Mabtin®

Trastuzumab for Injection (r-DNA Origin)

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, and PULMONARY TOXICITY
See full prescribing information for complete boxed warning.
Cardiomyopathy: *Mabtin® can result in sub-clinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue Mabtin® for cardiomyopathy.*
Infusion reactions, Pulmonary toxicity: *Discontinue Mabtin® for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.*

FORMS AND PRESENTATION
Mabtin® 150 (Single dose); powder for concentrate for solution for IV infusion.
Mabtin® 150 (Multi-dose); powder for concentrate for solution for IV infusion.
Mabtin® 440 (Multi-dose); powder for concentrate for solution for IV infusion.

COMPOSITION
Reconstituted Mabtin® concentrate contains approximately 21 mg/mL of trastuzumab, a humanized IgG1 monoclonal antibody expressed in Chinese hamster ovary cell suspension culture, and purified by affinity and ion-exchange chromatography including specific viral inactivation and removal procedures.
Excipients: L-Histidine, L-Histidine hydrochloride, Polysorbate 20, Trehalose dihydrate.

PHARMACOLOGICAL PROPERTIES

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

Mechanism of action
The humanized monoclonal IgG1 antibody trastuzumab is produced by recombinant DNA technology; and contains complementarily-determining regions from a mouse antibody (anti-p185) specific for the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2), along with human framework sequences.
Trastuzumab binds with high affinity and specificity to sub-domain IV, a juxta-membrane region of HER2's extracellular domain. Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signaling 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 tumor cells that overexpress HER2. Trastuzumab also preferentially mediates antibody-dependent cell-mediated cytotoxicity (ADCC) on tumor cells over expressing HER2.

Pharmacokinetic properties
A randomized, double-blind, parallel-group, comparative clinical study in patients with HER2-positive metastatic breast cancer showed that the pharmacokinetic profile of Mabtin® was similar to that of trastuzumab after single- and multi-dose intravenous infusions.
The following data for pharmacokinetics in various patient populations treated with trastuzumab is summarized from publicly available information.
Breast Cancer
A population pharmacokinetics method was used to model steady-state pharmacokinetics in metastatic breast cancer patients (given 4 mg/kg trastuzumab [loading], followed by 2 mg/kg weekly [maintenance]); in phase 1, phase 2 and pivotal phase 3 clinical trials. Table 1 shows steady-state values.

Table 1: Trastuzumab Steady-State Pharmacokinetic Parameters

Parameter	Mean Value
Terminal half-life	28.5 days (95% CI, 25.5 to 32.8 days)
Weekly AUC	578 mg x day/L
Clearance	0.225 L/day
Volume of distribution	2.95 L
Peak concentration	110 mg/L
Trough concentration	66 mg/L

Patients with early breast cancer were administered an initial loading dose of 8 mg/kg followed by a three weekly maintenance dose of 6 mg/kg for 1 year. The steady state mean Cmax was 225 µg/mL and mean Cmin was 68.9 µg/mL at day 21 of cycle 18, the last cycle of treatment for 1 year of treatment.
The pharmacokinetics do not appear to be affected by concomitant anthracycline/cyclophosphamide or paclitaxel chemotherapy, or concomitant anastrozole.
Advanced Gastric Cancer
A two compartment nonlinear population pharmacokinetic model was used to estimate the steady state pharmacokinetics in advanced gastric cancer patients (given 8 mg/kg trastuzumab [loading], followed by 6 mg/kg 3-weekly [maintenance]); in a phase 3 trial. At very low serum concentrations (below 10 µg/mL), non-linear clearance is 7-fold higher than linear clearance. At high serum concentrations, linear clearance dominates and the half-life is approximately 26 days. The mean predicted steady-state AUC (over a period of 3 weeks at steady state) is approximately 1213 mg day/L, and the median steady-state Cmax and Cmin are approximately 132 mg/L and 27.6 mg/L, respectively.

Pharmacokinetics in Special Populations
The pharmacokinetics of trastuzumab has not been explored in detailed studies in elderly patients, patients with renal impairment, or patients with hepatic impairment.
Distribution and elimination are not affected by age and renal impairment.

INDICATIONS

Metastatic Breast Cancer (MBC)
Mabtin® is indicated for the treatment of metastatic breast cancer patients who have human epidermal growth factor receptor 2- (HER2) - over expressing tumors.
- Mabtin® is indicated as monotherapy in patients who have already had two or more chemotherapy regimens for metastatic disease. Prior chemotherapy must have been an anthracycline and a taxane (at least), unless patients are unsuitable for these treatments. Hormonal therapy must also have been tried, and have failed, in hormone receptor-positive patients (unless patients are unsuitable for hormonal therapy).
- Mabtin® is indicated in combination with paclitaxel in patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.
- in combination with docetaxel in patients who have not received chemotherapy for their metastatic disease.
- and in combination with an aromatase inhibitor in postmenopausal patients with hormone-receptor positive MBC, who have not previously been treated with trastuzumab.

Early Breast Cancer (EBC)
Mabtin® is indicated for the treatment of adult patients with HER2 positive early breast cancer.
Mabtin® should only be used in MBC or EBC patients who have tumors with either over expression of HER2, or HER2 gene amplification.
- Mabtin® is indicated after surgery, neoadjuvant or adjuvant chemotherapy, and (if applicable) radiotherapy.
- Mabtin® should be used after adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.
- Mabtin® should be used in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin. Mabtin® should be used in combination with neoadjuvant chemotherapy followed by adjuvant Mabtin® therapy, for locally advanced disease (including inflammatory disease) or tumors of diameter > 2 cm.

Metastatic Gastric Cancer (MGC)
Mabtin® in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.
Mabtin® should be used in only those MGC patients whose tumors overexpress HER2, as defined by:
- IHC2+ plus a confirmatory SISH or FISH result, OR
- IHC 3+ result.

CONTRAINDICATIONS
- Hypersensitivity to trastuzumab murine proteins or to any other component of Mabtin®.
- Severe dyspnoea at rest due to complications of advanced malignancy
- Requiring supplementary oxygen therapy

Data in the following section (Warnings and Precautions) has been taken from publicly available data on trastuzumab.

WARNING AND PRECAUTIONS

Exacerbation of chemotherapy-induced neutropenia
Incidences of neutropenia, including febrile neutropenia, were reported in clinical trials in patients receiving trastuzumab in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. The incidence of septic death was similar among patients who received trastuzumab and those who did not. The risk of neutropenia may be slightly increased when trastuzumab is administered with docetaxel following anthracycline therapy.

Infusion-related reactions
Serious infusion-related reactions to trastuzumab infusion have been reported; and include dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, hypertension, supraventricular tachyarrhythmia, anaphylaxis, urticaria, angioedema and respiratory distress. The majority of these events occur during or within 2.5 hours of the start of the first infusion.
Patients may be at increased risk of a fatal infusion reaction if they are experiencing dyspnoea at rest, arising from complications of advanced malignancy or comorbidities. Should infusion reactions occur, discontinue trastuzumab infusion or slow the rate of infusion, and observe the patient until the symptoms resolve. Rarely, such reactions culminate in death. Most patients experienced resolution of symptoms and were given further infusions of trastuzumab. Supportive therapy, such as oxygen, epinephrine, antihistamine, bronchodilators, beta-agonists and corticosteroids, has been successfully used to treat serious reactions.

Pulmonary toxicity
Severe pulmonary events have been reported with trastuzumab, occasionally resulting in death. Cases of interstitial lung diseases including lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported; these events may occur as part of an infusion-related reaction or with a delayed onset. Risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies such as taxanes, gemcitabine, vinorelbine and radiation therapy. Patients may be at greater risk of severe reactions if they have symptomatic intrinsic lung disease; or extensive tumour involvement of the lungs, resulting in dyspnoea at rest. Therefore, such patients should not be treated with trastuzumab. Exercise caution for pneumonitis, especially in patients being treated concomitantly with taxanes.

Cardiac dysfunction
Trastuzumab therapy increases the risk 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 alone or in combination with paclitaxel following anthracycline (doxorubicin or epirubicin). These events can be moderate to severe and may be associated with death. Caution should be taken when treating patients with increased cardiac risk (e.g., hypertension, documented coronary artery disease, CHF, LVEF <55%, older age).
Since the half-life of trastuzumab is long, it may persist in the circulation for up to 27 weeks after stopping treatment. Patients who receive anthracyclines after stopping trastuzumab may possibly be at increased risk of cardiotoxicity. If possible, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping treatment, and monitor cardiac function carefully if anthracyclines are used. If left ventricular function continues to decrease, but patients remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of therapy has been seen. Trastuzumab and anthracycline should not be given concurrently in the adjuvant treatment setting (early breast cancer) or metastatic breast cancer setting. In patients with early breast cancer eligible for neoadjuvant-adjuvant chemotherapy, trastuzumab should only be used concurrently with anthracyclines in chemotherapy-naive patients and only with low-dose anthracycline regimens (maximum cumulative doses of doxorubicin 180 mg/m2 or epirubicin 360 mg/m2). In patients being concurrently treated with full course of low-dose anthracyclines and trastuzumab in the neoadjuvant setting, additional cytotoxic chemotherapy should not be given after surgery. Patients who are going to start trastuzumab, especially those with prior exposure to anthracycline and cyclophosphamide, should undergo baseline cardiac assessment, including history and physical examination, ECG, echocardiogram and/or MUGA scan. Repeat cardiac assessments every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of trastuzumab.
If left ventricular ejection fraction (LVEF) drops =10 ejection fraction (EF) points from baseline and to below 50%, treatment should be stopped and a repeat LVEF assessment should be performed within approximately 3 weeks. If LVEF does not improve, or declines further, or symptomatic congestive heart failure (CHF) develops, discontinuation of trastuzumab should be strongly considered, unless the benefits for the individual patient outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.
No prospective study has been done on the safety of continuing or resuming trastuzumab in patients who experience cardiotoxicity. In the pivotal trials, most patients who developed heart failure improved with standard treatments (including diuretics, cardiac glycosides, beta blockers and/or angiotensin converting enzyme inhibitors). In these trials, most patients with cardiac symptoms who also had evidence of a clinical benefit from trastuzumab treatment continued on therapy with trastuzumab without further clinical cardiac events.

Benzyl alcohol
Benzyl alcohol (1.1%) is used as a preservative in bacteriostatic water for injection in the 150 mg and 440 mg Mabtin® multidose vials. If a patient is known to be hypersensitive to benzyl alcohol, reconstitute Mabtin® with water for injection, and use only one dose per Mabtin® vial. DISCARD ANY UNUSED PORTION.

Effects on ability to drive and use machines
Trastuzumab has no or negligible influence on the ability to drive or use machines. Patients should be advised not to drive and use machines if they are experiencing infusion-related symptoms; until the symptoms abate.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy
It is not known whether trastuzumab can harm the foetus when administered to a pregnant woman or whether it can affect reproductive capacity. Animal reproduction studies done with trastuzumab revealed no evidence of impaired fertility or harm to the foetus.
Avoid administering Mabtin® to pregnant women, unless the potential benefit for the mother outweighs the potential risk to the foetus. Oligohydramnios, and cases of impaired foetal renal growth and/or function in association with oligohydramnios (some associated with fatal pulmonary hypoplasia of the foetus), skeletal abnormalities and neonatal death have been reported in pregnant women receiving trastuzumab.
Advise women of childbearing potential to use effective contraception during treatment with Mabtin®; and for at least 7 months thereafter. If a pregnant woman is treated with Mabtin®, close monitoring by a multidisciplinary team is desirable. Monitor women exposed to trastuzumab during pregnancy for oligohydramnios.

Lactation
Breast-feeding should be avoided during Mabtin® therapy. Women should not breast-feed during Mabtin® therapy and for 7 months after the last dose.

DRUG INTERACTIONS
Formal drug interaction studies with trastuzumab have not been performed in humans. In clinical trials of trastuzumab, no clinically significant interactions with the concomitant medications used were observed.The mean serum trough concentration of trastuzumab was consistently elevated approximately 1.5-fold, when administered in combination with paclitaxel as compared to trough concentrations of trastuzumab when administered in combination with an anthracycline and cyclophosphamide. Trastuzumab can increase the overall exposure of 7-deoxy-13 dihydro-doxorubicinone (D7D), a doxorubicin metabolite. The bioactivity of D7D and the clinical impact of the increase of this metabolite is not clear.

ADVERSE EFFECTS
The following undesirable effects are based on publicly available information categorized on the basis of frequency of occurrence of adverse reactions in different clinical trials and post-marketing information for trastuzumab.
Very common (≥1/10): Tremor, blood pressure decreased, blood pressure increased, heart beat irregular, palpitation, cardiac flutter, lip swelling, swelling face, muscle tightness (adverse reactions reported largely in association with infusion-related reactions); ejection fraction decreased; wheezing; dyspnoea; infection, nasopharyngitis, febrile neutropenia, anaemia, neutropenia, leukopenia, thrombocytopenia, weight decreased/weight loss, anorexia, weight increased, decreased appetite, insomnia, dizziness, headache, paraesthesia, hypoaesthesia, dysgeusia, conjunctivitis, lacrimation increased, lymphoedema, hot flush, cough, epistaxis, rhinorrhoea, oropharyngeal pain, diarrhoea, vomiting, nausea, abdominal pain, dyspepsia, constipation, stomatitis, erythema, rash, alopecia, nail disorder, Palmar-plantar erythrodysaesthesia syndrome, arthralgia, myalgia, asthenia, chest pain, chills, fatigue, influenza-like symptoms, infusion-related reaction, pain, pyrexia, mucosal inflammation, peripheral oedema, nail toxicity.
Common (≥1/100 to <1/10): Cardiac failure (congestive), pneumonia, pleural effusion; supraventricular tachyarrhythmia, hypotension; neutropenic sepsis, cystitis, herpes zoster, influenza, sinusitis, skin infection, rhinitis, upper respiratory tract infection, urinary tract infection, erysipelas, cellulitis, pharyngitis, hypersensitivity, anxiety, depression, thinking abnormal, peripheral neuropathy, hypertonia, somnolence, ataxia, dry eye,

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cardiomyopathy, hypertension, vasodilatation, asthma, lung disorder, pancreatitis, haemorrhoids, dry mouth, hepatocellular injury, hepatitis, liver tenderness, acne, dry skin, ecchymosis, hyperhydrosis, maculopapular rash, pruritus, onychoclasis, dermatitis, arthritis, back pain, bone pain, muscle spasms, neck pain, pain in extremity, renal disorder, breast inflammation/mastitis, malaise, oedema, contusion.
Uncommon (≥1/1,000 to <1/100): Sepsis, deafness, pericardial effusion, urticaria.
Rare (≥1/10,000 to <1/1,000): Paresis, pneumonitis, jaundice.
The most serious and/or common adverse reactions reported with trastuzumab are: cardiac dysfunction, infusion-related reactions and hypersensitivity, haematological toxicity, infections and pulmonary toxicity.

Cardiac dysfunction
Congestive heart failure (NYHA II-IV) is a common adverse reaction observed with trastuzumab and has been associated with fatal outcome.

Infusion-related reactions (IRRs) and Hypersensitivity
The following IRRs were seen in all trastuzumab trials: chills and/or fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress. Majority of IRRs are mild to moderate in intensity; usually occur during first, second or third infusion and lessen in frequency in subsequent infusions. Anaphylactoid reactions have been observed with trastuzumab in isolated cases.

Haematological toxicity
Febrile neutropenia is the most common haematological toxicity observed with trastuzumab. The common haematological toxicity are: anaemia, leukopenia, thrombocytopenia and neutropenia. When trastuzumab is administered with docetaxel following anthracycline therapy, the risk of neutropenia may be slightly increased.

Infections
In the adjuvant setting, the most common sites of infections include upper respiratory tract, skin and urinary tract.

Pulmonary toxicity
The following pulmonary adverse reactions were observed with trastuzumab: pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedma and respiratory insufficiency.

DOSAGE AND ADMINISTRATION
- Before starting Mabtin® treatment, HER2 testing is mandatory.
- Administer Mabtin® as intravenous infusion.
- Mabtin® is not to be administered as an intravenous push or bolus.
- Do not mix with other drugs.
- Patients with MBC and MGC should be treated until disease progression.
- Only a physician experienced in the administration of cytotoxic chemotherapy treatment should initiate treatment. Only a healthcare professional should administer Mabtin® and it should be administered by a healthcare professional prepared to manage anaphylaxis and an emergency kit should be available to manage any unexpected complications.
- Loading dose should be administered as a 90-minute intravenous infusion. If the initial loading dose is well tolerated, subsequent doses can be administered as a 30-minute infusion. Observe patients for at least six hours after the start of the first infusion and for two hours after the start of subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. If a patient displays infusion-associated symptoms, the infusion may be interrupted to help control the symptoms; and may be resumed once the symptoms have abated.

Metastatic Breast Cancer (MBC)
3-weekly dosing
- An initial loading dose of 8 mg/kg is recommended; a maintenance dose of 6 mg/kg at 3-weekly intervals is recommended, beginning 3 weeks after the loading dose.
- The loading dose should be administered as an intravenous infusion over approximately 90 minutes. The subsequent doses can be administered as a 30-minute infusion, if the initial loading dose was well tolerated.

Weekly dosing
- An initial loading dose of 4 mg/kg is recommended; a maintenance dose of 2 mg/kg at weekly intervals is recommended, beginning one week after the loading dose.
- The loading dose should be administered as an intravenous infusion over approximately 90 minutes. The subsequent doses can be administered as a 30-minute infusion, if the initial loading dose was well tolerated.

Administration in combination with paclitaxel or docetaxel
- In clinical trials, paclitaxel or docetaxel was administered the day following the first dose of trastuzumab. If the dose was well tolerated, paclitaxel/docetaxel was administered immediately after the subsequent doses of trastuzumab.

Administration in combination with an aromatase inhibitor
- In a clinical trial, trastuzumab and anastrozole were administered from day 1; without restrictions on the relative timing of administration of trastuzumab and anastrozole.

Early Breast Cancer (EBC)
Weekly dosing
- Initial loading dose of 4 mg/kg followed by 2 mg/kg every week concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide.

Three-weekly dosing
- An initial loading dose of 8 mg/kg is recommended; a maintenance dose of 6 mg/kg at 3-weekly intervals is recommended, beginning 3 weeks after the loading dose.

Metastatic Gastric Cancer (MGC)
Three-weekly dosing
- An initial loading dose of 8 mg/kg is recommended; a maintenance dose of 6 mg/kg at 3-weekly intervals is recommended, beginning 3 weeks after the loading dose.

Duration of Treatment of Breast cancer and gastric cancer
Patients with metastatic breast cancer or metastatic gastric cancer should be treated with trastuzumab until disease progression.
Patients with early breast cancer should be treated with trastuzumab for 1 year or until disease recurrence, whichever occurs first; it is not recommended to extend treatment in early breast cancer beyond one year.

Dose Reduction
During periods of reversible chemotherapy-induced myelosuppression, Trastuzumab may be continued; but observe the patient carefully for complications of neutropenia. Chemotherapy doses should be reduced or maintained as per the instructions for the specific regimen.
If left ventricular ejection fraction (LVEF) drops ≥10 ejection fraction (EF) points from baseline and to below 50%, treatment should be stopped and a repeat LVEF assessment should be performed within approximately 3 weeks. Discontinuation of trastuzumab should be strongly considered if LVEF does not improve, or declines further or symptomatic congestive heart failure (CHF) develops; unless the benefits outweigh the risks for the individual patient. All such patients should be referred for assessment by a cardiologist and followed up.

Missed Doses
For a dose missed by ≤ 1 week, administer the usual maintenance dose of trastuzumab (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg), as soon as possible, without waiting till the next planned cycle. Subsequent maintenance doses should then be given according to the previous schedule.
For a dose missed by >1 week, administer a re-loading dose of trastuzumab (weekly regimen: 4 mg/kg; three-weekly regimen: 8 mg/kg) over approximately 90 minutes; subsequent maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen 6 mg/kg respectively) should then be given (weekly regimen: every week; three-weekly regimen: every 3 weeks) from that point.

Use in special populations
From available data, disposition of trastuzumab is not altered with increasing age, renal impairment or serum creatinine levels.
Elderly patients in reported clinical trials did not receive reduced doses.

Children
The safety and efficacy of trastuzumab has not been established in paediatric patients (below 18 years of age) Mabtin® should not be used in these patients.

OVERDOSAGE
There is no information on overdose from human clinical trials. Single doses greater than 10 mg/kg of trastuzumab alone have not been administered in the clinical trials. Doses up to this level were well tolerated.

INCOMPATIBILITIES
Mabtin® should not be mixed or diluted with other products except those mentioned under "Special Precautions for Disposal and Other Handling" section.
Do NOT dilute with glucose solutions, since these cause aggregation of the protein.

Shelf-life of the reconstituted solution
150 mg (Single-dose use vial)
The reconstituted product is physically and chemically stable for 24 hours at 2-8°C after dissolving in sterile water for injection (not supplied). From a microbiological perspective, the reconstituted solution should be used immediately. Do not freeze the reconstituted solution.
440 mg/150 mg (Multi-dose use vials)
Reconstituted solutions made with bacteriostatic water for injection, as supplied, are stable (physico-chemically and microbiologically) for 28 days, when refrigerated at 2°C to 8°C. The reconstituted solution is suitable for multiple uses, as it contains preservative. Discard any remaining reconstituted solution after 28 days. Do not freeze the reconstituted solution.

Shelf-life of the solution for infusion containing the reconstituted product
150 mg (single-dose and multi-dose use vials) and 440 mg (multi-dose use vials)
Infusion solution (0.9% sodium chloride) containing the reconstituted drug product is physically and chemically stable for 48 hours at 2-8°C. From the perspective of microbiological safety, the Mabtin® infusion solution should be used immediately, unless reconstitution and dilution have taken place under aseptic conditions. If reconstitution and dilution have taken place under aseptic conditions, the infusion solution can be stored up to 48 hours when refrigerated at 2°C to 8°C.

STORAGE AND HANDLING INFORMATION
Store vials at 2°C to 8°C prior to reconstitution.
Store away from light.
Vials should not be used beyond the expiration date stamped on the vial; the reconstituted drug solution should be used as given above; and any unused portion must be discarded.
DO NOT FREEZE DRUG THAT HAS BEEN RECONSTITUTED.

Special Precautions for Disposal and Other Handling
- Appropriate aseptic technique should be used.
- Use of other reconstitution solvents should be AVOIDED.
- Reconstitution details are given in the table below:

Table 2: Reconstitution Details of 150 mg (Single- and Multi-dose Use) and 440 mg Vials (Multi-dose Use)

Type of vial	Reconstitution	Trastuzumab mg/mL	pH
150 mg (Single dose)	7.2 mL of Sterile WFI*	~21	~6.0
150 mg (Multiple dose)	7.2 mL of BWFI (Containing 1.1% benzyl alcohol)	~21	~6.0
440 mg (Multi dose)	20 mL of BWFI (Containing 1.1% benzyl alcohol)	~21	~6.0
BWFI: Bacteriostatic water for injection			
* Not Supplied			

During reconstitution, handle Mabtin® carefully. Causing excessive foaming during reconstitution or shaking the reconstituted solution may result in problems with the amount of Mabtin® that can be withdrawn from the vial.

Instructions for reconstitution - 150 mg vial (single-dose vial)
1) Slowly inject 7.2 mL of sterile water for injection into the vial containing the lyophilized Mabtin®, using a sterile syringe.
Direct the stream into the lyophilized cake.
2) To aid reconstitution, the vial should be swirled gently. DO NOT SHAKE.

Instructions for reconstitution - 150 mg vial (multi-dose vial)
1) Slowly inject 7.2 mL of bacteriostatic water for injection into the vial containing the lyophilized Mabtin®, using a sterile syringe. Direct the stream into the lyophilized cake.
2) To aid reconstitution, the vial should be swirled gently. DO NOT SHAKE.

Instructions for reconstitution - 440 mg vial (multi-dose vial)
1) Slowly inject 20 mL of bacteriostatic water for injection into the vial containing the lyophilized Mabtin®, using a sterile syringe. Direct the stream into the lyophilized cake.
2) To aid reconstitution, the vial should be swirled gently. DO NOT SHAKE.
Slight foaming of the product may be seen upon reconstitution; this is not unusual. The vial should be allowed to stand undisturbed for approximately 5 minutes. Reconstituted Mabtin® is a colorless to pale yellow, transparent solution. No particles should be visible.

Instructions for dilution:
Determine the volume of Mabtin® solution required:
• Based on a loading dose of 4 mg Mabtin®/kg, or a subsequent weekly dose of 2 mg Mabtin®/kg:

$$\text{Volume (mL)} = \frac{\text{Body weight (kg)} \times \text{dose (4 mg/kg for laoding or 2 mg/kg for maintenance)}}{\text{21 (mg/mL, concentration of reconstitued solution)}}$$

• Based on a loading dose of 8 mg Mabtin®/kg, or a subsequent 3-weekly dose of 6 mg Mabtin®/kg:

$$\text{Volume (mL)} = \frac{\text{Body weight (kg)} \times \text{dose (8 mg/kg for laoding or 6 mg/kg for maintenance)}}{\text{21 (mg/mL, concentration of reconstitued solution)}}$$

Withdraw the appropriate amount of solution from the vial, and add it to an infusion bag containing 250 mL of 0.9% sodium chloride solution.
- Glucose/dextrose-containing solutions should NOT be used.
- Mix the solution by inverting the bag gently (to avoid foaming).
- Once the infusion is prepared it should be administered immediately.
- If diluted aseptically, it may be stored for 24 hours (do not store above 30°C).

Inspect visually for particulate matter and discoloration prior to administration.
No incompatibilities have been observed between trastuzumab and polyvinylchloride, polyethylene or polypropylene bags.
Dispose of unused medicinal product in accordance with local regulations.

PACKAGING INFORMATION
Mabtin® 150 mg (Single-dose vial)
Mabtin® finished product 150 mg is filled in 15 mL USP type 1 glass vial.
Mabtin® 150 mg (Multi-dose vial)
Mabtin® finished product 150 mg is filled in 15 mL USP type 1 glass vial. The 150 mg pack is provided with 1 vial of 10 mL bacteriostatic water for injection (containing 1.1% benzyl alcohol as preservative), of which 7.2 ml is to be used for reconstitution.
Mabtin® 440 mg (Multi-dose vial)
Mabtin® finished product 440 mg is filled in 50 mL USP type 1 glass. The 440 mg pack is provided with 2 vials of bacteriostatic water for injection, 10 ml each (containing 1.1% benzyl alcohol as preservative) for reconstitution.

Manufactured by
Biocon Limited, India
For
Benta SAL,
Dbayeh - Lebanon
Date of Revision: May 2018.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists