

WARNINGS

Cardiomyopathy: Equituz administration can result in the development of ventricular dysfunction and congestive heart failure. Left ventricular function should be evaluated in all patients prior to and during treatment with Equituz. Discontinuation of Equituz treatment should be strongly considered in patients who develop a clinically significant decrease in left ventricular function. The incidence and severity of cardiac dysfunction was particularly high in patients who received Equituz in combination with anthracyclines and cyclophosphamide (see section 4.4).

Hypersensitivity reactions including anaphylaxis, infusion reactions, pulmonary events.

Equituz administration can result in severe hypersensitivity reactions (including anaphylaxis), infusion reactions and pulmonary events. These may be fatal. In most cases, symptoms occurred during or within 24 hours of administration of Equituz. Equituz infusion should be interrupted for patients experiencing dyspnoea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of Equituz should be strongly considered for patients who develop anaphylaxis, angioedema, or acute respiratory distress syndrome (see section 4.4).

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Equituz, 440 mg, powder and solvent for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 440 mg of trastuzumab, a humanised 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. Reconstituted Equituz concentrate contains 21 mg/mL trastuzumab.

Each solvent vial contains 20 mL sterile bacteriostatic water for injection with 1,1 % *m/v* benzyl alcohol as preservative.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for concentrate for solution for infusion. Powder is a porous mass from white to light yellow. Solvent is clear colourless or with yellowish shade liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Metastatic breast cancer (MBC)

Equituz is indicated for the treatment of patients with metastatic breast cancer whose tumours over-express HER2:

- As monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease.
- In combination with paclitaxel or 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 patients with hormone-receptor positive metastatic breast cancer.

Early breast cancer (EBC)

Equituz is indicated for the treatment of patients with HER2 positive early breast cancer:

- Following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).
- In combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- In combination with neoadjuvant chemotherapy followed by adjuvant Equituz, for locally advanced (including inflammatory) breast cancer or tumours > 2 cm in diameter.

Equituz should only be used in patients whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay.

Equituz should only be used in patients whose tumours have HER2 overexpression at a 3+ level as determined by immunohistochemistry.

Metastatic gastric adenocarcinoma (MGC)

Equituz in combination with capecitabine or 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 prior anti-cancer treatment for their metastatic disease.

Equituz should only be used in patients with metastatic gastric-adenocarcinoma whose tumours have HER2 overexpression as defined by IHC 2+ and a confirmatory silver *in situ* hybridisation (SISH) or fluorescence *in situ* hybridisation (FISH) result, or by an IHC 3+ result. Accurate and validated assay methods should be used (see section 4.4).

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

4.2 Posology and method of administration

Posology

HER2 testing is mandatory prior to initiation of Equituz therapy. Equituz should be administered by a qualified healthcare professional.

Equituz formulation is not intended for subcutaneous administration and should be administered via intravenous infusion only.

Early breast cancer (EBC), Metastatic breast cancer (MBC) and Metastatic gastric adenocarcinoma (MGC):

Weekly schedule

The following loading and subsequent doses are recommended for monotherapy and in combination with paclitaxel or docetaxel.

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

Subsequent doses: The recommended weekly dose of Equituz is 2 mg/kg body weight, beginning one week after the loading dose. If the loading dose was well tolerated, the subsequent dose can be administered as a 30-minute infusion.

Administration in combination with paclitaxel or docetaxel

Paclitaxel or docetaxel in metastatic disease may be administered the day following the first dose of Equituz or immediately after the subsequent doses of Equituz if the preceding dose of Equituz was well tolerated.

Administration in combination with an aromatase inhibitor

In a pivotal trial Equituz and anastrozole were administered on day 1. There were no restrictions on the relative timing of Equituz and anastrozole at administration. For the anastrozole dose, refer

to the anastrozole package insert.

Three weekly schedule

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

Duration of treatment

Patients with MBC or MGC should be treated with Equituz until progression of disease. Patients with EBC should be treated with Equituz for 1 year or until disease recurrence, whichever occurs first. Extending treatment in EBC beyond 1 year has been shown to be not more effective than treatment for one year.

Missed doses

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

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

Dose reduction

No reductions in the dose of Equituz were made during clinical trials. Patients may continue Equituz therapy during periods of reversible, chemotherapy induced, myelosuppression but they should be monitored carefully for complications of neutropenia during this time. The specific instructions to reduce or withhold the dose of chemotherapy should be followed.

Special dosing instructions

Elderly: Data suggests that the disposition of Equituz is not altered based on age. (See section 5.2 in special populations.) In clinical trials, elderly patients did not receive reduced doses of Equituz.

Children: Equituz is not recommended for use in children below 18 years of age because the safety and efficacy in paediatric patients have not been established.

Method of administration

Equituz loading dose should be administered as a 90-minute intravenous infusion. **Do not administer as an intravenous push or bolus.** Equituz intravenous infusion should be administered by a healthcare provider prepared to manage anaphylaxis and an emergency kit should be available.

Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms (see sections 4.4 and 4.8). Interruption or slowing the rate of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

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

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

4.3 Contraindications

Patients with known hypersensitivity to trastuzumab, murine proteins, or to any of the excipients in Equituz as listed in section 6.1.

Patients with severe dyspnoea at rest due to complications of advanced malignancy or the requirement for supplementary oxygen therapy.

Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Traceability

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

Equituz should only be initiated under supervision of a medical practitioner experienced in the treatment of cancer patients. **Refer to boxed warning.**

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

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

Cardiac dysfunction

General considerations

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

All candidates for treatment with Equituz, 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 Equituz. A careful risk-benefit assessment should be made before deciding to treat with Equituz.

Trastuzumab may persist in the circulation for up to 7 months after stopping Equituz treatment based on population pharmacokinetic analysis of all available data (see section 5.2). Patients who receive anthracyclines after stopping Equituz may possibly be at increased risk of cardiac dysfunction. If possible, medical practitioners should avoid anthracycline based therapy for up to 7 months after stopping Equituz. 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 medical practitioner should consider discontinuing therapy if no clinical benefit of Equituz therapy has been seen.

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

Metastatic breast cancer

Equituz 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 Equituz treatment, although the risk is lower than with concurrent use of Equituz 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 Equituz. In patients who receive anthracycline-containing chemotherapy further monitoring is recommended and should occur yearly up to 5 years from the last administration of Equituz, 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 Equituz and therefore treatment cannot be recommended in such patients.

Adjuvant treatment

Equituz 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 Equituz was administered after anthracycline-containing chemotherapy compared to administration with a non- anthracycline regimen of docetaxel and carboplatin and was more marked when Equituz was administered concurrently with taxanes than when administered sequentially to taxanes. Regardless of the regimen used, most symptomatic cardiac events occurred within the first 18 months.

Risk factors for a cardiac event identified in four large adjuvant studies included advanced age (>50 years), low 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 medicines. In patients receiving Equituz after completion of adjuvant chemotherapy, the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracycline given prior to initiation of Equituz and a body mass index (BMI) >25 kg/m².

Neoadjuvant-adjuvant treatment

In patients with EBC eligible for neoadjuvant-adjuvant treatment, Equituz concurrently with anthracyclines should be used with caution and only in chemotherapy-naïve patients. The maximum cumulative doses of the low-dose anthracycline regimens should not exceed 180 mg/m² (doxorubicin) or 360 mg/m² (epirubicin).

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

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

Infusion-related reactions (IRRs) and hypersensitivity

Serious infusion-related reactions (IRRs) to Equituz infusion including dyspnoea, hypotension, wheezing, hypertension, bronchospasm, supraventricular tachydysrhythmia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria and angioedema have been reported (see section 4.8). Pre-medication may be used to reduce risk of occurrence of these events. The majority of these events occur during or within 2,5 hours of the start of the first infusion. Should an infusion reaction occur the infusion should be discontinued, or the rate of infusion slowed and the patient should be monitored until resolution of all observed symptoms (see section 4.2). These symptoms can be treated with an analgesic/antipyretic such as pethidine or paracetamol, or an antihistamine

such as diphenhydramine. The majority of patients experienced resolution of symptoms and subsequently received further infusions of Equituz. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. In less frequent 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 Equituz (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 less frequent occasions, patients have experienced the onset of infusion symptoms and pulmonary symptoms more than six hours after the start of the Equituz infusion. Patients should be warned of the possibility of such a late onset and should be instructed to contact their medical practitioner if these symptoms occur.

Pulmonary events

Severe pulmonary events have been reported with the use of Equituz in the post-marketing setting (see section 4.8). These events have occasionally been fatal.

In addition, cases of interstitial lung disease (ILD), 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 (ILD) include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with ILD 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 with dyspnoea at rest due to complications of advanced malignancy and co-morbidities may be at risk of pulmonary events. Therefore, these patients should not be treated with Equituz (see section 4.3).

Other severe events reported in the post-marketing setting include pulmonary fibrosis.

Benzyl alcohol

The solvent for Equituz contains bacteriostatic water for injection with 1,1 % *m/v* benzyl alcohol as preservative. Benzyl alcohol may cause allergic reactions.

Benzyl alcohol, used as a preservative in bacteriostatic water for injection, has been associated with toxicity in neonates and children up to 3 years old. When administering Equituz to a patient with a known hypersensitivity to benzyl alcohol, Equituz should be reconstituted with water for injection, and only one dose per Equituz vial should be used. Any unused portion must be discarded.

4.5 Interaction with other medicines and other forms of interaction

There have been no formal medicine interaction studies performed with Equituz in humans.

The results of an interaction sub-study evaluating the pharmacokinetics of capecitabine and cisplatin when used with or without Equituz 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 Equituz. However, capecitabine itself showed higher concentrations and a longer half-life when combined with Equituz.

The data also suggested that the pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus Equituz.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

Equituz crosses the placenta. Treatment with Equituz is contraindicated during pregnancy (see section 4.3).

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

Breastfeeding

Equituz appears in the breast milk. Mothers breastfeeding their infants should not use Equituz (see section 4.3).

Fertility

There is no fertility data available.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients experiencing infusion-related symptoms should be advised not to drive or use machines until

symptoms resolved completely.

4.8 Undesirable effects

Summary of the safety profile

Amongst the most serious and/or frequent adverse reactions reported in Equituz usage to date are cardiac dysfunction, infusion-related reactions, haematotoxicity (in particular neutropenia), infections and pulmonary adverse reactions.

Tabulated list of adverse reactions

Presented in Table 1 are adverse reactions that have been reported in association with the use of intravenous Equituz 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 Equituz Monotherapy or in Combination with Chemotherapy in Pivotal Clinical Trials and in Post-Marketing

System organ class	Frequency	Adverse reaction
Infections and infestations	Frequent	Infection, nasopharyngitis, neutropenic sepsis, cystitis, influenza, sinusitis, skin infection, rhinitis, upper respiratory tract infection, urinary tract infection, pharyngitis
	Less frequent	Sepsis
	Not known	Meningitis
Neoplasms benign,	Not known	Malignant neoplasm progression, neoplasma

malignant and unspecified (incl. Cysts and polyps)		progression
Blood and lymphatic system disorders	Frequent	Febrile neutropenia, anaemia, neutropenia, decreased white blood cell/leukopenia, thrombocytopenia
	Not known	Hypoprothrombinaemia, immune thrombocytopenia, leukaemia
Immune system disorders	Frequent	Hypersensitivity
	Less frequent	⁺ Anaphylactic reaction, ⁺ anaphylactic shock
Metabolism and nutrition disorders	Frequent	Weight decreased/weight loss, anorexia
	Not known	Tumour lysis syndrome, hyperkalaemia
Psychiatric disorders	Frequent	Insomnia, anxiety, depression
	Not known	Abnormal thinking
Nervous system disorders	Frequent	¹ Tremor, dizziness, headache, paraesthesia, dysgeusia, peripheral neuropathy, hypertonia, somnolence
	Not known	Cerebral oedema
Eye disorders	Frequent	Conjunctivitis, increased lacrimation, dry eye
	Not known	Papilloedema, retinal haemorrhage, madarosis
Ear and labyrinth disorders	Less frequent	Deafness

Cardiac disorders	Frequent	¹ Decreased blood pressure, ¹ increased blood pressure, ¹ heart beat irregular, ¹ cardiac flutter, ejection fraction decreased*, ⁺ cardiac failure (congestive), ⁺¹ supraventricular tachydysrhythmia, cardiomyopathy, ¹ palpitation
	Less frequent	Pericardial effusion
	Not known	Cardiogenic shock, gallop rhythm present, cerebrovascular disorder
Vascular disorders	Frequent	Hot flush, ⁺¹ hypotension, vasodilatation
Respiratory, thoracic and mediastinal disorders	Frequent	⁺ Dyspnoea, cough, epistaxis, rhinorrhoea, ⁺ pneumonia, asthma, lung disorder, ⁺ pleural effusion
	Less frequent	⁺¹ Wheezing, pneumonitis
	Not known	⁺ Pulmonary fibrosis, ⁺ respiratory distress, ⁺ respiratory failure, ⁺ lung infiltration, ⁺ acute pulmonary oedema, ⁺ acute respiratory distress syndrome, ⁺ bronchospasm, ⁺ hypoxia, ⁺ decreased oxygen saturation, laryngeal oedema, orthopnoea, pulmonary oedema, interstitial lung disease, respiratory insufficiency, Cheyne-Stokes breathing
Gastrointestinal disorders	Frequent	Diarrhoea, vomiting, nausea, ¹ lip swelling, abdominal pain, dyspepsia, constipation,

		stomatitis, haemorrhoids, dry mouth
Hepato-biliary disorders	Frequent	Hepatitis, liver tenderness, hepatocellular injury
	Less frequent	Jaundice
	Not known	Pancreatitis, hepatic failure
Skin and subcutaneous disorders	Frequent	Erythema, rash, ¹ swelling face, alopecia, nail disorder, Palmar-plantar erythrodysaesthesia syndrome, acne, dry skin, ecchymosis, hyperhidrosis, maculopapular rash, pruritis, onychoclasia, dermatitis
	Less frequent	Urticaria
	Not known	Angioedema, Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia, ¹ muscle tightness, myalgia, arthritis, back pain, bone pain, muscle spasms, neck pain, pain in extremity
Renal and urinary disorders	Frequent	Renal disorder
	Not known	Glomerulonephritis membranous, renal failure, glomerulonephropathy
Pregnancy, puerperium and perinatal conditions	Not known	Oligohydramnios, renal hypoplasia, pulmonary hypoplasia
Reproductive system and breast disorders	Frequent	Breast inflammation/mastitis
General disorders and administration	Frequent	Asthenia, chest pain, chills, fatigue, influenza like symptoms, infusion related reaction,

site conditions		pain, pyrexia, mucosal inflammation, peripheral oedema, malaise, oedema
	Not known	Coma, paraneoplastic cerebellar degeneration
Injury, poisoning and procedural complications	Frequent	Contusion

⁺ 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 frequent adverse reaction associated with the use of Equituz and has been associated with a fatal outcome (see section 4.4). Signs and symptoms of cardiac dysfunction such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with Equituz (see section 4.4).

Infusion-related reactions (IRRs) and hypersensitivity

It is estimated that approximately 40 % of patients who are treated with Equituz 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 Equituz 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 Equituz (see section 4.4) and have been associated with a fatal outcome.

Anaphylactoid reactions have been observed in isolated cases.

Haematotoxicity

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

Pulmonary events

Severe pulmonary adverse reactions occur in association with the use of Equituz 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 Risk Management Plan are presented in Warnings and Precautions (see section 4.4).

Hepatic and renal toxicity in breast cancer treatment:

WHO Grade III or IV hepatic toxicity was observed in 12 % of patients following administration of Equituz as single medicine in the metastatic setting. This toxicity was associated with

progression of disease in the liver in 60 % of these patients.

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

Advanced Gastric-adenocarcinoma:

National Cancer Institute Common Toxicity Criteria Adverse Events (NCICTCAE) (v 3.0) grade ≥ 3 renal toxicity occurred in 5 % of patients.

NCICTCAE (v 3,0) grade ≥ 3 adverse event in hepatobiliary disorders: Hyperbilirubinaemia occurred in 1 % of patients.

Diarrhoea in breast cancer treatment:

Of patients treated with Equituz monotherapy in the metastatic setting, 27 % experienced diarrhoea.

Infection

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

Immunogenicity

In a neoadjuvant-adjuvant EBC treatment setting, 10,1 % (30/296) of patients treated with trastuzumab intravenous developed antibodies against trastuzumab. Neutralising 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 Equituz intravenous.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the “**6.04 Adverse Drug Reactions**

Reporting Form”, found online under SAHPRA’s publications:

<https://www.sahpra.org.za/Publications/Index/8>

4.9 Overdose

Symptoms of overdose may be exacerbated and/or exaggerated to those reported in side effects.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 26 Cytostatic agents

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

Equituz is a biosimilar medicine.

Mechanism of action

Trastuzumab is a recombinant DNA-derived humanised monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2).

The antibody is an IgG1 isotype that contains human framework regions with the complementarity-

determining regions of a murine anti-p185 HER2 antibody that binds to HER2. The HER2 proto-oncogene or c-erbB2 encodes for a single transmembrane spanning, receptor-like protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. Overexpression of HER2 is observed in 15 - 20 % of primary breast cancers and 6,8 - 42,6 % advanced gastric-adenocarcinoma.

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

Immunogenicity: Neutralising activity of anti-trastuzumab antibodies was revealed in 2,65 % patients receiving Equituz. Trastuzumab is characterised with low antibody occurrence rate and short life of anti-trastuzumab antibodies.

Clinical Efficacy

HER2-positive metastatic breast cancer

Study BCD-022-02 was an international, multicentre, randomized double-blind comparative clinical study in 225 patients with HER2-positive metastatic breast cancer.

The primary endpoint of the study was the overall response rate (complete responses + partial responses) in HER2(+) mBC subjects after receiving up to 6 cycles (18 weeks) of paclitaxel + trastuzumab therapy.

Patients were treated with trastuzumab at a loading dose of 8 mg/kg (once), followed by maintenance dose of 6 mg/kg every 3 weeks (5 administrations), + paclitaxel 175 mg/m² every 3 weeks as 3-hour intravenous infusion (6 administrations). Therapy continued for 6 cycles of

therapy (every 3 weeks), until progression of the disease or unbearable toxicity.

After the planned 6 cycles of therapy, patients with complete or partial response or stable disease, according to investigator's decision, were transferred to the follow-up and maintenance therapy period, within which they continued receiving unblinded maintenance therapy with trastuzumab until disease progression or unbearable adverse events. In this period, trastuzumab was administered in maintenance dose 6 mg/kg every 3 weeks.

The efficacy of the therapy was evaluated by determination of the overall response rate (partial response + complete response) by computed tomography (CT scan data) applying RECIST 1.1 criteria. CT scan was performed at the screening, after 3 therapy cycles and after 6 therapy cycles. If CT after 3 or 6 therapy cycles revealed the complete or partial response, another CT scan was performed in 4 weeks to confirm the response achieved. The best response reported in the study (6 therapy cycles) was then used for assessment.

Main population for efficacy analysis included those patients who received at least one dose of trastuzumab (intent to treat (ITT) population). This population included 223 patients. To confirm the conclusions based on results in ITT population, additional efficacy analysis was carried out in the per protocol (PP) population. The PP population included 206 patients.

According to CT-scan results in the ITT population, the overall response rate for Equituz (complete and partial response rate), that was the primary outcome measure for the efficacy analysis, was 49,6 % (95 % CI 40,08 - 59,07). There were 4 complete responses in the Equituz group, and partial responses were reported in 52 of 113 subjects. According to CT-scan results in the per protocol population, the overall response rate (complete and partial response rate) was 51,4 % (95 % CI 41,66 – 60,99). This confirmed the results of analysis in ITT population.

The results from the study concluded that efficacy of Equituz in patients with HER2-positive metastatic breast cancer is equivalent to the efficacy reported for trastuzumab in literature.

5.2 Pharmacokinetic properties

Based on the results from study BCD-022-02, the exposure and pharmacokinetics of Equituz after both single-dose and repeated dose administration are similar to the pharmacokinetics reported for trastuzumab in literature.

The pharmacokinetics (PK) of trastuzumab were reported in a population pharmacokinetic model analysis using pooled data from 1 582 subjects receiving trastuzumab 21 mg/mL IV. A two-compartment model with parallel linear and non-linear elimination from the central compartment described the trastuzumab concentration-time profile. Due to the non-linear elimination, total clearance increased with decreasing concentrations. Linear clearance was 0,127 l/day for metastatic and early breast cancer (MBC/EBC) and 0,176 l/day for metastatic gastric-adenocarcinoma (MGC). The nonlinear elimination parameter values were 8,81 mg/day for the maximum elimination rate (V_{max}) and 8,92 mg/l for the Michaelis-Menten constant (K_m). The central compartment volume was 2,62 liter for patients with breast cancer and 3,63 liter for patients with MGC.

The population predicted PK exposures (with 5th - 95th percentiles) and PK parameter values at clinically relevant concentrations (C_{max} and C_{min}) for breast cancer and MGC patients treated with the approved once weekly and three weekly dosing regimens are shown in Table 2 (Cycle 1) and Table 3 (steady-state) below.

Table 2: Population Predicted Cycle 1 PK Exposure Values (with 5th - 95th Percentiles) for IV Regimens in Breast Cancer and MGC Patients

Regimen	Primary	N	Cmin	Cmax	AUC
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	tumour type		(µg/mL)	(µg/mL)	(µg.day/mL)
8mg/kg + 6mg/kg three weekly	MBC/EBC	1 195	29,4 (5,8 - 59,5)	178 (117 - 291)	1 373 (736 - 2 245)
	MGC	274	23,1 (6,1 - 50,3)	132 (84,2 - 225)	1 109 (588 - 1 938)
4mg/kg + 2mg/kg weekly	MBC/ EBC	1 195	37,7 (12,3 - 70,9)	88,3 (58 - 144)	1 066 (586 - 1 754)

**Table 3: Population Predicted Steady State PK Exposure Values (with 5th - 95th Percentiles)
for Trastuzumab Dosing Regimens in Breast Cancer and MGC Patients**

Regimen	Primary tumour type	N	C _{min,ss} (µg/mL)	C _{max,ss} (µg/mL)	AUC _{ss} (µg.day/ mL)	Time to steady- state (week)	Total CL range at steady- state (l/day)
8mg/kg + 6mg/kg three weekly	MBC/ EBC	1 195	47,4 (5 - 115)	179 (107 - 309)	1 794 (673 - 3 618)	12	0,173 - 0,283
	MGC	274	32,9 (6,1 - 88,9)	131 (72,5 - 251)	1 338 (557 - 2 875)	9	0,189 - 0,337
4mg/kg + 2mg/kg weekly	MBC/ EBC	1 195	66,1 (14,9 - 142)	109 (51,0 - 209)	1 765 (647 - 3 578)	12	0,201 - 0,244

Trastuzumab washout

Trastuzumab washout time period results using population PK models indicated that at least 95 % of patients will reach serum trastuzumab concentrations that are <1 µg/mL by 7 months after the last dose.

Pharmacokinetics in special populations

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

Renal impairment

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

Elderly

Age has been shown to have no effect on the disposition of trastuzumab, (see section 4.2).

Pregnancy and lactation

In animal studies trastuzumab has been demonstrated to cross the placenta and to appear in breast milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

For vial containing 440 mg of trastuzumab:

α, α-trehalose dihydrate

L-histidine hydrochloride monohydrate

L-histidine

Polysorbate 20

For vial containing 20 mL of solvent:

Benzyl alcohol 1,1 % w/v

Water for injections

6.2 Incompatibilities

This medicine must not be mixed or diluted with other medicines except those mentioned under section 6.6.

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

6.3 Shelf life

Unopened vial

4 years

Reconstituted solution:

A vial of Equituz, reconstituted with bacteriostatic water for injection as supplied, is physically and chemically stable for 28 days when stored refrigerated at 2 – 8 °C. The reconstituted solution contains a preservative and is therefore suitable for multiple use. Any remaining reconstituted solution should be discarded after 28 days.

After aseptic reconstitution with sterile water for injection, chemical and physical stability of the reconstituted solution has been demonstrated for 24 hours at 2 – 8 °C. Any remaining reconstituted solution should be discarded.

Do not freeze the reconstituted solutions.

Solution for infusion:

Solutions of Equituz for infusion are physically and chemically stable in polyvinylchloride, polyethylene or polypropylene bags containing sodium chloride 9 mg/mL (0,9 %) solution for injection for 24 hours at 2 °C – 8 °C.

From a microbiological point of view, the the reconstituted solution of Equituz with water for injections and Equituz 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 normally not be longer than 24 hours at 2 °C - 8 °C, unless reconstitution and dilution has taken place under controlled and validated aseptic conditions. This medicine should not be used after the expiry date shown on the pack.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).

Do not freeze the reconstituted solution.

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

For storage conditions of the opened medicine, see section 6.3 and 6.6.

6.5 Nature and contents of container

Equituz, 440 mg powder vial is packaged in 50 mL colourless neutral hydrolytic class I glass vials, sealed with rubber bromobutyl stoppers, crimped with aluminium caps with red plastic "flip-off" lid. Each vial is labelled with a self-adhesive label.

Solvent for Equituz is supplied in 20 mL of in neutral glass type I vials, sealed with rubber bromobutyl stoppers and crimped with aluminium flip-off caps with red plastic "flip-off" lid.

Each carton contains one vial with powder and one vial with the solvent in a PVC blister.

6.6 Special precautions for disposal and other handling

Handling and disposal

Appropriate aseptic technique should be used.

Each vial containing 440 mg of trastuzumab is reconstituted with 20,0 mL of solvent containing 1,1 % *m/v* benzyl alcohol (supplied) or water for injections (not supplied). Use of other reconstitution solvents should be avoided.

This yields a 20 mL solution containing approximately 21 mg/mL trastuzumab, at a pH of approximately 6.0. The vial reconstituted with solvent containing 1,1 % *m/v* benzyl alcohol (supplied) is suitable for multiple use. The vial reconstituted with water for injections (not supplied) is for single-use.

Equituz should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted solution may result in

problems with the amount of Equituz that can be withdrawn from the vial.

The reconstituted solution should not be frozen.

Instructions for reconstitution

1. Using a sterile syringe, slowly inject 20 mL of bacteriostatic water for injection in the vial containing the lyophilised Equituz, directing the stream into the lyophilised 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 preparation results in a colourless to pale yellow transparent solution, free of visible particles.

When administering Equituz to a patient with a known hypersensitivity to benzyl alcohol (see section 4.4), Equituz should be reconstituted with water for injection (not supplied), which may also be used for single-dose preparation.

Instructions for dilution

Determine the volume of the solution required

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

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

- based on a loading dose of 8 mg trastuzumab per kilogram body weight, or a subsequent 3 weekly dose of 6 mg trastuzumab per kilogram body weight:

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

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of 0,9 % sodium chloride solution. Dextrose solution should not be used, see section 6.2 for incompatibilities. The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral medicines should be inspected visually for particulates and discolouration prior to administration. Once the infusion is prepared, it should be administered immediately. If diluted aseptically, it may be stored for 24 hours when refrigerated at 2 to 8 °C.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

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9. DATE of FIRST AUTHORISATION/RENEAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT