse reactions

Cardiac dysfunction Congestive heart failure (NYHA Class II – IV) is a common adve with the use of trastuzumab and has been associated with a fa symptoms of cardiac dysfunction such as dysphoea, orthophoe monary oedema, S3 gallop, or reduced ventricular ejection fract

# Fron

Tabulated list of adverse reactions

Summary of the safety profile

Information provided below is based on the innovator data.

igst the most serious and/or common adverse reactions reported in trastuzumab us-

age (IV and subcutaneous formulations) to date are cardiac dysfunction infusion-related

reactions, haematotoxicity (in particular neutropenia), infections and pulmonary adverse

	Frequency
	Very common Very common Very common
	Very common
	Very common Common
	Common Common
	Common Rare
	Not known
	Not known Not known
	Not known Not known
	Not known
	Not known Not known
	Not known Not known
	Not known Not known
	Not known
	Very common Very common
	Very common Very common
	Very common Very common
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	Very common Common
	Common Common
	Common Common
	Common
	Rare Not known
	Very common Very common
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ne-	Very common
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	Uncommon Not known
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us	Not known Not known
	Not known Not known
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	Very common
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	Very common Very common
	Very common
	Very common Very common
	Very common Very common
	Common Common
	Common
socia	tion with a fatal
ot av	tion with Infu- ailable. nd combined
atal c a, ind	reaction associated outcome. Signs and creased cough, pul- nave been observed
1	t Side

#### 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 adninistered 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 n subsequent infusion

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.

#### Pulmonarv 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, pulnonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency.

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 g3w 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

5 PHARMACOLOGICAL PROPERTIES

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

Trastuzumab is a recombinant humanized IaG1 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 eaion of HER2's e

# **Back Side**

dependent 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 formation 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<sup>™</sup> (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 nclusive) 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 1<sup>st</sup> 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<sup>2</sup> 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<sup>™</sup> 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<sup>™</sup> 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)

	Number of pati	ents (%)	Treatment difference	
Endpoint	Intas Trastuzumab (n=69)	Herclon™ (n=33)	(95% CI)	
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<sup>™</sup> 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 nfusion. Serum samples were collected from 20 patients (14 from Intas Trastuzumab and 6 from Herclon<sup>™</sup> 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<sup>™</sup> is provided in Table 4.

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

			· · /			
		Mean ± SD (untransformed data)				
	Parameter (Unit)	Intas Trastuzumab (n=13)	Herclon (n=6)			
	AUC <sub>0-22d</sub> (µg.h/ml)	24958.030 ± 7754.1302	25253.903 ± 7636.2143			
	C <sub>max</sub> (µg/ml)	199.144 ± 37.3145	244.827 ± 99.3967			
	T <sub>max</sub> (h) <sup>1</sup>	2.500 (1.500 - 8.000)	2.009 (1.000 - 4.000)			

AUC: area under the serum concentration versus time curve; C<sub>max</sub>: maximum serum concentration;  $T_{max}$ : time corresponding to Cmax

<sup>1</sup> Median (minimum-maximum) value reported for T\_

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 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<sub>c</sub>)) and opulation-predicted steady-state exposures (C<sub>min</sub>, C<sub>max</sub> 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<sub>m</sub>) 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

The population predicted PK exposure values (median with 5<sup>th</sup> - 95<sup>th</sup> Percentiles) and PK parameter values at clinically relevant concentrations (C and C) 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	<b>C</b> <sub>min</sub> (μg/ml)	<b>C</b> <sub>max</sub> (μg/ml)	
	MBC	805	28.7 (2.9 - 46.3)	182 (134 - 280)	[
8 mg/kg + 6 mg/kg q3w	EBC	390	30.9 (18.7 - 45.5)	176 (127 - 227)	
	AGC	274	23.1 (6.1 - 50.3)	132 (84.2 – 225)	
	MBC	805	37.4 (8.7 - 58.9)	76.5 (49.4 - 114)	ļ
4 mg/kg + 2 mg/kg qw	EBC	390	38.9 (25.3 - 58.8)	76.0 (54 7 - 104)	

#### Table 6: Population Predicted Steady State PK Exposure Values (median with 5<sup>th</sup> - 95<sup>th</sup> Percentiles) for Trastuzumab IV Dosing Regimens in Metastatic Breast

Regimen	Primary tumor type	N	C <sub>min,ss</sub> (μg/ml)	$\bm{C}_{_{\text{max,ss}}}\left(\mu g/ml\right)$	AUC (µg.day/ml)	Time to steady state* (week)
	мвс	805	44.2 (1.8 – 85.4)	179 (123 - 266)	1736 (618 - 2756)	12
8 mg/kg + 6 mg/kg q3w	EBC	390	53.8 (28.7 - 85.8)	184 (134 - 247)	1927 (1332 -2771)	15
0 0 1	AGC	274	32.9 (6.1 – 88.9)	131 (72.5 – 251)	1338 (557 - 2875)	9
4 mg/kg + 2	мвс	805	63.1 (11.7 - 107)	107 (54.2 - 164)	1710 (581 - 2715)	12
mg/k̃g q̃w	EBC	390	72.6 (46 - 109)	115 (82.6 - 160)	1893 (1309 -2734)	14

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 <sub>max,ss</sub> to C <sub>min,ss</sub> (L/day)	t <sub>1/2</sub> rang to C <sub>min,se</sub>		
8 mg/kg + 6 mg/ kg q3w	MBC	805	0.183 – 0.302	15.1 – 2		
	EBC	390	0.158 – 0.253	17.5 – 2		
	AGC	274	0.189 – 0.337	12.6 – 2		
4 mg/kg + 2 mg/ kg qw	MBC	805	0.213 - 0.259	17.2 – 2		
	EBC	390	0.184 – 0.221	19.7 – 2		

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

Trastuzumab washout Trastuzumab washout period was assessed following g1w or g3w 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  $\mu$ g/ml (approximately 3% of the population predicted C<sub>min ss</sub>, 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 ormulation 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

olysorbate 20

Water for injection

6.2 Incompatibilities This medicinal product must not be mixed or diluted with other medicinal products or disposal and other handling' except those mentioned under

#### Do not dilute with glucose/dextrose solutions since these cause aggregation of the 6.3 Shelf life

(1039 - 1895) (588 – 1938)

(597 – 1584) AGC: advanced gastric cancer; EBC: early breast cancer; MBC: metastatic breast cancer

150 mg single use vial One 20 ml USP type I glass vial containing 150 mg of Trastuzumab.

150 mg single use vial and 440 mg multiple use vial

for 48 hours when stored at 2°C to 8°C

6.4 Special precautions for storage

precautions for disposal and other handling".

6.5 Nature and contents of container

Store in a refrigerator at 2°C to 8°C.

36 months from date of manufacturing when stored at 2°C to 8°C.

Reconstituted solution from Trastuzumab 150 mg single use vial

Reconstituted solution from Trastuzumab 440 mg multiple use vial

is stable for only 48 hours and must be discarded thereafter.

Solution for infusion containing reconstituted product

hours when stored at temperature not more than 25°C.

50 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

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

(0.9% sodium chloride infusion solution in polyvinylchloride or non-polyvinylchloride bags

or low density polyethylene bottles) containing reconstituted product is stable for 24

For storage conditions of the opened medicinal product, see "Shelf-life" and "Special

reconstituted solution should be further diluted immediately. The infusion solution

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

philized cake.

- <u>150 mg single use vial</u>

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)

Allow the vial to stand undisturbed for approximately 5 minutes.

8°C; discard any unused trastuzumab after 48 hours. DO NOT FREEZE.

Swirl the vial gently to aid reconstitution, DO NOT SHAKE.

and should be essentially free of visible particulates.

below "Determine the volume of solution required"

Determine the dose (mg) of trastuzumab.

Gently invert the bag to mix the solution.

Discard after 24 hours. DO NOT FREEZE

440 mg multiple use vial

in the vial containing the lyophilized trastuzumab, directing the stream into the lyo-

Slight foaming of the product upon reconstitution may be present; it is not unusual.

The reconstituted solution results in a colourless to pale yellow transparent solution

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

Determine the volume of 21 mg/ml reconstituted trastuzumab solution required (see

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 solu-

• The trastuzumab solution for infusion should be administered immediately after

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

Using a sterile syringe, slowly inject 20 ml of bacteriostatic water for injection (sup-

Slight foaming of the product upon reconstitution may be present; it is not unusual.

The reconstituted solution results in a colourless to pale yellow transparent solution

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 tras-

tuzumab 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

plied with this product) in the vial containing the lyophilised trastuzumab, directing the

Use appropriate aseptic technique when performing following reconstitution steps:

and it can be used within 48 hours of reconstitution, it stored 2°C to 8°C.

Swirl the vial gently to aid reconstitution. DO NOT SHAKE.

and should be essentially free of visible particulates.

Allow the vial to stand undisturbed for approximately 5 minutes.

vial with 20 ml sterile water for injection (without preservative) to yield single use solution

preparation. If diluted aseptically, it is stable for 24 hours when stored at 2°C to 8°C.

immediately, store the reconstituted trastuzumab solution for up to 48 hours at 2°C to

ge from max,ss

Determine the dose (mg) of trastuzumab.

stream into the lyophilised cake.

- 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 solu-
- Gently invert the bag to mix the solution.
- · The trastuzumab solution for infusion should be administered immediately af

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:

Body weight (kg) x dose (4 mg/kg for leading or 2 mg/kg for maintenance) Volume (ml) = 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 Body weight (kg) x dose (8 mg/kg for leading or 6 mg/kg for maintenance) Volume (ml) =

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 Limite Plot No. 457 - 458, Village. Matoda, Bavla Road, Dist: Ahmedabad.

9. MANUFACTURING SITE FOR TRASTUZUMAB DRUG PRODUCT IN VIAL -(INTAS

## INTAS PHARMACEUTICALS LTD.

Plot No. 423/P/A, Sarkhej - Bavla Highway, Village - Moraiva, Taluka - Sanand, District - Ahmedabad-382 213, Gujarat, INDIA Version 00 dated 07-Aug-2018

