ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions

1. NAME OF THE MEDICINAL PRODUCT

Dazublys 150 mg powder for concentrate for solution for infusion.
Dazublys 420 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dazublys 150 mg powder for concentrate for solution for infusion.

One vial contains 150 mg of trastuzumab, a humanized IgG1 monoclonal antibody produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity and ion exchange chromatography, including specific viral inactivation and removal procedures.

Dazublys 420 mg powder for concentrate for solution for infusion.

One vial contains 420 mg of trastuzumab, a humanized IgG1 monoclonal antibody produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity and ion exchange chromatography, including specific viral inactivation and removal procedures.

The reconstituted Dazublys solution contains 21 mg/mL of trastuzumab.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

White to pale yellow lyophilized powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast cancer

Metastatic breast cancer

Dazublys 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.

- 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

Dazublys 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.

- in combination with neoadjuvant chemotherapy followed by adjuvant Dazublys therapy for locally advanced (including inflammatory) disease or tumors> 2 cm in diameter (see sections 4.4 and 5.1).

Dazublys should only be used in patients with metastatic or early breast cancer whose tumors have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay (see sections 4.4 and 5.1).

Metastatic gastric cancer

Dazublys 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 gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Dazublys should only be used in patients with metastatic gastric cancer (MGC) whose tumors have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result or by an IHC 3+ result. Accurate and validated assay methods should be used (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). Trastuzumab treatment should only be initiated by a physician experienced in the administration of cytotoxic chemotherapy (see section 4.4) and should be administered by a healthcare professional only.

Dazublys 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 treatment errors, it is important to check the vial labels to ensure that the drug being prepared and administered is Dazublys (trastuzumab) and not another trastuzumab-containing product (e.g., trastuzumab emtansine or trastuzumab deruxtecan).

Posology

Metastatic breast cancer

Three-weekly schedule

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

Weekly Schedule

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

Administration in combination with paclitaxel or docetaxel

In the pivotal trials (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 in combination 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 at administration (for dose, see the SmPC for anastrozole or other aromatase inhibitors).

Early breast cancer

Three-weekly and weekly schedule

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

See section 5.1 for chemotherapy combination dosing.

Metastatic gastric cancer

Three-weekly schedule

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

Breast cancer and gastric cancer

Duration of treatment

Patients with MBC or MGC should be treated with trastuzumab until the progression of the disease. Patients with EBC should be treated with trastuzumab 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 inhibitors for information on dose reduction or delays.

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

Missed doses

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

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

Special populations

Dedicated pharmacokinetic 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.

Pediatric population

There is no relevant use of trastuzumab in the pediatric population.

Method of administration

Trastuzumab loading dose should be administered as a 90-minute intravenous infusion. Do not administer as an intravenous push or bolus. Trastuzumab 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 is well tolerated, the subsequent doses can be administered as a 30-minute infusion.

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

Infusion Bags used for administering the trastuzumab finished product should be DEHP free.

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 specialized 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%, and older age.

All candidates for treatment with trastuzumab, but especially those with prior anthracycline and cyclophosphamide (AC) exposure, should undergo baseline cardiac assessment including history and physical examination, electrocardiogram (ECG), echocardiogram, and/or multigated acquisition (MUGA) scan or magnetic resonance imaging. Monitoring may help to identify patients who develop cardiac dysfunction. Cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of trastuzumab. A careful risk-benefit assessment should be made before deciding to treat with trastuzumab.

trastuzumab may persist in circulation for up to 7 months after stopping Dazublys 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, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

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

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

If symptomatic cardiac failure develops during trastuzumab therapy, it should be treated with standard medicinal products for CHF. Most patients who developed CHF or asymptomatic cardiac dysfunction in pivotal trials improved with standard CHF treatment consisting of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a beta-blocker. The majority of patients with cardiac symptoms and evidence of a clinical benefit of trastuzumab treatment continued

on therapy without additional clinical cardiac events.

Metastatic breast cancer

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

Early breast cancer

For patients with EBC, cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of trastuzumab. In patients who receive anthracycline-containing chemotherapy further monitoring is recommended and should occur yearly up to 5 years from the last administration of trastuzumab, or longer if a continuous decrease of LVEF is observed.

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

Adjuvant treatment

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

In patients with 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/m2.

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 trastuzumabin the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after

surgery. In other situations, the decision on the need for additional cytotoxic chemotherapy is determined based on individual factors.

Experience of concurrent administration of trastuzumab with low dose anthracycline regimens is currently limited to two trials (MO16432 and BO22227)

In the pivotal trial MO16432, trastuzumab was administered concurrently with neoadjuvant chemotherapy containing three cycles of doxorubicin (cumulative dose 180 mg/m2).
The incidence of symptomatic cardiac dysfunction was 1.7% in the trastuzumab arm.

In the pivotal study BO22227, trastuzumab was administered concurrently with neoadjuvant chemotherapy that contained four cycles of epirubicin (cumulative dose 300 mg/m^2); at a median follow-up exceeding 70 months, the incidence of cardiac failure/congestive cardiac failure was 0.3% in the trastuzumab intravenous 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 meperidine or paracetamol, or an antihistamine such as diphenhydramine. The majority of patients experienced resolution of symptoms and subsequently received further infusions of trastuzumab. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta- agonists, and corticosteroids. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with trastuzumab (see section 4.3).

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

Pulmonary events

Severe pulmonary events have been reported with the use of trastuzumab in the post-marketing setting (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.

Sodium

Dazublys contains less than 1 mmol of sodium (23 mg) per dose, that is to say essentially sodium-free.

Polysorbate-20

This medicine contains 0.6 mg or 1.7 mg of polysorbate 20 in each 150 mg/vial or 420 mg/vial which is equivalent to 0.6 mg/60 kg/7.4 mLor 1.7 mg/60 kg/20.8 mL, respectively. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

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

Effect of trastuzumab on the pharmacokinetics of other antineoplastic agents

Pharmacokinetic data from 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 IV loading dose followed by 6 mg/kg q3w or 2 mg/kg q1w IV, respectively).
However, trastuzumab may elevate the overall exposure of one doxorubicin metabolite, (7-deoxy-13 dihydro-doxorubicinone, D7D). The bioactivity of D7D and the clinical impact of the elevation of this metabolite was unclear.

Data from study JP16003, a single-arm study of trastuzumab (4 mg/kg IV loading dose and 2 mg/kg IV weekly) and docetaxel (60 mg/m2 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 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 lactation

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 and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving trastuzumab. Women who become pregnant should be advised ofthe 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 Cynomolgus monkeys at doses 25 times that of the weekly human maintenance dose of 2 mg/kg trastuzumab intravenous formulation from days 120 to 150 of pregnancy demonstrated that trastuzumab is secreted in the milk postpartum. The exposure to trastuzumab in utero and the presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 1 month of age. 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 theinfant is unknown, women should not breast-feed during trastuzumab therapy and for 7 months after the last dose.

Fertility

There is no fertility data available.

4.7 Effects on the ability to drive and use machines.

Dazublys has a minor influence on the ability to drive or use machines (see section 4.8). Dizziness and somnolence may 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 and/or common adverse reactions reported in trastuzumab usage

intravenous 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 in 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
	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

System organ class	Adverse reaction	Frequency
	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
	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

System organ class	Adverse reaction	Frequency
	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
	Pruritus	Common
	Onychoclasis	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

System organ class	Adverse reaction	Frequency
	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 edema, 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 (ie 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 fataloutcome.

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).

Details of risk minimisation measures that are consistent with the EU Risk Management Plan are presented in (section 4.4) Warnings and Precautions.

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.

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

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no experience with overdose in human clinical trials. Single doses of trastuzumab alone greaterthan 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: L01FD01

Dazublys is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Trastuzumab is a recombinant humanized IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2). Overexpression of HER2 is observed in 20% - 30% of primary breast cancers. Studies of HER2-positivity rates in gastric cancer (GC) using immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH) or chromogenic *in situ* hybridization (CISH) have shown that there is a broad variation of HER2-positivity ranging from 6.8% to 34.0% for IHC and 7.1% to 42.6% for FISH. Studies indicate that breast cancer patients whose tumors overexpress HER2 have a shortened disease-free survival compared to patients whose tumors do not overexpressHER2. 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. The 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. 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

Detection of HER2 overexpression or HER2 gene amplification in breast cancer

Trastuzumab should only be used in patients whose tumors 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 tumor blocks (see section 4.4). HER2 gene amplification should be detected using fluorescence *in situ* hybridization (FISH) or chromogenic in situ hybridization (CISH) of fixed tumor blocks. Patients are eligible for trastuzumab 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 specialized 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 verexpression assessment**
0	No staining is observed or membrane staining is observed in < 10% of the tumor cells	Negative
1+	A faint/barely perceptible membrane staining is detected in > 10% of the tumour cells. The cells areonly 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 nucleusin greater than 50% of tumors 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.

Detection of HER2 over expression or HER2 gene amplification in gastric cancer

Only an accurate and validated assay should be used to detect HER2 over expression or HER2 gene amplification. IHC is recommended as the first testing modality and in cases where HER2 gene amplification status is also required, either a silver-enhanced *in situ* hybridization (SISH) or a FISH technique must be applied. SISH technology is however, recommended to allow for the parallel evaluation of tumor histology and morphology. To ensure validation of testing procedures and the generation of accurate and reproducible results, HER2 testing must be performed in a laboratory staffed by trained personnel. Full instructions on assay performance and results interpretation shouldbe taken from the product information leaflet provided with the HER2 testing assays used.

In the ToGA (BO18255) trial, patients whose tumours were either IHC3 + or FISH positive were defined as HER2 positive and thus included in the trial. Based on the clinical trial results, the beneficial effects were limited to patients with the highest level of HER2 protein overexpression, defined by a 3 + score by IHC, or a 2 + score by IHC and a positive FISH result.

In a method comparison study (study D008548), a high degree of concordance (> 95%) was observed for SISH and FISH techniques for the detection of HER2 gene amplification in gastric cancer patients.

HER2 overexpression should be detected using an immunohistochemistry (IHC)-based assessment of fixed tumor blocks; HER2 gene amplification should be detected using in situ hybridization using either SISH or FISH on fixed tumor blocks.

The recommended scoring system to evaluate the IHC staining patterns is as stated in Table 3:

Table 3: Recommended Scoring System to Evaluate the IHC Staining Patterns in Gastric Cancer

Score	**Surgical specimen - staining pattern**	**Biopsy specimen – staining pattern**	**HER2 overexpression assessment**
0	No reactivity or membranous reactivity in < 10% of tumour cells	No reactivity or membranous reactivity in any tumour cell	Negative

1+	Faint/barely perceptible membranous reactivity in ≥ 10% of tumour cells; cells arereactive only in part of their Membrane	Tumour cell cluster with a faint/ barely perceptible membranous reactivity irrespective of percentage of tumour cells Stained	Negative
2+	Weak to moderate complete, basolateral or lateral membranous reactivity in ≥ 10% of tumour cells	Tumour cell cluster with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained	Equivocal
3+	Strong complete, basolateral or lateral membranous reactivity in ≥ 10% of tumour cells	Tumour cell cluster with a strong complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained	Positive

In general, SISH or 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.

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 patientswho 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 over1 hour) with or without trastuzumab, 60% of the patients had received prior anthracycline-based adjuvant chemotherapy. Patients were treated with trastuzumab until the 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. Greater 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 ~~i~~*n situ* hybridization (FISH). In this trial, 87% of patients entered had disease that was IHC3+, and 95% of patients entered had disease that was IHC3+ and/or FISH-positive.

Weekly dosing in metastatic breast cancer

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

Table 4: 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 n plus docetaxel3 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 durationof 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) and/or progesterone-receptor (PR)) positive postmenopausal patients. Progression-freee survival was doubled in the trastuzumab plus anastrozole arm compared to anastrozole (4.8 months versus 2.4 months). For the other parameters theimprovements 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 summarized in Table 5:

Table 5: 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 systemthan those treated with paclitaxel alone (12.6% versus 6.5%; p = 0.377).

Early breast cancer (adjuvant setting)

Early breast cancer is defined as non-metastatic primary invasive carcinoma of the breast.
In the adjuvant treatment setting, trastuzumab was investigated in 4 large multicenter, randomized 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, a 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 everythree 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.

Early breast cancer in the HERA trial was limited to operable, primary, invasive adenocarcinoma of the breast, with axillary nodes positive or axillary nodes negative if tumors 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 (tumor size > 1 cm and ER negative or tumor 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-upare

summarized in Table 6:

Table 6: Efficacy Results from Study BO16348

Parameter	Median follow-up12 months*		Median follow-up8 years**	
	Observation N = 1693	trastuzumab 1 Year N = 1693	Observation N = 1697***	trastuzumab [1] Year N = 1702***
Disease-free survival				
- No. patients with event	219 (12.9%)	127 (7.5%)	570 (33.6%)	471 (27.7%)
- No. patients without event	1474 (87.1%)	1566 (92.5%)	1127 (66.4%)	1231 (72.3%)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.54		0.76	
Recurrence-free survival				
- No. patients with event	208 (12.3%)	113 (6.7%)	506 (29.8%)	399 (23.4%)
- No. patients without event	1485 (87.7%)	1580 (93.3%)	1191 (70.2%)	1303 (76.6%)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.51		0.73	
Distant disease-free survival				
- No. patients with event	184 (10.9%)	99 (5.8%)	488 (28.8%)	399 (23.4%)
- No. patients without event	1508 (89.1%)	1594 (94.6%)	1209 (71.2%)	1303 (76.6%)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.50		0.76	
Overall survival (death)				
- No. patients with event	40 (2.4%)	31 (1.8%)	350 (20.6%)	278 (16.3%)
- No. patients without event	1653 (97.6%)	1662 (98.2%)	1347 (79.4%)	1424 (83.7%)
P-value versus Observation	0.24		0.0005	
Hazard Ratio versus Observation	0.75		0.76	

*Co-primary endpoint of DFS of 1 year 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 randomized 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 survivalrate 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 eventin 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 4cycles.

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

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

The efficacy results from the joint analysis of the NSABP B-31 and NCCTG 9831 trials at the time of the definitive analysis of DFS* are summarized in Table 7. 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 7: Summary of Efficacy results from the joint analysis of the NSABP B-31 and NCCTG N9831trials at the time of the definitive DFS analysis*

Parameter	AC→P (n = 1679)	AC→PH (n = 1672)	Hazard Ratio vsAC→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 forpatients 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 reconfirmsthe 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 8 below:

Table 8:Final Overall Survival Analysis from the joint analysis of trials NSABPB-31 and NCCTG N9831

Parameter	**AC→P (N = 2032)**	**AC→PH (N = 2031)**	**p-value versus AC→P**	**Hazard Ratioversus 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 benefitof 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 ocetaxel and carboplatin (DCarbH).

Docetaxel was administered as follows:

- intravenous docetaxel – 100 mg/m^2 as an intravenous infusion over 1 hour, given every 3weeks 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 3weeks 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 30-60 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 9 and 10. 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 9: Overview of Efficacy Analyses BCIRG 006 AC→D versus AC→DH

Parameter	**AC→D (n = 1073)**	**AC→DH (n = 1074)**	**Hazard Ratio vsAC→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 10: 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)
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 11:

Table 11: 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: trastuzumabCI = confidence interval

* At the time of the definitive analysis of DFS. Median duration of follow up was 1.8 years in the AC→P armand 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+ tumors were randomized 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 three weeks) was administered concurrently with 10 cycles of neoadjuvant chemotherapy as follows:

- Doxorubicin 60mg/m2 and paclitaxel 150 mg/m2, administered 3-weekly for 3 cycles, which was followed by
- Paclitaxel 175 mg/m2 administered 3-weekly for 4 cycles, which was followed by
- CMF on days 1 and 8 every four 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 12. The median duration of follow-up in the trastuzumab arm was 3.8 years.

Table 12: 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 the absence of any invasive cancer both in the breast and axillary nodes

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

Metastatic gastric cancer

trastuzumab has been investigated in one randomized, open-label phase III trial, ToGA (BO18255), in combination with chemotherapy versus chemotherapy alone.

Chemotherapy was administered as follows:

- capecitabine 1000 mg/m^2 orally twice daily for 14 days every 3 weeks for 6 cycles(evening of day 1 to the morning of day 15 of each cycle)

or

- intravenous 5-fluorouracil – 800 mg/m^2/day as a continuous intravenous infusion over 5days, given every 3 weeks for six cycles (days 1 to 5 of each cycle)

Either of which was administered with:

- cisplatin – 80 mg/m^2 every 3 weeks for six cycles on day 1 of each cycle.

The efficacy results from study BO18225 are summarized in Table 13:

Table 13: Efficacy Results from BO18225

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

FP + H: Fluoropyrimidine/cisplatin + trastuzumabFP: Fluoropyrimidine/cisplatin
a Odds ratio

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

Post-hoc subgroup analyses indicate that positive treatment effects are limited to targeting tumors with higher levels of HER2 protein (IHC 2+/FISH+ or IHC 3+). The median overall survival for the high HER2 expressing group was 11.8 months versus 16 months, HR 0.65 (95% CI 0.51-0.83), and the median progression-free survival was 5.5 months versus 7.6 months, HR 0.64 (95% CI 0.51-0.79) for FP versus FP + H, respectively. For overall survival, the HR was 0.75 (95% CI 0.51-1.11) in the IHC 2+/FISH+ group, and the HR was 0.58 (95% CI 0.41-0.81) in the IHC 3+/FISH+ group.

In an exploratory subgroup analysis performed in the TOGA (BO18255) trial there was no apparent benefit on overall survival with the addition of trastuzumab in patients with ECOG PS 2 at baseline [HR 0.96 (95% CI 0.51-1.79)], non-measurable [HR 1.78 (95% CI 0.87-3.66)] and locally advanced disease [HR 1.20 (95% CI 0.29-4.97)].

Pediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product in all subsets of the pediatric population for breast and gastric cancer (see section 4.2 for information on pediatric 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 tumor types, and healthy volunteers, in 18 Phase I, II, and III trials receiving trastuzumab IV. A two-compartment model with parallel linear and non-linear elimination from the central compartment described the trastuzumab concentration-time profile. Due to non-linear elimination, total clearance

increased with decreasing concentration. Therefore, no constant value for the half-life of trastuzumab canbe deduced. The t1/2 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 (Vc)), and population-predicted steady-state exposures (C_{min}, C_{max}, and AUC). Linear clearancewas 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 tumor type, body weight, serum aspartate aminotransferase, and albumin were identified as statistically significant covariates affecting the exposure of trastuzumab. However, the magnitude of the 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 (Cmax and Cmin) for MBC, EBC, and AGC patients treated with the approved q1w and q3w dosing regimens are shown in Table 14 (Cycle 1), Table 15 (steady-state), and Table 16 (PK parameters).

Table 14: Population Predicted Cycle 1 PK Exposure Values (median with 5th - 95th Percentiles) fortrastuzumab IV Dosing Regimens in MBC, EBC, and AGC Patients

Regimen	Primary tumor type	N	Cmin (mcg/mL)	Cmax (mcg/mL)	AUC0-21days (mcg.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 15: 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 tumor type	N	Cmin,ss* (mcg/mL)	Cmax,ss** (mcg/mL)	AUCss, 0-21days (mcg.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 16: Population Predicted PK Parameter Values at Steady State for trastuzumab Intravenous DosingRegimens in MBC, EBC and AGC Patients

Regimen	Primary tumor type	N	Total CL range from Cmax,ss to Cmin,ss (L/day)	t1/2 range from Cmax, ss to Cmin,ss (day)
8mg/kg + 6mg/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
4mg/kg + 2mg/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 mcg/mL (approximately 3% of the population predicted $C_{min, ss}$, or about 97% washout) by seven 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 levels 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. A study of trehalose, a major formulation excipient, did not revealany toxicities.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine
L-histidine hydrochloride monohydrate
α,α-trehalose dihydrate
Polysorbate 20 (E 432)**

** This medicine contains 0.6 mg or 1.7mg of polysorbate 20 in each 150 mg /vial or 420 mg/vial

which is equivalent to 0.6 mg/60 kg/7.4 mL or 1.7 mg/60 kg/20. 8 mL respectively Polysorbates may cause allergic reactions.

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 this causes aggregation of the protein.

6.3 Shelf life

Unopened vial

3 years

Aseptic reconstitution and dilution:

After aseptic reconstitution with sterile water for injection, the chemical and physical stability of the reconstituted solution was demonstrated for 48 hours at 2 °C – 8 °C.

After aseptic dilution in polyvinylchloride polyethylene or polypropylene bags containing sodium chloride 9 mg/mL (0.9%) solution for injection, chemical and physical stability of trastuzumab have been demonstrated for up to 48 hours at 5 °C ± 3 °C and 30 °C ± 2 °C.

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

6.4 Special precautions for storage

Store in a refrigerator (2° C – 8 °C).
Keep the container in the outer carton in order to protect from light.

Do not freeze the reconstituted solution.

For storage conditions of the opened medicinal product, see sections 6.3 and 6.6.

6.5 Nature and contents of the container

Dazublys 150 mg powder for concentrate for solution for infusion.

One 15 mL clear glass type I vial with butyl rubber stopper laminated with a fluoro-resin film containing 150 mg of trastuzumab.

Each carton contains one vial.

Dazublys 420 mg powder for concentrate for solution for infusion.

One 50 mL clear glass type I vial with butyl rubber stopper laminated with a fluoro-resin film containing 420 mg of trastuzumab.

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

Dazublys intravenous is provided in sterile, preservative-free, non-pyrogenic, single-use vials.

Appropriate aseptic technique should be used for reconstitution and dilution procedures. Care must be taken to ensure the sterility of prepared solutions. Since the medicinal product does not contain any anti-microbial preservative or bacteriostatic agents, an aseptic technique must be observed.

Aseptic preparation, handling, and storage:

Aseptic handling must be ensured when preparing the infusion. Preparation should be:

- performed under aseptic conditions by trained personnel in accordance with good practice rules, especially with respect to the aseptic preparation of parenteral products.
- prepared in a laminar flow hood or biological safety cabinet using standard precautions for the safe handling of intravenous agents.
- followed by adequate storage of the prepared solution for intravenous infusion to ensure maintenance of the aseptic conditions.

Dazublys 150 mg powder for concentrate for solution for infusion.

Each 150 mg vial of Dazublys is reconstituted with 7.2 mL of sterile water for injection (not supplied). Use of other reconstitution solvents should be avoided.

This yields a 7.4 mL solution for single-dose use, containing approximately 21 mg/mL trastuzumab at a pH of approximately 6.0. A volume overage of 4 % ensures that the labeled dose of 150 mg can be withdrawn from each vial.

Dazublys 420 mg powder for concentrate for solution for infusion.

Each 420 mg vial of Dazublys is reconstituted with 20 mL of sterile water for injection (not supplied). Use of other reconstitution solvents should be avoided.

This yields a 20.8 mL solution for single-dose use, containing approximately 21 mg/mL trastuzumab at a pH of approximately 6.0. A volume overage of 4 % ensures that the labeled dose of 420 mg can be withdrawn from each vial.

Dazublys Vial	**Volume of sterile water for injections**	**Final concentration**
150 mg Vial	7.2 mL	21 mg/mL
420 mg Vial	20 mL	21 mg/mL

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

The reconstituted solution should not be frozen.

Instructions for aseptic reconstitution:

1) Using a sterile syringe, slowly inject appropriate volume (as noted above) of sterile water for injection in the vial containing thelyophilized trastuzumab, directing the stream into the lyophilized cake.

2) Swirl the vial gently to aid reconstitution. DO NOT SHAKE!

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

Instructions for aseptic dilution of the reconstituted solution

Determine the volume of the solution required:

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

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

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

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

The appropriate amount of solution should be withdrawn from the vial using a sterile needle and syringe and added to an infusion bag containing 250 mL of 0.9 % sodium chloride solution. Do not use with glucose-containing solutions (see section 6.2). The bag should be gently inverted to mix the solution in order to avoid foaming.

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

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

No incompatibilities between trastuzumab and polyvinylchloride polyethylene or polypropylene bags have been observed. Infusion Bags used for administering the trastuzumab finished product should be DEHP free.

7. MARKETING AUTHORISATION HOLDER

CuraTeQ Biologics (Malta) Limited
Vault 14 Level 2,
Valletta Waterfront, Floriana,
FRN 1914, Malta

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1949/001
EU/1/25/1949/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization:
30 June 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the European Medicines Agency website: https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLEFOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLYAND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THEMARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINALPRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

CuraTeQ Biologics Private Limited,
Survey No. 77/78, Indrakaran Village, Kandi Mandal, SangaReddy District
Hyderabad - 502329,
India

Name and address of the manufacturer(s) responsible for batch release

APL Swift Services Malta Ltd. HF26, Hal Far Industrial Estate,
Qasam Industrijali Hal Far,
Birzebbugia, BBG 3000
Malta

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal products are subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The marketing authorization holder (MAH) shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result ofan important (pharmacovigilance or risk minimization) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Dazublys 150 mg powder for concentrate for solution for infusion
trastuzumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 150 mg trastuzumab. After reconstitution, 1 ml concentrate contains 21 mg of trastuzumab. To be reconstituted with 7.2 mL sterile water for injection.

3. LIST OF EXCIPIENTS

L-histidine hydrochloride monohydrate, L-histidine, polysorbate 20 (E 432), α,α-trehalose dihydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion.
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous infusion after reconstitution and dilution,
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze the reconstituted solution.
Keep the container in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused portion.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CuraTeQ Biologics (Malta) Limited
Vault 14 Level 2,
Valletta Waterfront, Floriana,
FRN 1914, Malta

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1949/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal products subject to medical prescription

15. INSTRUCTIONS ON USE

Do not shake after reconstitution.
For single use only.

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN

NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Dazublys 150 mg powder for concentrate
trastuzumab.

2. METHOD OF ADMINISTRATION

For intravenous use only

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Dazublys 420 mg powder for concentrate for solution for infusion
trastuzumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 420 mg trastuzumab. After reconstitution, 1 ml concentrate contains 21 mg of trastuzumab. To be reconstituted with 20 mL sterile water for injection.

3. LIST OF EXCIPIENTS

L-histidine hydrochloride monohydrate, L-histidine, polysorbate 20 (E 432), α,α-trehalose dihydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion.
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous infusion after reconstitution and dilution,
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze the reconstituted solution.

Keep the container in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused portion.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CuraTeQ Biologics (Malta) Limited
Vault 14 Level 2,
Valletta Waterfront, Floriana,
FRN 1914, Malta

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1949/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal products subject to medical prescription

15. INSTRUCTIONS ON USE

Do not shake after reconstitution.
For single use only.

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN

NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Dazublys 420 mg powder for concentrate
trastuzumab.

2. METHOD OF ADMINISTRATION

For intravenous use only

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Dazublys 150 mg powder for concentrate for solution for infusion
Dazublys 420 mg powder for concentrate for solution for infusion

trastuzumab

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

In this leaflet:

1. What is Dazublys, and what is it used for
2. What you need to know before you are given Dazublys
3. How Dazublys is given
4. Possible side effects
5. How to store Dazublys
6. Contents of the pack and other information

1. What is Dazublys, and what is it used for

Dazublys contains the active substance trastuzumab, which is a monoclonal antibody. Monoclonal antibodies attach to specific proteins or antigens. trastuzumab is designed to bind selectively to an antigen called human epidermal growth factor receptor 2 (HER2). HER2 is found in large amounts on the surface of some cancer cells, where it stimulates their growth. When trastuzumab binds to HER2, it stops the growth of such cells and causes them to die.

Your doctor may prescribe Dazublys for the treatment of breast and gastric cancer when:
- You have early breast cancer with high levels of a protein called HER2.
- You have metastatic breast cancer (breast cancer that has spread beyond the original tumor) with high levels of HER2. trastuzumab may be prescribed in combination with the chemotherapy medicine paclitaxel or docetaxel as the first treatment for metastatic breast cancer, or it may be prescribed alone if other treatments have proved unsuccessful. It is also used in combination with medicines called aromatase inhibitors in patients with high levels of HER2 and hormonereceptor-positive metastatic breast cancer (cancer that is sensitive to the presence of female sex hormones).
- You have metastatic gastric cancer with high levels of HER2 when it is in combination with the other cancer medicines, capecitabine or 5-fluorouracil and cisplatin.

2. What you need to know before you are given Dazublys

Do not use Dazublys if:

- you are allergic to trastuzumab, to murine (mouse) proteins, or to any of the other ingredients ofthis medicine (listed in section 6).
- you have severe breathing problems at rest due to your cancer or if you need oxygen treatment.

Warnings and precautions

Your doctor will closely supervise your therapy.

Heart checks

Treatment with Dazublys alone or with a taxane may affect the heart, especially if you have ever used an anthracycline (taxanes and anthracyclines are two other kinds of medicine used to treat cancer). The effects may be moderate to severe and could cause death. Therefore, your heart function will be checked before, during (every three months), and after (up to two to five years) treatment with Dazublys. If you develop any signs of heart failure (inadequate pumping of blood by the heart), your heart function may be checked more frequently (every six to eight weeks), you may receive treatment for heart failure, or you may have to stop Dazublys treatment.

Talk to your doctor, pharmacist, or nurse before you are given Dazublys if:

- you have had heart failure, coronary artery disease, heart valve disease (heart murmurs), high blood pressure, taking any high blood pressure medicine, or are currently taking any high blood pressure medicine.

- you have ever had or are currently using a medicine called doxorubicin or epirubicin (medicines used to treat cancer). These medicines (or any other anthracyclines) can damage heart muscle and increase the risk of heart problems with Dazublys.

- you suffer from breathlessness., especially if you are currently using a taxane. Dazublys can cause breathing difficulties, especially when it is first given. This could be more serious if you are already breathless. Very rarely, patients with severe breathing difficulties before treatment have died when they were given Dazublys.

- you have ever had any other treatment for cancer.

If you receive Dazublys with any other medicine to treat cancer, such as paclitaxel, docetaxel, an aromatase inhibitor, capecitabine, 5-fluorouracil, or cisplatin, you should also read the patient information leaflets for these products.

Children and adolescents

Dazublys is not recommended for anyone under the age of 18 years.

Other medicines and Dazublys

Tell your doctor, pharmacist, or nurse if you are taking, have recently taken, or may take any other medicines.

It may take up to 7 months for Dazublys to be removed from the body. Therefore, you should tell your doctor, pharmacist, or nurse that you have had Dazublys if you start any new medicine within seven monthsafter stopping treatment.

Pregnancy

- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist, or nurse for advice before taking this medicine.

- You should use effective contraception during treatment with Dazublys and for at leastseven months after treatment has ended.
- Your doctor will advise you of the risks and benefits of taking Dazublys during pregnancy. Inrare cases, a reduction in the amount of (amniotic) fluid that surrounds the developing baby within the womb has been observed in pregnant women receiving trastuzumab. This condition may be harmful to your baby in the womb and has been associated with the lungs not developing fully, resulting in fetal death.

Breast-feeding

Do not breastfeed your baby during Dazublys therapy and for seven months after the last dose of Dazublys, as this medication may pass to your baby through your breast milk. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Dazublys may affect your ability to drive a car or operate machines. If, during treatment, you experience symptoms such as dizziness, sleepiness, chills, or fever, you should not drive or use machines until these symptoms disappear.

Sodium

Dazublys contains less than 1 mmol of sodium (23 mg) per dose, that is to say essentially sodium-free.

Polysorbate 20

This medicine contains 0.6 mg or 1.7 mg of polysorbate 20 in each 150 mg/vial or 420 mg/vial which is equivalent to 0.6 mg/60 kg/7.4 mL or 1.7 mg/60 kg/20.8 mL, respectively. Polysorbates may cause allergic reactions.

3. How Dazublys is given

Before starting the treatment, your doctor will determine the amount of HER2 in your tumor. Only patients with a large amount of HER2 will be treated with Dazublys. Dazublys should only be given by a doctor or nurse. Your doctor will prescribe a dose and treatment regimen that is right for you. The dose of Dazublys depends on your body weight.

The first dose of your treatment is given over 90 minutes, and you will be observed by a health professional while it is being given in case you have any side effects. If the first dose is well tolerated, the next doses may be given over 30 minutes (see section 2 under “Warnings and precautions”). The number of infusions you receive will depend on how you respond to the treatment. Your doctor will discuss this with you.

Dazublys is given as an infusion into a vein (intravenous infusion, drip); this intravenous formulation is not for subcutaneous use and should be given as an intravenous infusion only.

In order to prevent medication errors, it is important to check the vial labels to ensure that the medicine is prepared and given is Dazublys (trastuzumab) and not another trastuzumab-containing product (e.g., trastuzumab emtansine or trastuzumab deruxtecan).

For early breast cancer, metastatic breast cancer, and metastatic gastric cancer, Dazublys is givenevery three weeks. Dazublys may also be given once a week for metastatic breast cancer.

If you stop using Dazublys

Do not stop using this medicine without talking to your doctor first. All doses should be taken at the

right time every week or every three weeks (depending on your dosing schedule). This helps your medicine work as well as it can.

It may take up to 7 months for Dazublys to be removed from your body. Therefore, your doctor may decide to continue to check your heart functions even after you finish treatment.

If you have any further questions about the use of this medicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

Like all medicines, trastuzumab can cause side effects, although not everybody gets them.
Some of these side effects may be serious and may lead to hospitalization.

During a Dazublys infusion, chills, fever, and other flu-like symptoms may occur. These are very common (may affect more than 1 in 10 people).
Other infusion-related symptoms are feeling sick(nausea), vomiting, pain, increased muscle tension and shaking, headache, dizziness, breathing difficulties, high or low blood pressure, heart rhythm disturbances (palpitations, heart fluttering, or irregular heartbeat), swelling of the face and lips, rash and feeling tired.
Some of these symptoms canbe serious, and some patients have died (see section 2 under “Warnings and precautions”).

These effects mainly occur with the first intravenous infusion (“drip” into your vein) and during the first few hours after the start of the infusion. They are usually temporary. You will be observed by a healthcare professional during the infusion and for at least six hours after the start of the first infusion and for two hours after the start of other infusions. If you develop a reaction, they will slow down or stop the infusion and may give you treatment to counteract the side effects. The infusion may be continued after the symptoms improve.

Occasionally, symptoms start later than six hours after the infusion begins. If this happens to you, contact your doctor immediately. Sometimes, symptoms may improve and then get worse later.

Serious side effects

Other side effects can occur at any time during treatment with Dazublys, not just related to an infusion.

Tell a doctor or nurse straight away if you notice any of the following side effects:

- Heart problems can sometimes occur during treatment and occasionally after treatment has stopped and can be serious. They include weakening of the heart muscle, possibly leading to heart failure, inflammation of the lining around the heart, and heart rhythm disturbances. This can lead tosymptoms such as breathlessness (including breathlessness at night), cough, fluid retention (swelling) in the legs or arms, and palpitations (heart fluttering or irregular heartbeat) (see section 2. Heart checks).

Your doctor will monitor your heart regularly during and after treatment, but you should tell your doctor immediately if you notice any of the above symptoms.

- Tumour lysis syndrome (a group of metabolic complications occurring after cancer treatment characterized by high blood levels of potassium and phosphate and low blood levels of calcium). Symptoms may include kidney problems (weakness, shortness of breath, fatigue, and confusion), heart problems (fluttering of the heart or a faster or slower heartbeat), seizures, vomiting or diarrhea, and tingling in the mouth, hands, or feet.

If you experience any of the above symptoms when your treatment with Dazublys has finished, you

should see your doctor and tell them that you have previously been treated with Dazublys.

Very common side effects of trastuzumab: may affect more than 1 in 10 people
- infections
- diarrhoea
- constipation
- heartburn (dyspepsia)
- fatigue
- skin rashes
- chest pain
- abdominal pain
- joint pain
- low counts of red blood cells and white blood cells (which help fight infection), sometimes with fever
- muscle pain
- conjunctivitis
- watery eyes
- nose bleeds
- runny nose
- hair loss
- tremor
- hot flush
- dizziness
- nail disorders
- weight loss
- loss of appetite
- inability to sleep (insomnia)
- altered taste
- low platelet count
- bruising
- numbness or tingling of the fingers and toes, which occasionally may extend to the rest of the limb
- redness, swelling, or sores in your mouth and/or throat
- pain, swelling, redness, or tingling of hands and/or feet
- breathlessness
- headache
- cough
- vomiting
- nausea

Common side effects of Trastuzumab: may affect up to 1 in 10 people
- allergic reactions
- throat infections
- bladder and skin infections
- inflammation of the breast
- inflammation of the liver
- kidney disorders
- increased muscle tone or tension(hypertonia)
- pain in the arms and/or legs
- itchy rash
- sleepiness (somnolence)
- haemorrhoids
- dry mouth and skin
- dry eyes
- sweating
- feeling weak and unwell
- anxiety
- depression
- asthma
- infection of the lungs
- lung disorders
- back pain
- neck pain
- bone pain

- itchiness
- acne
- leg cramps

Uncommon side effects of trastuzumab: may affect up to 1 in 100 people:
- deafness
- bumpy rash
- wheezing
- inflammation or scarring of the lungs

Rare side effects of trastuzumab: may affect up to 1 in 1000 people
- jaundice
- anaphylactic reactions

Other side effects that have been reported with trastuzumab use: frequency cannot be estimated from the available data
- abnormal or impaired blood clotting
- high potassium levels
- swelling or bleeding at the back of the eyes
- shock
- abnormal heart rhythm
- respiratory distress
- respiratory failure
- acute accumulation of fluid in the lungs
- acute narrowing of the airways
- abnormally low oxygen levels in the blood
- difficulty in breathing when lying flat
- liver damage
- swelling of the face, lips and throat
- kidney failure
- abnormally low levels of fluid around the baby in the womb
- failure of the lungs of the baby to develop in the womb
- abnormal development of the kidneys of the baby in the womb

Some of the side effects you experience may be due to your underlying cancer. If you receive Dazublys in combination with chemotherapy, some of them may also be due to the chemotherapy.

If you get any side effects, talk to your doctor, pharmacist, or nurse.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can provide more information on thesafety of this medicine.

5. How to store Dazublys

Dazublys will be stored by the health professionals at the hospital or clinic.

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiration date, which is stated on the outer carton and on the vial label after EXP. The expiry date refers to the last day of that month.
- The unopened vial should be stored in a refrigerator (2 °C – 8 °C).
- Do not freeze the reconstituted solution.

- Infusion solutions should be used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 48 hours at 2 °C – 8 °C.
- Keep the container in the outer carton in order to protect from light.
- Do not use Dazublys if you notice any particulate matter or discoloration prior to administration.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines that are no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Dazublys contains

- The active substance is trastuzumab. One vial contains either:
  - 150 mg trastuzumab that has to be dissolved in 7.2 mL of sterile water for injections, or 420 mg trastuzumab that has to be dissolved in 20 mL of sterile water for injections. The resulting solution contains approximately 21 mg/mL trastuzumab

- The other ingredient(s) are L-histidine hydrochloride monohydrate, L-histidine, α,α-trehalose dihydrate, and polysorbate 20 (E 432).

What trastuzumab looks like and the contents of the pack

trastuzumab is a powder for concentration solution for intravenous infusion, which is supplied in a glass vial with a rubber stopper containing 150 mg or 420 mg of trastuzumab. The powder is a white to paleyellow pellet. Each carton contains one vial of powder.

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Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for medical or healthcare professionals only

Dazublys intravenous is provided in sterile, preservative-free, non-pyrogenic, single use vials.
In order to prevent medication errors, it is important to check the vial labels to ensure that the medicinebeing prepared and given is Dazublys and not another trastuzumab-containing product (e.g. trastuzumab emtansine or trastuzumab deruxtecan).

Always keep this medicine in the closed original pack at a temperature of 2 ºC – 8 ºC in a refrigerator.

Appropriate aseptic technique should be used for reconstitution and dilution procedures. Care must be taken to ensure the sterility of prepared solutions. Since the medicinal product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed.

A vial of Dazublys aseptically reconstituted with sterile water for injections (not supplied) is chemically and physically stable for 48 hours at 2 ºC – 8 ºC after reconstitution and must not be frozen.

After aseptic dilution in polyvinylchloride polyethylene or polypropylene bags containing sodium chloride 9 mg/mL (0.9%) solution for injection, chemical and physical stability of Dazublys has been demonstrated for up to 48 hours at 5 °C ± 3 °C and 30 °C ± 2 °C.

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

Aseptic preparation, handling, and storage:

Aseptic handling must be ensured when preparing the infusion. Preparation should be:
- performed under aseptic conditions by trained personnel in accordance with good practice rules especially with respect to the aseptic preparation of parenteral products.
- prepared in a laminar flow hood or biological safety cabinet using standard precautions for thesafe handling of intravenous agents.
- followed by adequate storage of the prepared solution for intravenous infusion to ensure maintenance of the aseptic conditions.

Dazublys 150 mg powder for concentrate for solution for infusion.

Each 150 mg vial of Dazublys is reconstituted with 7.2 mL of water for injections (not supplied). Use of other reconstitution solvents should be avoided. This yields a 7.4 mL solution for single-dose use, containing approximately 21 mg/mL trastuzumab. A volume overage of 4 % ensures that the labelled dose of 150 mg can be withdrawn from each vial.

Dazublys 420 mg powder for concentrate for solution for infusion.

Each 420 mg vial of Dazublys is reconstituted with 20 mL of water for injections (not supplied). Use of other reconstitution solvents should be avoided. This yields a 20.8 mL solution for single-dose use, containing approximately 21 mg/mL trastuzumab. A volume overage of 4 % ensures that the labelled dose of 420 mg can be withdrawn from each vial.

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

Instructions for reconstitution:

1) Using a sterile syringe, slowly inject appropriate volume (as noted above)of water for injections in the vial containing the lyophilized Dazublys, directing the stream into the lyophilized cake.
2) Swirl vial gently to aid reconstitution. DO NOT SHAKE!

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

Determine the volume of the solution required:

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

Volume (mL) = **Body weight** (kg) x **dose** (**4** mg/kg for loading or **2** mg/kg for maintenance)
21 (mg/mL, concentration of reconstituted solution)

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

Volume (mL) = **Body weight** (kg) x **dose** (**8** mg/kg for loading or **6** mg/kg for maintenance)
21 (mg/mL, concentration of reconstituted solution)

The appropriate amount of solution should be withdrawn from the vial using a sterile needle and syringe and added to a polyvinylchloride polyethylene or polypropylene bags containing 250 mL of 0.9% sodium chloride solution. Do not use with glucose-containing solutions. The bag should be gently inverted to mix the solution to avoid foaming. Parenteral solutions should beinspected visually for particulates and discoloration prior to administration. Once the infusion is prepared it should be administered immediately. If diluted aseptically, it may be stored for 48 hours at 5 °C ± 3 °C and 30 °C ± 2 °C.