WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]
The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[BT-ON014 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug product co-packaged with diluent.

Drug product
One vial containing 420 mg of trastuzumab, a humanised IgG1 monoclonal antibody produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by chromatography including specific viral inactivation and removal procedures.

The reconstituted solution contains 21 mg/mL of trastuzumab.

Diluent
One vial containing 20 mL of bacteriostatic water for injection.

Excipients with known effect:
Each vial of [BT-ON014 trade name] contains 322.6 mg of sorbital (see section 4-4).

Each vial of bacteriostatic water for injection contains 231 mg of benzyl alcohol (see section 4-4).

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Drug product
[BT-ON014 trade name] is a sterile, off-white to pale yellow lyophilized powder for concentrate for solution for infusion. Upon reconstitution with bacteriostatic water for injection (BWFI), the powder yields a colourless to pale yellow transparent solution, free of visible particles.

Diluent
The bacteriostatic water for injection is a colourless, transparent solution, free of visible particles and is intended to use for the reconstitution of [BT-ON014 trade name] to yield a multi-dose solution containing 21 mg/mL trastuzumab at a pH of approximately 6.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Metastatic breast cancer

[BT-ON014 trade name] is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer (MBC):

- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease.
  Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments
- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

- in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease
- in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab.

Early breast cancer

[BT-ON014 trade name] is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC):

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) (see section 5.1)
- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel
- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter, as adjuvant therapy following neoadjuvant chemotherapy and surgery (see sections 4.4 and 5.1).

[BT-ON014 trade name] should only be used in patients with MBC or EBC whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay (see sections 4.4 and 5.1).

4.2 Posology and method of administration

HER2 testing is mandatory prior to initiation of therapy (see sections 4.4 and 5.1).

[BT-ON014 trade name] treatment should only be initiated by a health care provider experienced in the administration of cytotoxic chemotherapy (see section 4.4), and should be administered by a health care provider only.

[BT-ON014 trade name] intravenous formulation is not intended for subcutaneous administration and should be administered via an intravenous infusion only.

If an alternate route of administration is required, other trastuzumab products offering such an option should be used.

In order to prevent medication errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is [BT-ON014 trade name] and not trastuzumab emtansine.

Posology

Metastatic breast cancer

Three-weekly regimen

The recommended initial loading dose of [BT-ON014 trade name] is 8 mg/kg body weight. The recommended maintenance dose is 6 mg/kg body weight every three weeks, beginning three weeks after the loading dose.

Weekly regimen

The recommended initial loading dose of [BT-ON014 trade name] is 4 mg/kg body weight. The recommended weekly maintenance dose is 2 mg/kg body weight, beginning one week after the loading dose.

Administration with paclitaxel or docetaxel

In the pivotal trials (H0648g, M77001), paclitaxel or docetaxel was administered the day following the first dose of trastuzumab (for dose, see the Summary of Product Characteristics (SmPC) for paclitaxel or docetaxel) and immediately after the subsequent doses of trastuzumab if the preceding dose of trastuzumab was well tolerated.

Administration with an aromatase inhibitor

In the pivotal trial (BO16216) trastuzumab and anastrozole were administered from day 1. There were no restrictions on the relative timing of trastuzumab and anastrozole administration (for dose of anastrozole or other aromatase inhibitors, see the relevant SmPC).

Early breast cancer

As a *three-weekly regimen* the recommended initial loading dose of [BT-ON014 trade name] is 8 mg/kg body weight. The recommended maintenance dose of [BT-ON014 trade name] at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.

As a *weekly regimen* (initial loading dose of 4 mg/kg followed by 2 mg/kg every week) concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide.

See section 5.1 for chemotherapy combination dosing.

Duration of treatment

Patients with MBC should be treated with [BT-ON014 trade name] until progression of disease. Patients with EBC should be treated with [BT-ON014 trade name] for 1 year or until disease recurrence, whichever occurs first; extending treatment in EBC beyond one year is not recommended (see section 5.1).

Dose reduction

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

If left ventricular ejection fraction (LVEF) percentage drops ≥ 10 points from baseline and to below 50%, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further, or if symptomatic congestive heart failure (CHF) has developed, discontinuation of [BT-ON014 trade name] should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.

Missed doses

If the patient has missed a dose of [BT-ON014 trade name] 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 then be administered at the appropriate interval from the date this dose is given, i.e. every 7 or 21 days afterwards according to the weekly or three-weekly schedules respectively.

If the patient has missed a dose of [BT-ON014 trade name] by more than one week, another loading dose of [BT-ON014 trade name] should be administered over approximately 90 minutes (weekly regimen: 4 mg/kg; three-weekly regimen: 8 mg/kg) as soon as possible. Subsequent [BT-ON014 trade name] maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen 6 mg/kg respectively) should then be administered every 7 days or 21 days later according to the weekly or three-weekly schedules respectively.

Special populations

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

Paediatric population

There is no relevant use of [BT-ON014 trade name] in the paediatric population.

Method of administration

The initial loading dose of [BT-ON014 trade name] should be administered as a 90-minute intravenous infusion. Do not administer as an intravenous push or bolus.

[BT-ON014 trade name] intravenous infusion should be administered by a health care provider prepared to manage anaphylaxis and an emergency kit should be available. Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms (see sections 4.4 and 4.8). Interruption or slowing the rate of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

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

For instructions on reconstitution of [BT-ON014 trade name] before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to trastuzumab, murine proteins, or to any of the excipients listed in section 6.1.
- Severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded.

HER2 testing must be performed in a specialised laboratory which can ensure adequate validation of the testing procedures (see section 5.1).

Currently no data from clinical trials are available on re-treatment of patients with previous exposure to trastuzumab in the adjuvant setting**.**

Cardiac dysfunction

General considerations

Patients treated with trastuzumab are at increased risk for developing CHF (New York Heart Association [NYHA] Class II-IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving trastuzumab therapy alone or in combination with paclitaxel or docetaxel, particularly following anthracycline (doxorubicin or epirubicin) containing chemotherapy. These may be moderate to severe and have been associated with death (see section 4.8). In addition, caution should be exercised in treating patients with increased cardiac risk, e.g., hypertension, documented coronary artery disease, CHF, LVEF of < 55%, older age.

A careful risk-benefit assessment should therefore be made before deciding to treat with trastuzumab. All candidates for treatment with trastuzumab, but especially those with prior anthracycline and cyclophosphamide (AC) exposure, should undergo baseline cardiac assessment including history and physical examination, electrocardiogram (ECG), echocardiogram or multigated acquisition (MUGA) scan or magnetic resonance imaging. Formal cardiological assessment should be considered in patients in whom there are cardiovascular concerns following baseline screening.

Monitoring may help to identify patients who develop cardiac dysfunction. Cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of trastuzumab.

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 health care provider should consider discontinuing therapy if no clinical benefit of trastuzumab therapy has been seen.

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

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

Trastuzumab may persist in the circulation for up to 7 months after stopping [BT-ON014 trade name] treatment based on population pharmacokinetic analysis of all available data (see section 5.2). Patients who receive anthracyclines after stopping trastuzumab may possibly be at increased risk of cardiac dysfunction. If possible, health care providers should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Metastatic breast cancer

[BT-ON014 trade name] and anthracyclines should not be given concurrently in the MBC setting.

Patients with MBC who have previously received anthracyclines are also at risk of cardiac dysfunction with [BT-ON014 trade name] treatment, although the risk is lower than with concurrent use of [BT-ON014 trade name] and anthracyclines.

Early breast cancer

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

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

<u>Adjuvant treatment</u>

[BT-ON014 trade name] and anthracyclines should not be given concurrently in combination in the adjuvant treatment setting.

In patients with EBC an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when trastuzumab was administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin and was more marked when trastuzumab was administered concurrently with taxanes than when administered sequentially to taxanes. Regardless of the regimen used, most symptomatic cardiac events occurred within the first 18 months. In one of the 3 pivotal studies conducted in which a median follow-up of 5.5 years was available (BCIRG006) a continuous increase in the cumulative rate of symptomatic cardiac or LVEF events was observed in patients who were administered trastuzumab concurrently with a taxane following anthracycline therapy up to 2.37 % compared to approximately 1 % in the two comparator arms (anthracycline plus cyclophosphamide followed by taxane and taxane, carboplatin and trastuzumab).

Risk factors for a cardiac event identified in four large adjuvant studies included advanced age (>50 years), low LVEF (<55 %) at baseline, prior to or following the initiation of paclitaxel treatment, decline in LVEF by 10-15 points, and prior or concurrent use of anti-hypertensive medicinal products. In patients receiving trastuzumab after completion of adjuvant chemotherapy, the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracycline given prior to initiation of trastuzumab and a body mass index (BMI) >25 kg/m^2.

Neoadjuvant-adjuvant treatment

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

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

Experience of concurrent administration of trastuzumab with low dose anthracycline regimens is currently limited to the trial MO16432.

In the pivotal trial MO16432, trastuzumab was administered concurrently with neoadjuvant chemotherapy containing three cycles of doxorubicin (cumulative dose 180 mg/m^2).

The incidence of symptomatic cardiac dysfunction was 1.7 % in the trastuzumab arm.

Clinical experience is limited in patients above 65 years of age.

Infusion-related reactions (IRRs) and hypersensitivity

Serious IRRs to trastuzumab infusion including dyspnoea, hypotension, wheezing, hypertension, bronchospasm, supraventricular tachyarrhythmia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria and angioedema have been reported (see section 4.8). Pre-medication may be used to reduce risk of occurrence of these events.

The majority of these events occur during or within 2.5 hours of the start of the first infusion. Should an infusion reaction occur the infusion should be discontinued or the rate of infusion slowed and the patient should be monitored until resolution of all observed symptoms (see section 4.2). These symptoms can be treated with an analgesic/antipyretic such as pethidine or paracetamol, or an antihistamine such as diphenhydramine. The majority of patients experienced resolution of symptoms and subsequently received further infusions of trastuzumab. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta agonists, and corticosteroids.

In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome. Initial improvement followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported. Fatalities have occurred within hours and up to one week following infusion. On very rare occasions, patients have experienced the onset of infusion symptoms and pulmonary symptoms more than six hours after the start of the trastuzumab infusion. Patients should be warned of the possibility of such a late onset and should be instructed to contact their health care provider if these symptoms occur.

Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with trastuzumab (see section 4.3).

Pulmonary events

Severe pulmonary events have been reported with the use of trastuzumab in the post-marketing setting (see section 4.8). These events have occasionally been fatal. In addition, cases of interstitial lung disease including lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported. Risk factors

associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy. These events may occur as part of an infusion-related reaction or with a delayed onset.

Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with trastuzumab (see section 4.3). Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

Excipients
[BT-ON014 trade name] contains **sorbitol.** Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.

[BT-ON014 trade name] contains less than 1 mmol sodium (23 mg) per dose, that is to say, is essentially 'sodium-free'.

The bacteriostatic water for injection (diluent) contains **benzyl alcohol**. Benzyl alcohol may cause allergic reactions.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

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

Effect of trastuzumab on the pharmacokinetics of other antineoplastic agents

Pharmacokinetic data from studies BO15935 and M77004 in women with HER2-positive MBC suggested that exposure to *paclitaxel* and *doxorubicin* (and their major metabolites 6-α hydroxyl-paclitaxel, POH, and doxorubicinol, DOL) was not altered in the presence of trastuzumab (8 mg/kg or 4 mg/kg intravenous loading dose followed by 6 mg/kg q3w or 2 mg/kg q1w intravenous, respectively). However, trastuzumab may elevate the overall exposure of one doxorubicin metabolite, (7-deoxy-13 dihydro-doxorubicinone, D7D). The bioactivity of D7D and the clinical impact of the elevation of this metabolite were unclear.

Data from study JP16003, a single-arm study of trastuzumab (4 mg/kg IV loading dose and 2 mg/kg IV weekly) and docetaxel (60 mg/m^2 IV) in Japanese women with HER2- positive MBC, suggested that concomitant administration of trastuzumab had no effect on the single dose pharmacokinetics of *docetaxel*.

Study JP19959 was a sub study of BO18255 (ToGA) performed in male and female Japanese patients with advanced gastric cancer (AGC) to study the pharmacokinetics of *capecitabine* and *cisplatin* when used with or without trastuzumab. The results of this sub study 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.

Pharmacokinetic data from Study H4613g/GO01305 in patients with metastatic or locally advanced inoperable HER2-positive cancer suggested that trastuzumab had no impact on the PK of *carboplatin*.

Effect of antineoplastic agents on trastuzumab pharmacokinetics

By comparison of simulated serum trastuzumab concentrations after trastuzumab monotherapy (4 mg/kg loading/2 mg/kg q1w IV) and observed serum concentrations in Japanese women with HER2- positive MBC (study JP16003) no evidence of a PK effect of concurrent administration of *docetaxel* on the pharmacokinetics of trastuzumab was found.

Comparison of PK results from two phase II studies (BO15935 and M77004) and one phase III study (H0648g) in which patients were treated concomitantly with trastuzumab and *paclitaxel* and two phase II studies in which trastuzumab was administered as monotherapy (W016229 and MO16982), in women with HER2-positive MBC indicates that individual and mean trastuzumab trough serum concentrations varied within and across studies but there was no clear effect of the concomitant administration of paclitaxel on the pharmacokinetics of trastuzumab. Comparison of trastuzumab PK data from Study M77004 in which women with HER2-positive MBC were treated concomitantly with trastuzumab, paclitaxel and *doxorubicin* to trastuzumab PK data in studies where trastuzumab was administered as monotherapy (H0649g) or in combination with anthracycline plus cyclophosphamide or paclitaxel (Study H0648g), suggested no effect of doxorubicin and paclitaxel on the pharmacokinetics of trastuzumab.

Pharmacokinetic data from Study H4613g/GO01305 suggested that *carboplatin* had no impact on the PK of trastuzumab.

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

4.6 Fertility, pregnancy and breastfeeding

Women of childbearing potential

Women of childbearing potential should be advised to use effective contraception during treatment with trastuzumab and for 7 months after treatment has concluded (see section 5.2).

Pregnancy

Reproduction studies have been conducted in Cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg trastuzumab intravenous formulation and have revealed no evidence of impaired fertility or harm to the foetus. Placental transfer of trastuzumab during the early (days 20–50 of gestation) and late (days 120–150 of gestation) foetal development period was observed. It is not known whether trastuzumab can affect reproductive capacity. As animal reproduction studies are not always predictive of human response, trastuzumab should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus.

In the post-marketing setting, cases of foetal renal growth or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving trastuzumab. Women who become pregnant should be advised of the possibility of harm to the foetus. If a pregnant woman is treated with trastuzumab, or if a patient becomes pregnant while receiving trastuzumab or within 7 months following the last dose of trastuzumab, close monitoring by a multidisciplinary team is desirable.

Breast-feeding

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

Fertility

There are no data on the effects [BT-ON014 trade name] on human male or female fertility.

A fertility study conducted in female cynomolgus monkeys at doses up to 25 times the weekly recommended human dose of 2 mg/kg trastuzumab and has revealed no evidence of impaired fertility, as measured by menstrual cycle duration and female sex hormone levels. Studies to evaluate the effects of trastuzumab on male fertility have not been conducted (see 5.3).

4.7 Effects on ability to drive and use machines

[BT-ON014 trade name] may affect the ability to drive and use machines: symptoms such as dizziness and somnolence can occur during treatment with trastuzumab (see section 4.8). Patients experiencing infusion-related symptoms (see section 4.4) should be advised not to drive and use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

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

Presented in Table 1 are adverse reactions that have been reported in association with the use of intravenous trastuzumab alone or in combination with chemotherapy in pivotal clinical trials and in the post-marketing setting.

All the terms included are based on the highest percentage seen in pivotal clinical trials. In addition, terms reported in the post marketing setting are included in Table 1.

Table 1 *Undesirable effects reported with intravenous trastuzumab monotherapy or in combination with chemotherapy in pivotal clinical trials (N = 8386) and post-marketing*

System organ class	Adverse reaction	Frequency
Infections and infestations	Infection	Very common
	Nasopharyngitis	Very common
	Neutropenic sepsis	Common
	Cystitis	Common
	Influenza	Common
	Sinusitis	Common
	Skin infection	Common
	Rhinitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
	Pharyngitis	Common
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Malignant neoplasm progression	Not known
	Neoplasm progression	Not known
Blood and lymphatic system disorders	Febrile neutropenia	Very common
	Anaemia	Very common
	Neutropenia	Very common

System organ class	Adverse reaction	Frequency
	White blood cell count decreased/leukopenia	Very common
	Thrombocytopenia	Very common
	Hypoprothrombinaemia	Not known
	Immune thrombocytopenia	Not known
Immune system disorders	Hypersensitivity	Common
	[+] Anaphylactic reaction	Rare
	[+] Anaphylactic shock	Rare
Metabolism and nutrition disorders	Weight decreased/Weight loss	Very common
	Anorexia	Very common
	Tumour lysis syndrome	Not known
	Hyperkalaemia	Not known
Psychiatric disorders	Insomnia	Very common
	Anxiety	Common
	Depression	Common
Nervous system disorders	[1]Tremor	Very common
	Dizziness	Very common
	Headache	Very common
	Paraesthesia	Very common
	Dysgeusia	Very common
	Peripheral neuropathy	Common
	Hypertonia	Common
	Somnolence	Common
Eye disorders	Conjunctivitis	Very common
	Lacrimation increased	Very common
	Dry eye	Common
	Papilloedema	Not known
	Retinal haemorrhage	Not known
Ear and labyrinth disorders	Deafness	Uncommon
Cardiac disorders	[1] Blood pressure decreased	Very common
	[1] Blood pressure increased	Very common
	[1] Heart beat irregular	Very common
	[1] Cardiac flutter	Very common
	Ejection fraction decreased*	Very common
	[+] Cardiac failure(congestive)	Common
	[+1]Supraventricular tachyarrhythmia	Common
	Cardiomyopathy	Common
	[1]·Palpitation	Common
	Pericardial effusion	Uncommon
	Cardiogenic shock	Not known
	Gallop rhythm present	Not known
Vascular disorders	Hot flush	Very common
	[+1] Hypotension	Common
	Vasodilatation	Common
Respiratory, thoracic and mediastinal disorders	[+]Dyspnoea	Very common
	Cough	Very common
	Epistaxis	Very common

System organ class	Adverse reaction	Frequency
	Rhinorrhoea	Very common
	[+]Pneumonia	Common
	Asthma	Common
	Lung disorder	Common
	[+] Pleural effusion	Common
	[+1]Wheezing	Uncommon
	Pneumonitis	Uncommon
	[+] Pulmonary fibrosis	Not known
	[+] Respiratory distress	Not known
	[+] Respiratory failure	Not known
	[+] Lung infiltration	Not known
	[+] Acute pulmonary oedema	Not known
	[+] Acute respiratory distress syndrome	Not known
	[+]Bronchospasm	Not known
	[+] Hypoxia	Not known
	[+] Oxygen saturation decreased	Not known
	Laryngeal oedema	Not known
	Orthopnoea	Not known
	Pulmonary oedema	Not known
	Interstitial lung disease	Not known
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting	Very common
	Nausea	Very common
	[1] Lip swelling	Very common
	Abdominal pain	Very common
	Dyspepsia	Very common
	Constipation	Very common
	Stomatitis	Very common
	Haemorrhoids	Common
	Dry mouth	Common
Hepatobiliary disorders	Hepatocellular injury	Common
	Hepatitis	Common
	Liver tenderness	Common
	Jaundice	Rare
Skin and subcutaneous tissue disorders	Erythema	Very common
	Rash	Very common
	[1] Swelling face	Very common
	Alopecia	Very common
	Nail disorder	Very common
	Palmar-plantar erythrodysaesthesia syndrome	Very common
	Acne	Common
	Dry skin	Common
	Ecchymosis	Common
	Hyperhydrosis	Common
	Maculopapular rash	Common

System organ class	Adverse reaction	Frequency
	Pruritus	Common
	Onycholysis	Common
	Dermatitis	Common
	Urticaria	Uncommon
	Angioedema	Not known
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	[1] Muscle tightness	Very common
	Myalgia	Very common
	Arthritis	Common
	Back pain	Common
	Bone pain	Common
	Muscle spasms	Common
	Neck Pain	Common
	Pain in extremity	Common
Renal and urinary disorders	Renal disorder	Common
	Glomerulonephritis membranous	Not known
	Glomerulonephropathy	Not known
	Renal failure	Not known
Pregnancy, puerperium and perinatal conditions	Oligohydramnios	Not known
	Renal hypoplasia	Not known
	Pulmonary hypoplasia	Not known
Reproductive system and breast disorders	Breast inflammation/mastitis	Common
General disorders and administration site conditions	Asthenia	Very common
	Chest pain	Very common
	Chills	Very common
	Fatigue	Very common
	Influenza-like symptoms	Very common
	Infusion related reaction	Very common
	Pain	Very common
	Pyrexia	Very common
	Mucosal inflammation	Very common
	Peripheral oedema	Very common
	Malaise	Common
	Oedema	Common
Injury, poisoning and procedural complications	Contusion	Common

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

Description of selected adverse reactions

Cardiac dysfunction

Congestive heart failure (NYHA Class II – IV) is a common adverse reaction associated with the use of trastuzumab and has been associated with a fatal outcome (see section 4.4). Signs and symptoms of cardiac dysfunction such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with trastuzumab (see section 4.4).

In 3 pivotal clinical trials of adjuvant trastuzumab given in combination with chemotherapy, the incidence of grade 3/4 cardiac dysfunction (specifically symptomatic congestive heart failure) was similar in patients who were administered chemotherapy alone (i.e., did not receive trastuzumab) and in patients who were administered trastuzumab sequentially after a taxane (0.3-0.4 %). The rate was highest in patients who were administered trastuzumab concurrently with a taxane (2.0 %). In the neoadjuvant setting, the experience of concurrent administration of trastuzumab and low dose anthracycline regimen is limited (see section 4.4).

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

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

In the pivotal metastatic trials of intravenous trastuzumab, the incidence of cardiac dysfunction varied between 9 % and 12 % when it was combined with paclitaxel compared with 1 % – 4 % for paclitaxel alone. For monotherapy, the rate was 6 % – 9 %. The highest rate of cardiac dysfunction was seen in patients receiving trastuzumab concurrently with anthracycline/cyclophosphamide (27 %), and was significantly higher than for anthracycline/cyclophosphamide alone (7 % – 10 %). In a subsequent trial with prospective monitoring of cardiac function, the incidence of symptomatic CHF was 2.2 % in patients receiving trastuzumab and docetaxel, compared with 0 % in patients receiving docetaxel alone. Most of the patients (79 %) who developed cardiac dysfunction in these trials experienced an improvement after receiving standard treatment for CHF.

Infusion reactions, allergic-like reactions and hypersensitivity

It is estimated that approximately 40 % of patients who are treated with trastuzumab will experience some form of infusion-related reaction. However, the majority of infusion-related reactions are mild to moderate in intensity (NCI-CTC grading system) and tend to occur earlier in treatment, i.e., during infusions one, two and three and lessen in frequency in subsequent infusions. Reactions include chills, fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, respiratory distress, rash, nausea, vomiting and headache (see section 4.4). The rate of infusion-related reactions of all grades varied between studies depending on the indication, the data collection methodology, and whether trastuzumab was given concurrently with chemotherapy or as monotherapy.

Severe anaphylactic reactions requiring immediate additional intervention can occur usually during either the first or second infusion of trastuzumab (see section 4.4) and have been associated with a fatal outcome.

Anaphylactoid reactions have been observed in isolated cases.

Haematotoxicity

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

Pulmonary events

Severe pulmonary adverse reactions occur in association with the use of trastuzumab and have been associated with a fatal outcome. These include, but are not limited to, pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency (see section 4.4).

Immunogenicity

In the neoadjuvant-adjuvant EBC study (BO22227), at a median follow-up exceeding 70 months, 10.1 % (30/296) of patients treated with trastuzumab intravenous developed antibodies against trastuzumab. Neutralizing anti-trastuzumab antibodies were detected in post-baseline samples in 2 of 30 patients in the trastuzumab intravenous 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 trastuzumab intravenous.

Switching treatment between trastuzumab intravenous and trastuzumab subcutaneous formulation and vice versa.

Study MO22982 investigated switching between a trastuzumab intravenous and trastuzumab subcutaneous formulation with a primary objective to evaluate patient preference for either intravenous or the subcutaneous route of trastuzumab administration. In this trial, 2 cohorts (one using subcutaneous formulation in vial and one using subcutaneous formulation in administration system) were investigated using a 2-arm, cross-over design with 488 patients being randomised to one of two different three-weekly trastuzumab treatment sequences (intravenous [Cycles 1-4] → subcutaneous [Cycles 5-8], or subcutaneous [Cycles 1-4] → intravenous [Cycles 5-8]). Patients were either naïve to trastuzumab intravenous treatment (20.3 %) or pre-exposed to trastuzumab intravenous (79.7 %). For the sequence intravenous → subcutaneous (subcutaneous vial and subcutaneous formulation in administration system cohorts combined), adverse event rates (all grades) were described pre-switching (Cycles 1-4) and post-switching (Cycles 5-8) as 53.8 % vs. 56.4 %, respectively; for the sequence subcutaneous → intravenous (subcutaneous vial and subcutaneous formulation in administration system cohorts combined), adverse event rates (all grades) were described pre- and post-switching as 65.4 % vs. 48.7 %, respectively.

Pre-switching rates (Cycles 1-4) for serious adverse events, grade 3 adverse events and treatment discontinuations due to adverse events were low (< 5 %) and similar to post-switching rates (Cycles 5-8). No grade 4 or grade 5 adverse events were reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system. See section 7 for the supplier's contact details.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC03

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

Mechanism of action

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

Detection of HER2 overexpression or HER2 gene amplification

Trastuzumab should only be used in breast cancer patients whose tumours have HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay. HER2 overexpression should be detected using an immunohistochemistry (IHC)-based assessment of fixed tumour blocks (see section 4.4). HER2 gene amplification should be detected using fluorescence *in situ* hybridisation (FISH) or chromogenic *in situ* hybridisation (CISH) of fixed tumour blocks. Patients are eligible for [BT-ON014 trade name] treatment if they show strong HER2 overexpression as described by a 3+ score by IHC or a positive FISH or CISH result.

To ensure accurate and reproducible results, the testing must be performed in a specialised laboratory, which can ensure validation of the testing procedures.

The recommended scoring system to evaluate the IHC staining patterns is as stated in Table 2:

Table 2 *Recommended scoring system to evaluate the IHC staining patterns in breast cancer*

Score	**Staining pattern**	**HER2 overexpression assessment**
0	No staining is observed or membrane staining is observed in <10 % of the tumour cells	Negative
1+	A faint/barely perceptible membrane staining is detected in >10 % of the tumour cells. The cells are only stained in part of their membrane.	Negative
2+	A weak to moderate complete membrane staining is detected in >10 % of the tumour cells.	Equivocal
3+	Strong complete membrane staining is detected in >10 % of the tumour cells.	Positive

In general, FISH is considered positive if the ratio of the HER2 gene copy number per tumour cell to the chromosome 17 copy number is greater than or equal to 2, or if there are more than 4 copies of the HER2 gene per tumour cell if no chromosome 17 control is used.

In general, CISH is considered positive if there are more than 5 copies of the HER2 gene per nucleus in greater than 50 % of tumour cells.

For full instructions on assay performance and interpretation please refer to the package inserts of validated FISH and CISH assays. Official recommendations on HER2 testing may also apply.

For any other method that may be used for the assessment of HER2 protein or gene expression, the analyses should only be performed by laboratories that provide adequate state-of-the-art performance of validated methods. Such methods must clearly be precise and accurate enough to demonstrate overexpression of HER2 and must be able to distinguish between moderate (congruent with 2+) and strong (congruent with 3+) overexpression of HER2.

Clinical efficacy and safety

Metastatic breast cancer

Trastuzumab has been used in clinical trials as monotherapy for patients with MBC who have tumours that overexpress HER2 and who have failed one or more chemotherapy regimens for their metastatic disease (trastuzumab alone).

Trastuzumab has also been used in combination with paclitaxel or docetaxel for the treatment of patients who have not received chemotherapy for their metastatic disease. 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. In the pivotal trial of docetaxel (100 mg/m^2 infused over 1 hour) with or without trastuzumab, 60 % of the patients had received prior anthracycline-based adjuvant chemotherapy. Patients were treated with trastuzumab until progression of disease.

The efficacy of trastuzumab in combination with paclitaxel in patients who did not receive prior adjuvant anthracyclines has not been studied. However, trastuzumab plus docetaxel was efficacious in patients whether or not they had received prior adjuvant anthracyclines.

The test method for HER2 overexpression used to determine eligibility of patients in the pivotal trastuzumab monotherapy and trastuzumab plus paclitaxel clinical trials employed immunohistochemical staining for HER2 of fixed material from breast tumours using the murine monoclonal antibodies CB11 and 4D5. These tissues were fixed in formalin or Bouin's fixative. This investigative clinical trial assay performed in a central laboratory utilised a 0 to 3+ scale. Patients classified as staining 2+ or 3+ were included, while those staining 0 or 1+ were excluded. More than 70 % of patients enrolled exhibited 3+ overexpression. The data suggest that beneficial effects were greater among those patients with higher levels of overexpression of HER2 (3+).

The main test method used to determine HER2 positivity in the pivotal trial of docetaxel, with or without trastuzumab, was immunohistochemistry. A minority of patients was tested using fluorescence *in-situ* hybridisation (FISH). In this trial, 87 % of patients entered had disease that was IHC3+, and 95 % of patients entered had disease that was IHC3+ or FISH-positive.

Weekly dosing in metastatic breast cancer

The efficacy results from the monotherapy and combination therapy studies are summarised in Table 3:

Table 3. *Efficacy results from the monotherapy and combination therapy studies*

Parameter	**Monotherapy**	**Combination Therapy**			
	Trastuzumab[1] N = 172	**Trastuzumab plus paclitaxel[2] N = 68**	**Paclitaxel[2] N = 77**	**Trastuzumab plus docetaxel[3] N = 92**	**Docetaxel[3] N = 94**
Response rate (95 %CI)	18 % (13 - 25)	49 % (36 - 61)	17 % (9 - 27)	61 % (50-71)	34 % (25-45)
Median duration of response (months) (95 %CI)	9.1 (5.6-10.3)	8.3 (7.3-8.8)	4.6 (3.7-7.4)	11.7 (9.3 – 15.0)	5.7 (4.6-7.6)
Median TTP (months) (95 %CI)	3.2 (2.6-3.5)	7.1 (6.2-12.0)	3.0 (2.0-4.4)	11.7 (9.2-13.5)	6.1 (5.4-7.2)
Median Survival (months) (95 %CI)	16.4 (12.3-ne)	24.8 (18.6-33.7)	17.9 (11.2-23.8)	31.2 (27.3-40.8)	22.74 (19.1-30.8)

TTP = time to progression; "ne" indicates that it could not be estimated or it was not yet reached.

1. Study H0649g: IHC3+ patient subset
2. Study H0648g: IHC3+ patient subset
3. Study M77001: Full analysis set (intent-to-treat), 24 months results

Combination treatment with trastuzumab and anastrozole

Trastuzumab has been studied in combination with anastrozole for first line treatment of MBC in HER2-overexpressing, hormone-receptor (i.e., estrogen-receptor (ER) or progesterone-receptor (PR)) positive postmenopausal patients. Progression free survival was doubled in the trastuzumab 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 containing regimen after progression of disease.

Three -weekly dosing in metastatic breast cancer

The efficacy results from the non-comparative monotherapy and combination therapy studies are summarised in Table 4:

Table 4. *Efficacy results from the non-comparative monotherapy and combination therapy studies*

Parameter	**Monotherapy**		**Combination Therapy**	
	Trastuzumab[1] N = 105	**Trastuzumab[2] N = 72**	**Trastuzumab plus paclitaxel[3] N = 32**	**Trastuzumab plus docetaxel[4] N = 110**
Response rate (95 %CI)	24 % (15–35)	27 % (14–43)	59 % (41–76)	73 % (63–81)
Median duration of response (months) (range)	10.1 (2.8–35.6)	7.9 (2.1–18.8)	10.5 (1.8–21)	13.4 (2.1–55.1)

Median TTP (months) (95 %CI)	3.4 (2.8–4.1)	7.7 (4.2–8.3)	12.2 (6.2–ne)	13.6 (11–16)
Median Survival (months) (95 %CI)	ne	ne	ne	47.3 (32–ne)

TTP = time to progression; "ne" indicates that it could not be estimated or it was not yet reached.

1. Study WO16229: loading dose 8 mg/kg, followed by 6 mg/kg 3 weekly schedule
2. Study MO16982: loading dose 6 mg/kg weekly x 3; followed by 6 mg/kg 3-weekly schedule
3. Study BO15935
4. Study MO16419

Sites of progression

The frequency of progression in the liver was significantly reduced in patients treated with the combination of trastuzumab and paclitaxel, compared to paclitaxel alone (21.8 % versus 45.7 %; p = 0.004). More patients treated with trastuzumab and paclitaxel progressed in the central nervous system than those treated with paclitaxel alone (12.6 % versus 6.5 %; p = 0.377).

Early breast cancer (adjuvant setting)

EBC is defined as non-metastatic primary invasive carcinoma of the breast.

In the adjuvant treatment setting, trastuzumab was investigated in 4 large multicentre, randomised, trials.

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

EBC in the HERA trial was limited to operable, primary, invasive adenocarcinoma of the breast, with axillary nodes positive or axillary nodes negative if tumours at least 1 cm in diameter.

In the joint analysis of the NSABP B-31 and NCCTG N9831 studies, EBC 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).

In the BCIRG 006 study HER2 positive, EBC was defined as either lymph node positive or high-risk node negative patients with no (pN0) lymph node involvement, and at least 1 of the following factors:

tumour size greater than 2 cm, estrogen receptor and progesterone receptor negative, histological and/or nuclear grade 2-3, or age < 35 years).

The efficacy results from the BO16348 trial following 12 months* and 8 years** median follow-up are summarized in Table 5:

Table 5. *Efficacy results from study BO16348*

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

*Co-primary endpoint of DFS of 1 year versus observation met the pre-defined statistical boundary
**Final analysis (including crossover of 52 % of patients from the observation arm to trastuzumab)
***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 versus 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 arm.

A final analysis was performed after a median follow-up of 8 years, which showed that 1-year trastuzumab 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 treatment.

In this final analysis, extending trastuzumab 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 versus 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 NSABP B-31 and NCCTG N9831 studies trastuzumab was administered in combination with paclitaxel, following AC chemotherapy.

Doxorubicin and cyclophosphamide were administered concurrently as follows:

- intravenous push doxorubicin, at 60 mg/ m^2, given every 3 weeks for 4 cycles.
- intravenous cyclophosphamide, at 600 mg/ m^2 over 30 minutes, given every 3 weeks for 4 cycles

Paclitaxel, in combination with trastuzumab, was administered as follows:

- intravenous paclitaxel – 80 mg/ m^2 as a continuous intravenous infusion, given every week for 12 weeks.

  or

- intravenous paclitaxel – 175 mg/ m^2 as a continuous intravenous infusion, given every 3 weeks for 4 cycles (day 1 of each cycle).

The efficacy results from the joint analysis of the NSABP B-31 and NCCTG N9831 trials at the time of the definitive analysis of DFS* are summarized in Table 6. The median duration of follow up was 1.8 years for the patients in the AC→P arm and 2.0 years for patients in the AC→PH arm.

Table 6. *Summary of efficacy results from the joint analysis of the NSABP B-31 and NCCTG N9831 trials at the time of the definitive DFS analysis**

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

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

For the primary endpoint, DFS, the addition of trastuzumab 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 3-year disease-free survival rate estimates of 11.8 percentage points (87.2 % versus 75.4 %) in favour of the AC→PH (trastuzumab) arm.

At the time of a safety update after a median of 3.5-3.8 years follow up, an analysis of DFS reconfirmed the magnitude of the benefit shown in the definitive analysis of DFS. Despite the cross-over to trastuzumab in the control arm, the addition of trastuzumab to paclitaxel chemotherapy resulted in a 52 % decrease in the risk of disease recurrence. The addition of trastuzumab to paclitaxel chemotherapy also resulted in a 37 % decrease in the risk of death.

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→P H 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 Table 7 below:

Table 7. *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

DFS analysis was also performed at the final analysis of OS from the joint analysis of studies NSABP B-31 and NCCTG N9831. The updated DFS analysis results (stratified HR = 0.61; 95% CI [0.54, 0.69]) showed a similar DFS benefit compared to the definitive primary DFS analysis, despite 24.8 % patients in the AC→P arm who crossed over to receive trastuzumab. At 8 years, the disease-free survival rate was estimated to be 77.2 % (95 % CI: 75.4, 79.1) in the AC→PH arm, an absolute benefit of 11.8% compared with the AC→P arm.

In the BCIRG 006 study trastuzumab 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:

- intravenous docetaxel – 100 mg/m^2 as an intravenous 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

- intravenous docetaxel – 75 mg/m^2 as an intravenous infusion over 1 hour, given every 3 weeks for 6 cycles (day 2 of cycle 1, then day 1 of each subsequent cycle).

which was followed by:

- carboplatin – at target AUC = 6 mg/mL/min administered by intravenous infusion over 3060 minutes repeated every 3 weeks for a total of six cycles.

Trastuzumab was administered weekly with chemotherapy and 3- weekly thereafter for a total of 52 weeks.

The efficacy results from the BCIRG 006 are summarized in Tables 8 and 9. The median duration of follow up was 2.9 years in the AC→D arm and 3.0 years in each of the AC→DH and DCarbH arms.

Table 8. *Overview of efficacy analyses BCIRG 006 AC→D versus AC→DH*

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

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

Table 9. *Overview of efficacy analyses BCIRG 006 AC→D versus DCarbH*

Parameter	**AC→D (n = 1073)**	**DCarbH (n = 1074)**	**Hazard Ratio vs AC→D (95 % CI) p-value**
Disease-free survival No. patients with event	195	145	0.67 (0.54, 0.83) p = 0.0003
Distant recurrence No. patients with event	144	103	0.65 (0.50, 0.84) p = 0.0008
Death (OS event) No. patients with event	80	56	0.66 (0.47, 0.93) p = 0.0182

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 3-year disease-free survival rate estimates of 5.8 percentage points (86.7 % versus 80.9 %) in favour of the AC→DH (trastuzumab) arm and 4.6 percentage points (85.5 % versus 80.9 %) in favour of the DCarbH (trastuzumab) arm compared to AC→D.

In study BCIRG 006, 213/1075 patients in the DCarbH (TCH) arm, 221/1074 patients in the AC→DH (AC→TH) arm, and 217/1073 in the AC→D (AC→T) arm had a Karnofsky performance status ≤ 90 (either 80 or 90). No disease-free survival (DFS) benefit was noticed in this subgroup of patients (hazard ratio = 1.16, 95 % CI [0.73, 1.83] for DCarbH (TCH) versus AC→D (AC→T); hazard ratio 0.97, 95 % CI [0.60, 1.55] for AC→DH (AC→TH) versus AC→D).

In addition, a post-hoc exploratory analysis was performed on the data sets from the joint analysis (JA) NSABP B-31/NCCTG N9831* and BCIRG006 clinical studies combining DFS events and symptomatic cardiac events and summarised in Table 10:

Table 10. *Post-hoc exploratory analysis results from the joint analysis NSABP B-31/NCCTG N9831 and BCIRG006 clinical studies combining DFS events and symptomatic cardiac events*

	AC→PH (vs. AC→P) (NSABP B-31 and NCCTG N9831)*	**AC→DH (vs. AC→D) (BCIRG 006)**	**DCarbH (vs. AC→D) (BCIRG 006)**
Primary efficacy analysis DFS Hazard ratios (95 % CI) p-value	0.48 (0.39, 0.59) p < 0.0001	0.61 (0.49, 0.77) p < 0.0001	0.67 (0.54, 0.83) p = 0.0003
Long term follow-up efficacy analysis** DFS Hazard ratios (95 % CI) p-value	0.61 (0.54, 0.69) p < 0.0001	0.72 (0.61, 0.85) p < 0.0001	0.77 (0.65, 0.90) p = 0.0011
Post-hoc exploratory analysis with DFS and symptomatic cardiac events Long term follow-up** Hazard ratios (95 % CI)	0.67 (0.60, 0.75)	0.77 (0.66, 0.90)	0.77 (0.66, 0.90)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; D: docetaxel; Carb: carboplatin; H: trastuzumab CI = confidence interval
* At the time of the definitive analysis of DFS. Median duration of follow up was 1.8 years in the AC→P arm and 2.0 years in the AC→PH arm
** Median duration of long-term follow-up for the Joint Analysis clinical studies was 8.3 years (range: 0.1 to 12.1) for the AC→PH arm and 7.9 years (range: 0.0 to 12.2) for the AC→P arm; Median duration of long-term follow-up for the BCIRG 006 study was 10.3 years in both the AC→D arm (range: 0.0 to 12.6) arm and the DCarbH arm (range: 0.0 to 13.1), and was 10.4 years (range: 0.0 to 12.7) in the AC→DH arm

Early breast cancer (neoadjuvant-adjuvant setting)

So far, no results are available which compare the efficacy of trastuzumab administered with chemotherapy in the adjuvant setting with that obtained in the neo-adjuvant/adjuvant setting.

In the neoadjuvant-adjuvant treatment setting, study MO16432, a multicentre randomised trial, was designed to investigate the clinical efficacy of concurrent administration of trastuzumab with neoadjuvant chemotherapy including both an anthracycline and a taxane, followed by adjuvant trastuzumab, up to a total treatment duration of 1 year. The study recruited patients with newly diagnosed locally advanced (Stage III) or inflammatory EBC. Patients with HER2+ tumours were randomised to receive either neoadjuvant chemotherapy concurrently with neoadjuvant-adjuvant trastuzumab, or neoadjuvant chemotherapy alone.

In study MO16432, trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg maintenance every 3 weeks) was administered concurrently with 10 cycles of neoadjuvant chemotherapy as follows:

- Doxorubicin 60 mg/m^2 and paclitaxel 150 mg/m^2, administered 3-weekly for 3 cycles,

which was followed by
- Paclitaxel 175 mg/m^2 administered 3-weekly for 4 cycles,

which was followed by

- CMF on day 1 and 8 every 4 weeks for 3 cycles

which was followed after surgery by
- additional cycles of adjuvant trastuzumab (to complete 1 year of treatment)

The efficacy results from Study MO16432 are summarized in Table 11. The median duration of follow-up in the trastuzumab arm was 3.8 years.

Table 11. *Efficacy results from MO16432*

Parameter	**Chemo + Trastuzumab (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
Overall survival No. patients with event	 22	 33	Hazard Ratio (95 % CI) 0.59 (0.35, 1.02) p = 0.0555

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

An absolute benefit of 13 percentage points in favour of the trastuzumab arm was estimated in terms of 3-year event-free survival rate (65 % versus 52 %).

Paediatric population

See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

The pharmacokinetics of trastuzumab were evaluated in a population pharmacokinetic model analysis using pooled data from 1,582 subjects, including patients with HER2 positive MBC, EBC, AGC or other tumour types, and healthy volunteers, in 18 Phase I, II and III trials receiving trastuzumab. A two-compartment model with parallel linear and non-linear elimination from the central compartment described the trastuzumab concentration-time profile. Due to non-linear elimination, total clearance increased with decreasing concentration. Therefore, no constant value for half-life of trastuzumab can be deduced. The $t_{1/2}$ decreases with decreasing concentrations within a dosing interval (see Table 16). MBC and EBC patients had similar PK parameters (e.g., clearance (CL), the central compartment volume (V_c)) and population-predicted steady-state exposures (C_{min}, C_{max} and AUC). Linear clearance was 0.136 L/day for MBC, 0.112 L/day for EBC and 0.176 L/day for AGC. The non-linear elimination parameter values were 8.81 mg/day for the maximum elimination rate (V_{max}) and 8.92 µg/mL for the Michaelis-Menten constant (K_m) for the MBC, EBC, and AGC patients. The central compartment volume was 2.62 L for patients with MBC and EBC and 3.63 L for patients with AGC. In the final population PK model, in addition to primary tumour type, body-weight, serum aspartate aminotransferase and albumin were identified as statistically significant covariates affecting the exposure of trastuzumab. However, the magnitude of effect of these covariates on trastuzumab exposure suggests that these covariates are unlikely to have a clinically meaningful effect on trastuzumab concentrations.

The population predicted PK exposure values (median with 5th - 95th percentiles) and PK parameter values at clinically relevant concentrations (C_{max} and C_{min}) for MBC, EBC and AGC patients treated with the approved q1w and q3w dosing regimens are shown in Table 12 (cycle 1), Table 13 (steady- state), and Table 14 (PK parameters).

Table 12 Population predicted cycle 1 PK exposure values (median with 5th - 95th percentiles) for trastuzumab intravenous dosing regimens in MBC, EBC and AGC patients

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

Table 13 Population predicted steady state PK exposure values (median with 5th - 95th percentiles) for trastuzumab intravenous dosing regimens in MBC, EBC and AGC patients

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

*$C_{min,ss}$ – C_{min} at steady state
**$C_{max,ss}$ = C_{max} at steady state
*** time to 90% of steady-state

Table 14 Population predicted PK parameter values at steady state for trastuzumab intravenous dosing regimens in MBC, EBC and AGC patients

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

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

Circulating shed HER2-ECD
The exploratory analyses of covariates with information in only a subset of patients suggested that patients with greater shed HER2-ECD level had faster nonlinear clearance (lower K_m) ($P < 0.001$). There was a

correlation between shed antigen and SGOT/AST levels; part of the impact of shed antigen on clearance may have been explained by SGOT/AST levels.

Baseline levels of the shed HER2-ECD observed in MGC patients were comparable to those in MBC and EBC patients and no apparent impact on trastuzumab clearance was observed.

5.3 Preclinical safety data

There was no evidence of acute or multiple dose-related toxicity in studies of up to 6 months, or reproductive toxicity in teratology, female fertility or late gestational toxicity/placental transfer studies. Trastuzumab is not genotoxic.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Drug product
L-histidine hydrochloride
L-histidine
D-sorbitol
Macrogol 3350
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)

Diluent
Water for injection
Benzyl alcohol

6.2 Incompatibilities

This medicinal product must not be mixed or diluted with other medicinal products except those mentioned under section 6.6.

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

6.3 Shelf life

Unopened vial
48 months

In-use shelf life:
The reconstituted product is physico-chemically and microbiologically stable for 28 days when refrigerated at 2°C to 8°C after dissolving in the supplied bacteriostatic water for injection. See section 6.6

Infusion solution (0.9% sodium chloride) containing the reconstituted drug product is physically and chemically stable for 24 hours at 2°C to 8°C. From the perspective of microbiological safety, the [BT-ON014 trade name] 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 24 hours when refrigerated at 2°C to 8°C. See section 6-6

6.4 Special precautions for storage

Store at 2°C-8°C, in the original package in order to protect from light.

See section 6-3 for the storage of the reconstituted and further diluted product.

6.5 Nature and contents of container

Drug product

The packaging consists of a clear, colourless Type I glass vial, closed with a 20 mm chlorobutyl rubber stopper with fluoro-polymer laminate on the product contact side. The rubber stopper is sealed with an aluminium seal that has a plastic flip-off cap.

420 mg trastuzumab are filled into each vial.

Diluent

20mL of the diluent bacteriostatic water for injection are filled into a colorless Type I glass vials (USP/Ph. Eur.) and closed with a chlorobutyl rubber stopper with fluoro-polymer laminate on the product contact side. The rubber stopper is sealed with an aluminum seal that has a plastic flip-off cap component. The seal and cap do not come into contact with the diluent.

One vial of drug product and one vial of diluent are packed into one carton.

6.6 Special precautions for disposal and other handling

Handling

[BT-ON014 trade name] should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted solution may result in problems with the amount of product that can be withdrawn from the vial.

A volume over-fill of 4.8 % ensures that the labelled dose of 420 mg can be withdrawn from each vial.

The reconstituted solution should not be frozen.

Instructions for reconstitution

1. Appropriate aseptic technique should be used.
2. Using a sterile syringe, slowly inject 20 mL of bacteriostatic water for injection into the vial containing the lyophilised drug product, i.e., [BT-ON014 trade name]. Direct the stream into the lyophilised cake.
3. To aid reconstitution, the vial should be swirled gently. DO NOT SHAKE.
4. Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes.
    - The reconstituted product results in a colourless to pale yellow transparent solution and should be essentially free of visible particulates.
    - Reconstitution yields a 21 mL solution for multi-dose use, containing approximately 21 mg/mL trastuzumab, at a pH of approximately 6.0.
5. The reconstituted product is physico-chemically and microbiologically stable for 28 days when refrigerated at 2°C to 8°C after dissolving in the supplied bacteriostatic water for injection.

No incompatibilities between [BT-ON014 trade name] and polyvinylchloride, polyethylene or polypropylene bags have been observed.

Instructions for dilution

1. Determine the volume of [BT-ON014 trade name] solution required:
    • Based on a loading dose of trastuzumab of 4mg /kg, or a subsequent weekly dose of 2 mg /kg:

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

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

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

2. The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of 0.9 % sodium chloride solution. Do not use with glucose-containing solutions (see section 6.2).
3. The bag should be gently inverted to mix the solution in order to avoid foaming. Once the infusion is prepared it should be administered immediately. If reconstitution and dilution have taken place under aseptic conditions, the infusion solution can be stored up to 24 hours when refrigerated at 2°C to 8°C.

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

Disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

Biocon Biologics Limited
16 Great Queen Street
Covent Garden, London
United Kingdom
WC2B 5AH
Tel. No.: +91 80 6775 6775, +91 80 6775 1107
Fax No.: +91 80 6775 1030
Email: DrugSafety@biocon.com , ContactUs.BBL@biocon.com

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References

General reference sources for this SmPC:

EU Summary of product characteristics for Herceptin powder for concentrate for solution for infusion available at Herceptin, INN-trastuzumab (europa.eu). Accessed on 15 April, 2021

EU Summary of product characteristics for Ogivri powder for concentrate for solution for infusion available at Ogivri, INN trastuzumab (europa.eu). Accessed 15 April, 2021.

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines