WARNING: Preparation shall be supplied against the prescription of a Cancer Specialist

Trastuzumab for Injection

Biceltis®

बाइसेल्टिस

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Antineoplastic agent.

1.2 Type of Dosage Form and Strengths

Powder for concentrate for solution for infusion.

Strengths: 150mg and 440mg

1.3 Route of Administration

Intravenous infusion.

1.4 Sterile / Radioactive Statement

Sterile product.

1.5 Qualitative and Quantitative Composition

Active ingredient: trastuzumab.

Dosage Preparations: 150 mg single dose vials and 440 mg multidose vial containing powder for concentrate for solution for infusion. Reconstituted Biceltis concentrate contains 21 mg/mL of trastuzumab.

Excipients: L-Histidine hydrochloride, L-Histidine, α,α –Trehalose (dihydrate), Polysorbate 20 and Water for Injection.

Each multi-use vial of Biceltis contains 440 mg trastuzumab, 400 mg α,α-trehalose dihydrate, 9.9 mg L-histidine HCl, 6.4 mg L-histidine, and 1.8 mg polysorbate 20, USP. Reconstitution with 20 mL of the appropriate diluent (BWFI or SWFI) yields a solution, containing 21 mg/mL trastuzumab at a pH of approximately 6.

Each single-dose vial of Biceltis delivers 150 mg trastuzumab, 136.2 mg α,α-trehalose dihydrate, 3.36 mg L-histidine HCl monohydrate, 2.16 mg L-histidine, and 0.6 mg polysorbate 20. Reconstitution with 7.4 mL of sterile water for injection (SWFI) yields a

solution containing 21 mg/mL trastuzumab that delivers 7.15 mL (150 mg trastuzumab), at a pH of approximately 6.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication

Breast Cancer

Metastatic Breast Cancer:

a) Biceltis is indicated for the treatment of patients with metastatic breast cancer who have tumors that overexpress human epidermal growth factor receptor 2 (HER2)

b) Biceltis in combination with an aromatase inhibitor is indicated for the treatment of patients with HER2-positive and hormone receptor-positive metastatic breast cancer.

Early Breast Cancer (EBC)

Biceltis is indicated for treatment of patients with HER2 positive early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).

Biceltis is also indicated for adjuvant treatment of HER2 over-expressing node positive or node negative (ER/PR negative or with one 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

Biceltis is indicated for treatment of patients with HER2 positive early breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant Biceltis therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter.

Metastatic Gastric Cancer

Biceltis in combination with capecitabine or 5-fluorouracil and cisplatin for the treatment of patients with HER2-positive metastatic adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Biceltis 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 IHC 3+, as determined by an accurate and validated assay.

2.2 Dosage and Administration

General

HER2 testing is mandatory prior to initiation of Biceltis therapy.

Substitution by any other biological medicinal product requires the consent of the prescribing physician. The benefit-risk of alternating or switching between Biceltis and products that are biosimilar but not deemed interchangeable needs to be carefully considered when the safety and efficacy of alternating or switching has not been established.

Biceltis should be administered by a qualified health care professional.

It is important to check the product labels to ensure that the correct formulation (Biceltis IV) is being administered to the patient as prescribed.

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

Biceltis IV is not to be used for subcutaneous administration and should be administered as intravenous infusion.

Do not administer as an intravenous push or bolus.

Weekly schedule:

Loading dose: The recommended initial loading dose is 4 mg/kg body weight. Biceltis administered as a 90-minute intravenous infusion.

Subsequent doses: The recommended weekly dose of Biceltis is 2 mg/kg body weight. If the prior dose was well tolerated, the dose can be administered as a 30-minute infusion.

Alternative 3-weekly schedule: Initial loading dose of 8 mg/kg body weight, followed by 6 mg/kg body weight 3 weeks later and then 6 mg/kg repeated at 3-weekly intervals administered as infusions over approximately 90 minutes. If the prior dose was well tolerated, the dose can be administered as a 30-minute infusion.

Duration of treatment

Patients with metastatic breast cancer or metastatic gastric cancer should be treated with Biceltis until progression of disease or unmanageable toxicity. Patients with EBC should be treated for 1 year or until disease recurrence or unmanageable toxicity, whichever occurs first. Extending treatment in EBC beyond one year is not recommended (*see section 3.1.2 Clinical / Efficacy Studies*).

Missed doses

If the patient has missed a dose of Biceltis 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 Biceltis should be administered over approximately 90 minutes (weekly regimen: 4 mg/kg; three weekly regimen: 8 mg/kg) as soon as possible. Subsequent Biceltis 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.

Dose modification

If the patient develops an infusion-related reaction (IRR), the infusion rate of Biceltis IV may be slowed or interrupted (*see section 2.4 Warnings and Precautions*).

No reductions in the dose of Trastuzumab Injection 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. The specific instructions to reduce or hold the dose of chemotherapy should be followed.

2.2.1 Special Dosage Instructions

Geriatric use

Data suggest that the disposition of Trastuzumab Injection is not altered based on age (see Pharmacokinetics in Special Populations). In clinical trials, patients ≥ 65 years of age did not receive reduced doses of Trastuzumab Injection.

Paediatric use
The safety and efficacy of Biceltis in paediatric patients < 18 years of age has not been established.

2.3 Contraindications

Biceltis is contraindicated in patients with known hypersensitivity to trastuzumab or to any of its excipients.

2.4 Warnings and Precautions

2.4.1 General

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.

Biceltis therapy should only be initiated under supervision of a physician experienced in the treatment of cancer patients.

Infusion related reactions (IRRs)

IRRs are known to occur with the administration of Trastuzumab Injection *(see section 2.6. Undesirable Effects*).

IRRs may be clinically difficult to distinguish from hypersensitivity reactions.

Pre-medication may be used to reduce risk of occurrence of IRRs.

Serious IRRs to Trastuzumab Injection including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, supraventricular tachyarrhythmia and urticaria have been reported (*see section 2.6. Undesirable Effects*). Patients should be observed for IRRs. Interruption of an IV infusion may help control such symptoms and the infusion may be resumed when symptoms abate. These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. 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 who are experiencing dyspnoea at rest due to complications of advanced malignancy or co-morbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with Biceltis.

Pulmonary reactions

Severe pulmonary events have been reported with the use of Trastuzumab Injection IV in the post-marketing setting. These events have occasionally resulted in fatal outcome and may occur as part of an IRR or with a delayed onset. 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. Patients with 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 Biceltis.

Cardiac dysfunction

General considerations

Patients treated with Trastuzumab Injection are at increased risk of developing congestive heart failure (CHF) (New York Heart Association [NYHA] Class II-IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving Trastuzumab Injection therapy alone or in combination with taxane following anthracycline (doxorubicin or epirubicin)–containing chemotherapy. This may be moderate to severe and has been associated with death (*see section 2.6 Undesirable Effects*). In addition, caution should be exercised in treating patients with increased cardiac risk, e.g. hypertension, documented coronary artery disease, CHF, diastolic dysfunction, older age.

Population pharmacokinetic model simulations indicate that trastuzumab may persist in the circulation for up to 7 months after stopping Biceltis treatment (*see section 3.2 Pharmacokinetic Properties*). Patients who receive anthracycline after stopping Trastuzumab Injection may also be at increased risk of cardiac dysfunction.

If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping Biceltis. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Candidates for treatment with Biceltis, especially those with prior exposure to an anthracycline, should undergo baseline cardiac assessment including history and physical examination, electrocardiogram (ECG) and echocardiogram or multigated acquisition scanning (MUGA) scan. Monitoring may help to identify patients who develop cardiac dysfunction, including signs and symptoms of CHF. 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 Biceltis.

If LVEF percentage drops 10 points from baseline and to below 50%, Biceltis should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further, or if clinically significant CHF has developed, discontinuation of Biceltis should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

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 unless the benefits for the individual patient are deemed to outweigh the risks.

The safety of continuation or resumption of Trastuzumab Injection in patients who experience cardiac dysfunction has not been prospectively studied. If symptomatic cardiac failure develops during Biceltis therapy, it should be treated with standard medications for heart failure (HF). In the pivotal trials, most patients who developed HF or asymptomatic cardiac dysfunction improved with standard HF treatment consisting of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a β-blocker. The majority

of patients with cardiac symptoms and evidence of a clinical benefit of Trastuzumab Injection treatment continued with Trastuzumab Injection without additional clinical cardiac events.

Metastatic breast cancer (MBC)

Trastuzumab Injection and anthracyclines should not be given concurrently in the metastatic breast cancer setting.

Early breast cancer (EBC)

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

Patients with history of myocardial infarction (MI), angina pectoris requiring medication, history of or present CHF (NYHA Class II –IV), other cardiomyopathy, cardiac arrhythmia requiring medication, clinically significant cardiac valvular disease, poorly controlled hypertension (hypertension controlled by standard medication eligible), and hemodynamic effective pericardial effusion were excluded from adjuvant breast cancer clinical trials with Trastuzumab Injection.

Adjuvant treatment

Biceltis and anthracyclines should not be given concurrently in the adjuvant treatment setting.

In patients with EBC an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when Trastuzumab Injection IV was administered after anthracycline containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin. The incidence was more marked when Trastuzumab Injection IV 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.

Risk factors for a cardiac event identified in four large adjuvant studies included advanced age (> 50 years), low level of baseline and declining LVEF (< 55%), low LVEF prior to or following the initiation of paclitaxel treatment, Trastuzumab Injection treatment, and prior or concurrent use of anti-hypertensive medications. In patients receiving Trastuzumab Injection 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 Injection and a high body mass index (BMI >25 kg/m^2).

Neoadjuvant-adjuvant treatment

In patients with EBC eligible for neoadjuvant-adjuvant treatment, Biceltis concurrently with anthracyclines should be used with caution and only in chemotherapy-naive patients. The maximum cumulative doses of the low-dose anthracycline regimens should not exceed 180 mg/m^2 (doxorubicin) or 360 mg/m^2 (epirubicin).

If patients have been treated concurrently with low-dose anthracyclines and Biceltis in the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after surgery.

Clinical experience in the neoadjuvant-adjuvant setting is limited in patients above 65 years of age.

Benzyl alcohol

Benzyl alcohol, used as a preservative in bacteriostatic water for injection in the 440 mg multidose vial, has been associated with toxicity in neonates and children up to 3 years old. When administering Biceltis to a patient with a known hypersensitivity to benzyl alcohol, Biceltis should be reconstituted with water for injection, and only one dose per Biceltis vial should be used. Any unused portion must be discarded. Sterile water for injection, used to reconstitute 150 mg single dose vials, does not contain benzyl alcohol.

2.4.2 Drug Abuse and Dependence

No data to report.

2.4.3 Ability to Drive and Use Machines

Biceltis has a minor influence on the ability to drive and use machines. Dizziness and somnolence may occur during treatment with Biceltis (*see section 2.6 Undesirable effects*). Patients experiencing infusion-related symptoms (*see section 2.4 Warnings and Precautions*) should be advised not to drive or use machines until symptoms resolve completely.

2.5 Use in Special Populations

2.5.1 Females and Males of Reproductive Potential

Fertility

It is not known whether Biceltis can affect reproductive capacity. Animal reproduction studies revealed no evidence of impaired fertility or harm to the foetus (see *section 3.3.4 Reproductive toxicity*).

Contraception

Women of childbearing potential should be advised to use effective contraception during treatment with Biceltis IV and for 7 months after treatment has concluded (*see section 3.2 Pharmacokinetic Properties*).

2.5.2 Pregnancy

Biceltis should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus. In the post marketing setting, cases of foetal renal growth and/or function impairment in association with oligohydramnios, some of which resulted in fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving Trastuzumab Injection.

Women who become pregnant should be advised of the possibility of harm to the foetus. If a pregnant woman is treated with Biceltis, or if a patient becomes pregnant while receiving Biceltis or within 7 months following last dose of Biceltis, close monitoring by a multidisciplinary team is desirable.

Labour and Delivery

No data to report

2.5.3 Lactation

It is not known whether trastuzumab is secreted in human milk. As human immunoglobulin G (IgG) is secreted into human milk, and the potential for harm to the infant is unknown, breastfeeding should be avoided during Biceltis therapy (*see section 3.2.3 on Other, Lactation*].

2.5.4 Paediatric Use

The safety and efficacy of Biceltis in paediatric patients below the age of 18 have not been established.

2.5.5 Geriatric Use

Data suggest that the disposition of Biceltis is not altered based on age (*see section 3.2.5 Pharmacokinetics in Special Populations*).

2.5.6 Renal Impairment

In a population pharmacokinetic analysis, renal impairment was shown not to affect trastuzumab disposition.

2.5.7 Hepatic Impairment

No data to report.

2.6 Undesirable Effects

2.6.1 Clinical Trials

Table 1 summarizes the adverse drug reactions (ADRs) that have been reported in association with the use of Biceltis alone or in combination with chemotherapy in pivotal clinical trials. All the terms included are based on the highest percentage seen in pivotal clinical trials.

As Biceltis is commonly used with other chemotherapeutic agents and radiotherapy it is often difficult to ascertain the causal relationship of an adverse event to a particular drug/radiotherapy.

The corresponding frequency category for each adverse drug reaction is based on the following convention: 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 should be presented in order of decreasing seriousness.

Table 1 Summary of adverse drug reactions occurring in patients treated with Biceltis in clinical trials

System organ class	Adverse reaction*	Frequency
Infections and infestations	Nasopharyngitis	Very Common
	Infection	Very common
	Influenza	Common
	Neutropenic sepsis	Common
	Pharyngitis	Common
	Sinusitis	Common
	Rhinitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
Blood and lymphatic system disorders	Anaemia	Very common
	Thrombocytopenia	Very common
	Febrile neutropenia	Very common
	White blood cell count decreased/leukopenia	Very Common
	Neutropenia	Very Common
Immune system disorders	Hypersensitivity	Common
	Anaphylactic shock	rare

Metabolism and nutrition disorders	Weight decreased	Very common
	Weight increased	Very common
	Decreased appetite	Very common
Psychiatric disorders	Insomnia	Very common
	Depression	Common
	Anxiety	Common
Nervous system disorders	Dizziness	Very common
	Headache	Very common
	Paraesthesia	Very common
	Hypoaesthesia	Very common
	Dysgeusia	Very common
	Hypertonia	Common
	Peripheral neuropathy	Common
	Somnolence	Common
Eye disorders	Lacrimation increased	Very common
	Conjunctivitis	Very common
Ear and labyrinth disorders	Deafness	Uncommon
Cardiac disorders	Ejection fraction decreased	Very common
	[+1]Supraventricular tachyarrhythmia	Common
	[+]Cardiac failure (congestive)	Common
	Cardiomyopathy	Common
	[1]Palpitation	Common
	Pericardial Effusion	Uncommon
Vascular disorders	Lymphoedema	Very common
	Hot flush	Very common
	[+1]Hypotension	Common
	Hypertension	Common
	Vasodilation	Common
Respiratory, thoracic and mediastinal disorders	[+]Dyspnoea	Very common
	Epistaxis	Very common
	Oropharyngeal pain	Very common
	Cough	Very common
	Rhinorrhoea	Very common
	Asthma	Common
	Lung disorder	Common
	[+]Pleural effusion	Common
	Pneumonia	Common
	Pneumonitis	Uncommon
	Wheezing	Uncommon
	Diarrhoea	Very common

Gastrointestinal disorders	Vomiting	Very common
	Nausea	Very common
	Abdominal pain	Very common
	Dyspepsia	Very common
	Constipation	Very common
	Stomatitis	Very common
Hepatobiliary disorders	Hepatocellular injury	Common
	Jaundice	Rare
Skin and subcutaneous tissue disorders	Erythema	Very common
	Rash	Very common
	Alopecia	Very common
	Palmar-plantar erythrodysaesthesia syndrome	Very common
	Nail disorder	Very common
	Acne	Common
	Dermatitis	Common
	Dry skin	Common
	Hyperhydrosis	Common
	Maculopapular rash	Common
	Pruritus	Common
	Onychoclasis	Common
	Urticaria	Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	Myalgia	Very common
	Arthritis	Common
	Back pain	Common
	Bone pain	Common
	Muscle spasms	Common
	Neck pain	Common
	Pain in extremity	Common
General disorders and administration site conditions	Asthenia	Very common
	Chest pain	Very common
	Chills	Very common
	Fatigue	Very common
	Influenza-like illness	Very common
	Infusion/Administration related reaction	Very common
	Pain	Very common
	Pyrexia	Very common
	Peripheral oedema	Very common
	Mucosal inflammation	Very common

	Oedema	Common
	Injection site pain**	Common
	Malaise	Common
Injury, poisoning and procedural complications	Nail toxicity	Very common

* Adverse drug reactions (ADRs) were identified as events that occurred with at least a 2% difference compared to the control arm in at least one of the major randomised clinical trials.
** Injection site pain was identified as an ADR in the SC arm in the BO22227 study. ADRs were added to the appropriate system organ class (SOC) category and are presented in a single table according to the highest incidence seen in any of the major clinical trials.
+ 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.

Additional information for selected adverse drug reactions

Infusion/Administration-related reactions (IRRs/ARRs) / Hypersensitivity

IRRs/ARRs such as chills and/or fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress were seen in all trastuzumab clinical trials and for the IV and the SC formulation (*see section 2.4 Warnings and Precautions*).

IRRs/ARRs may be clinically difficult to distinguish from hypersensitivity reactions.

The rate of IRRs/ARRs of all grades varied between studies depending on the indication, whether trastuzumab was given concurrently with chemotherapy or as monotherapy and data collection methodology.

In MBC, the rate of IRRs/ARRs ranged from 49% to 54% in the trastuzumab containing arm compared to 36% to 58% in the comparator arm (which may have contained other chemotherapy). Severe (grade 3 and above) ranged from 5% to 7% in the trastuzumab containing arm compared to 5 to 6% in the comparator arm.

In EBC, the rate of IRRs/ARRs ranged from 18% to 54% in the trastuzumab containing arm compared to 6% to 50% in the comparator arm (which may have contained other chemotherapy). Severe (grade 3 and above) ranged from 0.5% to 6% in the trastuzumab containing arm compared to 0.3 to 5% in the comparator arm.

In the neoadjuvant-adjuvant EBC treatment setting (BO22227), the rates of IRRs/ARRs were in line with the above and were 37.2% in the Biceltis IV arm to 47.8% in the Biceltis SC arm. Severe (grade 3) IRRs/ARRs were 2.0% and 1.7% in the Biceltis IV and Biceltis SC arms, respectively during the treatment phase. There were no grade 4 or 5 IRRs/ARRs.

Anaphylactoid reactions were observed in isolated cases.

Cardiac dysfunction

Congestive heart failure (NYHA Class II-IV) is a common adverse reaction to Trastuzumab Injection. It has been associated with fatal outcome. Signs and symptoms of cardiac dysfunction such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S_3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with Trastuzumab Injection (see section 2.4 Warnings and Precautions).

Metastatic Breast Cancer

Depending on the criteria used to define cardiac dysfunction, the incidence in the pivotal metastatic trials varied between 9% and 12% in the Trastuzumab Injection + paclitaxel group, compared with 1% – 4% in the paclitaxel alone group. For Trastuzumab Injection monotherapy, the rate was 6% – 9%. The highest rate of cardiac dysfunction was seen in patients receiving concurrent Trastuzumab Injection + anthracycline/cyclophosphamide (27%), and was significantly higher than in the anthracycline/cyclophosphamide alone group (7% – 10%). In a subsequent trial with prospective monitoring of cardiac function, the incidence of symptomatic heart failure was 2.2% in patients receiving Trastuzumab Injection 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.

Early Breast Cancer (adjuvant setting)

In three pivotal clinical trials of adjuvant trastuzumab given in combination with chemotherapy the incidence of grade 3/4 cardiac dysfunction (symptomatic CHF) was similar in patients who were administered chemotherapy alone and in patients who were administered Trastuzumab Injection sequentially after a taxane (0.3 - 0.4%). The rate was highest in patients who were administered Trastuzumab Injection concurrently with a taxane (2.0%). At 3 years, the cardiac event rate in patients receiving AC→P (doxorubicin plus cyclophosphamide followed by paclitaxel) + H (trastuzumab) was estimated at 3.2%, compared with 0.8% in AC→P treated patients. No increase in the cumulative incidence of cardiac events was seen with further follow up at 5 years.

At 5.5 years, the rates of symptomatic cardiac or LVEF events were 1.0%, 2.3%, and 1.1% in the AC→D (doxorubicin plus cyclophosphamide, followed by docetaxel), AC→DH (doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab), and DCarbH (docetaxel, carboplatin and trastuzumab) treatment arms, respectively. For symptomatic CHF (NCI-CTC Grade 3-4), the 5-year rates were 0.6%, 1.9%, and 0.4% in the AC→D, AC→DH, and DCarbH treatment arms, respectively. The overall risk of developing symptomatic cardiac events was low and similar for patients in the AC→D and DCarbH arms; relative to both the AC→D and DCarbH arms there was an increased risk of developing a symptomatic cardiac event for patients in the AC→DH arm, being discernable by a continuous increase in the cumulative rate of symptomatic cardiac or LVEF events up to 2.3% compared to approximately 1% in the two comparator arms (AC→D and DCarbH).

When Trastuzumab Injection 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. After a median follow-up of 3.6 years the incidence of severe CHF and left ventricular dysfunction after 1 year Trastuzumab Injection therapy remained low at 0.8% and 9.8%, respectively.

In study BO16348, after a median follow-up of 8 years the incidence of severe CHF (NYHA Class III-IV) in the Trastuzumab Injection 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 $\geq$50% after the event) was evident for 71.4 % of Trastuzumab Injection-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 Injection.

In the joint analysis of studies NSABP B-31 and NCCTG N9831, with a median follow-up of 8.1 years for the AC→PH group (doxorubicin plus cyclophosphamide, followed by paclitaxel plus trastuzumab), the per patient incidence of new onset cardiac dysfunction, as determined by LVEF, remained unchanged compared to the analysis performed at a median follow up of 2.0 years in the AC→PH group: 18.5% of AC→PH patients with an LVEF decrease of ≥10% to below 50%. Reversibility of left ventricular dysfunction was reported in 64.5% of patients who experienced a symptomatic CHF in the AC→PH group being asymptomatic at latest follow up, and 90.3% having full or partial LVEF recovery.

Early Breast Cancer (neoadjuvant-adjuvant setting)

In the pivotal trial MO16432, Biceltis 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 Biceltis arm.

In the pivotal trial BO22227, Biceltis was administered concurrently with neoadjuvant chemotherapy that contained four cycles of epirubicin (cumulative dose 300 mg/m^2); at a median follow-up exceeding 70 months, the incidence of cardiac failure / congestive cardiac failure was 0.3% in the Biceltis IV arm. In patients with lower body weights (<59 kg, the lowest body weight quartile) the fixed dose used in the Biceltis SC arm was not associated with an increased risk of cardiac events or significant drop in LVEF.

Advanced Gastric Cancer

In the BO18255 study, at screening, the median LVEF value was 64% (range 48%-90%) in the Fluoropyrimidine/Cisplatin arm (FP) arm and 65% (range 50%-86%) in the Trastuzumab Injection IV plus Fluoropyrimidine/Cisplatin arm (H+FP) arm.

The majority of the LVEF decreases noted in BO18255 study were asymptomatic, with the exception of one patient in the Trastuzumab Injection-containing arm whose LVEF decrease coincided with cardiac failure.

Table 2: Summary of LVEF Change from baseline (BO18255 study)

LVEF Decrease: Lowest Post screening Value	**Fluoropyrimidine/Cisplatin (N = 290) (% of patients in each treatment arm)**	**Trastuzumab/ Fluoropyrimidine/ Cisplatin (N = 294) (% of patients in each treatment arm)**
*LVEF decrease of ≥ 10% to a value of <50%	1.1%	4.6%
Absolute Value < 50%	1.1%	5.9%
*LVEF decrease of ≥10% to a value of ≥50%	11.8%	16.5%

*Only includes patients whose method of assessment at that visit is the same as at their initial assessments (FP, n = 187 and H +FP, n = 237)

Table 3: Cardiac Adverse Events (BO18255 study)

	Fluoropyrimidine/Cisplatin (N = 290) (% of patients in each treatment arm)	**Trastuzumab/Fluoropyrimidine/ Cisplatin (N = 294) (% of patients in each treatment arm)**
Total Cardiac Events	6%	6%
≥Grade 3 NCI CTCAE v3.0	*3%	**1%

* 9 patients experienced 9 Events
** 4 patients experienced 5 Events

Overall, there were no significant differences in cardiac dysfunction between the treatment arm and the comparator arm.

Haematological toxicity

Breast Cancer

Haematological toxicity is infrequent following the administration of Trastuzumab Injection monotherapy in the metastatic setting, WHO Grade 3 leukopenia, thrombocytopenia and anaemia occurring in < 1% of patients. No WHO Grade 4 toxicities were observed. There was an increase in WHO Grade 3 or 4 haematological toxicity in patients treated with the combination of Trastuzumab Injection and paclitaxel compared with patients receiving paclitaxel alone (34% versus 21%). Haematological toxicity was also increased in patients

receiving Trastuzumab Injection and docetaxel, compared with docetaxel alone (32% grade 3/4 neutropenia versus 22%, using NCI-CTC criteria). The incidence of febrile neutropenia/neutropenic sepsis was also increased in patients treated with Trastuzumab Injection plus docetaxel (23% versus 17% for patients treated with docetaxel alone).

Using NCI-CTC criteria, in the BO16348 study, 0.4% of Trastuzumab Injection-treated patients experienced a shift of 3 or 4 grades from baseline, compared with 0.6% in the observation arm.

Advanced Gastric Cancer

The most frequently reported AEs, of Grade ≥ 3 occurring with an incidence rate of at least 1% by trial treatment, that were categorised under the Blood and Lymphatic System Disorders SOC are shown below:

Table 4: Frequently reported AEs grade ≥ 3 in blood and lymphatic system disorders SOC

	Fluoropyrimidine/Cisplatin (N = 290) (% of patients in each treatment arm)	**Trastuzumab/Fluoropyrimidine/ Cisplatin (N = 294) (% of patients in each treatment arm)**
Neutropenia	30%	27%
Anaemia	10%	12%
Febrile neutropenia	3%	5%
Thrombocytopenia	3%	5%

The total percentage of patients who experienced an AE of ≥ grade 3 NCI-CTCAE v3.0 that has been categorised under this SOC were 38% in the FP arm and 40% in the FP + H arm.

Overall, there were no significant differences in haematotoxicity between the treatment arm and the comparator arm.

Hepatic and renal toxicity

Breast Cancer

WHO Grade 3 or 4 hepatic toxicity was observed in 12% of patients following administration of Trastuzumab Injection IV as single agent, in the metastatic setting. This toxicity was associated with progression of disease in the liver in 60% of these patients.

WHO Grade 3 or 4 hepatic toxicity was less frequently observed among patients receiving Trastuzumab Injection IV and paclitaxel than among patients receiving paclitaxel alone (7% compared with 15%). No WHO Grade 3 or 4 renal toxicity was observed.

Advanced Gastric Cancer

In the BO18255 study no significant differences in hepatic and renal toxicity were observed between the two treatment arms.

NCI-CTCAE (version 3.0) grade ≥3 renal toxicity was not significantly higher in patients receiving Trastuzumab Injection IV than those in the F+P arm (3% and 2% respectively).

NCI-CTCAE (version 3.0) grade ≥3 adverse event in the Hepatobiliary Disorders SOC: Hyperbilirubinaemia was the only reported AE and was not significantly higher in patients receiving Trastuzumab Injection IV than those in the F+P arm (1% and < 1% respectively).

Diarrhoea

Breast Cancer

Of patients treated with Trastuzumab Injection IV monotherapy in the metastatic setting 27% experienced diarrhoea. An increase in the incidence of diarrhoea, primarily mild to moderate in severity, has also been observed in patients receiving Trastuzumab Injection in combination with paclitaxel compared with patients receiving paclitaxel alone.

In the BO16348 study, 8% of Trastuzumab Injection-treated patients experienced diarrhoea during the first year of treatment.

Advanced Gastric Cancer

In the BO18255 study, 109 patients (37%) participating in the Trastuzumab Injection-containing treatment arm versus 80 patients (28%) in the comparator arm experienced any grade diarrhoea. Using NCI-CTCAE v3.0 severity criteria, the percentage of patients experiencing grade ≥ 3 diarrhoea was 4% in the FP arm versus 9% in the FP+H arm.

Infection

An increased incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections has been observed in patients treated with Trastuzumab Injection.

Switching treatment from Biceltis IV to Biceltis SC and vice versa (SC formulation not approved and not available in India)

Study MO22982 investigated switching from Biceltis IV to Biceltis SC, and vice versa, in patients with HER2 positive EBC, with a primary objective to evaluate patient preference for either Biceltis IV infusion or Biceltis SC injection. In this trial, 2 cohorts (one using Biceltis SC Vial and one using Biceltis SC SID) were investigated using a 2-arm, cross-over design with patients being randomized to one of two different q3w Biceltis treatment sequences (Biceltis IV (Cycles 1-4) → Biceltis SC (Cycles 5-8), or Biceltis SC (Cycles 1-4) → Biceltis IV (Cycles 5-

8)). Patients were either naïve to Biceltis IV treatment (20.3%) or pre-exposed to Biceltis IV (79.7%) as part of ongoing adjuvant treatment for HER2 positive EBC. Overall, switches from Biceltis IV to Biceltis SC and vice versa were well tolerated. Pre-switch rates (Cycles 1-4) for SAEs, Grade 3 AEs and treatment discontinuations due to AEs were low (<5%) and similar to post-switch rates (Cycles 5-8). No Grade 4 or Grade 5 AEs were reported.

Biceltis SC safety and tolerability in EBC patients (SC formulation not approved and not available in India)

Study MO28048 investigating the safety and tolerability of Biceltis SC as adjuvant therapy enrolled HER2 positive EBC patients in either a Biceltis SC Vial cohort (N=1868 patients, including 20 patients receiving neoadjuvant therapy) or a Biceltis SC SID cohort (N=710 patients, including 21 patients receiving neoadjuvant therapy). The primary analysis included patients with a median follow-up of up to 23.7 months. No new safety signals were observed and results were consistent with the known safety profile for Biceltis IV and Biceltis SC. In addition, treatment of lower body weight patients with Biceltis SC fixed dose in adjuvant EBC was not associated with increased safety risk, AEs and SAEs, compared to the higher body weight patients. The final results of study BO22227 at a median follow-up exceeding 70 months were also consistent with the known safety profile for Biceltis IV and Biceltis SC, and no new safety signals were observed.

2.6.2 Post marketing Experience

The following adverse drug reactions have been identified from post marketing experience with Biceltis (Table 5).

Table 5: Adverse Reactions reported in the post marketing setting

System organ class	Adverse reaction
Blood and lymphatic system disorders	Hypoprothrombinaemia Immune thrombocytopenia
Immune system disorders	Anaphylactoid reaction
	Anaphylactic reaction
Metabolism and nutrition disorders	Tumour lysis syndrome
Eye disorders	Madarosis
Cardiac disorders	Cardiogenic shock
	Tachycardia
Respiratory, thoracic and mediastinal disorders	Bronchospasm
	Oxygen saturation decreased
	Respiratory failure
	Interstitial lung disease

	Lung infiltration
	Acute respiratory distress syndrome
	Respiratory distress
	Pulmonary fibrosis
	Hypoxia
	Laryngeal oedema
Renal and urinary disorders	Glomerulonephropathy
	Renal failure
Pregnancy, puerperium and perinatal conditions	Pulmonary hypoplasia
	Renal hypoplasia
	Oligohydramnios

2.6.3 Adverse Events

Table below indicates adverse events that historically have been reported in patients who have received Trastuzumab Injection. As no evidence of a causal association has been found between Trastuzumab Injection and these events, these events are not considered expected for the purposes of regulatory reporting.

Table 6: Adverse Events

System organ class	**Adverse Event**
Infections and infestations	Meningitis
	Bronchitis
Blood and lymphatic system disorders	Leukaemia
Nervous system disorders	Cerebrovascular disorder
	Lethargy
	Coma
Ear and labyrinth disorders	Vertigo
Respiratory, Thoracic and Mediastinal system disorders	Hiccups
	Dyspnoea exertional
Gastrointestinal disorders	Gastritis
	Pancreatitis
Musculoskeletal and connective tissue disorders	Musculoskeletal pain
Renal and urinary disorders	Dysuria
Reproductive system and breast disorders	Breast pain
General disorders and administration site conditions	Chest discomfort

2.7 Overdose

There is no experience with overdose in human clinical trials. Single doses higher than 10 mg/kg have not been tested.

2.8 Interactions with other medicinal products and other forms of interaction

There have been no formal drug interaction studies performed with Biceltis in humans. Clinically significant interactions between Biceltis and the concomitant medications used in clinical trials have not been observed (*see section 3.2 Pharmacokinetic Properties*).

In studies where Biceltis was administered in combination with docetaxel, carboplatin, or anastrozole, the pharmacokinetics of these medications was not altered nor was the pharmacokinetics of trastuzumab altered.

Concentrations of paclitaxel and doxorubicin (and their major metabolites 6-α hydroxylpaclitaxel, POH, and doxorubicinol, DOL) were not altered in the presence of trastuzumab. However, trastuzumab may elevate the overall exposure of one doxorubicin metabolite, (7deoxy-13 dihydro-doxorubicinone, D7D). The bioactivity of D7D and the clinical impact of the elevation of this metabolite is unclear. No changes were observed in trastuzumab concentrations in the presence of paclitaxel and doxorubicin.

The results of a drug interaction substudy evaluating the pharmacokinetics of capecitabine and cisplatin when used with or without trastuzumab 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 pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus Trastuzumab.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

Trastuzumab is a recombinant humanised monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). The antibody is an IgG_1 isotype that contains human framework regions with the complementarity determining regions of a murine anti-p185 HER2 antibody that binds to human HER2.

The HER2 proto-oncogene or c-erbB2 encodes for a single transmembrane spanning, receptor like protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. Overexpression of HER2 is observed in 15%-20% of primary breast cancer The overall rate of HER2 positivity in advanced gastric cancers as observed during screening for study BO18255 is 15% for IHC3+ and IHC2+/FISH+ or 22.1% when applying the broader definition of IHC3+ or FISH+. A consequence of HER2 gene amplification is an increase in

HER2 protein expression on the surface of these tumour cells, which results in a constitutively activated HER2 protein.

Studies indicate that breast cancer patients whose tumors have amplification or overexpression of HER2 have a shortened disease-free survival compared to patients whose tumors do not have amplification or overexpression of HER2.

Trastuzumab has been shown, both in in-vitro assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2. In vitro, trastuzumab-mediated antibody dependent cell-mediated cytotoxicity (ADCC) has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

3.1.2 Clinical / Efficacy Studies

Breast Cancer

Metastatic Breast Cancer

Trastuzumab Injection monotherapy has been used in clinical trials for patients with metastatic breast cancer who have tumors that overexpress HER2 and who have failed one or more chemotherapy regimens for their metastatic disease.

Trastuzumab Injection has also been used in clinical trials in combination with paclitaxel or an anthracycline (doxorubicin or epirubicin) plus cyclophosphamide as first line therapy for patients with metastatic breast cancer who have tumors that overexpress HER2.

Patients who had previously received anthracycline-based adjuvant chemotherapy were treated with paclitaxel (175 mg/m^2 infused over 3 hours) with or without Trastuzumab Injection. Patients could be treated with Trastuzumab Injection until progression of disease.

Trastuzumab Injection monotherapy, when used as second- or third-line treatment of women with metastatic breast cancer which overexpresses HER-2, results in an overall tumor response rate of 15% and a median survival of 13 months.

The use of Trastuzumab Injection in combination with paclitaxel as first-line treatment of women with metastatic breast cancer that overexpresses HER-2 significantly prolongs the median time to disease progression, compared with patients treated with paclitaxel alone. The increase in median time to disease progression for patients treated with Trastuzumab Injection and paclitaxel is 3.9 months (6.9 months vs. 3.0 months). Tumor response and one year survival rate are also increased for Trastuzumab Injection in combination with paclitaxel versus paclitaxel alone.

Trastuzumab Injection has also been studied in a randomised, controlled trial, in combination with docetaxel, as first-line treatment of women with metastatic breast cancer. The combination of Trastuzumab Injection and docetaxel significantly increased response rate (61% versus 34%) and prolonged the median time to disease progression, (by 5.6 months), compared with patients treated with docetaxel alone. Median survival was also significantly

increased in patients receiving the combination, compared with those receiving docetaxel alone (31.2 months versus 22.7 months).

Combination treatment with Trastuzumab Injection and anastrozole

Trastuzumab Injection has been studied in combination with anastrozole for first line treatment of metastatic breast cancer in HER2 overexpressing, hormone-receptor (i.e. estrogen-receptor (ER) and/or progesterone-receptor (PR)) positive patients. Progression free survival was doubled in the Trastuzumab Injection plus anastrozole arm compared to anastrozole (4.8 months versus 2.4 months). For the other parameters the improvements seen for the combination were; for overall response (16.5% versus 6.7%); clinical benefit rate (42.7% versus 27.9%); time to progression (4.8 months versus 2.4 months). For time to response and duration of response no difference could be recorded between the arms. The median overall survival was extended by 4.6 months for patients in the combination arm. The difference was not statistically significant, however more than half of the patients in the anastrozole alone arm crossed over to a Trastuzumab Injection containing regimen after progression of disease. Fifty two percent of the patients taking Trastuzumab Injection plus anastrozole survived for at least 2 years compared to 45% taking anastrozole alone.

Early Breast Cancer

In the adjuvant treatment setting, Trastuzumab Injection was investigated in 4 large multicenter, randomised, phase 3 trials:

- Study BO16348 was designed to compare one and two years of three-weekly Trastuzumab Injection treatment versus observation in patients with HER2-positive early breast cancer following surgery, established chemotherapy and radiotherapy (if applicable). In addition, a comparison of two years of Trastuzumab Injection treatment versus one year of Trastuzumab Injection treatment was performed. Patients assigned to receive Trastuzumab Injection were given an initial loading dose of 8 mg/kg, followed by 6 mg/kg every three weeks for either one or two years.
- Studies NSABP B-31 and NCCTG N9831 that comprise the joint analysis were designed to investigate the clinical utility of combining Trastuzumab Injection IV treatment with paclitaxel following AC chemotherapy; additionally the NCCTG N9831 study investigated adding Trastuzumab Injection sequentially to AC-paclitaxel chemotherapy in patients with HER2-positive early breast cancer following surgery.
- Study BCIRG 006 was designed to investigate combining Trastuzumab Injection IV treatment with docetaxel either following AC chemotherapy or in combination with docetaxel and carboplatin in patients with HER2-positive early breast cancer following surgery.

Early breast cancer in the BO16348 study was limited to operable, primary, invasive adenocarcinoma of the breast, with axillary nodes-positive or axillary nodes-negative tumours of at least 1 cm in diameter.

The efficacy results from the BO16348 study are summarized in the following table:

Table 7: Efficacy Results (BO16348 study): Results at 12months* and 8 years of median follow-up**

	Median follow-up 12 months		Median follow-up 8 years	
Parameter	Observation N=1693	Trastuzumab Injection 1 Year N = 1693	Observation N= 1697***	Trastuzumab Injection 1 Year N = 1702***
Disease-free survival				
- No. patients with event	219 (12.9%)	127 (7.5%)	570 (33.6%)	471 (27.7%)
- No. patients without event	1474 (87.1%)	1566 (92.5%)	1127 (66.4%)	1231 (72.3%)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.54		0.76	
Recurrence-free survival				
- No. patients with event	208 (12.3%)	113 (6.7%)	506 (29.8%)	399 (23.4%)
- No. patients without event	1485 (87.7%)	1580 (93.3%)	1191 (70.2%)	1303 (76.6%)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.51		0.73	
Distant disease-free survival				
- No. patients with event	184 (10.9%)	99 (5.8%)	488 (28.8%)	399 (23.4%)
- No. patients without event	1508 (89.1%)	1594 (94.6%)	1209 (71.2%)	1303 (76.6%)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.50		0.76	
Overall survival (death)				
- No. patients with event	40 (2.4%)	31 (1.8%)	350 (20.6%)	278 (16.3%)
- No. patients without event	1653 (97.6%)	1662 (98.2%)	1347 (79.4%)	1424 (83.7%)
P-value versus Observation	0.24		0.0005	
Hazard Ratio versus Observation	0.75		0.76	

*Co-primary endpoint of DFS of 1 year vs observation met the pre-defined statistical boundary

**Final analysis (including crossover of 52% of patients from the observation arm to Biceltis)
*** There is a discrepancy in the overall sample size due to a small number of patients who were randomised after the cut-off date for the 12-month median follow-up analysis

The efficacy results from the interim efficacy analysis crossed the protocol pre-specified statistical boundary for the comparison of 1-year of Trastuzumab Injection vs. observation. After a median follow-up of 12 months, the hazard ratio (HR) for disease free survival (DFS) was 0.54 (95% CI 0.44, 0.67) which translates into an absolute benefit, in terms of a 2-year disease-free survival rate, of 7.6 percentage points (85.8% versus 78.2%) in favour of the Trastuzumab Injection arm.

A final analysis was performed after a median follow-up of 8 years, which showed that 1 year Trastuzumab Injection treatment is associated with a 24% risk reduction compared to observation only (HR=0.76, 95% CI 0.67, 0.86). This translates into an absolute benefit in terms of an 8-year disease free survival rate of 6.4 percentage points in favour of 1 year Trastuzumab Injection treatment.

In this final analysis, extending Trastuzumab Injection treatment for a duration of two years did not show additional benefit over treatment for 1 year [DFS HR in the intent to treat (ITT) population of 2 years vs 1 year=0.99 (95% CI: 0.87, 1.13), p-value=0.90 and OS HR=0.98 (0.83, 1.15); p-value= 0.78]. The rate of asymptomatic cardiac dysfunction was increased in the 2-year treatment arm (8.1% versus 4.6% in the 1-year treatment arm). More patients experienced at least one grade 3 or 4 adverse event in the 2-year treatment arm (20.4%) compared with the 1-year treatment arm (16.3%).

In the joint analysis of the NSABP B-31 and NCCTG N9831 studies, early breast cancer was limited to women with operable breast cancer at high risk, defined as HER2-positive and axillary lymph node-positive or HER2-positive and lymph node-negative with high risk features (tumour size > 1 cm and ER negative or tumour size > 2 cm, regardless of hormonal status). Trastuzumab Injection was administered in combination with paclitaxel, following AC chemotherapy. Paclitaxel was administered as follows:

- Intravenous paclitaxel - 80 mg/m^2 as a continuous IV infusion, given every week for 12 weeks, or
- Intravenous paclitaxel - 175 mg/m^2 as a continuous IV infusion, given every 3 weeks for 4 cycles (day 1 of each cycle).

Table 8: Summary of Efficacy results from the joint analysis studies NSABP B-31 and NCCTG N9831 at the time of the definitive DFS analysis*:

Parameter	AC→P (N=1679)	AC→PH (N=1672)	p-value versus AC→P	Hazard Ratio versus AC→P (95% CI)
Disease-free survival No. patients with event (%)	261 (15.5)	133 (8.0)	< 0.0001	0.48 (0.39, 0.59)
Distant Recurrence No. patients with event (%)	193 (11.5)	96 (5.7)	< 0.0001	0.47 (0.37, 0.60)
Death (OS event): No. patients with event (%)	92 (5.5)	62 (3.7)	0.014**	0.67 (0.48, 0.92)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: trastuzumab
* at median duration of follow up of 1.8 years for the patients in the AC→P arm and 2.0 years for patients in the AC→PH arm
** p value for OS did not cross the pre-specified statistical boundary for comparison of AC→PH vs. AC→P Source: Table 15 Clinical Study Report: Joint Analysis of B-31 and N9831, 04 February 2006, Genentech, Inc.

For the primary endpoint, DFS, the addition of Trastuzumab Injection to paclitaxel chemotherapy resulted in a 52% decrease in the risk of disease recurrence. The hazard ratio translates into an absolute benefit, in terms of a 3-year disease-free survival rate, of 11.8 percentage points (87.2% versus 75.4%) in favour of the AC→PH (Trastuzumab Injection) arm.

The pre-planned final analysis of OS from the joint analysis of studies NSABP B-31 and NCCTG N9831 was performed when 707 deaths had occurred (median follow-up 8.3 years in the AC→PH group). Treatment with AC→PH resulted in a statistically significant improvement in OS compared with AC→P (stratified HR=0.64; 95% CI [0.55, 0.74]; log-rank p value < 0.0001). At 8 years, the survival rate was estimated to be 86.9% in the AC→PH arm and 79.4% in the AC→P arm, an absolute benefit of 7.4% (95% CI 4.9%, 10.0%).

The final OS results from the joint analysis of studies NSABP B-31 and NCCTG N9831 are summarized in the following table:

Table 9: Final Overall Survival Analysis from the joint analysis of trials NSABP B-31 and NCCTG N9831:

Parameter	AC→P (N=2032)	AC→PH (N=2031)	p-value versus AC→P	Hazard Ratio versus AC→P (95% CI)

Death (OS event): No. patients with event (%)	418 (20.6%)	289 (14.2%)	< 0.0001	0.64 (0.55, 0.74)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: trastuzumab

In the BCIRG 006 study, HER2-positive, early breast cancer was limited to either lymph node-positive or high risk node-negative patients, defined as negative (pN0) lymph node involvement, and at least 1 of the following factors: tumour size greater than 2 cm, oestrogen receptor and progesterone receptor negative, histologic and/or nuclear grade 2 - 3, or age < 35 years. Trastuzumab Injection was administered either in combination with docetaxel, following AC chemotherapy (AC-DH) or in combination with docetaxel and carboplatin (DCarbH).

Docetaxel was administered as follows:

- intravenously (100 mg/m^2 as an IV infusion over 1 hour) given every 3 weeks for 4 cycles (day 2 of first docetaxel cycle, then day 1 of each subsequent cycle), or
- intravenously (75 mg/m^2 as an IV infusion over 1 hour) given every 3 weeks for 6 cycles (day 2 of cycle 1, then day 1 of each cycle).

Docetaxel therapy was followed by carboplatin (at target AUC = 6 mg/ml/min) administered by IV infusion over 30-60 minutes repeated every 3 weeks for a total of 6 cycles

The efficacy results from the BCIRG 006 study are summarized in the following tables:

Table 10: Overview of Efficacy Analyses AC→D versus AC→DH (BCIRG 006 study)

Parameter	AC→D (N=1073)	AC→DH (N=1074)	p-value versus AC→D (log-rank)	Hazard Ratio versus AC→D (95% CI)
Disease-free survival				
No. patients with event	195	134	< 0.0001	0.61 (0.49, 0.77)
Distant recurrence				
No. patients with event	144	95	< 0.0001	0.59 (0.46, 0.77)
Overall Survival (Death)				
No. patients with event	80	49	0.0024	0.58 (0.40, 0.83)

AC→D = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→DH = doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; CI = confidence interval

Table 11: Overview of Efficacy Analyses AC→D versus DCarbH (BCIRG 006 study)

Parameter	AC→D (N=1073)	DCarbH (N=1075)	p-value versus AC→D (log-rank)	Hazard Ratio versus AC→D (95% CI)
Disease-free survival				
No. patients with event	195	145	0.0003	0.67 (0.54, 0.83)
Distant recurrence				
No. patients with event	144	103	0.0008	0.65 (0.50, 0.84)
Death (OS event)				
No. patients with event	80	56	0.0182	0.66 (0.47, 0.93)

AC→D = doxorubicin plus cyclophosphamide, followed by docetaxel; DCarbH = docetaxel, carboplatin and trastuzumab; CI = confidence interval

In the BCIRG 006 study for the primary endpoint, DFS, the hazard ratio translates into an absolute benefit, in terms of a 3-year disease-free survival rate, of 5.8 percentage points (86.7% versus 80.9%) in favour of the AC→DH (Trastuzumab Injection) arm and 4.6 percentage points (85.5% versus 80.9%) in favour of the DCarbH (Trastuzumab Injection) arm compared to AC→D.

For the secondary endpoint overall survival, treatment with AC→DH reduced the risk of death by 42% when compared to AC→D (hazard ratio 0.58 [95% CI: 0.40, 0.83] p = 0.0024, log-rank test) and the risk of death was reduced by 34% for patients treated with DCarbH compared to patients treated with AC→D (hazard ratio 0.66 [95% CI: 0.47, 0.93], p = 0.0182). In the BCIRG 006 study at the second interim analysis, 185 randomised patients had died: 80 patients (7.5%) in the AC→D arm, 49 patients (4.6%) in the AC→DH arm, and 56 patients (5.2%) in the DCarbH arm. The median duration of follow-up was 2.9 years in the AC→D arm and 3.0 years in both the AC→DH and DCarbH arms.

In the neoadjuvant-adjuvant treatment setting, Trastuzumab Injection was evaluated in two phase 3 trials.

- Study MO16432 investigated a total of 10 cycles of neoadjuvant chemotherapy [an anthracycline and a taxane (AP+H followed by P+H, followed by CMF+H] concurrently with neoadjuvant-adjuvant Biceltis, or neoadjuvant chemotherapy alone, followed by adjuvant Biceltis for up to a total treatment duration of 1 year) in newly diagnosed locally advanced (Stage III) or inflammatory HER2-positive breast cancer patients.

- Study BO22227 was designed to demonstrate non-inferiority of treatment with Biceltis SC versus Biceltis IV based on co-primary PK and efficacy endpoints (trastuzumab C_{trough} at pre-dose Cycle 8, and pCR rate at definitive surgery, respectively). Patients with HER2positive, operable or locally advanced breast cancer (LABC) including inflammatory breast cancer received eight cycles of either Biceltis IV or Biceltis SC concurrently with chemotherapy (docetaxel followed by FEC), followed by surgery, and continued therapy with Biceltis SC or Biceltis IV as originally randomised for an additional 10 cycles, for a total of one year of treatment.

The efficacy results from Study MO16432 are summarized in the table below. The median duration of follow-up in the Trastuzumab Injection arm was 3.8 years.

Table 12: Overview of Efficacy Analyses (MO16432 study)

Parameter	Chemo + Trastuzumab Injection (n=115)	Chemo only (n=116)	
Event-free survival No. patients with event	46	59	Hazard Ratio (95% CI) 0.65 (0.44, 0.96) p=0.0275
Total pathological complete response* (95% CI)	40% (31.0, 49.6)	20.7% (13.7, 29.2)	p=0.0014

* Defined as absence of any invasive cancer both in the breast and axillary nodes

For the primary endpoint, EFS, the addition of Trastuzumab Injection to the neoadjuvant chemotherapy followed by adjuvant Trastuzumab Injection for a total duration of 52 weeks resulted in a 35% reduction in the risk of disease recurrence/progression. The hazard ratio translates into an absolute benefit, in terms of 3-year event-free survival rate estimates of 13 percentage points (65% versus 52%) in favour of the Trastuzumab Injection arm.

In Study BO22227 the analysis of the efficacy co-primary endpoint, pCR, defined as absence of invasive neoplastic cells in the breast, resulted in rates of 40.7% (95% CI: 34.7, 46.9) in the trastuzumab IV arm and 45.4% (95% CI: 39.2%, 51.7%) in the trastuzumab SC arm, a difference of 4.7% in favour of the trastuzumab SC arm. The lower boundary of the one-sided 97.5% confidence interval for the difference in pCR rates was -4.0, whereas the pre-defined non-inferiority margin was -12.5%, establishing the non-inferiority of trastuzumab SC for the co-primary endpoint

Table 13: Summary of pathological Complete Response (pCR) (BO22227 HannaH Study)

	Biceltis IV (N = 263)	Biceltis SC (N=260)
pCR (absence of invasive neoplastic cells in breast	107 (40.7%)	118 (45.4%)
Non-responders	156 (59.3%)	142 (54.6%)
Exact 95% CI for pCR Rate[1]	(34.7; 46.9)	(39.2; 51.7)
Difference in pCR (SC minus IV arm)	4.70	
Lower bound one-sided 97.5% CI for the difference in pCR[2]	- 4.0	

[1] Confidence interval for one sample binomial using Pearson-Clopper method

[2] Continuity correction of Anderson and Hauck (1986) has been used in this calculation

Analyses with longer term follow-up of a median duration exceeding 40 months supported the non-inferior efficacy of Biceltis SC compared to Biceltis IV with comparable results of both EFS and OS (3-year EFS rates of 73% in the Biceltis IV arm and 76% in the Biceltis SC arm, and 3year OS rates of 90% in the Biceltis IV arm and 92% in the Biceltis SC arm).

For non-inferiority of the PK co-primary endpoint, steady-state trastuzumab C_{trough} value at the end of treatment Cycle 7, refer to section 3.2. Pharmacokinetic Properties.

The final analysis at a median follow-up exceeding 70 months showed similar EFS and OS between patients who received Biceltis IV and those who received Biceltis SC. The 6-year EFS rate was 65% in both arms (ITT population: HR=0.98 [95% CI: 0.74;1.29]) and the OS rate, 84% in both arms (ITT population: HR=0.94 [95% CI: 0.61;1.45]).

Metastatic Gastric Cancer

The efficacy results from the BO18255 study are summarized in table 14 . Patients were recruited to the trial who were previously untreated for HER2-positive inoperable locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction not amenable to curative therapy. The primary endpoint was overall survival which was defined as the time from the date of randomization to the date of death from any cause. At the time of the analysis a total of 349 randomized patients had died: 182 patients (62.8%) in the control arm and 167 patients (56.8%) in the treatment arm (4). The majority of the deaths were due to events related to the underlying cancer.

The overall survival was significantly improved in the Trastuzumab Injection + capecitabine/5FU and cisplatin arm compared to the capecitabine/5-FU and cisplatin arm (p = 0.0046, LogRank test). The median survival time was 11.1 months with capecitabine/5-FU and cisplatin and 13.8 months with Trastuzumab Injection + capecitabine/5-FU and cisplatin. The risk of death was decreased by 26% (Hazard Ratio [HR] 0.74 95% CI [0.60-0.91]) for patients in the Trastuzumab Injection arm compared to the capecitabine/5-FU arm.

Post-hoc subgroup analyses indicate that targeting tumors with higher levels of HER2 protein (IHC 2+/FISH+ and IHC 3+/regardless of the FISH status) results in a greater treatment effect. The median overall survival for the high HER2 expressing group was 11.8 months versus 16 months, HR 0.65 (95%CI 0.51-0.83) and the median progression free survival was 5.5 months vs. 7.6 months, HR 0.64 (95% CI 0.51-0.79) for capecitabine/5-FU and cisplatin and Trastuzumab Injection + capecitabine/5-FU and cisplatin respectively.

In a method comparison study a high degree of concordance (>95%) was observed for SISH and FISH techniques for the detection of HER2 gene amplification in gastric cancer patients.

Table 14 Summary of Efficacy* from study BO18255

Parameter	FP N = 290	FP+H N = 294	HR (95% CI)	p-value
Overall Survival, Median months	11.1	13.8	0.74 (0.60-0.91)	0.0046
Progression-Free Survival, Median months	5.5	6.7	0.71 (0.59-0.85)	0.0002
Time to Disease Progression, Median months	5.6	7.1	0.70 (0.58-0.85)	0.0003
Overall Response Rate, %	34.5%	47.3%	1.70[a] (1.22, 2.38)	0.0017
Duration of Response, Median months	4.8	6.9	0.54 (0.40-0.73)	< 0.0001

FP: Fluoropyrimidine/cisplatin
FP+H: Fluoropyrimidine/cisplatin + Trastuzumab Injection [a] Odds ratio

3.1.3 Immunogenicity

In the neoadjuvant-adjuvant EBC study (BO22227), at a median follow-up exceeding 70 months, 10.1% (30/296) of patients treated with Biceltis IV and 15.9% (47/295) of patients receiving Biceltis SC Vial developed antibodies against trastuzumab. Neutralizing anti-trastuzumab antibodies were detected in post-baseline samples in 2 of 30 patients in the Biceltis IV arm and 3 of 47 patients in the Biceltis SC arm.

The clinical relevance of these antibodies is not known. The presence of anti-trastuzumab antibodies had no impact on pharmacokinetics, efficacy [determined by pathological complete response (pCR) and event free survival (EFS)] and safety [determined by occurrence of administration related reactions (ARRs)] of Biceltis IV and Biceltis SC.

3.2 Pharmacokinetic Properties

The pharmacokinetics of trastuzumab were evaluated in a population pharmacokinetic model analysis using pooled data from 1,582 subjects from 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 the nonlinear elimination, total clearance increased with decreasing concentrations. Linear clearance was 0.127 L/day for breast cancer (MBC/EBC) and 0.176 L/day for advanced gastric cancer (AGC). The nonlinear elimination parameter values were 8.81 mg/day for the maximum elimination rate (V_{max}) and 8.92 mg/L for the Michaelis-Menten constant (Km). The central compartment volume was 2.62 L for patients with breast cancer and 3.63 L for patients with AGC.

The population predicted PK exposures (with 5^{th} - 95^{th} Percentiles) and PK parameter value at clinically relevant concentrations (C_{max} and C_{min}) for breast cancer and AGC patients treated with the approved q1w and q3w dosing regimens are shown in Table 15 (Cycle 1) and Table 16 (steady state) below.

Table 15: Population Predicted Cycle 1 PK Exposure Values (with 5^{th} - 95^{th} Percentiles) for IV Regimens in Breast Cancer and AGC Patients

Regimen	Primary tumor type	N	Cmin (µg/mL)	Cmax (µg/mL)	AUC (µg.day/mL)
8mg/kg + 6mg/kg q3w	MBC/EBC	1195	29.4 (5.8 - 59.5)	178 (117 - 291)	1373 (736 - 2245)
	AGC	274	23.1 (6.1 - 50.3)	132 (84.2 - 225)	1109 (588 - 1938)
4mg/kg + 2mg/kg qw	MBC/EBC	1195	37.7 (12.3 - 70.9)	88.3 (58 - 144)	1066 (586 - 1754)

Table 16: Population Predicted Steady State PK Exposure Values (with 5^{th} - 95^{th} Percentiles) for trastuzumab IV Dosing Regimens in Breast Cancer and AGC Patients

Regimen	Primary tumor type	N	Cmin,ss (µg/mL)	Cmax,ss (µg/mL)	AUCss (µg.day/mL)	Time to steady-state (week)	Total CL range at Steady state (L/day)

8mg/kg + 6mg/kg q3w	MBC/EBC	1195	47.4 (5 - 115)	179 (107 - 309)	1794 (673 - 3618)	12	0.173 - 0.283
	AGC	274	32.9 (6.1 - 88.9)	131 (72.5 - 251)	1338 (557 - 2875)	9	0.189 - 0.337
4mg/kg + 2mg/kg qw	MBC/EBC	1195	66.1 (14.9 - 142)	109 (51.0 - 209)	1765 (647 - 3578)	12	0.201 - 0.244

Trastuzumab washout

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

3.2.1 Absorption

No text.

3.2.2 Distribution

No text.

3.2.3 Metabolism

No text.

3.2.4 Elimination

No text.

3.2.5 Pharmacokinetic in Special Populations

Detailed pharmacokinetic studies in the geriatric population and those with renal or hepatic impairment have not been carried out.

Renal Impairment

Detailed pharmacokinetic studies in patients with renal impairment have not been carried out. In a population pharmacokinetic analysis, renal impairment was shown not to affect trastuzumab disposition.

Geriatric population

Age has been shown to have no effect on the disposition of trastuzumab (see Dosage and administration).

3.3 Nonclinical safety

Trastuzumab was well tolerated in mice (non-binding species) and Macaque monkeys (binding species) in single- and repeat-dose toxicity studies of up to 6 months duration, respectively.

There was no evidence of acute or chronic toxicity identified.

3.3.1 Carcinogenicity

No carcinogenicity studies have been performed to establish the carcinogenic potential of Biceltis.

3.3.2 Genotoxicity

No data to report.

3.3.3 Impairment of Fertility

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 Biceltis IV and have revealed no evidence of impaired fertility.

3.3.4 Reproductive Toxicity

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 Injection IV and have revealed no evidence of impaired fertility or harm to the foetus. However, when assessing the risk of reproductive toxicity to humans, it is also important to consider the significance of the rodent form of the HER2 receptor in normal embryonic development and the embryonic death in mutant mice lacking this receptor. Placental transfer of trastuzumab during the early (days 20-50 of gestation) and late (days 120-150 of gestation) foetal development period was observed.

3.3.5 Other

Lactation

A study conducted in lactating Cynomolgus monkeys at doses 25 times that of the weekly human maintenance dose of 2 mg/kg Trastuzumab Injection IV from days 100 to 150 of pregnancy demonstrated that trastuzumab is secreted in the milk postpartum. The exposure to trastuzumab in utero and 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.

4. DESCRIPTION

Trastuzumab is a humanized IgG1 kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. Trastuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture which may contain the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Biceltis (trastuzumab) for injection is a sterile, white to pale yellow, preservative-free lyophilized powder with a cake-like appearance, for intravenous administration.

5. PHARMACEUTICAL PARTICULARS

5.1 Storage

Vials

Store vials at 2°C–8°C.

This medicine should not be used after the expiry date (Expiry Date) shown on the pack.

Shelf-life of the reconstituted solution

- *440 mg vials (multidose vials)*

Reconstituted solutions made with bacteriostatic water for injection for the 440 mg vial of Biceltis, as supplied, are stable for 28 days when stored refrigerated at 2°C-8°C. The reconstituted solution contains preservative and is therefore suitable for multiple use. Any remaining reconstituted solution should be discarded after 28 days.

When administering Biceltis to a patient with a known hypersensitivity to benzyl alcohol (*see section 2.4 Warnings and Precautions / 2.4.1 General / Benzyl alcohol*), Biceltis should be reconstituted with sterile water for injection. In case Biceltis is reconstituted with sterile water for injection, only one dose per Biceltis vial should be used. The reconstituted solution should be used immediately. Any unused portion must be discarded.

Do not freeze the reconstituted solution.

Shelf-life of the solution for infusion containing the reconstituted product

The infusion solution (0.9% sodium chloride infusion solution) containing the reconstituted product is physically and chemically stable for 24 hours at 2°C - 8°C.

From a microbiological point of view, the Biceltis infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use is the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

- *150 mg vials (single-dose vial) Shelf-life of the reconstituted solution*

The reconstituted product is physically and chemically stable for 48 hours at 2°C - 8°C after reconstitution with sterile water for injection.

From a microbiological point of view, the reconstituted solution should be further diluted in infusion solution immediately. If not, in-use storage times and conditions prior to use is the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Do not freeze the reconstituted solution.

Shelf-life of the solution for infusion containing the reconstituted product

The infusion solution (0.9% sodium chloride infusion solution) containing the reconstituted product is physically and chemically stable up to 7 days at 2°C - 8°C and 24 hours at room temperature (≤30°C).

From a microbiological point of view, the Biceltis infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use is the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

5.2 Special Instruction for Use, Handing and Disposal

Appropriate aseptic technique should be used.

The 440 mg vial of Biceltis is reconstituted with 20 ml of Bacteriostatic Water for Injection, containing 1.1% w/v benzyl alcohol I.P. (as a preservative), as supplied. This yields a solution for multiple uses, containing 21 mg/ml trastuzumab, at a pH of approximately 6.0. Use of other reconstitution solvents should be avoided except for sterile water for injection in case of a patient with a known hypersensitivity to benzyl alcohol.

The 150 mg vial of Biceltis is reconstituted with 7.2 mL of sterile water for injection.

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

Instructions for Reconstitution - 440 mg vial:

1. Using a sterile syringe, slowly inject 20 ml of Bacteriostatic Water for Injection into the vial containing the lyophilized Biceltis, directing the stream into the lyophilized cake.
2. Swirl vial gently to aid reconstitution. DO NOT SHAKE!

Instructions for Reconstitution – 150 mg vial:

1. Using a sterile syringe, slowly inject 7.2 mL of sterile water for injection into the vial containing the lyophilized Biceltis, directing the stream into the lyophilized cake.
2. Swirl vial gently to aid reconstitution. DO NOT SHAKE!

Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The reconstituted Biceltis results in a colourless to pale yellow transparent solution and should be essentially free of visible particles.

Instructions for dilution:

Determine the volume of the solution required

- based on a loading dose of 4 mg trastuzumab/kg body weight, or a maintenance dose of 2 mg trastuzumab/kg body weight:

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

- 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:

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

The appropriate amount of solution should be withdrawn from the vial using a sterile needle and syringe and added to an infusion bag containing 250 ml of 0.9% sodium chloride. Dextrose (5%) solution should not be used (*see section 5.3 Incompatibilities*). The bag should be gently inverted to mix the solution in order to avoid foaming. Care must be taken to ensure the sterility of prepared solutions. Since the medicinal product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration. Once the infusion is prepared it should be administered immediately (*see section on Storage*).

5.3 Incompatibilities

No incompatibilities between Biceltis and polyvinylchloride, polyethylene or polypropylene bags have been observed.

Dextrose (5%) solution should not be used since it causes aggregation of the protein.

Biceltis should not be mixed or diluted with other drugs.

5.4 Packs

150 mg vial:

1 pack containing 1 vial of Biceltis with 150 mg trastuzumab Currently, this strength is not marketed in India.

440 mg vial:

1 pack containing 1 vial with 440 mg trastuzumab + 1 vial with 20 ml Solvent for Trastuzumab 440 mg (bacteriostatic water for injection containing Benzyl alcohol I.P. 1.1% w/v as a preservative)

5.5 Shelf-life

48 months when stored under the recommended storage conditions.

5.6 Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).
- Dispose of the full container according to local requirements.

5.7 Patient counselling information

Cardiomyopathy

- Advise patients to contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness.

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential that Biceltis exposure during pregnancy or within 7 months prior to conception can result in fetal harm. Advise female patients to contact their healthcare provider with a known or suspected pregnancy.

- Advise women who are exposed to Biceltis during pregnancy or who become pregnant within 7 months following the last dose of Biceltis that there is a pregnancy pharmacovigilance program that monitor pregnancy outcomes.
- Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of Biceltis.

Keep out of reach of children

6. DETAILS OF MANUFACTURER

Manufactured by:
F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, CH-4070 Basel, Switzerland at:

1. Genentech Inc., 4625 NW Brookwood Parkway, Hillsboro, OR 97124, USA ***(Trastuzumab Vial 440mg)***
2. Genentech Inc., DNA Way, South San Francisco 94080, California, USA ***(Trastuzumab Vial 440mg)***
3. F. Hoffmann-La Roche Ltd, Wurmisweg, CH-4303 Kaiseraugst, Switzerland ***(Solvent Vial 20ml)***
4. M/s. Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim, Germany ***(Trastuzumab Vial 150mg)***

[NOTE: Please refer outer carton and vial label for manufacturing site details of Trastuzumab Vial 440mg]

Imported and Marketed by:
Roche Products (India) Pvt. Ltd.,
C/O. Parekh Integrated Services Pvt. Ltd,
Gala No. A1, First Floor, Warehouse no. 6,
BGR Logistics Park, NH-3, Zone 5,
Bhiwandi, Maharashtra (India) – 421302

Distributed and Marketed by:

Cipla Ltd.
Cipla House, Peninsula Business Park,
Ganpatrao Kadam Marg,
Lower Parel, Mumbai 400 013, India.

7. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

12-52/2004-DC dated 11 October 2002 (Trastuzumab vial 440mg)

12-46/2000-DC dated 25 January 2008 (Trastuzumab vial 150mg)

8. DATE OF REVISION

Current at February 2021, Version 13.0