

Data Sheet

Herceptin[®]

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

Antineoplastic agent

Pharmaceutical Form

Type of dosage form

Powder for concentrate for solution for infusion.

Route of administration

Intravenous infusion.

Sterile/radioactive statement

Sterile product.

Qualitative and Quantitative Composition

Active ingredient

Trastuzumab.

Dosage Preparations: 150 mg single-dose vial and 440 mg multi-dose vial containing powder for concentrate for solution for infusion. Reconstituted Herceptin concentrate contains 21 mg/mL of trastuzumab.

Excipients

Herceptin 150 mg and 440 mg vials:

L-histidine hydrochloride, L-histidine, α,α -trehalose dihydrate, polysorbate 20.

Solvent vial (for use with the 440 mg vial only):

Water for Injection containing 1.1% benzyl alcohol (Bacteriostatic Water for Injection).

Appearance

Herceptin is a white to pale yellow lyophilised powder. The solvent is a clear to slightly opalescent liquid.

Indications

Metastatic breast cancer

Herceptin is indicated for the treatment of patients with metastatic breast cancer who have tumours that overexpress HER2:

- a) as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease; or
- b) in combination with taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease; or
- c) in combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone-receptor positive metastatic breast cancer.

Early breast cancer

Herceptin is also indicated for the treatment of HER2-positive early breast cancer in women with a normal Left Ventricular Ejection Fraction following surgery, sequentially or concurrently with chemotherapy and, if applicable, radiotherapy.

Advanced gastric cancer

Herceptin is indicated in combination with cisplatin and either capecitabine or 5-FU for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Dosage and Administration

HER2 testing is mandatory prior to initiation of Herceptin therapy (see Warnings and Precautions, Detection of HER2 Overexpression or Gene Amplification). Herceptin should be administered by a healthcare professional prepared to manage anaphylaxis and adequate life support facilities should be available. Treatment may be administered in an outpatient setting.

Herceptin should be administered as an intravenous infusion.

DO NOT ADMINISTER HERCEPTIN AS AN INTRAVENOUS PUSH OR BOLUS.

Breast Cancer

Herceptin may be used in **metastatic breast cancer** with the once weekly dose schedule, or the, alternative three-weekly schedule. The alternative schedule has been tested in clinical trials but has not been compared directly with the standard weekly regimen. In clinical studies, patients with metastatic breast cancer were treated with Herceptin until progression of disease.

For treatment of **early breast cancer**, either the once weekly schedule or the three weekly schedule, with loading and subsequent doses, may be used. Patients should be treated for a maximum of 12 months or until disease recurrence.

Once Weekly Dose Schedule

Loading dose

The recommended initial loading dose of Herceptin is 4 mg/kg body weight administered as a 90-minute intravenous infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see Undesirable Effects). Interruption of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

Subsequent doses

The recommended weekly maintenance dose of Herceptin is 2 mg/kg body weight. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30 minute infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see Undesirable Effects).

Three-Weekly Dose Schedule

Loading dose

The recommended initial loading dose of Herceptin is 8 mg/kg body weight administered as a 90-minute intravenous infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see Undesirable Effects). Interruption of the infusion and/or medication may help to control such symptoms. The infusion may be resumed when symptoms abate.

Subsequent doses

The recommended three-weekly maintenance dose of Herceptin is 6 mg/kg body weight administered as a 90-minute intravenous infusion. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30 minute infusion. Patients should be observed for fevers and chills or other infusion-associated symptoms (see Undesirable Effects).

Switching patients from established weekly schedule to three-weekly doses

The first 6 mg/kg dose should be given a week after the last 2 mg/kg dose. As a precaution, all 6 mg/kg doses should be administered as a 90-minute intravenous infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see Undesirable Effects). Interruption of the infusion and/or medication may help to control such symptoms. The infusion may be resumed when symptoms abate. Subsequent maintenance doses of 6 mg/kg are given three-weekly.

Advanced Gastric Cancer

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

In clinical trials, patients with advanced gastric cancer were treated with Herceptin until progression of disease.

Refer to Clinical Efficacy Studies, Advanced Gastric Cancer for chemotherapy combination dosing.

Missed doses

If the patient misses a dose of Herceptin by one week or less, then the usual maintenance dose of Herceptin (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 Herceptin maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg respectively) should then be given according to the previous schedule.

If the patient misses a dose of Herceptin by more than one week, a re-loading dose of Herceptin should be given over approximately 90 minutes (weekly regimen: 4 mg/kg; three-weekly regimen: 8 mg/kg). Subsequent Herceptin maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg respectively) should then be given according to the previous schedule.

Dose reduction

No reductions in the dose of Herceptin were made during clinical trials. Patients may continue Herceptin 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 hold the dose of chemotherapy should be followed.

Special Dosage Instructions

Elderly

Data suggest that the disposition of Herceptin is not altered based on age (see Pharmacokinetics in Special Populations). In clinical trials, elderly patients did not receive reduced doses of Herceptin.

Children

The safety and efficacy of Herceptin in paediatric patients have not been established.

Contraindications

Herceptin is contraindicated in patients with known hypersensitivity to trastuzumab or to any other component of the product.

Warnings and Precautions

General

Herceptin therapy should only be initiated under supervision of a physician experienced in the treatment of cancer patients.

Benzyl alcohol, used as a preservative in Bacteriostatic Water for Injection in the 440 mg multidose vial, has been associated with toxicity in neonates and children up to 3 years old. When administering Herceptin to a patient with a known sensitivity to benzyl alcohol, Herceptin should be reconstituted with water for injection, and only one dose per Herceptin vial should be used. Any unused portion

must be discarded. Sterile water for injection, used to reconstitute the 150 mg single dose vials, does not contain benzyl alcohol.

Infusion reactions

Serious adverse reactions to Herceptin infusion including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress have been reported infrequently. The Herceptin infusion should be discontinued and the patient monitored until resolution of any observed symptoms. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists and corticosteroids (see Undesirable Effects). In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome. Patients who are experiencing dyspnoea at rest due to complications of advanced malignancy or comorbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should be treated with extreme caution and the risk versus the benefit considered for each patient (see Undesirable Effects).

Pulmonary toxicity

Severe pulmonary events have been reported with the use of Herceptin in the post-marketing setting. These events have occasionally resulted in a fatal outcome. In addition, cases of interstitial lung disease including pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported. These events may occur as part of an infusion-related reaction or with a delayed onset. Patients with symptomatic intrinsic lung disease or with extensive tumour involvement of the lungs, resulting in dyspnoea at rest, may be at greater risk of severe reactions (see Undesirable Effects) and should only be treated with Herceptin following consideration of the risk versus benefit.

Cardiac toxicity

Heart failure (New York Heart Association [NYHA] class II - IV) has been observed in patients receiving Herceptin therapy alone or in combination with paclitaxel following anthracycline (doxorubicin or epirubicin)-containing chemotherapy. This may be moderate to severe and has been associated with death (see Undesirable Effects).

Caution should be exercised in treating patients with symptomatic heart failure, a history of hypertension, or documented coronary artery disease, and patients 50 years and above should Herceptin be used concurrently with chemotherapy. Candidates for treatment with Herceptin, (especially those with prior anthracycline and cyclophosphamide (AC) exposure), should undergo baseline cardiac assessment including history and physical examination, ECG, echocardiogram, and/or MUGA scan. A careful risk-benefit assessment should be made before deciding to treat with Herceptin.

Cardiac function should be further monitored every three months while on treatment. Assessment of Left Ventricular Ejection Fraction (LVEF) should be monitored by an echocardiogram or a MUGA scan. The same method used for baseline assessment should be used throughout treatment. Monitoring may help to identify patients who develop cardiac dysfunction.

Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g. every 6 - 8 weeks). If patients have a continued decrease in left ventricular function, but remain

asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of Herceptin therapy has been seen.

If LVEF drops 10 percentage points from baseline and to below 50%, Herceptin should be withheld and a repeat LVEF assessment performed within approximately three weeks. If LVEF has not improved, or declined further, discontinuation of Herceptin should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

If symptomatic cardiac failure develops during Herceptin therapy, it should be treated with the standard medications for this purpose. Discontinuation of Herceptin therapy should be strongly considered in patients who develop clinically significant heart failure unless the benefits for an individual patient are deemed to outweigh the risks.

The safety of continuation or resumption of Herceptin in patients who experience cardiotoxicity has not been prospectively studied. However, most patients who developed heart failure in the pivotal trials improved with standard medical treatment. This included diuretics, cardiac glycosides, and/or angiotensin-converting enzyme inhibitors. The majority of patients with cardiac symptoms and evidence of a clinical benefit of Herceptin treatment continued on weekly therapy with Herceptin without additional clinical cardiac events.

Breast Cancer

Caution should be exercised in early breast cancer patients with an LVEF of 55% or less.

In early breast cancer, there are insufficient clinical data available about the benefit/risk balance in the following patients and consequently treatment cannot be recommended in such patients:

- History of documented congestive heart failure
- High-risk uncontrolled arrhythmias
- Angina pectoris requiring medication
- Clinically significant valvular disease
- Evidence of transmural infarction on ECG
- Poorly controlled hypertension

Advanced Gastric Cancer

In advanced gastric cancer, the following patients were excluded from Study BO18255 (ToGA) according to the study protocol:

- History of documented congestive heart failure
- Angina pectoris requiring medication
- Evidence of transmural myocardial infarction on ECG
- Poorly controlled hypertension (systolic BP >180 mmHg or diastolic BP >100 mmHg)
- Clinically significant valvular heart disease
- High risk uncontrollable arrhythmias
- Baseline LVEF <50% (measured by echocardiography or MUGA).

Refer to Undesirable Effects, Cardiac toxicity.

Detection of HER2 Overexpression or Gene Amplification

Herceptin should only be used in patients whose tumours have HER2 overexpression or HER2 gene amplification. HER2 overexpression should be detected using an immunohistochemistry (IHC)-based assessment of fixed tumour blocks. HER2 gene amplification should be detected using in situ

hybridisation (ISH) of fixed tumour blocks. Examples of ISH include fluorescence in situ hybridisation (FISH), chromogenic in situ hybridisation (CISH) and silver in situ hybridisation (SISH).

The recommended scoring systems to evaluate IHC staining patterns are shown below in Table 1 (breast cancer) and Table 2 (advanced gastric cancer).

In general, FISH is considered to show gene amplification if the ratio of the HER2 gene copy number per tumour cell to the chromosome 17 copy number is greater than or equal to 2.2, or if there are more than 6 copies of the HER2 gene per tumour cell, if no chromosome 17 control is used.

In general, CISH and SISH are considered to show gene amplification if there are more than 6 copies of the HER2 gene per nucleus in greater than 50% and 30% of tumour cells respectively.

For full instructions on assay performance and interpretation please refer to the package inserts of validated FISH, CISH and SISH assays.

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

Breast Cancer

Herceptin treatment is only appropriate if there is strong HER2 overexpression, as described by a 3+ score by IHC or a positive ISH result. For patients with an intensity score of 2+ on IHC, confirmation of HER2 positive status by ISH is mandatory. It is also recommended for patients with 3+ staining by IHC.

Table 1: Scoring of IHC Staining Patterns for Breast Cancer Tumour Samples

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

Adapted from DAKO HercepTest™ package insert

Advanced Gastric Cancer

Herceptin treatment is only appropriate if there is HER2 overexpression, as described by a 3+ IHC score. For cases with a score of less than 3+ by IHC, confirmation of HER2 positive status by ISH is mandatory.

Table 2: Scoring of IHC Staining Patterns for Gastric Cancer Tumour Samples

Staining Intensity Score	Staining pattern	HER2 Overexpression Assessment
0	No reactivity or membranous reactivity in <10% of tumour cells	Negative
1+	Faint/barely perceptible membranous reactivity in >10% of tumour cells; cells are reactive only in part of their membrane	Negative
2+	Weak to moderate complete, basolateral or lateral membranous reactivity in >10% of tumour cells	Equivocal
3+	Strong complete, basolateral or lateral membranous reactivity in >10% of tumour cells Biopsy (not surgery) samples with cohesive IHC 3+ clones are considered positive irrespective of percentage of tumour cells stained	Positive

Interactions

There have been no formal interaction studies performed with Herceptin in humans. Clinically significant interactions with the concomitant medication used in clinical trials have not been observed (see Pharmacokinetic Properties).

Paclitaxel pharmacokinetics determined during the fourth cycle of the alternative 3-weekly Herceptin regimen ($n = 25$) were not altered appreciably, relative to parameters determined during the initiation of paclitaxel, prior to introduction of Herceptin. Similarly, docetaxel pharmacokinetics determined during the first dose of Herceptin in the standard weekly regimen ($n = 10$) were not altered appreciably relative to those determined 2 weeks earlier for docetaxel alone.

Use in Special Populations

Pregnancy

Pregnancy Category: B2

Herceptin should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus. In the post-marketing setting, cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving Herceptin. Women of childbearing potential should be advised to use effective contraception during treatment with Herceptin and for at least 6 months after treatment has concluded. Women who become pregnant should be advised of the possibility of harm to the foetus. If a pregnant woman is treated with Herceptin, close monitoring by a multidisciplinary team is desirable. It is not known whether Herceptin can affect reproductive capacity. Animal reproduction studies revealed no evidence of impaired fertility or harm to the foetus (See Preclinical Safety, Teratogenicity).

Nursing mothers

It is not known whether trastuzumab is secreted in human milk. As human IgG is secreted into human milk, and the potential for harm to the infant is unknown, breast-feeding should be avoided during Herceptin therapy and for 6 months after the last dose of Herceptin (See Preclinical Safety, Other).

Undesirable Effects

Clinical Trials

Metastatic Breast Cancer

Herceptin monotherapy or in combination with chemotherapy

Patients received Herceptin as monotherapy or in combination with paclitaxel in the two pivotal clinical trials. Approximately 50% of patients can be expected to experience adverse reactions. The most common adverse reactions are infusion-related symptoms, such as fever and chills, usually following the first infusion of Herceptin.

Adverse reactions attributed to Herceptin in $\geq 10\%$ of patients in the two pivotal clinical trials were the following:

Body as a whole: abdominal pain, asthenia, chest pain, chills, fever, headache, pain
Digestive: diarrhoea, nausea, vomiting
Musculoskeletal: arthralgia, myalgia
Skin and appendages: rash

In another randomised clinical trial, patients with metastatic breast cancer received docetaxel, with or without Herceptin. The following table displays common non-haematological adverse events which were reported in $\geq 10\%$ of patients, by study treatment:

Table 3: Common Non-haematological Adverse Events Reported in (10% of Patients, by Study Treatment

Body System	Adverse Event	Herceptin + docetaxel n = 92 (%)	Docetaxel n = 94 (%)
General disorders and administration site conditions	asthenia	45	41
	oedema peripheral	40	35
	fatigue	24	21
	mucosal inflammation	23	22
	pyrexia	29	15
	pain	12	9
	lethargy	7	11
	chest pain	11	5
	influenza-like illness	12	2
	rigors	11	1
Skin and subcutaneous tissue disorders	alopecia	67	54
	nail disorder	17	21
	rash	24	12
	erythema	23	11
Gastrointestinal disorders	nausea	43	41
	diarrhoea	43	36
	vomiting	29	22
	constipation	27	23

Body System	Adverse Event	Herceptin + docetaxel n = 92 (%)	Docetaxel n = 94 (%)
	stomatitis	20	14
	abdominal pain	12	12
	dyspepsia	14	5
Nervous system disorders	paraesthesia	32	21
	headache	21	18
	dysgeusia	14	12
	hypoesthesia	11	5
Musculoskeletal and connective tissue disorders	myalgia	27	26
	arthralgia	27	20
	pain in extremity	16	16
	back pain	10	14
	bone pain	14	6
Respiratory, thoracic and mediastinal disorders	cough	13	16
	dyspnoea	14	15
	pharyngolaryngeal pain	16	9
	epistaxis	18	5
	rhinorrhoea	12	1
Infections and infestations	nasopharyngitis	15	6
Eye disorders	lacrimation increased	21	10
	conjunctivitis	12	7
Vascular disorders	lymphoedema	11	6
Metabolism and nutrition disorders	anorexia	22	13
Investigations	weight increased	15	6
Psychiatric disorders	insomnia	11	4
Injury, poisoning and procedural complications	nail toxicity	11	7

Herceptin in combination with anastrozole

The TAnDEM trial was a randomised open-label study, comparing Herceptin + anastrozole with anastrozole alone in patients with metastatic breast cancer (see Clinical Efficacy Studies, Metastatic Breast Cancer). In the TAnDEM trial, there was no change in the nature or frequency of adverse effects compared with previous trials in the metastatic population.

Adverse reactions attributed to Herceptin in > 1% and < 10% of patients treated for **metastatic breast cancer** were the following:

<i>Body as a whole:</i>	back pain, influenza-like illness, infection, neck pain, malaise, hypersensitivity reaction
<i>Cardiovascular:</i>	vasodilation, supraventricular tachyarrhythmia, hypotension, heart failure, cardiomyopathy, palpitation
<i>Digestive:</i>	anorexia, constipation, dyspepsia
<i>Haeme and lymphatic</i>	leucopenia
<i>Metabolic:</i>	peripheral oedema, oedema
<i>Musculoskeletal:</i>	bone pain
<i>Nervous:</i>	anxiety, depression, dizziness, insomnia, paraesthesia, somnolence, hypertonia, peripheral neuropathy
<i>Respiratory:</i>	asthma, cough increased, dyspnoea, epistaxis, lung disorders, pleural effusion, pharyngitis, rhinitis, sinusitis
<i>Urogenital:</i>	urinary tract infection
<i>Skin and appendages:</i>	pruritus, sweating, nail disorders, dry skin, alopecia, acne, maculopapular rash

Early Breast Cancer

The HERA trial was a randomised, open label study in patients with HER2-positive early breast cancer (see Clinical Efficacy Studies, Early Breast Cancer). Table 4 displays adverse events which were reported at a median follow-up of 1 year in $\geq 1\%$ of patients, by study treatment.

Table 4: Adverse Events Reported at a median follow-up of 1 year in $\geq 1\%$ of Patients, by Study Treatment

Body System	Adverse Event	Observation Only <i>n</i> = 1708 No. (%)	Herceptin 1 year <i>n</i> = 1678 No. (%)
	Total Pts with at least one AE Total number of AEs	792 (46) 2251	1179 (70) 5248
Musculoskeletal and connective tissue disorders	arthralgia*	98 (6)	137 (8)
	back pain*	59 (3)	91 (5)
	pain in extremity	45 (3)	60 (4)
	myalgia*	17 (<1)	63 (4)
	bone pain	26 (2)	49 (3)
	shoulder pain	29 (2)	30 (2)
	chest wall pain	24 (1)	26 (2)
	muscle spasms*	3 (<1)	45 (3)
	musculoskeletal pain	11 (<1)	17 (1)
Infections and infestations	nasopharyngitis*	43 (3)	135 (8)
	influenza*	9 (<1)	69 (4)
	upper respiratory tract infection*	20 (1)	46 (3)
	urinary tract infection	13 (<1)	39 (2)
	rhinitis	6 (<1)	36 (2)
	sinusitis	5 (<1)	26 (2)
	cystitis	11 (<1)	19 (1)
	pharyngitis	9 (<1)	20 (1)
	bronchitis	9 (<1)	18 (1)
	herpes zoster	9 (<1)	17 (1)
General disorders and administration site conditions	fatigue*	44 (3)	128 (8)
	oedema peripheral*	38 (2)	79 (5)
	pyrexia*	6 (<1)	100 (6)
	asthenia*	30 (2)	75 (4)
	chills*	-	85 (5)
	chest pain*	22 (1)	45 (3)
	influenza illness	3 (<1)	40 (2)
	oedema	7 (<1)	18 (1)
chest discomfort	2 (<1)	20 (1)	
Gastrointestinal disorders	diarrhoea*	16 (<1)	123 (7)
	nausea*	19 (1)	108 (6)
	vomiting*	10 (<1)	58 (3)
	abdominal pain	16 (<1)	40 (2)
	constipation	17 (<1)	33 (2)
	abdominal pain upper	15 (<1)	29 (2)
	dyspepsia	9 (<1)	30 (2)
	gastritis	11 (<1)	20 (1)
	stomatitis	1 (<1)	26 (2)
Nervous system disorders	headache*	49 (3)	161 (10)
	dizziness*	29 (2)	60 (4)
	paraesthesia	11 (<1)	29 (2)
	vertigo	7 (<1)	25 (1)
Vascular disorders	hot flush	84 (5)	98 (6)
	hypertension*	35 (2)	64 (4)

	Adverse Event	Observation Only n = 1708 No. (%)	Herceptin 1 year n = 1678 No. (%)
	lymphoedema	40 (2)	42 (3)
Skin and subcutaneous tissue	rash*	10 (<1)	70 (4)
	pruritus	10 (<1)	40 (2)
	nail disorder*	-	43 (3)
	onychorrhexis	1 (<1)	36 (2)
	erythema	7 (<1)	24 (1)
Respiratory, thoracic and mediastinal disorders	cough*	34 (2)	81 (5)
	dyspnoea	26 (2)	56 (3)
	pharyngolaryngeal pain	8 (<1)	32 (2)
	dyspnoea exertional	15 (<1)	21 (1)
	rhinorrhoea	5 (<1)	24 (1)
	epistaxis	1 (<1)	24 (1)
Reproductive system and breast disorders	breast pain	19 (1)	24 (1)
Psychiatric	insomnia	31 (2)	58 (3)
	depression	34 (2)	51 (3)
	anxiety	19 (1)	39 (2)
Cardiac disorders	palpitations*	12 (<1)	48 (3)
	cardiac failure congestive	5 (<1)	30 (2)
	tachycardia	5 (<1)	20 (1)
Investigations	ejection fraction decreased*	11 (<1)	58 (3)
	weight increased	17 (<1)	29 (2)
Renal and urinary disorders	dysuria	2 (<1)	17 (1)

* Adverse Events that were reported at higher incidence ($\geq 2\%$ difference) in the Herceptin group compared with the observation group and therefore may be attributable to Herceptin.

At a median follow-up of two-years in the HERA trial, there were more episodes of at least one Grade 3-4 adverse event and of serious adverse events with Herceptin than in the observation group ($p < 0.0001$). The only Grade 3-4 adverse event experienced by five or more patients in the observation group ($n = 1,698$) was hypertension (5). The Grade 3-4 adverse events experienced by five or more patients in the Herceptin group ($n = 1,703$) were: hypertension (12), depression (8), diarrhoea (7), congestive cardiac failure (7), vomiting (6), arthralgia (6), cardiac failure (5), hot flush (5), headache (5), and back pain (5).

The B-31 and N9831 trials were phase III, randomised, open-label trials in patients with HER2-positive early breast cancer (see Clinical Efficacy Studies, Early Breast Cancer). The following non-cardiac adverse reactions of Grade 2-5 occurred in at least one of these trials at an incidence of at least 2% greater among patients randomised to Herceptin + chemotherapy as compared to chemotherapy alone: arthralgia, myalgia, fatigue, infection, hot flashes, anaemia, dyspnoea, rash/desquamation, neutropenia, headache, insomnia and nail changes. The majority of these events were Grade 2 in severity.

Advanced Gastric Cancer

Study BO18255 (ToGA) trial was a randomised, open-label study of Herceptin in combination with a fluoropyrimidine and cisplatin (FP) versus chemotherapy alone in patients with advanced gastric cancer (see Clinical Efficacy Studies, Advanced Gastric Cancer). The common adverse events (>10%) are presented in Table 5.

Table 5: Adverse Events Occurring in ≥10% of Patients Treated for Advanced Gastric Cancer

Body System/ Adverse Event	FP (n=290) n (%)	Herceptin + FP (n=294) n (%)
Gastrointestinal Disorders		
Nausea	184 (63)	197 (67)
Vomiting	134 (46)	147 (50)
Diarrhoea	80 (28)	109 (37)
Constipation	93 (32)	75 (26)
Stomatitis	43 (15)	72 (24)
Abdominal Pain	42 (14)	46 (16)
Blood And Lymphatic System Disorders		
Neutropenia	165 (57)	157 (53)
Anaemia	61 (21)	81 (28)
Thrombocytopenia	33 (11)	47 (16)
General Disorders And Administration Site Conditions		
Fatigue	82 (28)	102 (35)
Asthenia	53 (18)	55 (19)
Pyrexia	36 (12)	54 (18)
Mucosal Inflammation	18 (6)	37 (13)
Metabolism And Nutrition Disorders		
Anorexia	133 (46)	135 (46)
Skin And Subcutaneous Tissue Disorders		
Palmar-Plantar Erythrodysesthesia Syndrome	64 (22)	75 (26)
Alopecia	27 (9)	32 (11)
Investigations		
Weight Decreased	40 (14)	69 (23)
Renal And Urinary Disorders		
Renal Impairment	39 (13)	47 (16)
Respiratory, Thoracic And Mediastinal Disorders		
Hiccups	28 (10)	34 (12)
Nervous System Disorders		
Dizziness	28 (10)	31 (11)
Infections And Infestations		
Nasopharyngitis	17 (6)	37 (13)

FP: Fluoropyrimidine/cisplatin

The following information is relevant to all indications:

Infusion-related symptoms

During the first infusion of Herceptin, chills and/or fever are observed commonly in patients. Other signs and/or symptoms may include nausea, vomiting, pain, rigors, headache, cough, dizziness, rash, asthenia and hypertension. These symptoms are usually mild to moderate in severity, and occur infrequently with subsequent Herceptin infusions. These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine (see Dosage and Administration). Some adverse reactions to Herceptin infusion including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress can be serious and potentially fatal (see Warnings and Precautions).

Hypersensitivity reaction

Anaphylactoid reactions were observed in isolated cases.

Cardiac toxicity

Breast Cancer

Signs and symptoms of cardiac dysfunction, such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S₃ gallop, or reduced ejection fraction, have been observed in patients treated with Herceptin (see Warnings and Precautions). Depending on the criteria used to define cardiac dysfunction, the incidence in the pivotal metastatic trials varied between 9% and 12% in the Herceptin + paclitaxel subgroup, compared with 1% - 4% for the paclitaxel alone subgroup. For Herceptin monotherapy, the rate was 6% - 9%. The highest rate of cardiac dysfunction was seen in patients receiving Herceptin + anthracycline/cyclophosphamide (27% - 28%), which was significantly higher than the rate reported for patients in the anthracycline/cyclophosphamide alone subgroup (7% - 10%). In a subsequent trial with prospective monitoring of cardiac function, the incidence of symptomatic heart failure was 2.2% in patients receiving Herceptin and docetaxel, compared with 0% in patients receiving docetaxel alone.

In the early breast cancer HERA trial, 2.1% of women developed symptomatic heart failure with 0.6% developing severe heart failure (NYHA class III-IV) in the one year Herceptin arm. In the B-31 and N9831 early breast cancer trials, at a median follow-up of two years, the three-year cumulative incidences of severe heart failure or death from cardiac causes were 4.1% and 2.9% respectively in the Herceptin groups versus 0.8% and 0% respectively in the control groups.

As the mean terminal half-life of Herceptin is approximately 3 weeks, trastuzumab may persist in the circulation for up to 15 weeks after stopping treatment. Since the use of an anthracycline during this period could possibly be associated with an increased risk of cardiac dysfunction, a thorough assessment of the risks versus the potential benefits is recommended in addition to careful cardiac monitoring.

Advanced Gastric Cancer

In Study BO18255 (ToGA), at screening, the median LVEF value was 64% (range 48% - 90%) in the FP arm and 65% (range 50% - 86%) in the Herceptin + FP arm.

The majority of the LVEF decreases noted in ToGA were asymptomatic, with the exception of 1 patient in the Herceptin arm whose LVEF decrease coincided with cardiac failure.

Table 6: Summary of LVEF Change from Screening

LVEF Decrease[#]: Lowest Post-screening Value	FP (n=290) (% of patients in each treatment arm)	FP + H (n=294) (% of patients in each treatment arm)
LVEF decrease ≥10% to <50%	2 (1.1%)	11(4.6%)
Absolute Value <50%	2 (1.1%)	14 (5.9%)
LVEF decrease ≥ 10% to ≥ 50%	22 (11.8%)	39 (16.5%)

FP: Fluoropyrimidine/cisplatin; FP+H: Fluoropyrimidine/cisplatin + Herceptin; [#]Only includes patients whose method of assessment at that visit is the same as at their initial assessments (FP: n = 187 and FP + H: n = 237)

Table 7: Cardiac Adverse Events

	FP (n=290) (% of patients in each treatment arm)	FP +H (n=294) (% of patients in each treatment arm)
Total Cardiac Events	6% ^a	6% ^b
≥ Grade 3 ^c	3%	1%

FP: Fluoropyrimidine/cisplatin; FP+H: Fluoropyrimidine/cisplatin + Herceptin; ^a 9 patients experienced 9 Events; ^b 4 patients experienced 5 Events; ^c NCI-CTC criteria (V3.0)

Overall, there were no significant differences in cardiotoxicity between the treatment arm and the comparator arm.

Haematological toxicity

Breast Cancer

Haematological toxicity is infrequent following the administration of Herceptin monotherapy in the metastatic setting, WHO Grade 3 leucopenia, thrombocytopenia and anaemia occurring in < 1% of patients. No WHO Grade 4 toxicities were observed.

There was an increase in WHO Grade 3 or 4 haematological toxicity in patients treated with the combination of Herceptin and paclitaxel compared with patients receiving paclitaxel alone (34% vs. 21%). Haematological toxicity was also increased in patients receiving Herceptin and docetaxel, compared with docetaxel alone (32% grade 3/4 neutropenia versus 22%, using HCl-CTC criteria). The incidence of febrile neutropenia/neutropenic sepsis was also increased in patients treated with Herceptin + docetaxel (23% versus 17% for patients treated with docetaxel alone).

Using NCI-CTC criteria, in the HERA trial (median follow-up 1 year), 0.4% of Herceptin-treated patients experienced a shift of 3 or 4 grades from baseline, compared with 0.6% in the observation arm.

Advanced Gastric Cancer

The most frequently reported adverse events categorised under the Blood and Lymphatic System Disorders SOC (Grade ≥3) are shown below (Table 8) by trial treatment.

Table 8: Blood and Lymphatic System Disorders (SOC) Adverse Events >1%

	FP (n=290) (% of patients in each treatment arm)	FP + H (n=294) (% of patients in each treatment arm)
Neutropenia	30%	27%
Anaemia	10%	12%
Febrile Neutropenia	3%	5%
Thrombocytopenia	3%	5%

FP: Fluoropyrimidine/cisplatin; FP+H: Fluoropyrimidine/cisplatin + Herceptin

The total percentage of patients who experienced an adverse event of ≥ Grade 3 NCI CTCAE v3.0 categorised under this SOC were 38% in the FP arm and 40% in the FP + H arm.

Overall, there were no significant differences in haematotoxicity between the treatment arm and the comparator arm.

Hepatic and renal toxicity

Breast Cancer

WHO Grade 3 or 4 hepatic toxicity was observed in 12% of patients following administration of Herceptin as single agent, in the metastatic setting. This toxicity was associated with progression of disease in the liver in 60% of these patients.

WHO Grade 3 or 4 hepatic toxicity was less frequently observed among patients receiving Herceptin and paclitaxel than among patients receiving paclitaxel (7% compared with 15%). No WHO Grade 3 or 4 renal toxicity was observed.

Advanced Gastric Cancer

In Study BO18255 (ToGA) no significant differences in hepatic and renal toxicity were observed between the two treatment arms.

Grade ≥ 3 renal toxicity was not significantly higher in patients receiving Herceptin than those in the fluoropyrimidine/cisplatin arm (3% and 2% respectively).

Grade ≥ 3 adverse events in the Hepatobiliary Disorders SOC: Hyperbilirubinaemia was the only reported adverse event and was not significantly higher in patients receiving Herceptin than those in the fluoropyrimidine/cisplatin arm (1% and $<1\%$ respectively).

Diarrhoea

Breast Cancer

Of patients treated with Herceptin monotherapy in the metastatic setting, 27% experienced diarrhoea. An increase in the incidence of diarrhoea, primarily mild to moderate in severity, has also been observed in patients receiving Herceptin in combination with paclitaxel compared with patients receiving paclitaxel alone.

In the HERA trial (median follow-up 1 year), 7% of Herceptin-treated patients had diarrhoea.

Advanced Gastric Cancer

In Study BO18255 (ToGA), 109 patients (37%) in the Herceptin treatment arm versus 80 patients (28%) in the comparator arm experienced any grade diarrhoea. Four percent (4%) of patients in the fluoropyrimidine/cisplatin arm experienced Grade ≥ 3 diarrhoea vs. 9% in the Herceptin arm.

Infection

An increased incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections, has been observed primarily in patients treated with Herceptin + paclitaxel compared with patients receiving paclitaxel alone.

Serious adverse reactions

At least one case of the following serious adverse reactions has occurred in at least one patient treated with Herceptin alone or in combination with chemotherapy in clinical trials.

<i>Body as a whole:</i>	hypersensitivity reaction, anaphylaxis and anaphylactic shock, ataxia, sepsis, chills and fever, asthenia, fever, rigor, headache, paresis, chest pain, fatigue
<i>Cardiovascular:</i>	cardiomyopathy, congestive heart failure, increased congestive heart failure, decreased ejection fraction, hypotension, pericardial effusion, bradycardia, cerebrovascular disorder
<i>Digestive:</i>	hepatocellular damage, diarrhoea, nausea and vomiting
<i>Haeme and lymphatic:</i>	leukaemia, febrile neutropenia, neutropenia, thrombocytopenia
<i>Infections:</i>	cellulitis, erysipelas
<i>Respiratory:</i>	bronchospasm, respiratory distress, acute pulmonary oedema, respiratory insufficiency, pneumonitis
<i>Skin and appendages:</i>	rash

Post-Marketing Experience

The following additional serious adverse reactions have been reported in at least one patient during post-marketing experience:

<i>Body as a whole:</i>	infusion-related symptoms, peripheral oedema, bone pain, coma, meningitis, cerebral oedema, abnormal thinking
<i>Cardiovascular:</i>	cardiac failure, cardiogenic shock, pericarditis, hypertension
<i>Digestive:</i>	pancreatitis, hepatic failure, jaundice
<i>Haeme and lymphatic:</i>	anaemia, hypoprothrombinaemia
<i>Musculoskeletal</i>	myalgia
<i>Respiratory:</i>	interstitial lung disease including pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema, respiratory insufficiency, pulmonary fibrosis, dyspnoea, hypoxia, laryngeal oedema,
<i>Renal:</i>	glomerulonephropathy, renal failure
<i>Skin and appendages:</i>	dermatitis, urticaria
<i>Special senses</i>	deafness

Interstitial lung disease

Risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy.

Overdosage

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

Pharmacological Properties and Effects

Pharmacodynamic Properties

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 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 25% - 30% of primary breast cancers and 6.8% - 42.6% of advanced gastric cancers. A consequence of HER2 gene amplification is an increase in HER2 protein expression on the surface of these tumour cells, which results in a constitutively activated HER2 receptor.

Studies indicate that patients whose tumours have amplification or overexpression of HER2 have a shortened disease-free survival compared to patients whose tumours do not have amplification or overexpression of HER2.

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.

Clinical efficacy studies

Metastatic Breast Cancer

Herceptin monotherapy or in combination with chemotherapy

Herceptin monotherapy has been used in clinical trials for patients with metastatic breast cancer who have tumours that overexpress HER2 and who have failed one or more chemotherapy regimens for their metastatic disease.

Herceptin has also been used in clinical trials in combination with paclitaxel or an anthracycline (doxorubicin or epirubicin) plus cyclophosphamide (AC) as first line therapy for patients with metastatic breast cancer who have tumours that overexpress HER2.

Patients who had previously received anthracycline-based adjuvant chemotherapy were treated with paclitaxel (175 mg/m² infused over 3 hours) with or without Herceptin. Patients could be treated with Herceptin until progression of disease.

Herceptin monotherapy, when used as second- or third-line treatment of women with metastatic breast cancer which overexpresses HER2, results in an overall tumour response rate of 15% and a median survival of 13 months.

The use of Herceptin in combination with paclitaxel as first-line treatment of women with metastatic breast cancer that overexpresses HER2 significantly prolongs the median time to disease progression, compared with patients treated with paclitaxel alone. The increase in median time to

disease progression for patients treated with paclitaxel is 3.9 months (6.9 months vs. 3.0 months). Tumour response and one year survival rate are also increased for Herceptin in combination with paclitaxel versus paclitaxel alone.

Herceptin has also been studied in a randomised, controlled trial, in combination with docetaxel, as first-line treatment of women with metastatic breast cancer. The combination of Herceptin and docetaxel significantly increased response rate (61% vs. 34%) and prolonged the median time to disease progression, (by 5.6 months) compared with patients treated with docetaxel alone. Median survival was also significantly increased in patients receiving the combination, compared with those receiving docetaxel alone (31.2 months vs. 22.7 months).

Herceptin in combination with anastrozole

The TAnDEM trial was a multi-centre, randomised, open-label, phase III study comparing Herceptin + anastrozole with anastrozole alone for the first-line treatment of metastatic breast cancer in HER2 overexpressing, hormone-receptor (i.e. oestrogen-receptor (ER) and/or progesterone-receptor (PR)) positive post-menopausal patients. Two hundred and seven patients were randomised to receive oral anastrozole (1 mg/day) with or without Herceptin (4 mg/kg loading dose, followed by 2 mg/kg weekly). Patients who had previously received Herceptin were excluded from this trial.

Median progression free survival was doubled in the Herceptin + anastrozole arm compared to the anastrozole alone arm (4.8 months vs. 2.4 months; $p = 0.0016$). For the other parameters, the improvements seen for Herceptin + anastrozole were; overall response (16.5% vs. 6.7%); clinical benefit rate (42.7% vs. 27.9%); time to progression (4.8 months vs. 2.4 months). For time to response and duration of response no difference could be recorded between the arms. There was no significant difference in overall survival, however, more than half of the patients in the anastrozole alone arm crossed over to a Herceptin-containing regimen after progression of disease.

Early Breast Cancer

In the adjuvant setting, Herceptin was investigated in a multicentre, randomised, trial (HERA) designed to compare one year of three-weekly Herceptin treatment versus observation in patients with HER2 positive early breast cancer following surgery, established chemotherapy and radiotherapy (if applicable). Patients assigned to receive Herceptin were given an initial loading dose of 8 mg/kg, followed by 6 mg/kg every three weeks for one year.

The efficacy results from the HERA trial are summarised in the following table:

Table 9: Efficacy Results from the HERA Trial (median follow-up of 2 years; intention-to-treat analysis)

Parameter	Observation <i>n</i> = 1698	Herceptin 1 Year <i>n</i> = 1703	<i>p</i> -value vs. Observation (log rank test)	Hazard Ratio vs. Observation (95% CI)
Disease-free survival - No. patients with event - No. patients without event	321 (18.9%) 1377 (81.1%)	218 (12.8%) 1485 (87.2%)	< 0.0001	0.64 (0.54 - 0.76)
Distant disease-free survival - No. patients with event - No. patients without event	233 (13.7%) 1465 (86.3%)	152 (8.9%) 1551 (91.1%)	< 0.0001	0.60 (0.49 - 0.73)
Overall survival (death) - No. patients with event - No. patients without event	90 (5.3%) 1608 (94.7%)	59 (3.5%) 1644 (96.5%)	= 0.0115	0.66 (0.47 - 0.91)

The hazard ratios translate into absolute benefits, in favour of the Herceptin arm, of a 3-year disease-free survival rate of 6.3 percentage points (80.6% vs. 74.3%) and a 3-year overall survival rate of 2.7 percentage points (92.4% vs. 89.7%).

Herceptin has also been investigated in the adjuvant setting in two phase III, multi-centre, randomised, open-label trials (NSABP B-31 and NCCTG N9831). The trials were designed to compare the efficacy and safety of adjuvant chemotherapy with or without Herceptin. Patients assigned to receive Herceptin were given an initial loading dose of 4 mg/kg, followed by 2 mg/kg once a week for a total of 52 weeks.

The US Food and Drug Administration (FDA) approved a joint-analysis plan to combine data from B-31 and N9831. In the combined analysis, the two concurrent chemotherapy + Herceptin arms (trastuzumab group) were compared with the two chemotherapy alone arms (control group).

Efficacy results from the combined analysis of the B-31 and N9831 trials are summarised in the following table:

Table 10: Efficacy Results from the B-31/N9831 Combined Analysis (median follow-up of 2 years; intention-to-treat analysis)

End point	Number of patients			Hazard Ratio (95% CI)	p-value* by log-rank test
	Trastuzumab Group n = 1672	Control Group n = 1679	Total n = 3351		
Disease-free survival	133	261	394	0.48 (0.39 - 0.59)	< 0.0001
Time to recurrence	117	235	352	0.47 (0.38 - 0.59)	< 0.0001
Time to distant recurrence	96	193	289	0.47 (0.37 - 0.61)	< 0.0001
Overall survival	62	92	154	0.67 (0.48 - 0.93)	0.015

* All p-values are two-sided.

Advanced Gastric Cancer

Study BO18255 (ToGA) was a randomised, open-label, multicentre phase III study investigating Herceptin in combination with a fluoropyrimidine and cisplatin (FP) versus chemotherapy alone as first-line therapy in patients with HER2 positive, inoperable, locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction.

Patients were eligible if they had 3+ levels of HER2 overexpression based on a 0 - 3+ scale by IHC assessment of tumour tissue and/or those whose tumours had HER2 gene amplification as determined by a FISH test (see Warnings and Precautions, Detection of HER2 Overexpression or HER2 Gene Amplification).

After satisfying the screening eligibility criteria, including assessment of HER2 status, patients were randomly assigned (1:1) to receive either Herceptin (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks) + fluoropyrimidine/cisplatin (FP+H) or FP alone. The chemotherapy regimen was chosen

between 5-FU/cisplatin and capecitabine/cisplatin at the investigator's discretion and could be determined on an individual patient basis.

The efficacy results from ToGA are summarised in Table 11. The primary endpoint was overall survival, defined as the time from the date of randomization to the date of death from any cause. At the time of analysis a total of 349 randomised patients had died: 182 patients (62.8%) in the control arm and 167 patients (56.8%) in the treatment arm. The majority of the deaths were due to events related to the underlying cancer.

Overall survival was significantly improved in the FP + H arm compared to the FP arm ($p = 0.0046$, log-rank test). The median survival time was 11.1 months with FP and 13.8 months with FP + H. The risk of death was decreased by 26% (HR = 0.74; 95% CI 0.60 - 0.91) for patients in the FP + H arm compared to the FP arm (4).

Post-hoc subgroup analyses indicate that targeting tumours with higher levels of HER2 protein (IHC 2+/FISH+ and IHC 3+/regardless of FISH status) results in a greater treatment effect. The median overall survival for the high HER2 expressing group was 11.8 months versus 16 months, HR = 0.65 (95% CI 0.51 - 0.83) and the median progression free survival was 5.5 months vs. 7.6 months, HR = 0.64 (95% CI 0.51 - 0.79).

Table 11: Summary of Efficacy from Study BO18255

Herceptin dosage regimen	Every 3 weeks			
Chemotherapy regimens (FP)	<ul style="list-style-type: none"> • Capecitabine: 1000 mg/m² orally twice daily for 14 days every 3 weeks for 6 cycles (Days 1 to 15 of each cycle). • 5-FU: 800 mg/m²/day as a continuous IV infusion over 5 days, given every 3 weeks for 6 cycles (Days 1 to 5 of each cycle). The 5-FU infusion could be started at the same time as the cisplatin infusion on Day 1. • Cisplatin: 80 mg/m² every 3 weeks for 6 cycles (on Day 1 of each cycle) as a 2h IV infusion with hydration and premedication (steroids and anti-emetics). 			
Efficacy Parameters	FP n=290	FP+H n=294	HR (95% CI)	p-value
Overall Survival, Median months	11.1	13.8	0.74 (0.60-0.91)	0.0046
Progression-Free Survival, Median months	5.5	6.7	0.71 (0.59-0.85)	0.0002
Time to Disease Progression, Median months	5.6	7.1	0.70 (0.58-0.85)	0.0003
Overall Response Rate, %	34.5	47.3	1.70 ^a (1.22, 2.38)	0.0017
Duration of Response, Median months	4.8	6.9	0.54 (0.40-0.73)	<0.0001

FP: Fluoropyrimidine/cisplatin; FP+H: Fluoropyrimidine/cisplatin + Herceptin; ^a Odds ratio

Progression-free-survival: time between day of randomization and first documentation of progressive disease (PD) or date of death, whichever occurred first. *Time to disease progression*: time between randomization and first occurrence of PD. *Overall response*: occurrence of either a confirmed complete (CR) or a partial (PR) best overall response as determined by RECIST criteria from confirmed radiographic evaluations of target and non-target

lesions. *Duration of response*: time from when response (CR or PR) was first documented to the first documented disease progression. This was only calculated for patients who had a best overall response of CR or PR.

Immunogenicity

Human anti-trastuzumab antibodies were detected in 1 of 903 patients, who had no allergic manifestations.

Pharmacokinetic Properties

The pharmacokinetics of trastuzumab has been studied in patients with metastatic breast cancer and early breast cancer. In Phase I studies, short duration intravenous infusions of 10, 50, 100, 250 and 500 mg trastuzumab once weekly in patients demonstrated dose-dependent pharmacokinetics. Mean half-life increased and clearance decreased with increased dose level.

Steady state pharmacokinetics in breast cancer

A population pharmacokinetic method, using data from Phase I, Phase II and pivotal Phase III studies, was used to estimate the steady state pharmacokinetics in patients with metastatic breast cancer administered trastuzumab at a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg. In this assessment, the typical clearance of trastuzumab was 0.241 L/day (for a body weight of 68 kg) and the typical volume of distribution of the central compartment V_c was 3.02 L, with a corresponding elimination half-life of approximately 3 weeks. These data are supported by the most recent population PK report which describes the clearance as 0.231 L/day and the volume of distribution of 2.79 L with a corresponding elimination half-life of approximately 3 weeks. Steady state pharmacokinetics therefore should be reached by approximately 15 weeks (105 days or 5 elimination half-lives). The same time interval would be predicted for trastuzumab elimination after discontinuation of Herceptin therapy.

An assessment in early breast cancer patients administered Herceptin at an initial loading dose of 8 mg/kg followed by a three weekly maintenance dose of 6 mg/kg achieved steady state trough concentrations of 63 mg/L, by cycle 13. The concentrations were comparable to those reported previously in patients with metastatic breast cancer.

The administration of concomitant chemotherapy (either anthracycline/cyclophosphamide, paclitaxel or docetaxel) did not appear to influence the pharmacokinetics of trastuzumab.

Steady state pharmacokinetics in advanced gastric cancer

A two compartment population pharmacokinetic method, using data from the Phase III study BO18255 (ToGA) was used to estimate the steady state pharmacokinetics in patients with advanced gastric cancer administered Herceptin 3-weekly at a loading dose of 8 mg/kg followed by a 3-weekly maintenance dose of 6 mg/kg. In this assessment, for a typical patient with gastric cancer (male weighing 68 kg and over expressing HER2), the clearance of trastuzumab was 0.378 L/day and the volume of distribution in the central compartment was 3.91 L, with a corresponding median elimination half-life of 14.5 days. The median predicted steady-state AUC values (over a period of 3 weeks at steady state) is equal to 1030 mg• day/L, the median steady-state C_{max} is equal to 128 mg/L and the median steady-state C_{min} values is equal to 23 mg/L.

Pharmacokinetics in Special Populations

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

Elderly

Age has been shown to have no effect on the disposition of trastuzumab (see Dosage and Administration).

Preclinical Safety

Teratogenicity

Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg Herceptin and have revealed no evidence of impaired fertility or harm to the foetus. However, when assessing the risk of reproductive toxicity to humans, it is also important to consider the significance of the rodent form of the HER2 receptor in normal embryonic development and the embryonic death in mutant mice lacking this receptor. Placental transfer of trastuzumab during the early (days 20 - 50 of gestation) and late (days 120 - 150 of gestation) foetal development period was observed.

Other

Lactation

A study conducted in lactating cynomolgus monkeys at doses 25 times that of the weekly human maintenance dose of 2 mg/kg Herceptin demonstrated that trastuzumab is secreted in the milk. The presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 1 month of age.

Pharmaceutical Particulars

Storage

Vials

Store vials at 2°C – 8°C.

This medicine should not be used after the expiry date shown on the pack.

Shelf-life of the reconstituted solution

Herceptin 440 mg vial

Reconstituted solutions made with Bacteriostatic Water for Injection for the 440 mg vial of Herceptin, as supplied, are stable for **28 days when stored refrigerated at 2 °C – 8 °C**. The reconstituted solution contains preservative and is therefore suitable for multiple use. Any remaining reconstituted

solution should be discarded after 28 days. If sterile water is used to reconstitute the 440 mg vial, the solution is stable for only **24 hours**, and must be discarded thereafter.

Do not freeze the reconstituted solution.

Herceptin 150 mg vial

The 150 mg vials are reconstituted with sterile water for injection and are for single use only.

The reconstituted product is physically and chemically stable for **48 hours at 2 °C – 8 °C** (refrigerate, do not freeze) after dissolving with water for injections.

From a microbiological point of view, the reconstituted solution should be further diluted immediately. If not further diluted immediately, in-use storage times and conditions prior to dilution are the responsibility of the user. The shelf-life of the reconstituted solution is **24 hours at 2 °C – 8 °C**, unless reconstitution has taken place in controlled and validated aseptic conditions in which case the shelf-life is **48 hours at 2 °C – 8 °C**.

Shelf-life of the solution for infusion containing the reconstituted product

The infusion solution (0.9% sodium chloride infusion solution) containing the reconstituted product is physically and chemically stable for **24 hours (do not store above 30 °C)**.

From a microbiological point of view, the Herceptin 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 to 8 °C**, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

Special Instructions for Use, Handling and Disposal

Appropriate aseptic technique should be used.

The 440 mg vial of Herceptin is reconstituted with 20 mL of Bacteriostatic Water for Injection, containing 1.1% benzyl alcohol, as supplied. This yields a solution for multiple use, containing 21 mg/mL trastuzumab, at a pH of approximately 6.0. Use of other reconstitution solvents should be avoided.

The 150 mg vial of Herceptin is reconstituted with 7.2 mL of sterile water for injection.

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

Instructions for reconstitution – 440 mg vial:

1. Using a sterile syringe, slowly inject 20 mL of sterile Bacteriostatic Water for Injection into the vial containing the lyophilised Herceptin, directing the stream into the lyophilised cake.
2. Swirl vial gently to aid reconstitution. **DO NOT SHAKE!**

Instructions for reconstitution – 150 mg vial:

- 1) Using a sterile syringe, slowly inject 7.2 mL of sterile water for injection into the vial containing the lyophilised Herceptin, 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 Herceptin results in a colourless to pale yellow transparent solution and should be essentially free of visible particles.

Instructions for dilution

Weekly schedule

Determine the volume of the reconstituted solution required based on a loading dose of 4 mg trastuzumab/kg body weight, or a maintenance dose of 2 mg trastuzumab/kg body weight:

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

Three-weekly schedule

Determine the volume of the reconstituted solution required based on a loading dose of 8 mg trastuzumab/kg body weight, or a maintenance dose of 6 mg trastuzumab/kg body weight:

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

Preparation and Stability of the Admixture

The appropriate amount of reconstituted solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of 0.9% sodium chloride. Dextrose (5%) solution should not be used (see 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 discoloration prior to administration. Once the infusion is prepared it should be administered immediately (see Storage).

Incompatibilities

No incompatibilities between Herceptin and polyvinylchloride, polyethylene or polypropylene bags have been observed.

Dextrose (5%) solution should not be used since it causes aggregation of the protein.

Herceptin should not be mixed or diluted with other medicines.

Disposal

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

Medicine Classification

Prescription medicine.



Packs

Herceptin 150 mg single-dose vials: each pack contains one vial of Herceptin (150 mg trastuzumab).

Herceptin 440 mg multi-dose vials: each pack contains one vial of Herceptin (440 mg trastuzumab) and one 20 mL vial of Bacteriostatic Water for Injection.

Name and Address

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