TRAZIMERA

Trastuzumab

150 mg powder for concentrate for solution for infusion
440 mg powder for concentrate for solution for infusion

Reference market: Switzerland

AfME markets using the same Label: Saudi Arabia

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Trazimera 150 mg powder for concentrate for solution for infusion
Trazimera 440 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient
Trastuzumab (genetically engineered using CHO [Chinese hamster ovary] cells).

1 vial of Trazimera contains:
white powder for concentrate for solution for infusion, 150 mg trastuzumab.
Reconstituted Trazimera concentrate (water for injection not included) contains 21 mg/ml trastuzumab.

1 vial of Trazimera contains:
white powder for concentrate for solution for infusion, 440 mg trastuzumab.
Reconstituted Trazimera concentrate (water for injection not included) contains 21 mg/ml trastuzumab.

Excipients with known effect:
L-histidine hydrochloride monohydrate, L-histidine, sucrose, polysorbate 20.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White powder for concentrate for solution for infusion.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Breast cancer
Before beginning treatment with Trazimera, the overexpression of HER2 must have been demonstrated in the patient's tumour tissue immunohistochemically with 3+ or using molecular biological methods [determination of HER2 gene amplification by fluorescence in-situ hybridisation (FISH) or chromogenic in-situ hybridisation (CISH)].

Metastatic breast cancer
Trazimera is indicated for the treatment of patients with metastatic breast cancer when the tumours overexpress HER2:

a. as monotherapy for the treatment of patients who have received at least one or more chemotherapy regimens for their metastatic disease.
b. in combination with paclitaxel or docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.
c. in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone receptor positive metastatic breast cancer, not previously treated for their metastatic disease.

No data are available on patients with breast cancer who received trastuzumab as an adjuvant treatment in the early stage.

Early-stage breast cancer
Trazimera is indicated for the treatment of adult patients with HER2 positive early-stage breast cancer

- following surgery, chemotherapy (neoadjuvant or adjuvant) and (if applicable) radiation therapy.

- 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 trastuzumab therapy, for locally advanced (including inflammatory) disease or tumours >2 cm in diameter.

Metastatic gastric cancer or gastro-oesophageal junction cancer
Trazimera in combination with capecitabine or intravenous 5-fluorouracil and cisplatin is indicated for the treatment of patients with HER2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received chemotherapy for their metastatic disease. Trazimera should only be used in patients with metastatic gastric cancer whose tumours overexpress HER2 defined by IHC2+ and confirmed by a positive FISH+ or silver in-situ hybridisation result (SISH), or IHC3+ determined by a validated assay.

4.2. Posology and method of administration

Posology
Trazimera treatment should only be initiated by a doctor experienced in the treatment of cancer patients. A validated HER2 test is obligatory prior to initiation of therapy (see Pharmacological Properties).
In order to avoid medication errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Trazimera (trastuzumab) and not a medicinal product with the active ingredient trastuzumab emtansine.
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Metastatic breast cancer - weekly treatment regimen
Trazimera should be administered by intravenous infusion. Do not administer by intravenous bolus injection.
The following initial and subsequent doses are recommended for monotherapy and for the combination with chemotherapy:

Monotherapy

Initial dose
The recommended initial dose of Trazimera is 4 mg/kg body weight and should be given as an intravenous infusion over a period of 90 minutes.

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

Combination therapy with paclitaxel or docetaxel
Dosage of Trazimera in combination therapy is equivalent to that of monotherapy. Paclitaxel or docetaxel is administered on the day following the first treatment dose with Trazimera. Subsequently, paclitaxel or docetaxel can be administered every 3 weeks immediately after the following Trazimera doses, if the preceding administration of Trazimera has been well tolerated. For the dosage of paclitaxel or docetaxel, see the relevant Information for Healthcare Professionals.

Combination therapy with an aromatase inhibitor
Dosage of Trazimera in combination therapy is equivalent to that of monotherapy. In the marketing authorisation study, trastuzumab and anastrozole were administered on the first day. There were no restrictions on relative timing when the two were administered concomitantly. For the dosage of anastrozole, see the relevant Information for Healthcare Professionals. If the patient receives tamoxifen, this should be discontinued at least one day before initiation of combination therapy.

Metastatic breast cancer - three-weekly treatment schedule
Monotherapy and combination therapy

As an alternative to weekly administration, the following three-weekly regimen is recommended in monotherapy and in combination with paclitaxel, docetaxel or an aromatase inhibitor.
The initial dose of Trazimera is 8 mg/kg body weight followed by 6 mg/kg body weight 3 weeks later. The subsequent Trazimera doses of 6 mg/kg body weight are repeated at 3-week intervals. Administration takes place by infusion for about 90 minutes. If the initial dose is well tolerated, the maintenance dose can be administered as a 30-minute infusion.

Early-stage breast cancer
For the following treatment regimens, Trazimera is administered until recurrence or for a total of 52 weeks.

Weekly administration
For weekly administration, the initial dose is 4 mg/kg body weight, followed by 2 mg/kg body weight each week.

Three-weekly administration
For three-weekly use, the recommended initial dose of Trazimera is 8 mg/kg body weight. The recommended dose of Trazimera at 3-week intervals is 6 mg/kg body weight, initiated 3 weeks after the initial dose.

If Trazimera is continued following a combination with chemotherapy alone, 6 mg/kg body weight is administered at 3-week intervals.
How trastuzumab was investigated in combination with chemotherapy is discussed in the "Properties/Effects" section clinical studies on early-stage breast cancer.

Advanced gastric cancer or gastro-oesophageal junction cancer - *three-week treatment regimen*
The initial dose is 8 mg/kg body weight followed by 6 mg/kg body weight 3 weeks later. The subsequent Trazimera doses of 6 mg/kg body weight are repeated at 3-week intervals. Administration takes place by infusion for approx. 90 minutes. If the initial dose is well tolerated, the maintenance dose can be administered as a 30-minute infusion.

Duration of treatment
Patients with metastatic breast cancer or advanced gastric cancer and gastro-oesophageal junction cancer should be treated with Trazimera until disease progression or until the occurrence of uncontrollable toxicity.
Patients with early-stage breast cancer should be treated for 1 year or until the disease reappears or until the occurrence of uncontrollable toxicity, whichever occurs first. Treatment of early-stage breast cancer is not recommended for a duration of more than one year (see section Pharmacological Properties).

Dose adjustment following undesirable effects

If the patient develops an infusion associated reaction (IAR), the rate of infusion of Trazimera should be slowed down or the infusion should be discontinued and the patient should be monitored until all observed symptoms have subsided (see Special warnings and precautions for use).

No dose reduction for trastuzumab has occurred in clinical trials. In phases of reversible, chemotherapy-induced myelosuppression, treatment with Trazimera can be continued, but patients should be carefully monitored for complications due to neutropenia during this time. The special instructions for dose reduction or interval prolongation for chemotherapy must be observed.

If the left ventricular ejection fraction (LVEF) falls by ³10 percentage points below the baseline level or below 50%, the treatment should be suspended and a new LVEF measurement should be made within around 3 weeks. If the LVEF does not improve, falls further or symptomatic congestive heart failure (CHF) develops, the discontinuation of treatment with Trazimera should be seriously considered unless it is assumed that the benefit to the individual patient outweighs the risk. These patients should be referred to a cardiologist for examination and should continue to be monitored.

Special dosage instructions

Elderly patients
Based on the data it is assumed that the availability of trastuzumab in not age-dependent (see "Pharmacokinetics in special patient groups").
In clinical trials, patients ≥65 years did not receive reduced doses of trastuzumab.

*Children and adolescents*The use and safety of trastuzumabin children and adolescents <18 years has not yet been investigated.

Missed dose
If the patient has missed a Trazimera dose within a period of one week at the most, the usual maintenance dose (weekly treatment regimen: 2 mg/kg body weight; three-weekly treatment regimen: 6 mg/kg body weight) should be administered as soon as possible (do not wait until the next scheduled cycle). Subsequent Trazimera maintenance doses should be administered 7 or 21 days later, in accordance with either the weekly or three-week treatment regimen.

If the patient has missed a Trazimera dose for a period of more than one week, an initial dose of Trazimera over 90 minutes should be administered again as soon as possible (weekly therapy regimen: 4 mg/kg body weight; three-weekly treatment regimen: 8 mg/kg body weight). Subsequent Trazimera maintenance doses (weekly treatment regimen: 2 mg/kg body weight; three-week treatment schedule: 6 mg/kg body weight) should be administered 7 or 21 days later, in accordance with the weekly or three-week treatment schedule.

4.3. Contraindications

Trazimera is contraindicated in patients with a known hypersensitivity to trastuzumab, hamster (CHO) cell protein or any of the excipients of the medicinal product or solvent.
In metastatic breast cancer and in adjuvant treatment, Trazimera and anthracyclines should not be administered concomitantly. In neoadjuvant treatment, the concomitant administration of Trazimera and anthracyclines must be applied with caution, and only in chemotherapy-naive patients.
Trazimera is contraindicated in patients who suffer from resting dyspnoea due to their advanced malignant disease or comorbidities.

4.4. Special warnings and precautions for use

The sterile water for injection used to reconstitute the Trazimera vials for single dosing.
Infusion associated reactions
Infusion associated reactions, some of which were severe, were observed in patients treated with Trazimera (typical symptoms e.g. dyspnoea, hypotension, nausea, fever, bronchial spasm, tachycardia, reduced oxygen saturation, urticaria and exanthema). These undesirable effects may occur as a result of an infusion associated reaction or as a delayed reaction. To reduce the risk of infusion associated reactions, pre-medication may be administered.
Patients should be monitored for infusion associated reactions. Interrupting the infusion may help to control these symptoms. The infusion can be resumed once the symptoms subside. These symptoms may be treated with an analgesic/antipyretic agent such as pethidine or paracetamol or an antihistamine such as diphenhydramine. Serious reactions have been successfully treated with symptomatic therapy, such as administration of oxygen, beta agonists and corticoids. In rare cases, these reactions are associated with a clinical course that may have a fatal outcome. Patients suffering from resting dyspnoea due to their advanced malignant disease or comorbidities may be at increased risk of fatal reactions to the infusion. Therefore, these patients should not be treated with Trazimera (see "Contraindications").
Infusion associated reactions may be difficult to clinically distinguish from hypersensitivity reactions.

Cardiotoxicity
General information
Patients treated with Trazimera are at increased risk of NYHA Class II-IV congestive heart failure or asymptomatic cardiac dysfunction. This has been observed with trastuzumab monotherapy and in combination with taxanes after anthracycline (doxorubicin, epirubicin) therapy. Cardiac failure may be moderate to severe and lead to death (see "Undesirable effects"). Patients with elevated cardiac risk (e.g.

hypertension, coronary heart disease, congestive heart failure, diastolic dysfunction, increased age) should be treated with caution.

In metastatic breast cancer and in adjuvant treatment, Trazimera and anthracyclines should not be administered concomitantly. For neoadjuvant treatment, concomitant administration of Trazimera and anthracyclines must take place with caution, and only in chemotherapy-naive patients (see "Contraindications"). The maximum cumulative dose of low-dose anthracycline therapy should not exceed 180 mg/m^2 (doxorubicin) or 360 mg/m^2 (epirubicin). Patients who have been treated with neoadjuvant therapy with low doses of anthracyclines in combination with Trazimera should not be administered additional cytotoxic chemotherapy after surgery. Clinical experience with neoadjuvant-adjuvant therapy in patients over 65 years is limited.

Most symptomatic cardiac adverse effects occurred within the first 18 months, irrespective of the regimen used. Cumulative incidence did not increase after 3 years. The majority of cases of left ventricular dysfunction improved after discontinuation of trastuzumabtherapy and/or initiation of cardiac drug therapy.

Population pharmacokinetic model simulations suggest that trastuzumab may still be present in the bloodstream for up to 7 months after discontinuation of treatment with intravenously or subcutaneously administered trastuzumab (see "Pharmacokinetics"). Patients who receive anthracycline after discontinuation of Trazimera are also likely to be at increased risk of cardiotoxicity.

If possible, anthracycline therapy should be avoided for up to 7 months after discontinuation of Trazimera.
Before treatment with Trazimera, especially in patients previously treated with anthracycline, heart function should be monitored, including medical history and physical examination as well as ECG, echocardiogram and/or MUGA scan. For the early detection of cardiac dysfunction, patients should also continue to undergo heart function monitoring every 3 months during treatment, and after discontinuation of treatment every 6 to 24 months after the final administration of Trazimera. Patients receiving chemotherapy containing anthracycline should continue to be monitored yearly for up to 5 years after the final administration of Trazimera, or longer if a continuous reduction of LVEF is observed.

If LVEF decreases by 10 or more percentage points or drops below 50% compared to baseline, administration of Trazimera should be discontinued temporarily and a repeated LVEF measurement should be made within approximately 3 weeks. If LVEF has not improved in the meantime, or if clinically significant cardiac failure has developed, discontinuation of Trazimera should be urgently considered unless in individual cases the benefit is assessed to outweigh the risks. Patients who develop asymptomatic cardiac dysfunction should be monitored more frequently (e.g. every 6-8 weeks). If patients show a persistent drop in left ventricular function but remain asymptomatic, the doctor should consider discontinuing treatment unless the benefit to the patient in question is regarded as being greater than the risks. These patients should be referred to a cardiologist for examination and should continue to be monitored.
The safety of continuing or resuming trastuzumabin patients with cardiac dysfunction has not been prospectively investigated. If symptomatic cardiac failure occurs during Trazimera treatment, it should be treated with the standard medication for cardiac failure. In the pivotal studies, the condition of most patients who developed cardiac failure or asymptomatic cardiac dysfunction improved under therapy with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and beta blockers.

Adjuvant and neoadjuvant treatment
Patients with a history of myocardial infarction, angina pectoris requiring medication, with a prior history of or with existing congestive heart failure (NYHA Class II-IV), other cardiomyopathies, cardiac arrhythmias requiring medication, clinically significant cardiac valve disease, inadequately controlled hypertension (apart from hypertension controlled with standard medication) and pericardial effusion with an effect on haemodynamic parameters were excluded from adjuvant breast cancer studies with trastuzumab.

In patients with early-stage breast cancer, an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when trastuzumab was administered after anthracycline-containing chemotherapy versus a non-anthracycline-containing treatment such as docetaxel or carboplatin. The incidence was greater when trastuzumab was administered concomitantly with taxanes than when administered sequentially after taxanes. Regardless of the treatment regimen used, most symptomatic cardiac side effects occurred within the first 18 months.

The risk factors for cardiac side effects were advanced age (>50 years), a low baseline value and decreasing LVEF (<55%), a low LVEF before or after initiating treatment with paclitaxel, trastuzumab treatment and previous or concomitant use of antihypertensive medicinal products. In patients receiving trastuzumab after discontinuing adjuvant chemotherapy, the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracyclines administered prior to initiating trastuzumab treatment and a higher body mass index (BMI>25 kg/m^2).

Pulmonary reactions
Serious undesirable effects on the lungs during treatment with trastuzumab have been reported in the post-marketing phase (see "Undesirable effects"). These cases occasionally had a fatal outcome and may occur as part of an infusion associated reaction or as a delayed reaction. In addition, interstitial pulmonary disease including lung infiltration, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported.

Risk factors associated with interstitial pulmonary disease include other, previously or concomitantly performed anti-neoplastic therapies that are known to be associated with interstitial pulmonary disease, such as taxanes, gemcitabine, vinorelbine and radiation therapy. Patients who suffer from resting dyspnoea due to complications of advanced malignant disease and comorbidities may have an increased risk of pulmonary events. Therefore, these patients should not be treated with Trazimera.

4.5. Interaction with other medicinal products and other forms of interaction

Pharmacokinetic/pharmacodynamic interactions
No formal interaction studies with trastuzumab have been performed in humans. Clinically relevant interactions between trastuzumab and the accompanying medicinal products used in clinical trials have not been observed.

Pharmacokinetic interactions

In vivo data

In studies where trastuzumab was administered in therapeutic doses in combination with docetaxel, carboplatin or anastrozole, neither the pharmacokinetics of these medicinal products nor those of trastuzumab were altered.

The concentrations of paclitaxel and doxorubicin [as well as their main metabolites 6-α-hydroxyl paclitaxel (POH) and doxorubicinol (DOL)] were unchanged in the presence of trastuzumab. However, trastuzumab may increase the total exposure to one doxorubicin metabolite [7-deoxy-13-dihydro-doxorubicinone (D7D)]. The bioactivity of D7D and the clinical effect of increasing this metabolite are uncertain. No changes in trastuzumab concentrations were observed in the presence of paclitaxel and doxorubicin.

The results of a drug interaction substudy to assess the pharmacokinetics of capecitabine and cisplatin when administered with or without trastuzumab suggest that exposure to the bioactive metabolites (e.g. 5-FU) of capecitabine was not influenced by concomitant administration of cisplatin and cisplatin plus trastuzumab, respectively. However, capecitabine itself showed higher concentrations and a longer half-life in combination with trastuzumab. The data also suggest that the pharmacokinetics of cisplatin were not influenced by concomitant administration of capecitabine or capecitabine plus trastuzumab.

4.6. Fertility, pregnancy and breast-feeding

Pregnancy

Women of childbearing age

Women of childbearing age should use effective contraception during treatment with Trazimera and for 7 months after completion of the treatment (see "Pharmacokinetics").

The medicinal product has harmful pharmacological effects on the pregnancy and/or the foetus/neonate.

Trazimera should not be used during pregnancy, unless absolutely necessary, i.e. the potential benefit to the mother outweighs the potential risk to the foetus.
In the post-marketing setting, cases of foetal renal growth (e.g. renal hypoplasia) and/or function impairment associated with oligohydramnios, including some with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving trastuzumab. Women who become pregnant should be advised of the possibility of harm to the foetus. If a pregnant woman is treated with Trazimera, or if a patient becomes pregnant during treatment with Trazimera or within 7 months after the last dose of Trazimera, close monitoring by a multidisciplinary team is indicated.

Breast-feeding

In a study in which cynomolgus monkeys received doses from day 120 to 150 of their gestation that corresponded to 25 times the weekly maintenance dose of trastuzumab i.v. of 2 mg/kg in humans, showed that trastuzumab is secreted postpartum in breast milk. The trastuzumab exposition in utero and the presence of trastuzumab in the serum of breast-fed infant monkeys was not associated with undesirable effects on their growth or development from the time of birth to the age of one month. It is not known whether trastuzumab is secreted in human milk. However, since human IgG is secreted from the serum to the mother's milk and the risk potential for the infant is not known, breast-feeding should not take place during therapy with Trazimera.

Fertility

It is not known whether Trazimera can affect reproductive ability when administered to pregnant women.
Reproduction studies were performed on cynomolgus monkeys with dosages up to 25 times the weekly maintenance dose of trastuzumab in humans of 2 mg/kg body weight. Trastuzumab was shown to cross the placenta in the early (gestation day 20 to 50) and the late (gestation day 120-to 150) stage of foetal development. However, the studies did not reveal any harm to foetuses or impairment of fertility.

4.7. Effects on ability to drive and use machines

Trastuzumab has low influence on the ability to drive and the capability to use machines. During treatment with trastuzumab dizziness or sleepiness may occur (see section «Undesirable effects»). Patients with infusion associated symptoms (see section “Warnings and precautions”) should be advised not to drive or use machines until the symptoms disappeared completely.

4.8. Undesirable effects

Summary of safety profile:

The most serious and/or most frequently reported undesirable effects in treatment with trastuzumab are cardiotoxicity, infusion reactions, haematotoxicity (mainly neutropenia), infections and pulmonary adverse events.
NYHA Class II-IV cardiotoxicity (cardiac failure) is a common undesirable effect associated with treatment with trastuzumab and may have a fatal outcome (see "Warnings and precautions").

An estimated 49-54% (MBC) and 18-54% (EBC) of patients treated with trastuzumab will experience infusion-related reactions of some kind. However, most of these infusion-related undesirable effects are mild to moderate (according to NCI-CTC criteria) and occur mainly in the first few treatments, especially during the first three infusions, with frequency decreasing in the following infusions.

Reactions include chills, fever, nausea, urticaria, exanthema, dyspnoea, bronchial spasm, tachycardia and hypotension (see "Warnings and precautions").
Severe anaphylactic reactions requiring immediate additional intervention occur very rarely and when they do, are normally encountered during the first or second infusion of trastuzumab (see "Warnings and precautions").

Leucopenia, febrile neutropenia anaemia and thrombocytopaenia occur very commonly. Frequently occurring adverse events include neutropenia. The frequency with which hypoprothrombinaemia occurs is not known.
Serious pulmonary undesirable effects associated with trastuzumab are rare, but have occasionally been associated with a fatal outcome. These include lung infiltration, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency (see "Warnings and precautions").

List of undesirable effects
Frequency categories are listed based on MedDRA terminology: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 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).

Undesirable effects and undesirable events which have been reported with the use of intravenous trastuzumab alone or in combination with chemotherapy in marketing authorisation clinical studies and after post-marketing are listed below.
The frequency information relates to the maximum percentage frequencies of undesirable effects which have been observed in marketing authorisation clinical studies.

Table of Adverse Drug Events Reported During Clinical or Postmarketing Experience

System organ class	**Very common (≥ 1/10)**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Rare**	**Very rare**	**Not Known**
Infections and infestations	Infection (24%) , Nasopharyngitis (17%)	Cystitis, influenza, pharyngitis, skin infections sinusitis, , rhinitis, upper respiratory tract infection, urinary tract infection, neutropenic sepsis				Meningitis, bronchitis *Neoplasms benign, malignant, and unspecified (incl. cysts and polyps).* Progressive malignant neoplasia, progressive neoplasia
Blood and lymphatic system disorders	Neutropenia (47%), Anaemia (28%), thrombocytopenia (16%), febrile neutropenia (23%), leukopenia (15%)			Severe immune thrombocytopaenia with bleeding have been observed which may occur within a few hours after the infusion		Hypoprothrombinaemia, leukaemia, immune thrombocytopaenia
Immune system disorders		Hypersensitivity		Anaphylactic reaction, anaphylactic shock		
Metabolic and nutrition disorders	Anorexia (46%), Weight increase (15%), weight decreased					Hyperkalaemia, tumour lysis syndrome

System organ class	Very common (≥ 1/10)	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare	Very rare	Not Known
	(23%), appetite decreased (20%)					
Psychiatric disorders	Insomnia (11%)	Anxiety, depression				Lethargy, paraneoplastic cerebellar degeneration
Nervous system disorders	Paraesthesia (50%), headache (25%), lightheadedness (21%), dysgeusia (19%), hypoaesthesia 11%), tremor	Taste reduction, hypertonia (muscule hypertonia), peripheral neuropathy, giddiness, sleepiness				Lethargy, coma, cerebrovascular disorders
Eye disorders	Conjunctivitis (38%), lacrimation increased (21%),	Dry eye.				Papillary oedema, retinal haemorrhage, madarosis
Ear and labyrinth disorders			Deafness			
*Cardiac disorders**	Ejection fraction decreased (11%), $cardiac flutter , $heartbeats irregular (10%)	$Supraventricular tachyarrhythmia, (congestive) heart failure, cardiomyopathy, $palpitations	Pericardial effusion			Cardiogenic shock, gallop rhythm present, tachycardia
Vascular disorders	Hot flushes (17%), lymphoedema (11%)	$Hypotension, $hypertension, vasodilatation				
Respiratory, thoracic and mediastinal disorders	Epistaxis (18%), , rhinorrhoea (18%), cough (16%), oropharyngeal pain (15%), dyspnoea (14%),	Asthma, pulmonary disease, pleural effusion, pneumonia	Pneumonitis, $wheezing			Interstitial pulmonary disease including lung infiltration, pulmonary fibrosis, respiratory insufficiency, respiratory arrest, acute pulmonary oedema, acute respiratory distress, bronchospasm, laryngeal oedema, orthopnoea, exertional dyspnoea, hiccups, acute respiratory distress syndrome, respiratory distress syndrome, oxygen saturation decreased, hypoxia, Cheyne-Stokes respiration
Gastrointestinal disorders	Nausea (78%), diarrhoea (50%), vomiting (50%),	Dry mouth, haemorrhoids	Pancreatitis			Gastritis

System organ class	Very common (≥ 1/10)	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare	Very rare	Not Known
	stomatitis (40%), constipation (27%), abdominal pains (20%), , dyspepsia (14%), $lip swelling , , ,					
Hepatobiliary disorders		Hepatitis, liver sensitivity, liver cell damage		Jaundice		
Skin and subcutaneous tissue disorders	Alopecia (94%), palmar-plantar erythrodyaesthesia (26%), erythema (23%), rash (24%), , nail toxicity (11%), nail disorders (17%), $face oedema	Acne, dry skin, subcutaneous bleeding, hyperhidrosis, maculopapular rash, pruritus, onychoclasis, dermatitis	Urticaria			Angioedema, onychorrhexis, Stevens Johnson syndrome
Musculoskeletal and connective tissue disorders	Arthralgia (28%), $muscle tightness, myalgia (35%)	Arthritis, back pain, bone pain, muscle cramps, neck pain, pain in limb, musculoskeletal pain				
Renal and urinary disorders		Renal disorder				Membranous glomerulonephritis, glomerulonephropathy, renal failure, dysuria
Reproductive system and breast disorders		Breast inflammation/mastitis, breast pain				
General disorders and administration site conditions	Asthenia (51%), chest pain (11%), chills (15%), fatigue (53%), influenza-like illness (23%), infusion associated reactions (74%), pain (12%), fever (12%), peripheral oedema (17%), mucosal inflammation (23%).	Malaise, oedema				

$ Means that the incidence shown is the total incidence of several terms. Percentages are not available for individual undesirable effects.

Undesirable effects after market launch
In the post-marketing setting, rare cases of severe immune thrombocytopaenia with hemorrhage have been observed which may occur within a few hours after the infusion.

Description of selected undesirable effects

Immunogenicity
In a neoadjuvant/adjuvant study (B022227), antibodies to trastuzumab were detected during follow-up with a median duration of more than 70 months in 10.1% (30/296) of patients (treatment-related antibodies as well as antibodies occurring more frequently as a result of treatment). In 2 out of 30 trastuzumab patients, neutralising antibodies were found in samples taken from the beginning of the study. The clinical relevance of these antibodies is not known. However, pharmacokinetics, efficacy [determined by pathological complete response (pCR)] or safety [determined by the frequency of infusion associated reactions] of trastuzumab did not appear to be adversely affected by these antibodies to trastuzumab.

** Cardiological long-term follow-up period in early-stage breast cancer.*
After one year of treatment with trastuzumab and a median follow-up period of 8 years, in study BO16348, the frequency of severe chronic heart failure (NYHA class III & IV) was 0.8%, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6%.
The reversibility of severe chronic heart failure (defined as the result of at least two consecutive left ventricular ejection fractions with values ≥50% after the event) was apparent for 71.4% of the affected patients. Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated in 79.5% of affected patients. Approximately 17% of events caused by cardiac dysfunction occurred after discontinuing treatment with trastuzumab.
In the joint evaluation of studies NSABP B-31 and NCCTG N9831 with a median follow-up period duration of 8.1 years, the patient-associated frequency of newly occurring cardiac dysfunction, measured using LVEF, remained unchanged in the AC→PH group (doxorubicin plus cyclophosphamide, followed by paclitaxel plus trastuzumab) compared to the evaluation performed in the AC→PH group after a median follow-up period of 2.0 years: a ≥10% reduction in LVEF to under 50% was observed in 18.5% of AC→PH patients. Reversibility of left ventricular dysfunction was observed in 64.5% of patients in the AC → PH group who had symptomatic congestive heart failure and were asymptomatic at the last follow-up examination, and in 90.3% of patients who exhibited complete or partial LVEF recovery.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after market 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 pharmacovigilance centre (NPC) reporting system.

To report any side effect(s):

- **Saudi Arabia**

National Pharmacovigilance Centre (NPC)
- Call center: 19999
- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa/

- **Other GCC States**

- Please contact the relevant competent authority.

4.9. Overdose

Clinical trials have shown no experience of overdose in humans. Individual doses of more than 10 mg/kg body weight have not been tested.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC code: L01FD01
Trazimera is a trastuzumab biosimilar. Biosimilarity to the trastuzumab reference product has been shown in comparability studies regarding pharmaceutical quality, biological activity, pharmacokinetics, efficacy and safety.

Mechanism of action

Trastuzumab is a recombinant humanised monoclonal IgG_1 kappa antibody produced in CHO (Chinese Hamster Ovary) cells with murine hypervariable regions of the variable region. The antibody specifically binds to the extracellular domain of human epidermal growth factor receptor 2 (HER2).
The HER2 proto-oncogene (or c-erbB2) codes for a receptor-like transmembranous single-stranded protein 185 kDa in size, structurally related to the epidermal growth factor receptor. Overexpression of HER2 is observed in 15% to 20% of all primary breast cancers. The overall rate of HER2 positivity in advanced gastric cancer in relation to IHC3+ or IHC2+/FISH+ observed during the screening for study BO18255 is 15%. When a broader definition for IHC3+ or FISH+ for HER2 positivity is used, the rate is 22.1%. HER2 protein amplification on the cell surface of these tumour cells, which is associated with a strong activation of the HER2 protein, increases with HER2 gene amplification.

As studies show, breast cancer patients with tumours that overexpress HER2 have a shorter disease-free survival time than patients without HER2-overexpressing tumours.
It has been shown both in vitro and in animals that trastuzumab inhibits the proliferation of human tumour cells that overexpress HER2. Trastuzumab is a mediator for antibody-dependent cell-mediated cytotoxicity (ADCC). In vitro data show trastuzumab-mediated ADCC, preferably on HER2-overexpressing cancer cells.

Detection of HER2 overexpression or HER2 gene amplification in breast cancer
Trazimera should only be used to treat patients whose tumours have HER2 overexpression or HER2 gene amplification. HER2 overexpression should be diagnosed by an immunohistochemical assay (IHC) of fixed tumour blocks (see "Dosage Administration"). HER2 gene amplification should be demonstrated by fluorescence in-situ hybridisation (FISH) or chromogenic in-situ hybridisation (CISH) of fixed tumour blocks. Patients are eligible for therapy with Trazimera if they have strong HER2 overexpression as described under the 3+ classification for IHC or a positive FISH or CISH result.

In order to obtain accurate and reproducible results, testing must be conducted in specialised laboratories that can ensure validation of the test methods.

The following rating system is recommended for the assessment of IHC staining patterns:

Classification of staining intensity	*Staining pattern*	*Assessment of HER2 overexpression*
0	No staining or membrane staining is observed in <10% of the tumour cells	Negative
1+	Weak/barely perceptible membrane staining is observed in >10% of the tumour cells. The cells are stained only on parts of their membrane.	Negative
2+	Weak to moderate staining of the entire membrane can be observed in >10% of the tumour cells.	Equivocal
3+	Moderate to strong complete membrane staining is observed in >10% of the tumour cells.	Positive

The result of the FISH test is generally classified as positive if the ratio between the number of HER2 gene copies per tumour cell and the number of copies of chromosome 17 is greater than or equal to 2, or if chromosome 17 is not carried as a control - if more than 4 copies of the HER2 gene are present per tumour cell.

The result of the CISH test is generally classified as positive if over 50% of the tumour cells have more than 5 copies of the HER2 gene per cell nucleus.
For complete information on the performance and interpretation of these tests, see the package brochures of validated FISH and CISH assays.

Detection of HER2 overexpress*ion or HER2 gene amplification in metastatic* gastric cancer *or* gastro-oesophageal junction cancer
Only a reliable and validated test may be used to determine HER2 overexpression or HER2 gene amplification. IHC is recommended as the first test modality. In cases where an additional HER2 gene amplification status is required, either a silver in-situ hybridisation (SISH) or FISH method must be used. In order to obtain accurate and reproducible results, testing must be conducted in specialised laboratories that can ensure validation of the test methods. For complete information on the performance and interpretation of these tests, see the product information for validated FISH and SISH assays.

In the ToGA study, patients with either IHC3+ or FISH-positive tumours were defined as HER2 positive and included in the study. Based on the clinical trial results, the positive effects were limited to patients with the highest HER2 protein overexpression levels, defined by IHC3+ or IHC2+ and a positive FISH score.

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

Trazimera should only be used in patients whose tumour has a strong HER2 overexpression, i.e., IHC3+ or IHC2+ plus a positive FISH or SISH result.
The amplification of the HER2 gene can be detected by in-situ hybridisation, e.g. FISH or SISH of fixed tumour blocks.
The following rating system is recommended for the assessment of IHC staining patterns:

Classification	*Surgical specimen - Staining pattern*	*Biopsy specimen - Staining pattern*	*Assessment of HER2 overexpression*
0	No reactivity or membrane reactivity in <10% of tumour cells	No reactivity or membrane reactivity in any tumour cells	Negative
1+	Weak/barely perceptible membrane reactivity in ≥10% of tumour cells; the cells are reactive only at parts of their membrane	Tumour cell clusters with weak/barely perceptible membrane reactivity independent of the percentage of stained tumour cells	Negative
2+	Weak to moderate complete or basolateral membrane reactivity in ≥10% of tumour cells	Tumour cell clusters with weak to moderate complete basolateral or lateral membrane reactivity independent of the percentage of stained tumour cells	Equivocal
3+	Strong complete, basolateral or lateral membrane reactivity in ≥10% of tumour cells	Tumour cell clusters with a strong complete, basolateral or lateral membrane reactivity independent of the percentage of stained tumour cells	Positive

In general, the result of the FISH or SISH test is classified as positive if the ratio between the number of HER2 gene copies per tumour cell and the number of copies of chromosome 17 is greater than or equal to 2.
HER2 expression is predominantly found in the intestinal histological subtype. In contrast to breast cancer, immunohistochemical staining is usually incomplete in gastric cancer.
HER2 can be detected as a free molecule in the plasma (shedding). However, the extent of HER2 expression in the plasma does not correlate with the clinical course. There is no information on shedding in gastric cancer.

Clinical efficacy
Metastatic breast cancer

Trastuzumab has been administered as a monotherapeutic agent in clinical trials to patients with metastatic breast cancer whose tumours overexpressed HER2 and who had not responded to one or more chemotherapies of their metastatic disease (trastuzumab alone).

Trastuzumab has also been used in combination with paclitaxel or docetaxel for the treatment of patients who had not previously received chemotherapy for their metastatic breast cancer. Patients who had previously received adjuvant anthracycline chemotherapy received paclitaxel (175 mg/m^2, infusion duration 3 hours) with or without trastuzumab. In the pivotal study of docetaxel (100 mg/m^2 infused over 1 hour) with or without trastuzumab, 60% of patients previously received adjuvant anthracycline-based chemotherapy. Patients were treated with trastuzumab until progression of disease.
The efficacy of trastuzumab combined with paclitaxel in patients who have not received adjuvant chemotherapy with anthracyclines has not been studied. However, trastuzumab plus docetaxel was effective in all patients - whether or not they received adjuvant anthracycline.

The test method for HER2 overexpression used in the Pivotal study (trastuzumab monotherapy and trastuzumab plus paclitaxel) to determine patient suitability was based on immunohistochemical staining of HER2 on fixed material from breast cancer tumours using monoclonal mouse antibodies CB11 and 4D5. These tissues were fixed in formalin or Bouin's solution. This assay of the clinical trial was performed in a central laboratory using a scale of 0 to 3+. Patients whose staining was classified as 2+ and 3+ were included, while those with a staining of 0 or 1+ were excluded. More than 70% of patients demonstrated an overexpression of 3+. The data suggest that the positive effects were more pronounced in patients with severe overexpression of HER2 (3+).

In the pivotal study of docetaxel with or without trastuzumab, immunohistochemistry was the significant test method for the determination of HER2 overexpression. A minority of patients were tested using FISH. In this study, 87% of included patients had an IHC3+ overexpression and 95% of patients were IHC3+ and/or FISH-positive.

Combination therapy with trastuzumab and paclitaxel or docetaxel:
The efficacy data from the studies on monotherapy and combination therapy (with paclitaxel or docetaxel) are summarised in the following table:

Parameter	*Combination therapy*				*Monotherapy*
	Trastuzumab plus paclitaxel[1]	*Paclitaxel*[1]	*Trastuzumab plus cocetaxel*[2]	*Docetaxel*[2]	Trastuzumab [1]
	n=68	n=77	n=92	n=94	n=172
Median response time (months) (95% confidence interval)	8.3 (7.3-8.8)	4.6 (3.7-7.4)	11.7 (9.3-15.0)	5.7 (4.6-7.6)	9.1 (5.6-10.3)
Median TTP (months) (95% confidence interval)	7.1 (6.2-12.0)	3.0 (2.0-4.4)	11.7 (9.2-13.5)	6.1 (5.4-7.2)	3.2 (2.6-3.5)
Median survival time (months) (95% confidence interval)	24.8 (18.6-33.7)	17.9 (11.2-23.8)	31.2 (27.3-40.8)	22.7 (19.1-30.8)	16.4 (12.3-n.k.)
Response rate (%) (95% confidence interval)	49% (36-61)	17% (9-27)	61% (50-71)	34% (25-45)	18% (13-25)

TTP = time to progression; "n.k." means that the value could not be determined or had not been reached yet.
[1]IHC3+ patient subgroup
[2]"Full Analysis" population (intent-to-treat)

Combination treatment with trastuzumab and anastrozole:
Trastuzumab was tested in combination with anastrozole for first-line therapy in HER2-overexpressing and hormone receptor-positive (e.g. oestrogen receptor (ER) positive and/or progesterone receptor (PR)

positive) postmenopausal patients with metastatic breast cancer who had not received chemotherapy for their metastatic disease. Patients with brain metastases were also excluded. Progression-free survival was significantly improved in the group with trastuzumab plus anastrozole compared to anastrozole alone (4.8 months versus 2.4 months, p = 0.0016). In addition, the following parameters were improved by the addition of trastuzumab: overall response (16.5% versus 6.7%), clinical benefit rate (42.7% versus 27.9%) and duration until disease progression (4.8 months versus 2.4 months). There was no difference between the two groups concerning the time to response and the duration of the response. The median overall survival time was extended by 4.6 months in patients with combination therapy. The difference was not statistically significant. It should be taken into account here that more than half of patients from the group with anastrozole as a monotherapeutic agent switched to a trastuzumab -containing therapy after disease progression (crossover). 52% of patients receiving trastuzumab plus anastrozole survived for at least 2 years compared to 45% of patients who received anastrozole at the initiation of treatment (difference not statistically significant).

Early-stage breast cancer
For adjuvant therapy, trastuzumab was tested in four randomised, multi-centre Phase III trials:
The aim of the study BO16348 (HERA) was to compare 3-week therapy with trastuzumab (over 1 and 2 years) with observation in patients with early-stage HER2-positive breast cancer. Patients received surgery, established chemotherapy and (if applicable) radiation therapy beforehand. In addition, the 2-year treatment with trastuzumab was compared with the corresponding one-year treatment. Patients assigned to treatment with trastuzumab received an initial dose of 8 mg/kg body weight, and subsequently 6 mg/kg body weight every 3 weeks for one or two years.
In the study BO16348 (HERA), early-stage HER2-positive breast cancers were limited to primary operable invasive adenocarcinomas of the breast with positive axillary lymph nodes or negative axillary lymph nodes for tumours with a diameter of at least 1 cm.
The results on efficacy in study BO16348 (HERA) are summarised in the following table:

Efficacy results (BO16348/HERA study) of trastuzumab (treatment for 1 year) versus non-treatment: Results of median follow-up period after 12 months and 8 years***

Parameter	*Median follow-up period 12 months*		*Median follow-up period 8 years*	
	No Trastuzumab, only observation	*Trastuzumab, 1 year*	*No Trastuzumab, only observation*	*Trastuzumab, 1 year*
	n=1693	n=1693	n=1697***	n=1702***
Disease-free survival				
Number of patients with event	219 (12.9%)	127 (7.5%)	570 (33.6%)	471 (27.7%)
Number of patients without event	1474 (87.1%)	1566 (92.5%)	1127 (66.4%)	1231 (72.3%)
P-value vs. follow-up period Hazard ratio vs. observation	<0.0001 0.54		<0.0001 0.76	
Recurrence-free survival				
Number of patients with event	208 (12.3%)	113 (6.7%)	506 (29.8%)	399 (23.4%)
Number of patients without event	1485 (87.7%)	1580 (93.3%)	1191 (70.2%)	1303 (76.6%)
P-value vs. follow-up period Hazard ratio vs. observation	<0.0001 0.51		<0.0001 0.73	
Survival without disease of other organs				

Number of patients with event	184 (10.9%)	99 (5.8%)	488 (28.8%)	399 (23.4%)
Number of patients without event	1508 (89.1%)	1594 (94.6%)	1209 (71.2%)	1303 (76.6%)
P-value vs. follow-up period Hazard ratio vs. follow-up period	<0.0001 0.50		<0.0001 0.76	
Overall survival rate (deaths)				
Number of patients with event	40 (2.4%)	31 (1.8%)	350 (20.6%)	278 (16.3%)
Number of patients without event	1653 (97.65%)	1662 (98.2%)	1347 (79.4%)	1424 (83.7%)
P-value vs. follow-up period Hazard ratio vs. follow-up period	0.24 0.75		0.0005 0.76	

* The co-primary endpoint of disease-free survival after one year versus observation was within the predefined statistical limits
** Final analysis (including 52% of patients from the observation arm who switched to the trastuzumab arm)
*** There is a discrepancy in the overall sample size due to the fact that one small patient group was randomised after the sampling date of the 12-month median follow-up period

In the interim analysis, efficacy results exceeded the statistical limits pre-defined in the protocol for the comparison of one-year therapy with trastuzumab versus observation. After a median follow-up period of 12 months, the hazard ratio (HR) for disease-free survival was 0.54 (95% CI 0.44, 0.67), which is an absolute benefit of 7.6 percentage points (85.8% vs. 78.2%) of disease-free survival after two years in favour of the trastuzumab arm.

A final analysis conducted after a median follow-up period of 8 years showed that treatment with trastuzumab reduced the risk by 24% compared to the pure observation group (HR=0.76, 95% CI 0.67, 0.86). This equates to an absolute benefit of 6.4 percentage points of disease-free survival after 8 years in favour of the trastuzumab arm (one-year treatment).
In this final analysis, prolongation of trastuzumab treatment to two years showed no additional benefit compared to one-year treatment [HR disease-free survival in the intent to treat (ITT) population of 2 years vs. 1 year=0.99 (95% CI: 0.87, 1.13), p-value=0.90 and HR total survival=0.98 (0.83, 1.15); p-value=0.78]. The rate of asymptomatic cardiac dysfunction increased in the 2-year treatment arm (8.1% vs. 4.6% in the 1-year treatment arm). In the 2-year treatment arm, more patients experienced at least one adverse event of Grade 3 or Grade 4 (20.4%) than in the 1-year treatment arm (16.3%).

The studies NCCTG N9831 and NSAPB B-31, which were jointly evaluated, were designed to investigate the clinical benefit of the combination of trastuzumab (H) treatment with paclitaxel (P) following AC (doxorubicin plus cyclophosphamide) chemotherapy. The study NCCTG N9831 additionally investigated the administration of trastuzumab sequentially to chemotherapy with AC/paclitaxel in patients with HER2-positive breast cancer in the early stage following surgery.

In the joint evaluation of the NCCTG N9831 and NSAPB B-31 studies, early-stage breast cancers were confined to women with high-risk, operable tumours, defined as HER2 positive with positive axillary lymph nodes or HER2-positive with negative axillary lymph nodes in the presence of high-risk markers (size >1 cm and ER negative or tumour size >2 cm independent of hormonal state).
Trastuzumab was administered in combination with paclitaxel following AC chemotherapy. Paclitaxel was administered as follows:

- intravenous paclitaxel - 80 mg/m^2 as a long-term IV infusion, administered every week for 12 weeks

or

- intravenous paclitaxel - 175 mg/m^2 as a long-term IV infusion, administered every 3 weeks over 4 cycles (day 1 of each cycle).

Trastuzumab IV was administered weekly in the NCCTG 9831 and NSABP B-31 studies along with chemotherapy: initial dose 4 mg/kg body weight as a 90-minute infusion, followed by 2 mg/kg body weight as a 30-minute infusion. Treatment with trastuzumab was continued for a period of 1 year from the date of first administration.
At the time of interim analysis, the median duration of follow-up period was 1.8 years for the AC→P arm and 2.0 years for the AC→PH arm.

Summary of the efficacy results of the joint evaluation of studies NCCTG 9831 and NSABP B-31 at the time of final evaluation of disease-free survival:*

Parameter	*AC→P n=1679*	*AC→P+H n=1672*	*P-value*	*Hazard Ratio*
Disease-free survival				
- Patients with event	261 (15.5%)	133 (8.0%)	<0.0001	0.48 (0.39-0.59)
- Patients without event	1418 (84.5%)	1539 (92.0%)		
Recurrence				
- Patients with event	235 (14.0%)	117 (7.0%)	<0.0001	0.47 (0.37-0.58)
- Patients without event	1444 (86.0%)	1555 (93.0%)		
Distant recurrence (metastasis)				
- Patients with event	193 (11.5%)	96 (5.7%)	<0.0001	0.47 (0.37-0.60)
- Patients without event	1486 (88.5%)	1576 (94.3%)		
Overall survival				
- Patients with event	92 (5.5%)	62 (3.7%)	0.014 **	0.67 (0.48-0.92)
- Patients without event	1587 (94.5%)	1610 (96.3%)		

* For a median follow-up period of 1.8 years for the patients in the AC→P arm and 2.0 years for the patients in the AC→PH arm
** p-value for overall survival does not exceed the pre-determined statistical limit for the comparison between AC→PH and AC→P.

With regard to the primary endpoint, disease-free survival, the addition of trastuzumab to chemotherapy with paclitaxel resulted in a 52% reduction in the risk of disease recurrence. Regarding the rate of 3-year disease-free survival, the hazard ratio reflects an absolute benefit of 11.8 percentage points (87.2% vs 75.4%) in favour of the AC→PH (trastuzumab) arm.
The pre-planned final analysis of overall survival in the context of the joint evaluation of the NSABP B-31 and NCCTG N9831 studies was conducted after the occurrence of 707 deaths (median follow-up period 8.3 years in the AC→PH group). Treatment with AC→PH resulted in a statistically significant prolongation of overall survival compared to treatment with AC→P (stratified HR=0.64, 95% CI [0.55, 0.74], log rank p value <0.0001). After 8 years the survival rate was estimated to be 86.9% in the AC→PH arm and 79.4% in the AC→P arm; This represents an absolute benefit of 7.4% (95% CI 4.9%, 10.0%).

The BCIRG 006 study investigated the combination of trastuzumab and docetaxel either following AC chemotherapy or trastuzumab in combination with docetaxel and carboplatin in patients with early-stage HER2-positive breast cancer following surgery.
In the BCIRG 006 study, the HER2-positive breast cancers were either limited to patients with positive lymph nodes or to patients with high-risk negative lymph nodes, defined as negative (pN0) lymph node involvement and at least 1 of the following factors: tumour size >2 cm, oestrogen receptor and progesterone receptor negative, histological and/or nuclear Grade 2-3 or age <35 years.
In the BCIRG 006 study, trastuzumab was administered either in combination with docetaxel following AC chemotherapy (AC-DH) or in combination with docetaxel and carboplatin (DCarbH).

Docetaxel was administered as follows:

- intravenous - 100 mg/m^2 in the form of an IV infusion over 1 hour, administered every 3 weeks over 4 cycles (day 2 of docetaxel cycle 1, then day 1 of each additional cycle)

or

- intravenous - 75 mg/m^2 in the form of an IV infusion over 1 hour, administered every 3 weeks over 6 cycles (day 2 of cycle 1, then day 1 of each additional cycle),

followed by carboplatin - at a target AUC of 6 mg/ml/min as an IV infusion over 30-60 minutes, administered every 3 weeks for a total of 6 cycles.

Trastuzumab IV was administered weekly along with chemotherapy: initial dose 4 mg/kg body weight as a 90-minute infusion, followed by 2 mg/kg body weight as a 30-minute infusion. After discontinuing therapy with chemotherapy, trastuzumab was administered every 3 weeks (initial dose 8 mg/kg body weight as a 90-minute infusion, followed by 6 mg/kg body weight as a 30-minute infusion). Treatment with trastuzumab was continued for a period of 1 year from the date of first administration.

The median duration of follow-up period was 2.9 years in the AC→D arm and 3.0 years in the AC→DH arm and in the DCarbH arm.

The efficacy results of the BCIRG 006 study are summarised in the following tables:

Overview of efficacy analyses AC→D versus AC→DH (BCIRG 006 study*)*

Parameter	*AC→D (n=1073)*	*AC→DH (n=1074)*	*P-value vs. AC→D (log rank)*	*Hazard Ratio vs. AC→D (95% CI)*
Disease-free survival				
- Number of patients with event	195 (18.2%)	134 (12.5%)	<0.0001	0.61 (0.49-0.77)
- Number of patients without event	878 (81.8%)	940 (87.5%)		
Distant metastases				
- Number of patients with event	144 (13.4%)	95 (8.8%)	<0.0001	0.59 (0.46-0.77)
- Number of patients without event	929 (86.6%)	979 (91.2%)		
Death (event concerning overall survival)				
- Number of patients with event	80 (7.5%)	49 (4.6%)	0.0024	0.58 (0.40-0.83)
- Number of patients without event	993 (92.5%)	1025 (95.4%)		

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

Overview of efficacy analyses AC → D versus DCarbH (study BCIRG 006)

Parameter	*AC→D (n=1073)*	*DCarbH (n=1075)*	*P-value vs. AC→D (log rank)*	*Hazard Ratio vs. AC→D (95% CI)*
Disease-free survival				
- Number of patients with event	195 (18.2%)	145 (13.5%)	0.0003	0.67 (0.54-0.83)
- Number of patients without event	878 (81.8%)	930 (86.5%)		
Distant metastases				
- Number of patients with event	144 (13.4%)	103 (9.6%)	0.0008	0.65 (0.50-0.84)
- Number of patients without event	929 (86.6%)	972 (90.4%)		
Death (event concerning overall survival)				
- Number of patients with event	80 (7.5%)	56 (5.2%)	0.0182	0.66 (0.47-0.93)
- Number of patients without event	993 (92.5%)	1019 (94.8%)		

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

With respect to the primary endpoint, event-free survival, the hazard ratio in the BCIRG 006 study represents an absolute benefit in 3-year disease-free survival of 5.8 percentage points (86.7 vs. 80.9%) in favour of the AC → DH (trastuzumab) arm and 4.6 percentage points (85.5 vs. 80.9%) in favour of the DCarbH (trastuzumab) arm compared to AC→D.

With respect to the secondary endpoint, overall survival, the treatment with AC→DH reduced the risk of death by 42% compared to AC→D; In the patients treated with DCarbH, the risk of death was reduced by 34% compared to AC→D.
In the study BCIRG 006, 213/1075 patients in the DCarbH arm, 221/1074 patients in the AC→DH arm and 217/1073 in the AC→D arm had a Karnofsky index of ≤90 (either 80 or 90). No benefit for disease-free survival was found in this patient subgroup (hazard ratio=1.16, 95% CI [0.73, 1.83] for DCarbH vs. AC→D, hazard ratio 0.97, 95% CI [0.60, 1.55] for AC→DH vs. AC→D).

Neoadjuvant/Adjuvant treatment
The MO16432 (NOAH) study investigated the administration of trastuzumab along with a total of 10 cycles of neoadjuvant chemotherapy containing both an anthracycline and a taxane (doxorubicin (A) and paclitaxel (P) plus trastuzumab (H) followed by P+H, followed by cyclophosphamide/methotrexate/fluorouracil (CMF) plus H, followed by adjuvant trastuzumab up to a total treatment duration of 1 year) in patients with newly diagnosed locally advanced (stage III) or inflammatory HER-2 positive breast cancer.

The median duration of the follow-up period in the trastuzumab arm was 3.8 years. Pathological complete remission is defined as the absence of an invasive tumour in the breast as well as in the axillary lymph nodes.

Parameter	*Chemotherapy + Trastuzumab (n=115)*	*Chemotherapy alone (n=116)*	
Event-free survival			Hazard ratio (95% CI)
Number of patients with an event	46	59	0.65 (0.44, 0.96) p=0.0275
Overall pathological complete remission (95% CI)	40% (31.0, 49.6)	20.7% (13.7, 29.2)	p=0.0014

With respect to the primary endpoint, event-free survival, the addition of trastuzumab to neoadjuvant chemotherapy followed by adjuvant trastuzumab for a total of 52 weeks resulted in a 35% reduction in the risk of recurrence/progression of the disease (hazard ratio: 0.65 [95% CI: 0.44-0.96]; p<0.0275). After 3 years, 65% of the patients in the trastuzumab arm and 52% in the control arm were without an event. This reflects an improvement of 13% in favour of the trastuzumab arm.

CNS metastases
In the HERA study, a difference of 0.3% in relation to CNS metastases was determined in the trastuzumab group with regard to the localisation of first recurrences (1.2% of patients compared with 0.9% of patients in the control group). Overall, however, the incidence of CNS metastases (primary and secondary recurrence) was similar in the two therapy groups (23 patients in the observation group compared to 25 in the trastuzumab group). This indicates the likelihood that, at the end of adjuvant chemotherapy, micrometastases were present in the CNS with approximately equal frequency in the two treatment groups.

According to the joint evaluation of the NCCTG N9831 and NSAPB B-31 studies, isolated brain metastases were the initial event in the trastuzumab group more frequently than in the control group (21 vs. 11 in the B-31 study and 12 versus 4 in the N9831 study). Patients in the B-31 study were followed up for further recurrences after the occurrence of the first distant metastases. In this study, brain metastases were diagnosed as a first or secondary event in 28 patients of the trastuzumab group and 35 patients of the control group (hazard ratio 0.79, p=0.35).

Thus the incidence of brain metastases in the trastuzumab group was not higher than in the control group. The varying frequency of the occurrence of brain metastases as the first event in patients in the control group can likely be attributed to an earlier relapse in another organ system.

Metastatic adenocarcinoma of the stomach or gastro-oesophageal junction:
The efficacy results of the BO18255 study are summarised in the following table. The study included patients who had not yet received treatment for metastatic adenocarcinoma of the stomach or gastro-oesophageal junction. The primary endpoint was overall survival. At the time of analysis, a total of 349 of the randomised patients had died: 182 patients (62.8%) in the control arm and 167 patients (56.8%) in the treatment arm. The causes of most deaths were related to the underlying cancer.

In the trastuzumab+ capecitabine/5-FU and cisplatin arm, overall survival was significantly better than in the arm with capecitabine/5-FU and cisplatin (p=0.0046, log rank test). Median duration of survival was 11.1 months when treated with capecitabine/5-FU and cisplatin, and 13.8 months with trastuzumab + capecitabine/5-FU and cisplatin. The risk of death in the trastuzumab arm decreased by 26% compared to patients in the capecitabine/5-FU arm (hazard ratio [HR] 0.74 95% CI [0.60-0.91]).
Post-hoc analyses of the subgroups showed that treatment of tumours with higher HER2 protein concentrations (IHC2+ / FISH+ and IHC3+/ independent of the FISH status) resulted in a more pronounced treatment effect. Mean overall survival of the group with increased HER2 expression was 11.8 months versus 16 months, HR 0.65 (95% CI 0.51-0.83), and the mean survival-free survival was 5.5 months versus 7.6 months, HR 0.64 (95% CI 0.51-0.79) for capecitabine /5-FU and cisplatin and for trastuzumab + capecitabine /5-FU and cisplatin, respectively.

Summary of efficacy data (BO18255 study):

Population/Parameter	*FP n = 290*	*H+FP n = 294*	*HR (95% CI)*	*P-value*
Total population:				
Median overall survival (in months)	11.1	13.8	0.74 (0.60-0.91)	0.0046
Median progression-free survival (in months)	5.5	6.7	0.71 (0.59-0.85)	0.0002
Total response rate, %	34.5%	47.3%	1.70[a] (1.22-2.38)	0.0017
IHC3+ *(n=287)*				
Median overall survival (in months)	12.5	17.9	0.59 (0.43-0.81)	n.a.[b]
Median progression-free survival (in months)	5.7%	8.4%	0.59 (0.45-0.78)	n.a.[b]
IHC2+ and FISH+ (n= 159)				
Median overall survival (in months)	10.8	12.3	0.75 (0.51-1.11)	n.a.[b]
Median progression-free survival (in months)	5.0	5.7	0.73 (0.53-1.03)	n.a.[b]
Gastric cancer				
Median overall survival (in months)	11.1	14.6	0.76 (0.60-0.96)	n.a.[b]
Median progression-free survival (in months)	5.4	6.3	0.73 (0.60-0.90)	n.a.[b]
Gastro-oesophageal junction				
Median overall survival (in months)	8.6	10.9	0.67 (0.42-1.08)	n.a.[b]
Median progression-free survival (in months)	5.6	7.6	0.61 (0.40-0.93)	n.a.[b]

FP: fluoropyrimidine/cisplatin
H+FP: fluoropyrimidine/cisplatin + trastuzumab
[a] odds ratio
[b] p-values for subgroups are not listed because the power is not sufficient to show differences between the study arms.

5.2. Pharmacokinetic properties

The pharmacokinetics of trastuzumab were assessed in a population pharmacokinetics model analysis which used pooled data from 1582 subjects who received intravenous trastuzumab from 18 studies of phase I, II and III.

Absorption
No information

Distribution

In the following tables, the population-related PK exposure prognoses (with the 5th-95th percentile) and the PK parameter values were shown at clinically relevant concentrations (C_{max} and C_{min}) in breast cancer patients and in AGC patients who were treated with the permitted dose regimes q1w and q3w.

Population-related PK exposure prognoses in cycle 1 (with the median 5th-95th percentile) for intravenous regimens in breast cancer and AGC patients

Dosage	*Primary tumour type*	*N*	*C_{min} (µg/ml)*	*C_{max} (µg/ml)*	*AUC (µg day/ml)*
8 mg/kg + 6 mg/kg q3w	MBC/EBC	1195	29.4 (5.8-59.5)	178 (117-291)	1373 (736-2245)
	AGC	274	23.1 (6.1-50.3)	132 (84.2-225)	1109 (588-1938)
4 mg/kg + 2 mg/kg qw	MBC/EBC	1195	37.7 (12.3-70.9)	88.3 (58-144)	1066 (586-1754)

Population-related PK exposure prognoses in steady-state *(with the 5th-95th percentile) for intravenous regimens in breast cancer and AGC patients*

Dosage	*Primary tumour type*	*N*	*$C_{min,ss}$ (µg/ml)*	*$C_{max,ss}$ (µg/ml)*	*AUC_{ss} (µg.day/ml)*	*Time to steady-state (weeks)*	*Total CL range in steady-state (l/day)*
8 mg/kg + 6 mg/kg q3w	MBC/EBC	1195	47.4 (5-115)	179 (107-309)	1794 (673-3618)	12	0.173-0.283
	AGC	274	32.9 (6.1-88.9)	131 (72.5-251)	1338 (557-2875)	9	0.189-0.337
4 mg/kg + 2 mg/kg qw	MBC/EBC	1195	66.1 (14.9-142)	109 (51.0-209)	1765 (647-3578)	12	0.201-0.244

Metabolism
No information.

Elimination
Trastuzumab washout
The washout period for trastuzumab was assessed using the respective population PK model following intravenous and subcutaneous administration. The results of these simulations indicate that at least 95% of the patients achieved trastuzumab serum concentrations of <1 µg/ml 7 months after the last dose (approximately 3% of the population-related prognosticised Cmin, ss and approx. 97% washout).

Circulating HER2 antigen
Breast cancer: Measurable concentrations of the circulating extracellular domain of the HER2 receptor ("shed antigen") were detected in the serum of 64% of patients with HER2-overexpressing breast tumours (up to 1880 ng/ml; median=11 ng/ml). Patients with higher baseline values of circulating HER2 antigen tended to have lower minimal serum concentrations of trastuzumab. Most patients with increased circulating antigen levels achieved target serum concentrations for trastuzumab by week 6 over the course of the weekly dosing regimen. No significant relationship could be observed between the baseline value of the circulating antigen and clinical efficacy.
In patients with gastric cancer or gastro-oesophageal junction cancer, no data are available on the amounts of circulating HER2 antigen.

Linearity/non-linearity
A two-compartment model with parallel linear and non-linear elimination from the central compartment described the concentration-time profile of trastuzumab. Due to the non-linear elimination, the overall clearance increased with decreasing concentrations. The linear clearance was 0.127 l/day for breast cancer (MBC/EBC) and 0.176 l/day for AGC. The maximum elimination rate (V_{max}) was 8.81 mg/day for non-linear elimination and the Michaelis-Menten constant (Km) was 8.92 mg/l. The volume in the central compartment was 2.62 l in patients with breast cancer and 3.63 l in patients with AGC.

Pharmacokinetics of special patient groups

Hepatic impairment
No detailed pharmacokinetic studies have been conducted in patients with hepatic impairment.

Renal impairment
No detailed pharmacokinetic studies have been conducted in patients with renal impairment. It was shown in a population pharmacokinetic analysis that renal impairment does not affect the availability of trastuzumab.
No effect was found for serum creatinine on the pharmacological availability of trastuzumab.
Elderly patients
No detailed pharmacokinetic studies have been conducted in elderly patients. The age of the patients had no influence on the trastuzumab pharmacokinetics.

5.3. Preclinical safety data

Safety pharmacology/Long-term toxicity (or repeat dose toxicity)

Trastuzumab was well tolerated by mice (non-binding species) and cynomolgus monkeys (binding species) in single dose toxicity studies and toxicity studies with repeated doses of up to 6 months in duration. No signs of acute or chronic toxicity have been identified.
Two non-clinical toxicity studies to clarify the cardiotoxic effects of trastuzumab were performed with long-tailed macaques (cynomolgus monkeys).
The effects of trastuzumab were studied in animals suffering from manifest cardiac damage caused by pretreatment with doxorubicin. After conclusion of treatment with trastuzumab, no changes occurred within parameters that indicate cardiac muscle necrosis. The results showed changes in one parameter, e-point septal separation (EPSS), but not in two other parameters - fractional shortening (FS) and velocity of circumferential fibre shortening (Vcf) that would have indicated impaired cardiac function.
In one study, the adverse effects of combination therapy with doxorubicin and trastuzumab on cardiac function as well as on erythrocytes and leukocytes were compared with the corresponding adverse effects of monotherapy with the respective medicinal products. The adverse effects of combination therapy had a slightly higher degree of severity and a longer duration than the adverse effects of monotherapy with doxorubicin. Monotherapy with trastuzumab did not show any undesirable effects.

Carcinogenicity
No carcinogenicity studies have been conducted to investigate the carcinogenic potential of Trazimera.

Reproductive toxicity
Reproduction studies conducted with Cynomolgus monkeys with doses of trastuzumab up to 25 times the weekly human dose of 2 mg/kg showed no signs of fertility impairment in women. The influence on the fertility of male animals has not been tested. Studies on teratogenicity and toxicity at the end of gestation and on placental transfer did not indicate any reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

L-histidine hydrochloride monohydrate, L-histidine, sucrose, polysorbate 20.

6.2. Incompatibilities

No incompatibility has been observed between trastuzumab and polyvinyl chloride, polyethylene or polypropylene bags as well as glass bottles.
Glucose solution (5%) should not be used since it induces protein aggregation.
Trazimera should not be mixed or diluted with other medicinal products since no compatibility studies were conducted.

6.3. Shelf-life

Do not use this medicine after the expiry date which is stated on the container after EXP:. The expiry date refers to the last day of that month.

Before first opening:
48 months.

Trazimera 150 mg for single dosing and Trazimera 440 mg for single dosing when reconstituted with sterile water for injection
Trazimera is intended to be reconstituted with sterile water for injection for single dosing.

Stability of the reconstituted concentrate of Trazimera 150 mg and Trazimera 440 mg when sterile water for injection is used
After reconstitution with sterile water for injection, the reconstituted concentrate is physically and chemically stable for up to 48 hours at 2 °C to 8 °C.
For microbiological reasons, the reconstituted concentrate should be immediately diluted further into the infusion solution. If it is not possible, in-use storage times and conditions of the ready solution before use are the responsibility of the user and should be no longer than 24 hours at 2 °C to 8 °C, unless the reconstitution has taken place in controlled and validated aseptic conditions.
Do not freeze the reconstituted concentrate.

6.4. Special precautions for storage

Keep out of the reach of children.

Store the vial of powder for concentrate for solution for infusion in the refrigerator (2-8 °C).

Unopened vials of Trazimera may be stored at room temperature (up to 30°C) in the original packaging protected from light for a single period of up to 3 months. Once removed from refrigeration and stored under these conditions, discard after 3 months.

6.5. Nature and content of container

150 mg:
1 vial of Trazimera (Trastuzumab)

440 mg:
Pack of 1 vial of Trazimera (Trastuzumab)

Trazimera is packaged in a Type I clear glass vial with a chlorobutyl stopper and crimp seal having a flip-off cap.

6.6. Special precautions for disposal and other handling

Handling instructions for Trazimera 150 mg

Preparation for use:
The vial of Trazimera is reconstituted with 7.2 ml sterile water for injection (not supplied). Do not use other reconstitution agents. This results in 7.4 ml solution for a single dose containing 21 mg/ml trastuzumab and having a pH of about 6.0.
During reconstitution of Trazimera and dilution to the infusion solution, avoid shaking and excessive foam formation to prevent any possible precipitation and a reduction of the dissolved amount of Trazimera. Rapid injection from a syringe must also be avoided.

Instructions for reconstitution:
1. Using a sterile syringe, slowly inject 7.2 ml of sterile water for injection into the Trazimera powder in the vial.
2. Thoroughly swirl the vial. DO NOT SHAKE!

Slight foam formation during the reconstitution process is not unusual. Allow the vial to rest for about 5 minutes after reconstitution. The solution should subsequently be essentially free of visible particles. The reconstituted preparation is a colourless to slightly yellow brown transparent solution.

Handling instructions for Trazimera 440 mg
Preparation for use:
A suitable aseptic method should be used.
For the preparation, water for injection can also be used. Such preparations must be used immediately and the residues discarded. The use of other solvents is to be avoided.

During reconstitution of Trazimera and dilution to the infusion solution, avoid shaking and excessive foam formation to prevent any possible precipitation and a reduction of the dissolved amount of Trazimera. Rapid injection from a syringe must also be avoided.

Instructions for reconstitution:
1. Using a sterile syringe, slowly inject 20 ml of water into the existing Trazimera powder in the vial.
2. Thoroughly swirl the vial. DO NOT SHAKE!

Slight foam formation during the reconstitution process is not unusual. Allow the vial to rest for about 5 minutes after reconstitution. The solution should subsequently be essentially free of visible particles. The reconstituted preparation is a colourless to slightly yellow brown transparent solution.

Handling instructions for vials of Trazimera
Dilution of the reconstituted solution
The volume of reconstituted solution required to treat the affected patient is determined as follows:
- Based on an initial dose of trastuzumab 4 mg/kg body weight or trastuzumab 2 mg/kg body weight doses administered weekly:

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

- Based on an initial dose of trastuzumab 8 mg/kg body weight or additional doses of trastuzumab 6 mg/kg body weight administered every three weeks:

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

A corresponding amount of the reconstituted solution should be withdrawn from the vial (either from a 150 mg or 440 mg container) using a sterile needle or syringe and added to an infusion bag or glass bottle with 250 ml of 0.9% sodium chloride solution. Do not use glucose solution (5%) (see "Incompatibilities"). The bag or glass bottle should be carefully rotated to mix the solution without foaming.
When preparing the concentrate and the ready infusion solution particular attention should be paid to ensure sterility of the solutions.
Parenteral medicinal products should be examined by means of visual inspection prior to administration for suspended particles and discolouration.
The infusion should be used immediately after preparation. If diluted under aseptic conditions, it can be stored at 2-8 °C for 24 hours.

Disposal
After treatment or expiry, unused medicinal products must be returned in the original packaging to the place where dispensed (doctor or pharmacist) for proper disposal.

7. MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder
Pfizer AG, Zürich, Switzerland

Manufacturer:
Pfizer Manufacturing Belgium NV, Rijksweg, Puurs, Belgium

8. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 20/12/2020

9. DATE OF REVISION OF THE TEXT

March 2022.