Attachment 1: Product information for AusPAR Herceptin Trastuzumab Roche Products Pty Ltd 2011-01528-3-4 Final 17 December 2012. This Product Information was approved at the time this AusPAR was published.

NAME OF THE MEDICINE

HERCEPTIN®

trastuzumab

CAS-180288-69-1

HERCEPTIN (trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). The antibody is an IgG_1 kappa that contains human framework regions with the complementarity-determining regions of a murine anti-p185 HER2 antibody that binds to HER2. Trastuzumab is composed of 1,328 amino acids and has a molecular weight of ~148 kDa.

The humanized antibody against HER2 is produced by recombinant mammalian cells (Chinese hamster ovary (rch)) in suspension culture in a nutrient medium and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.

DESCRIPTION

HERCEPTIN is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) infusion.

HERCEPTIN is available as a single-dose vial containing 60 mg or 150 mg of trastuzumab with the following excipients: histidine hydrochloride, histidine, trehalose dihydrate and polysorbate 20.

Reconstitution of the 60 mg vial with 3.0 mL of sterile water for injection yields 3.1 mL of a single-dose solution containing approximately 21 mg/mL trastuzumab, at a pH of approximately 6.0. A volume overage of 7.5% ensures that the labelled dose can be withdrawn from each vial.

Reconstitution of the 150 mg vial with 7.2 mL of sterile water for injection yields 7.4 mL of a single-dose solution containing approximately 21 mg/mL trastuzumab, at a pH of approximately 6.0. A volume overage of 4% ensures that the labelled dose can be withdrawn from each vial.

PHARMACOLOGY

Pharmacodynamics

The HER2 (or c-erbB2) proto-oncogene 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 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 overexpress HER2 have a particularly aggressive form of tumour and a shortened disease-free survival compared to patients whose tumours do not have amplification or overexpress 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. In animal models *in vivo*, murine anti-HER2 antibody inhibited the growth of human tumours overexpressing HER2, indicating that the humanized antibody (trastuzumab) is likely also to have anti-proliferative activity *in vivo* against human breast tumours expressing high levels of HER2.

Pharmacokinetics

The pharmacokinetics of trastuzumab have been studied in patients with breast cancer (metastatic and localised) and advanced gastric cancer. Formal drug-drug interaction studies have not been performed for HERCEPTIN.

Breast Cancer

Short duration IV infusions of 10, 50, 100, 250, and 500 mg HERCEPTIN once weekly in patients demonstrated non-linear pharmacokinetics where clearance decreased with increased dose.

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 metastatic breast cancer patients. For a typical patient (body weight of 68 kg) the clearance of trastuzumab was 0.241 L/day and volume of distribution of the central (Vc) and peripheral (Vp) compartments were 3.02 L, and 2.68 L respectively, with a corresponding elimination half-life ranging from approximately 28-38 days. These indicate steady state pharmacokinetics should therefore be reached by approximately 27 weeks, with median predicted AUC at steady state (over a three week period) of 1677 mg· day/L with weekly dosing and 1793 mg· day/L with 3-weekly (once every three weeks) dosing. The estimated median peak and trough concentrations were 104 mg/L and 64.9 mg/L (weekly) and 189 mg/L and 47.3 mg/L (3-weekly) respectively. Comparable steady state trough concentrations of 63 mg/L (by cycle 13) have been reported in localised breast cancer patients administered HERCEPTIN 3-weekly.

It is expected that serum trastuzumab levels will fall to less than 5% of the trough levels at steady state approximately 27 weeks (190 days or 5 elimination half-lives) after a dose discontinuation.

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

Detectable concentrations of the circulating extracellular domain of the HER2 receptor (shed antigen) are found in the serum of some patients with HER2 overexpressing tumours. Determination of shed antigen in baseline serum samples revealed that 64% (286/447) of patients had detectable shed antigen, which ranged as high as 1880 µg/L (median = 11 µg/L). Patients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations of trastuzumab. However, with weekly dosing, most patients with elevated shed antigen levels achieved target serum concentrations of trastuzumab (>20 mg/L) by week 6.

Gastric Cancer

Short duration IV infusions of 8 mg/kg followed by 6 mg/kg HERCEPTIN every 3 weeks in patients with advanced gastric cancer demonstrated concentration-dependent clearance comprised of predominantly linear and non-linear components. At very low serum concentrations (below 10µg/mL) non-linear clearance comprises nearly all of the total clearance (7-fold higher than linear clearance). At higher concentrations (25µg/mL) the non-linear clearance component decreases to approximately one-half of total clearance, whilst at higher concentrations (> 75µg/L) clearance becomes predominantly linear.

Steady State Pharmacokinetics in Advanced Gastric Cancer

A two compartment non-linear population pharmacokinetic model, based on data from the Phase III study BO18255 (ToGA) was used to estimate the steady state pharmacokinetics in patients with advanced gastric cancer administered HERCEPTIN at a loading dose of 8 mg/kg followed by a 3-weekly maintenance dose of 6 mg/kg. At high serum concentrations, total clearance is dominated by linear clearance and the half-life is approximately 26 days. Steady state C_{min} is reached in approximately 168 days, due to the non-linear clearance component. The mean predicted steady-state AUC value (over a period of 3 weeks at steady state) is approximately 1213 mg· day/L, and the mean steady-state C_{max} and C_{min} values are approximately 132 mg/L and 27.6 mg/L respectively. It is expected that serum trastuzumab levels will fall to less than 5% of the trough levels at steady state, approximately 19 weeks after a dose discontinuation.

There are no data on the level of circulating extracellular domain of the HER2 receptor (shed antigen) in the serum of gastric cancer patients.

Pharmacokinetics in Special Populations

Detailed pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. The data from Study H0649g suggest that the disposition of trastuzumab is not altered by patient characteristics such as age or serum creatinine. The population pharmacokinetic analysis also shows that the estimated creatinine clearance (Cockcroft and Gault) does not correlate with the pharmacokinetics of trastuzumab.

Use in Elderly: Age has been shown to have no effect on the disposition of trastuzumab (see **DOSAGE AND ADMINISTRATION**).

CLINICAL TRIALS

Locally Advanced Breast Cancer

Locally advanced breast cancer is defined as the absence of metastatic disease and meeting one or more of the following criteria: inflammatory breast cancer, a primary tumour that extends to the chest wall or skin, tumour > 5 cm with any positive lymph node(s), any tumour with disease in supraclavicular nodes, infraclavicular nodes or internal mammary nodes, any tumour with axillary lymph nodes fixed to one another or other structures.

HERCEPTIN in Combination with Neoadjuvant Chemotherapy

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The use of HERCEPTIN for the neoadjuvant-adjuvant treatment of locally advanced breast cancer has been studied in Study MO16432 (NOAH), a multicentre randomized trial, designed to investigate the concurrent administration of HERCEPTIN with neoadjuvant chemotherapy, including both an anthracycline and a taxane, followed by adjuvant HERCEPTIN, up to a total treatment duration of 1 year. The study recruited patients with newly diagnosed locally advanced (Stage III) or inflammatory breast cancer. Patients with HER2+ tumours were randomized to receive either neoadjuvant chemotherapy concurrently with neoadjuvant-adjuvant HERCEPTIN (*n* = 116), or neoadjuvant chemotherapy alone (*n* = 118).

HERCEPTIN was administered concurrently with 10 cycles of neoadjuvant chemotherapy as follows;

- Doxorubicin (60 mg/m^2) and paclitaxel (150 mg/m^2) in combination with HERCEPTIN (8 mg/kg loading dose, followed by 6 mg/kg maintenance, administered 3-weekly) for 3 cycles, followed by
- Paclitaxel (175 mg/m^2) and HERCEPTIN (6mg/kg, administered 3-weekly) for 4 cycles, followed by
- CMF on day 1 and 8 every 4 weeks for 3 cycles, in combination with 4 cycles of HERCEPTIN (6mg/kg administered 3-weekly), followed by
- up to 7 additional cycles of HERCEPTIN (6mg/kg, administered 3-weekly) alone to complete 1 year after starting HERCEPTIN

The primary endpoint for the study, event-free survival (EFS), was defined as the time from randomization to disease recurrence or progression (local, regional, distant or contralateral), or death of any cause. The efficacy results from NOAH (full analysis population, defined as all patients who were randomized in the study following the intent-to-treat principle, with the exception of 3 patients whose data could not be evaluated) are summarized in the table below. The median duration of follow-up in the HERCEPTIN arm was 3.8 years.

Table 1: Overview of Efficacy Analyses MO16432 (NOAH)

Parameter	**Chemo + Herceptin *n* = 115**	**Chemo only *n* = 116**	**p-value**	**HR (95% CI)**
Event-free survival (EFS)				
No. patients with event	46	59	p = 0.0275	0.65 (0.44, 0.96)
Total pathological complete response^	40%	20.7%		
(95% CI)	(31.0, 49.6)	(13.7, 29.2)	p = 0.0014	

^ defined as absence of any invasive cancer both in the breast and axillary nodes; HR: hazard ratio

The addition of HERCEPTIN to neoadjuvant chemotherapy, followed by adjuvant HERCEPTIN for a total duration of 52 weeks, resulted in a 35% reduction in the risk of disease recurrence/progression. The hazard ratio translates into an absolute benefit, in terms of 3-year event-free survival rate estimates of 13 percentage points (65 % vs. 52 %) in favour of the HERCEPTIN arm.

To date, results are not available comparing the efficacy of HERCEPTIN administered with chemotherapy in the adjuvant setting with that obtained in the neoadjuvant/adjuvant setting.

Localised Breast Cancer

Localised breast cancer is defined as non-metastatic, primary, invasive carcinoma of the breast.

HERCEPTIN in Combination with Adjuvant Chemotherapy

The use of HERCEPTIN in the setting of localised breast cancer (after surgery and in association with chemotherapy and, if applicable, radiotherapy) has been studied in four multicentre randomized phase III trials of patients with HER2 positive breast cancer who have completed surgery. In these clinical trials, localised breast cancer was limited to operable, primary adenocarcinoma of the breast with positive axillary nodes or node negative disease with additional indicators of a higher degree of risk. The design of these studies is summarized in Table 2 and efficacy results are presented in Tables 3-6.

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Table 2: Clinical Trials in Localised Breast Cancer

	HERA trial ***n* = 3386**	**NSAPB B-31 and NCCTG N9831 trials (joint analysis)** ***n* = 3763**	**BCIRG 006** ***n* = 3222**
Eligible patients	Node positive or node negative [*n* = 1098] and tumour size >1 cm; *Protocol initially unrestricted but amended and node negative patients with tumours ≤1 cm [n =93, 8.5%] and node negative patients with tumours >1 and ≤2 cm [n = 509,46.4%] were included*	Node positive or node negative [*n* = 190] and tumour size • >2 cm regardless of hormonal status; or • >1 cm and ER–ve [*n* = 63 node-negative and tumour size ≤2 cm])	Node positive or node negative and at least 1 of the following: • tumour size > 2 cm and ER and PR -ve, or • histologic and/or nuclear grade 2-3, or • age < 35 years.
Herceptin dosage regimen	Loading dose 8 mg/kg, followed by 6 mg/kg (q3w)	Loading dose 4 mg/kg, followed by 2 mg/kg (q1w)	Loading dose 4 mg/kg, followed by 2 mg/kg (q1w). After chemo, 6 mg/kg (q3w)
Duration of Herceptin treatment	52 weeks	52 weeks	52 weeks
Chemotherapy regimen(s)	Various	AC (q3w) followed by IV paclitaxel as a continuous IV infusion (**AC→P)**. Paclitaxel: 80 mg/m^2 q1w for 12 weeks or 175 mg/m^2 q3w for 4 cycles (day 1 of each cycle)	AC followed by docetaxel **(AC→D)** or docetaxel and carboplatin (**DCarb)** Docetaxel (IV infusion over 60 min): **(AC→D):** 100 mg/m^2 q3w for 4 cycles or **(DCarb):** 75 mg/m^2 q3w for 6 cycles Carboplatin (at target AUC): 6 mg/mL/min (IV infusion over 30 - 60 min) q3w for a total of 6 cycles.
Timing of Herceptin in relation to chemotherapy	After completion of (neo)adjuvant [a]	Concurrent **(AC→PH)** or sequential (**AC→P→H)**	Concurrent **(AC→DH** and **DCarbH)**
Median follow-up	1 year (initial evaluation) [2 years (follow-up evaluation [b])]	2 years	3 years

AC = doxorubicin + cyclophosphamide; q3w = every 3 weeks; q1w = weekly chemo = chemotherapy; [a] 89% of subjects received adjuvant chemotherapy; 5% received neoadjuvant chemotherapy and 6% received a combination of neoadjuvant and adjuvant chemotherapy. [b] The 2 year follow-up analysis of the 1 year treatment and observation arms of the HERA study had data based on published literature and was not evaluated in detail by the TGA.

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

Table 3: Efficacy Results from the HERA Trial

Parameter	**Observation**	**Herceptin**	**p-value**	**HR (95% CI)**
<u>Disease recurrence</u>				
Rate (Herceptin vs. observation) (1 year analysis)	12.9%	7.5%	<0.0001	0.54 (0.44,0.67)
Rate (Herceptin vs. observation) (2 year analysis [a])	18.9%	12.8%	<0.0001	0.64 (0.54,0.76)
<u>Survival</u>				

Deaths (Herceptin vs. observation) (1 year analysis)	2.4%	1.8%	0.24	0.75 (0.47,1.21)
Deaths (Herceptin vs. observation) (2 year analysis [a])	5.3%	3.5%	0.0115	0.66 (0.47,0.91)

HR: Hazard ratio; [a] The 2 year follow-up analysis of the 1 year treatment and observation arms of the HERA study had data based on published literature and was not evaluated in detail by the TGA.

The HERA study included a subgroup of patients (*n* = 602) with small tumours (<2 cm) and node-negative disease. In this subgroup, the relative risk reduction was similar to the overall trial population (HR = 0.50; 95% CI 0.21 - 1.15). However, the benefit in terms of absolute difference in rate of recurrence after 1 year of follow-up was smaller (2.7% recurrence rate with Herceptin vs. 5.5% with observation).

The efficacy results from the joint analysis of the NCCTG 9831 and NSABP B-31 trials are summarized in the following table:

Table 4: Efficacy Results from NSAPB B-31 and NCCTG N9831 trials (joint analysis)

Parameter	**AC→P**	**AC→PH**	**p-value**	**HR (95% CI)**
Disease recurrence Rate (Herceptin vs. observation)	15.5%	8.0%	< 0.0001	0.48 (0.39, 0.59)
Survival Deaths (Herceptin vs. observation)	5.5%	3.7%	0.014	0.67 (0.48, 0.92)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: Herceptin; HR: Hazard ratio

The efficacy results from the BCIRG 006 are summarized in the following tables:

Table 5: Overview of Efficacy Analyses BCIRG 006 AC→D versus AC→DH

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

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

Table 6: Overview of Efficacy Analyses BCIRG 006 AC→D versus DCarbH

Parameter	**AC→D *n* = 1073**	**DCarbH *n* = 1075**	**p-value**	**HR (95% CI)**
Disease-free survival (DFS) No. patients with event	195	145	0.0003	0.67 (0.54, 0.83)
Death (OS event) No. patients with event	80	56	0.00182	0.66 (0.47,0.93)

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

The optimal duration of adjuvant trastuzumab therapy is not known and may be clarified only in further randomized trials. Outcomes of an alternative dosage schedule involving treatment for nine weeks are reported in a published paper of trial data (Joensuu et al, 2006. *NEJM).*

Metastatic Breast Cancer

There are no data available to establish the efficacy of HERCEPTIN for the treatment of metastatic disease in patients who have previously received the medicine for the treatment of localised disease.

The safety and efficacy of HERCEPTIN has been studied in randomized, controlled clinical trials in combination with chemotherapy (Studies H0648g, M77001 and TaNDEM) and in an open-label monotherapy clinical trial (Study H0649g) for the treatment of metastatic breast cancer. All trials studied patients with metastatic breast cancer whose tumours overexpress HER2. Patients were eligible if they had 2+ or 3+ levels of overexpression based on a 0 - 3+ scale by immunohistochemical (IHC) assessment of tumour tissue or whose tumours have HER2 gene amplification as determined by Fluorescence In Situ Hybridization (FISH) test (see **DOSAGE AND ADMINISTRATION, Detection of HER2 Overexpression or HER2 Gene Amplification**).

HERCEPTIN in Combination with Chemotherapy

Study H0648g was an open-label, randomized controlled, multinational trial of chemotherapy-alone and in combination with HERCEPTIN. Patients with previously untreated metastatic breast cancer were treated with either an anthracycline (doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2) plus cyclophosphamide (600 mg/m^2) with or without HERCEPTIN or paclitaxel (175 mg/m^2 infused over 3 hours) with or without HERCEPTIN. Patients on HERCEPTIN treatment received 4 mg/kg intravenous loading dose on Day 0, followed by weekly infusions of 2 mg/kg from Day 7, which they could continue to receive until evidence of disease progression. Patients who had previously received anthracycline based adjuvant therapy were treated with paclitaxel whereas those who were anthracycline naïve were treated with an anthracycline + cyclophosphamide.

The prospectively defined, primary intent-to-treat analysis indicated that the combination of HERCEPTIN and chemotherapy significantly prolonged time to disease progression (progression-free survival) compared with chemotherapy-alone as first-line treatment of women with metastatic breast cancer who had tumours that overexpressed HER2. The addition of HERCEPTIN to chemotherapy extended the median time to disease progression by 2.8 months representing a 61% increase (p=0.0001).

Both anthracycline-treated and paclitaxel-treated patients benefited from HERCEPTIN treatment, although the effect appeared to be greater in the paclitaxel stratum. The efficacy of HERCEPTIN treatment was further supported by the secondary endpoints of response rate, duration of response and one-year survival (see Table 7 below).

One-year survival rates (the prospectively defined survival endpoint) were significantly better for the HERCEPTIN + chemotherapy versus chemotherapy-alone (79% vs. 68%; p=0.008). With a median follow-up of approximately two years, overall survival is improved for patients initially treated with HERCEPTIN + chemotherapy compared with those receiving chemotherapy-alone (25.4 vs. 20.3 months; p=0.025) with a relative risk of death of 0.769 (95% CI 0.607 - 0.973; p=0.028).

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Figure 1 Survival Time: Anthracycline ± HERCEPTIN (Study H0648g)

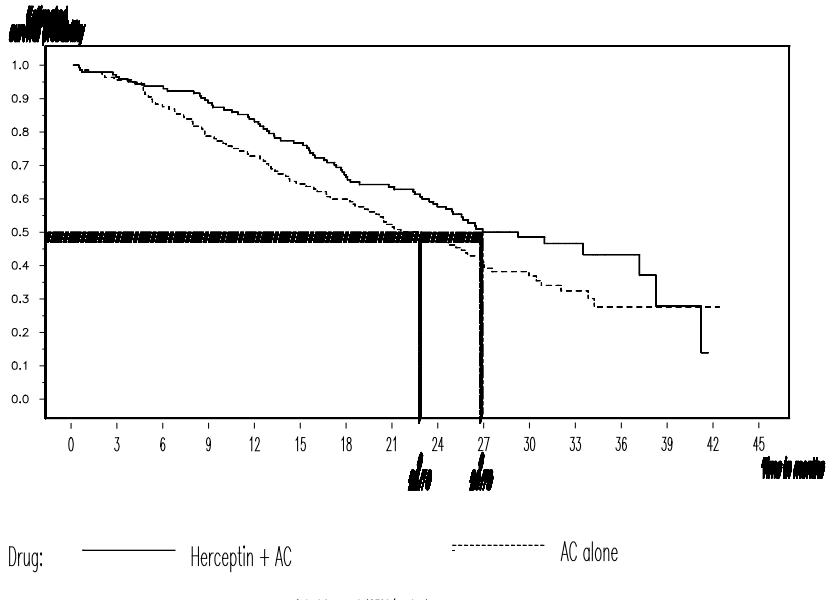
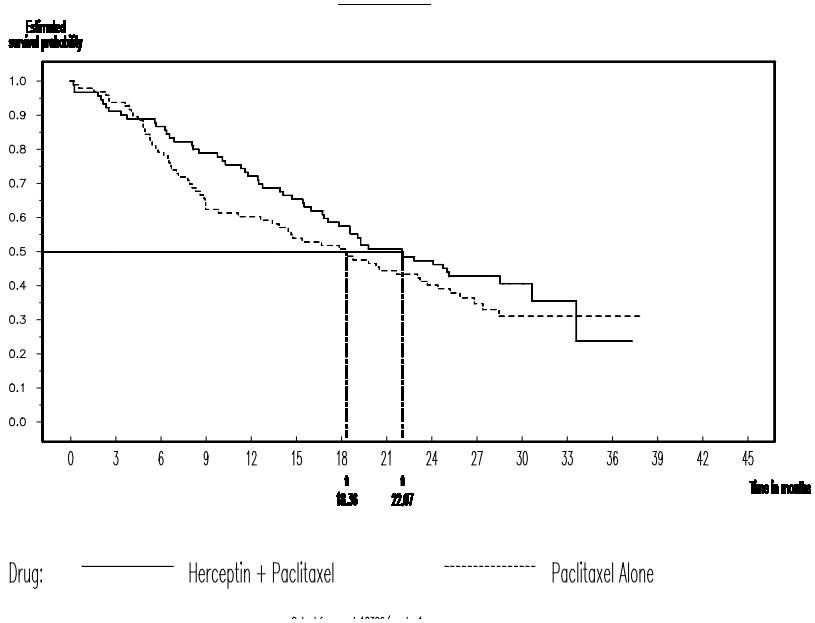


Figure 2 Survival Time: Paclitaxel ± HERCEPTIN (Study H0648g)

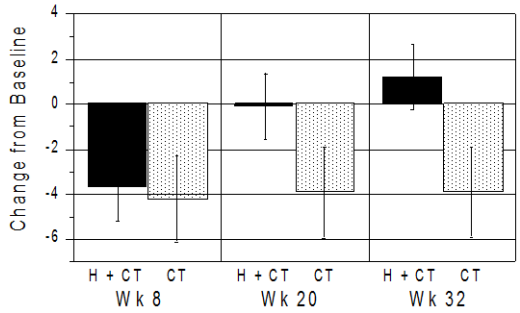


The relative overall survival advantage with the addition of HERCEPTIN was observed in both subgroups: AC [26.8 months (H + AC) vs. 22.8 months (AC-alone); *p*=0.052] and paclitaxel [22.1 months (H + P) vs. 18.4 months (P-alone); *p*=0.273] (see also Figures 1 and 2). The analysis of overall survival was, however, greatly confounded by subsequent HERCEPTIN treatment of each of control arms' patients, following disease progression, in the open-label extension study, H0659g (59%

of patients in the AC-alone group, and 75% of patients in the paclitaxel-alone group subsequently received HERCEPTIN). Hence, the survival advantage seen above, for HERCEPTIN + chemotherapy treatment versus chemotherapy-alone (which includes patients who subsequently received HERCEPTIN) may underestimate the benefit to patients.

Importantly, the efficacy described above was obtained without a significant negative impact on the quality of life. Global quality of life decreased equally in both the chemotherapy-alone group and the HERCEPTIN + chemotherapy group and was most likely related to the effects of cytotoxic chemotherapy. However, at weeks 20 and 32, the global quality of life score had returned to baseline or better than baseline in the group receiving HERCEPTIN + chemotherapy, while it remained low in the chemotherapy-alone arm (see Figure 3 below).

Figure 3 Changes from Baseline in Health-Related Quality-of-Life Scores in Study H0648g



H = HERCEPTIN; CT = chemotherapy

Study M77001 was a multinational, multi-centre, randomized, controlled trial investigating the safety and efficacy of HERCEPTIN in combination with docetaxel, as first-line treatment in HER2 positive metastatic breast cancer patients. One hundred and eighty six patients received docetaxel (100 mg/m^2 infused over 1 hour on Day 2) with or without HERCEPTIN (4 mg/kg loading dose, followed by 2 mg/kg weekly). Sixty percent of patients had received prior anthracycline based adjuvant chemotherapy. HERCEPTIN with docetaxel was shown to be efficacious in patients whether or not they had received prior adjuvant anthracyclines and regardless of their estrogen and/or progesterone receptor status.

The combination of HERCEPTIN + docetaxel significantly increased response rate (61% vs. 34%) and prolonged the median time to disease progression by 4.9 months compared with patients treated with docetaxel-alone (see Table 7). Median survival was also significantly increased in patients receiving the combination therapy compared with those receiving docetaxel-alone (30.5 months vs. 22.1 months) (see Figure 4).

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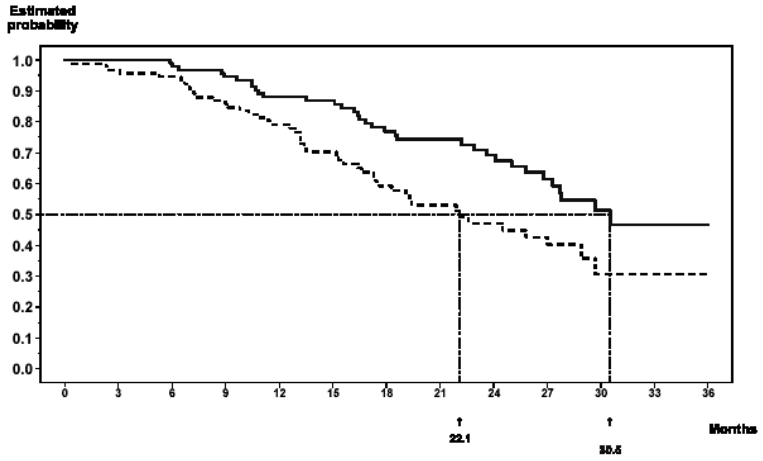
Figure 4 Survival Time: Docetaxel ± HERCEPTIN (Study M77001)



Drug: ——— Herceptin + docetaxel ---------- docetaxel-alone

Table 7: Efficacy Outcomes with Combination Therapy for Metastatic Breast Cancer

	H0648g						M77001	
	H + chemo ***n* = 235**	**Chemo alone** ***n* = 234**	**H + AC** ***n* = 143**	**AC alone** ***n* = 138**	**H + P** ***n* = 92**	**P alone** ***n* = 96**	**H + D** ***n* = 92**	**D alone** ***n* = 94**
Median Time to Disease Progression (months, 95% CI)	7.4 (7.0, 9.0)	4.6 (4.4, 5.4)	7.8 (7.3, 9.4)	6.1 (4.9, 7.1)	6.9 (5.3, 9.9)	3.0 (2.1, 4.3)	10.6 (7.6, 12.9)	5.7 (5, 6.5)
***p*-value** [a]	*p*=0.0001		*p*=0.0004		*p*=0.0001		*p*=0.0001	
Response Rate (%)	50	32	56	42	41	17	61	34
***p*-value** [b]	*p*<0.0001		*p*=0.0197		*p*=0.0002		*p*=0.0002	
Median Duration of Response (months, 95% CI)	9.1 (7.7,11)	6.1 (5.5,7.8)	9.1 (7.4,12.2)	6.7 (5.8, 8.2)	10.5 (7.3, 12.5)	4.5 (3.9, 6.4)	11.4 (8.3, 15.0)	5.5 (4.4, 6.2)
***p*-value** [a]	*p*=0.0002		*p*=0.0047		*p*=0.0124		*p*=0.0002	
Overall Survival (months, 95% CI)	24.8 (22.3,33.7)	20.5 (17.9,25.3)	33.4 (22.8,38.1)	22.8 (18.3,29.8)	22.1 (16.9,33.7)	18.4 (12.7,23.8)	30.5 (26.8, ne)	22.1 (17.6, 28.9)
***p*-value** [a]	*p*=0.0540		*p*=0.1021		*p*=0.2597		*p*=0.0062	

H = HERCEPTIN; Chemo = chemotherapy; AC = anthracycline + cyclophosphamide; P = paclitaxel; D = docetaxel

[a] *p* = log-rank test; [b] *p* = Chi-square test, ne = could not be estimated or not yet reached.

HERCEPTIN in Combination with Anastrozole

The TAnDEM trial was a multi-centre, randomized, 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 randomized 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 received HERCEPTIN for localised disease 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.

HERCEPTIN Monotherapy

Study H0649g was a multinational, multi-centre, single arm trial of HERCEPTIN as monotherapy in 222 women with HER2 overexpressing metastatic breast cancer. All patients had relapsed following treatment with the best available agents (e.g. anthracyclines and taxanes) and were heavily pre-treated. Two-thirds of the patients had prior adjuvant chemotherapy and all patients had tumour progression following at least one prior regimen of cytotoxic chemotherapy for metastatic disease. Ninety-four percent of the patients had prior anthracycline therapy, approximately 60% had prior paclitaxel therapy and 26% had prior bone marrow or stem cell transplants. Together with HER2 overexpression, which is associated with poorer clinical outcomes, aggressive disease was also suggested by nodal status at diagnosis and by the disease-free interval. Twenty-seven percent of patients had 10 or more positive nodes at the time of diagnosis. Thirty-eight percent of patients had a disease-free interval of less than one year prior to enrolment.

Patients received an intravenous loading dose of 4 mg/kg HERCEPTIN on Day 0, followed by weekly intravenous infusions of 2 mg/kg until there was evidence of disease progression. Patients who developed progressive disease could stop treatment, continue on the 2 mg/kg weekly dose or receive an increased intravenous dose of 4 mg/kg, as the investigator deemed appropriate. The primary efficacy parameter was tumour response rate.

HERCEPTIN as second- or third-line therapy induced objective, durable tumour responses in women with metastatic breast cancer who had tumours that overexpressed HER2. There were 8 complete responses and 26 partial responses yielding an overall response rate of 15%. The durability of the responses was particularly notable. The median duration of the responses was 9.1 months at the cut-off date for analysis (see Table 8 below).

Table 8: Efficacy Outcomes with Monotherapy Study H0649g

Outcome Measure	n	Time (months) Kaplan-Meier Estimate of Median (range)
Duration of response	34	9.1 (2–26+)
Time to disease progression	213	3.1 (0–28+)
Time to Treatment Failure	213	2.4 (0–28+)
Survival Time	213	12.8 (0.5–30+)

The clinical significance of the objective tumour responses in this group of patients was supported by the quality-of-life and survival data. Responders had clinically meaningful improvements in physical function, role function, social function, global quality of life and fatigue scale scores during HERCEPTIN treatment. Most responders were still alive at data cut-off (28/34; 82%). The Kaplan-Meier estimate of median survival for all treated patients at the data cut-off date was 12.8 months.

Evidence of efficacy for HERCEPTIN monotherapy is based upon response rates. No data are available to demonstrate improvement in survival or quality of life.

Advanced Gastric Cancer

Study BO18255 (ToGA) was a randomized, 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 **DOSAGE AND ADMINISTRATION, 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 summarized in Table 9. 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 randomized patients had died: 182 patients (62.8%) in the control arm and 167 patients (56.8%) in the treatment arm. The majority of the deaths were due to events related to the underlying cancer.

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.

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 9: Summary of Efficacy from Study BO18255

Herceptin dosage regimen	Every 3 weeks			
Chemotherapy regimens (FP)	• Capecitabine: 1000 mg/m^2 orally twice daily for 14 days every 3 weeks for 6 cycles (Days 1 to 15 of each cycle). • 5-FU: 800 mg/m^2/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/m^2 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

Nine hundred and three patients treated with HERCEPTIN, alone or in combination with chemotherapy, have been evaluated for antibody production. Human anti-trastuzumab antibodies were detected in 1 patient, who had no allergic manifestations.

INDICATIONS

Localised Breast Cancer

HERCEPTIN is indicated for the treatment of HER2-positive localised breast cancer following surgery, and in association with chemotherapy and, if applicable, radiotherapy.

Locally Advanced Breast Cancer

HERCEPTIN is indicated for the treatment of HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant HERCEPTIN.

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;

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.

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.

CONTRAINDICATIONS

HERCEPTIN is contraindicated in patients with known hypersensitivity to trastuzumab, Chinese hamster ovary cell proteins or to any other component of the product.

In the treatment of localised or locally advanced breast cancer, HERCEPTIN is contraindicated in patients with a left ventricular ejection fraction of less than 45% and those with symptomatic heart failure.

Attachment 1: Product information for AusPAR Herceptin Trastuzumab Roche Products Pty Ltd 2011-01528-3-4 Final 17 December 2012. This Product Information was approved at the time this AusPAR was published.

PRECAUTIONS

General

HERCEPTIN therapy should only be initiated under the supervision of a physician experienced in the treatment of cancer patients. Usual clinical care should be taken to prevent microbial contamination of the intravenous access sites used to deliver HERCEPTIN therapy. 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.

If HERCEPTIN is used concurrently with cytotoxic chemotherapy, the specific guidelines used to reduce or hold the dose of chemotherapy should be followed. Patients may continue HERCEPTIN therapy during periods of reversible chemotherapy-induced myelosuppression, renal toxicity or hepatic toxicity.

Cardiotoxicity

Heart failure (New York Heart Association [NYHA] class II-IV) has been observed in patients receiving HERCEPTIN therapy alone or in combination with chemotherapy. This may be moderate to severe and has been associated with death.

Caution should be exercised in treating patients with symptomatic heart failure, a history of hypertension, or documented coronary artery disease. 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 during treatment (e.g. every 3 months). 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.

As the half-life of trastuzumab is approximately 28 – 38 days, trastuzumab may persist in the circulation for up to 27 weeks after stopping HERCEPTIN treatment (see **Pharmacokinetics**). Patients who receive anthracycline after stopping HERCEPTIN may also be at increased risk of cardiac dysfunction. If possible, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping HERCEPTIN. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

If LVEF drops 10 percentage points from baseline (and to below 50% in patients with a normal baseline measurement) HERCEPTIN should be withheld and a repeat LVEF assessment performed within approximately 3 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

The probability of cardiac dysfunction was highest in patients who received HERCEPTIN concurrently with anthracyclines. As the mean terminal half-life of HERCEPTIN is approximately 28 - 38 days, trastuzumab may persist in the circulation for up to 27 weeks after stopping treatment (see **Pharmacokinetics**). 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. The data also suggests that advanced age may increase the probability of cardiac dysfunction.

For localised or locally advanced breast cancer, all patients should have a determination of left ventricular ejection fraction (LVEF) prior to treatment. Use of HERCEPTIN is contraindicated in patients with localised or locally advanced disease and a LVEF of less than 45% and those with symptomatic heart failure. Patients with a LVEF of 45 - 55% at baseline should be monitored regularly for symptoms of heart failure during HERCEPTIN treatment.

In localised breast cancer (HERA trial) and locally advanced breast cancer (NOAH trial), the following patients were excluded; therefore, there are no data about the risk/benefit ratio 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

In locally advanced breast cancer (NOAH trial), the following patients were also excluded; therefore, there are no data about the risk/benefit ratio and, consequently, treatment cannot be recommended in such patients:

- Patients with New York Heart Association (NYHA) class ≥ II disease i.e. cardiac disease with limitation of physical activity.
- Patients with LVEF < 55% by MUGA scan or echocardiography.

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).

Hypersensitivity Reactions including Anaphylaxis

Severe hypersensitivity reactions have been infrequently reported in patients treated with HERCEPTIN. Signs and symptoms include anaphylaxis, urticaria, bronchospasm, angioedema, and/or hypotension. In some cases, the reactions have been fatal. The onset of symptoms generally occurred during an infusion, but there have also been reports of symptom onset after the completion of an infusion. Reactions were most commonly reported in association with the initial infusion.

HERCEPTIN infusion should be interrupted in all patients with severe hypersensitivity reactions. In the event of a hypersensitivity reaction, appropriate medical therapy should be administered, which may include adrenaline, corticosteroids, diphenhydramine, bronchodilators and oxygen. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.

Infusion Reactions

In clinical trials, infusion reactions consisted of a symptom complex characterized by fever and chills, and on occasion included nausea, vomiting, pain (in some cases at tumour sites), headache, dizziness, dyspnoea, hypotension, rash, asthenia and hypertension. These reactions were usually mild to moderate in severity (see **ADVERSE EFFECTS**).

In the post-marketing setting, rare occurrences of severe infusion reactions leading to a fatal outcome have been associated with the use of HERCEPTIN. More severe adverse reactions to HERCEPTIN infusion reported include bronchospasm, hypoxia and severe hypotension. These severe reactions were usually associated with the initial infusion of HERCEPTIN and generally occurred during or immediately following the infusion. However, the onset and clinical course were variable. For some patients, symptoms progressively worsened and led to further pulmonary complications (see **Pulmonary Events**). In other patients with acute onset of signs and symptoms, initial improvement was followed by clinical deterioration. Delayed post-infusion events with rapid clinical deterioration have also been reported. Rarely, severe infusion reactions culminated in death within hours or up to one week following an infusion.

HERCEPTIN should be discontinued in the event of a severe infusion related reaction, until resolution of the symptoms. Serious reactions have been treated successfully with supportive therapy such as oxygen, intravenous fluids, beta-agonists and corticosteroids.

Pulmonary Events

Severe pulmonary events leading to death have been reported with the use of HERCEPTIN in the post-marketing setting. Signs, symptoms and clinical findings include dyspnoea, interstitial lung disease including lung infiltrates, pleural effusions, respiratory distress, non-cardiogenic pulmonary oedema, pulmonary insufficiency, hypoxia, pneumonitis, pulmonary fibrosis and acute respiratory distress syndrome and pneumonia. Interstitial pneumonitis has been reported as a rare but serious complication in clinical trials of HERCEPTIN in localised breast cancer. These events may occur as part of an infusion-related reaction (see **Infusion Reactions**) 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 and should only be treated with HERCEPTIN following consideration of the risk versus benefit.

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.

Effects on Fertility

A study in female cynomolgus monkeys revealed no evidence of impaired fertility at intravenous trastuzumab doses up to 25 mg/kg twice weekly, corresponding to serum trough levels (serum C_{min}) about 15 times higher than that in humans receiving the recommended weekly dose of 2 mg/kg. However, the binding affinity of trastuzumab to epidermal growth factor receptor 2 protein in cynomolgus monkeys is unclear (see **Use in Pregnancy**).

Use in Pregnancy – Category B2

In studies in cynomolgus monkeys, placental transfer of trastuzumab was observed during the early (days 20 - 50 of gestation) and late (days 120 - 150 of gestation) foetal development period. No evidence of harm to the foetus was seen in cynomolgus monkeys at intravenous trastuzumab doses up to 25 mg/kg twice weekly, corresponding to serum trough levels (serum C_{min}) about 15 times higher than that in humans receiving the recommended weekly dose of 2 mg/kg. However, the binding affinity of trastuzumab to epidermal growth factor receptor 2 protein in cynomolgus monkeys is unclear.

It is not known whether HERCEPTIN can affect reproductive capacity. As the animal studies of trastuzumab may not be relevant to human, HERCEPTIN should be avoided during pregnancy and since trastuzumab may persist in the circulation for up to 27 weeks, pregnancy should be avoided for 6 months after the last dose of HERCEPTIN, unless the anticipated benefit for the mother outweighs the unknown risk to the foetus.

In the post-marketing setting, cases of foetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving 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.

Use in Lactation

A study conducted in lactating cynomolgus monkeys dosed intravenously with trastuzumab at 25 mg/kg twice weekly (serum C_{min} about 15 times higher than that in humans receiving the recommended weekly dose of 2 mg/kg) demonstrated that trastuzumab is excreted in the milk. The presence of trastuzumab in the serum of infant monkeys was not associated with adverse effects on their growth or development from birth to 1 month of age. However, the binding affinity of trastuzumab to epidermal growth factor receptor 2 protein in cynomolgus monkeys is unclear.

It is not known whether trastuzumab is excreted 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.

Paediatric Use

The safety and efficacy of HERCEPTIN in patients under the age of 18 years have not been established.

Use in the Elderly

HERCEPTIN has been administered to 133 patients who were 65 years of age or over. The risk of cardiac dysfunction may be increased in elderly patients. The reported clinical experience is not adequate to determine whether older patients respond differently from younger patients. Elderly patients did not receive reduced doses of HERCEPTIN in clinical trials. However, greater sensitivity to HERCEPTIN in some older patients cannot be ruled out.

Genotoxicity

Trastuzumab did not induce gene mutations in bacteria, nor did it cause chromosomal damage *in vitro* (chromosome aberration assay in human lymphocytes) or *in vivo* (mouse micronucleus test).

Carcinogenicity

No studies on the carcinogenic potential of HERCEPTIN have been conducted to date.

Use in Renal Impairment

Data suggest that the disposition of HERCEPTIN is not altered based on serum creatinine levels up to 177 µmol/L (see **Pharmacokinetics**).

Use in Hepatic Impairment

The use of HERCEPTIN in patients with hepatic impairment has not been studied.

INTERACTIONS WITH OTHER MEDICINES

No formal drug interaction studies have been performed with HERCEPTIN in humans. Clinically significant interactions with concomitant medication used in clinical trials have not been observed. A comparison of serum levels of HERCEPTIN given in combination with cisplatin, doxorubicin or epirubicin-plus-cyclophosphamide has not suggested the possibility of any interaction.

Administration of paclitaxel in combination with HERCEPTIN resulted in a slightly less than two-fold decrease in trastuzumab clearance in a non-human primate study and in a 1.5-fold increase in HERCEPTIN serum levels in clinical studies. 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.

A pharmacokinetic interaction substudy of BO18255 (ToGA) performed in male and female Japanese patients with advanced gastric cancer showed that co-administration of trastuzumab and capecitabine and cisplatin had no significant effects on the pharmacokinetics of the two chemotherapy agents

compared with co-administration of the two agents without trastuzumab. The pharmacokinetics of trastuzumab were not evaluated in this study.

Ability to Drive and Use Machines

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

ADVERSE EFFECTS

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

Presented in Table 10 below are adverse reactions that have been reported in association with the use of HERCEPTIN alone, or in combination with chemotherapy in the below pivotal clinical trials as well as in the post-marketing setting.

Localised Breast Cancer

- **BO16348 (HERA):** HERCEPTIN arm (n=1678). Control arm (n=1708)
- **B-31/N9831 Joint Analysis:** HERCEPTIN arms (n=2345). Control arm (n=1673)
- **BCIRG 006:** HERCEPTIN arm (n=2133). Control arm (n=1041)
- **BO16216 (TanDEM):** HERCEPTIN arm (n=161). Control arm (n=161)

Locally Advanced Breast Cancer

- **MO16432 (NOAH):** HERCEPTIN arm (n=115). Control arm (n=116)

Metastatic Breast Cancer (MBC)

- **H0648g / H0649g:** HERCEPTIN arms (n=469 and n=222 respectively)
- **M77001:** HERCEPTIN arm (n=92). Control arm (n=94).

Advanced Gastric Cancer

- **BO18255 (ToGA):** HERCEPTIN arm (n=294). Control arm (n=290)

All terms included are based on the highest percentage seen in pivotal clinical trials.

Table 10: Adverse Reactions

System organ class	Adverse reaction	Frequency
Infections and infestations	[+]Pneumonia	Common (<1 %)
	Neutropenic sepsis	Common
	Cystitis	Common

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System organ class	Adverse reaction	Frequency
	Herpes zoster	Common
	Infection	Common
	Influenza	Common
	Nasopharyngitis	Common
	Sinusitis	Common
	Skin infection	Common
	Rhinitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
	Erysipelas	Common
	Cellulitis	Common
	Sepsis	Uncommon
Neoplasms benign, malignant and unspecified (incl. Cysts and polyps)	Malignant neoplasm progression	Not known
	Neoplasm progression	Not known
Blood and lymphatic system disorders	Febrile Neutropenia	Very common
	Anaemia	Common
	Neutropenia	Common
	Thrombocytopenia	Common
	White blood cell count decreased / leukopenia	Common
	Hypoprothrombinaemia	Not known
Immune system disorders	Hypersensitivity	Common
	[+]Anaphylactic reaction	Not known
	[+]Anaphylactic shock	Not known
Metabolism and nutrition disorders	Weight Decreased/Weight Loss	Common
	Anorexia	Common
	Hyperkalaemia	Not known
Psychiatric disorders	Anxiety	Common
	Depression	Common
	Insomnia	Common
	Thinking abnormal	Common
Nervous system disorders	[1]Tremor	Very common
	Dizziness	Very common
	Headache	Very common
	Peripheral neuropathy	Common
	Paraesthesia	Common
	Hypertonia	Common

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System organ class	Adverse reaction	Frequency
	Somnolence	Common
	Dysgeusia	Common
	Ataxia	Common
	Paresis	Rare
	Brain oedema	Not known
Eye disorders	Conjunctivitis	Very common
	Lacrimation increased	Very Common
	Dry eye	Common
	Papilloedema	Not known
	Retinal haemorrhage	Not known
Ear and Labyrinth Disorders	Deafness	Uncommon
Cardiac disorders	[1] Blood pressure decreased	Very common
	[1] Blood pressure increased	Very common
	[1] Heart beat irregular	Very common
	[1]Palpitation	Very common
	[1]Cardiac flutter	Very common
	[+]Cardiac failure (congestive)	Common (2 %)
	[+1]Supraventricular tachyarrhythmia	Common
	Cardiomyopathy	Common
	Ejection fraction decreased^	Very Common
	Pericardial effusion	Uncommon
	Cardiogenic shock	Not known
	Pericarditis	Not known
	Bradycardia	Not known
	Gallop rhythm present	Not known
Vascular disorders	Hot flush	Very Common
	[+1] Hypotension	Common
	Vasodilatation	Common
Respiratory, thoracic and mediastinal disorders	[+1]Wheezing	Very common
	[+]Dyspnoea	Very common (14 %)
	Cough	Very Common
	Epistaxis	Very Common
	Rhinorrhoea	Very Common
	Asthma	Common
	Lung disorder	Common
	Pharyngitis	Common
	[+]Pleural effusion	Uncommon
	Pneumonitis	Rare
	[+]Pulmonary fibrosis	Not known

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System organ class	Adverse reaction	Frequency
	[+]Respiratory distress	Not known
	[+]Respiratory failure	Not known
	[+]Lung infiltration	Not known
	[+]Acute pulmonary oedema	Not known
	[+]Acute respiratory distress syndrome	Not known
	[+]Bronchospasm	Not known
	[+]Hypoxia	Not known
	[+]Oxygen saturation decreased	Not known
	Laryngeal oedema	Not known
	Orthopnoea	Not known
	Pulmonary oedema	Not known
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting	Very common
	Nausea	Very common
	[1] Lip swelling	Very common
	Abdominal pain	Very common
	Pancreatitis	Common
	Dyspepsia	Common
	Haemorrhoids	Common
	Constipation	Common
	Dry mouth	Common
Hepatobiliary disorders	Hepatocellular Injury	Common
	Hepatitis	Common
	Liver Tenderness	Common
	Jaundice	Rare
	Hepatic Failure	Not known
Skin and subcutaneous disorders	Erythema	Very common
	Rash	Very common
	[1] Swelling face	Very common
	Palmar-plantar erythrodysaesthesia syndrome	Very common
	Acne	Common
	Alopecia	Common
	Dry skin	Common
	Ecchymosis	Common
	Hyperhydrosis	Common
	Maculopapular rash	Common
	Nail disorder	Common
	Pruritus	Common

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

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

The following information is relevant to all indications.

Infusion Reactions

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 paracetamol or pethidine and an antihistamine such as diphenhydramine (see **Dosage**). Some adverse reactions to HERCEPTIN infusions including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress can be serious and potentially fatal (see **PRECAUTIONS**).

Hypersensitivity Reactions

Anaphylactoid reactions were observed in isolated cases (see **PRECAUTIONS**).

Cardiac Toxicity

Breast Cancer

Cardiac dysfunction was observed during clinical trials in patients treated with HERCEPTIN (see **PRECAUTIONS**). Reduced ejection fraction and signs and symptoms of heart failure, such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, and S_3 gallop, have been observed in patients treated with HERCEPTIN. 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 study M77001 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.

The incidence of cardiac adverse events from retrospective analysis of data from the study of HERCEPTIN + paclitaxel versus paclitaxel alone and the HERCEPTIN monotherapy study is shown in Table 11.

Table 11: Overview of Cardiac Adverse Event Incidence (n, %) [95% CI]

	H0648g						**H0649g**
	H + P ***n* = 91**	**P alone** ***n* = 95**	***p*-value (χ2)**	**H + AC** ***n* = 143**	**AC** ***n* = 135**	***p*-value (χ2)**	**H alone** ***n* = 21**
Symptomatic heart failure "anthracycline typical" (a)	8 (8.8) [3.9-16.6]	4 (4.2) [1.2-10.4]	0.204	40 (28.0) [20.8-36.1]	13 (9.6) [5.2-15.9]	<0.001	18 (8.5) [5.1-13.0]
Cardiac diagnosis other than heart failure (b)	4 (4.4) [1.2-10.9]	7 (7.4) [3.0-14.6]	0.390	8 (5.6) [2.5-10.7]	9 (6.7) [3.1-12.3]	0.709	7 (3.3) [1.3-6.7]

H+P: HERCEPTIN + paclitaxel; P alone: paclitaxel alone; H+AC: HERCEPTIN + anthracyclines; H alone: Herceptin monotherapy; Categories are mutually exclusive: patients assigned in hierarchical fashion according to ranking in table.

a preferred terms: congestive heart failure, cardiomyopathy, heart failure, left ventricular failure, lung oedema or other search terms and CRF information indicating cardiac failure (eg. a combination of shortness of breath, dyspnoea, cough increased, pulmonary congestion on X-ray, echo or MUGA findings).

b cardiac condition most likely not related to adriamycin toxicity (eg. pericardial tamponade, syncope, stroke, angina pectoris, myocardial ischemia, myocardial infarction, ascites).
Includes preferred terms: cardiovascular disorder, shock, respiratory failure, respiratory distress, hypoxia, asthma, dyspnoea, cough increased, oedema, peripheral oedema, heart arrest, hypotension, palpitation, bradycardia, tachycardia, arrhythmia which are not further specified in the text of the adverse event forms in the CRF as being definitely related to malignant disease. Any other events with insufficient information for assessment of aetiology.

The incidence of symptomatic congestive heart failure in the study of HERCEPTIN + docetaxel versus docetaxel alone (M77001) is shown in Table 12:

Table 12: Overview of Cardiac Adverse Event Incidence (n, %)

	HERCEPTIN +Docetaxel *n* = 92	**Docetaxel *n* = 94**
Symptomatic heart failure	2 (2.2%)	0%

In this study, all patients had a baseline cardiac ejection fraction of greater than 50%. In the HERCEPTIN + docetaxel arm, 64% had received a prior anthracycline compared with 55% in the docetaxel-alone arm.

For HERCEPTIN + anastrozole, the rate of symptomatic congestive heart failure was <1% versus 0% in the anastrozole-alone arm. Asymptomatic LVEF drops were experienced by 5.8% of patients in the HERCEPTIN + anastrozole arm versus 0% in the anastrozole-alone arm.

Cardiac endpoints measured during the HERA trial in patients with localised breast cancer are shown in Table 13 below.

Table 13: Primary and Secondary Cardiac Endpoints Measured During the HERA Trial

	Observation *n* = 1708 n (%)	**HERCEPTIN 1 Year *n* = 1678 n (%)**
Incidence of Primary Cardiac Endpoint†	1 (0.1)	10 (0.6)
Incidence of Secondary Cardiac Endpoint‡	9 (0.5)	51 (3.0)

†symptomatic CHF (NYHA class III or IV) and a drop in LVEF of at least 10 points from baseline and to below 50% or cardiac death; ‡ significant asymptomatic (NYHA class I) or mildly symptomatic (NYHA class II) LVEF drop

The incidence of NYHA Class III or IV heart failure (or cardiac death) in the B-31 and N9831 trials for HERCEPTIN in localised breast cancer was 3.8% and 3.0% respectively (AC-TH), compared with 1.1% and 0% in the respective observation groups (AC-T). In a published trial (Joensuu et al, 2006, *NEJM*) no patients who received nine weeks of HERCEPTIN experienced cardiac failure.

Advanced Gastric Cancer

In Study BO18255 (ToGA), at screening, the median LVEF value was 64% (range 48% - 90%) in the fluoropyrimidine/cisplatin (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 14: Summary of LVEF Change from Screening

LVEF Decrease[#]: Lowest Post-screening Value	**FP (*n* = 290) (% patients in each treatment arm)**	**FP + H (*n* = 294) (% 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 15: Cardiac Adverse Events

	FP (*n* = 290) (% patients in each treatment arm)	**FP +H (*n* = 294) (% 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

Monotherapy– Study H0649g
Haematological toxicity is infrequent following the administration of HERCEPTIN as monotherapy in the metastatic setting, WHO Grade 3 leucopenia, thrombocytopenia and anaemia occurring in <1% of patients. No WHO Grade 4 toxicities were observed.

Combination Therapy – Studies H0648g and M77001
WHO Grade 3 or 4 haematological toxicity was observed in 63% of patients treated with HERCEPTIN and an anthracycline/cyclophosphamide compared to an incidence of 62% in patients treated with the anthracycline/cyclophosphamide combination without HERCEPTIN.

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 vs. 22%, using NCI-CTC criteria). The incidence of febrile neutropenia/neutropenic sepsis was also increased in patients treated with Herceptin + docetaxel (23% vs. 17% for patients treated with docetaxel-alone).

Localised Setting – HERA Study
Using NCI-CTC criteria, in the HERA trial, 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 categorized under the Blood and Lymphatic System Disorders SOC (Grade ≥3) are shown below (Table 16) by trial treatment.

Table 16: Blood and Lymphatic System Disorders (SOC) Adverse Events >1%

	FP (*n* = 290)	**FP + H (*n* = 294)**

	(% patients in each treatment arm)	(% 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 categorized 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

Monotherapy– Study H0649g
WHO Grade 3 or 4 hepatic toxicity was observed in 12% of patients following administration of HERCEPTIN as monotherapy in the metastatic setting. This toxicity was associated with progression of disease in the liver in 60% of these patients. No WHO Grade 3 or 4 renal toxicity was observed.

Combination Therapy – Study H0648g
WHO Grade 3 or 4 hepatic toxicity was observed in 6% of patients treated with HERCEPTIN and an anthracycline/cyclophosphamide compared with an incidence of 8% in patients treated with the anthracycline/cyclophosphamide combination without HERCEPTIN. No WHO Grade 3 or 4 renal toxicity was observed.

WHO Grade 3 or 4 hepatic toxicity was less frequently observed among patients receiving HERCEPTIN and paclitaxel than among patients receiving paclitaxel-alone (7% vs.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

Monotherapy– Study H0649g
Of patients treated with HERCEPTIN monotherapy in the metastatic setting, 27% experienced diarrhoea.

Combination Therapy – Studies H0648g and M77001
An increase in the incidence of diarrhoea, primarily mild to moderate in severity, has been observed in patients receiving HERCEPTIN in combination with chemotherapy compared with patients receiving chemotherapy-alone or HERCEPTIN-alone.

Localised Setting – HERA Study
In the HERA trial, 7% of HERCEPTIN treated patients experienced 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 + chemotherapy compared with patients receiving chemotherapy-alone or HERCEPTIN-alone.

Laboratory Abnormalities

Febrile neutropenia occurs very commonly. Commonly occurring adverse reactions include anaemia, leukopenia, thrombocytopenia and neutropenia. The frequency of occurrence of hypoprothrombinemia is not known.

DOSAGE AND ADMINISTRATION

HER2 testing is mandatory prior to initiation of HERCEPTIN therapy (refer to **Detection of HER2 Protein Overexpression and Gene Amplification** below).

Dosage

DO NOT ADMINISTER HERCEPTIN AS AN INTRAVENOUS PUSH OR BOLUS.

Patients should be observed for fever and chills or other infusion-associated symptoms (see **ADVERSE EFFECTS**). Interruption of the infusion and/or medication may help to control such symptoms. The infusion may be resumed when symptoms abate.

Localised Breast Cancer

The optimal dosage regimen and treatment duration have not been defined. A favourable risk/benefit ratio has been demonstrated with the following regimens (see **CLINICAL TRIALS**).

Three weekly regimen (HERA trial)
In the HERA study, treatment with HERCEPTIN was commenced following surgery and completion of neoadjuvant or at least 4 cycles of adjuvant chemotherapy. Patients were treated with HERCEPTIN in total for 1 year.

Loading Dose: an initial loading dose of 8 mg/kg body weight administered as an intravenous infusion over approximately 90 minutes.

Subsequent Doses: 3 weeks after the loading dose administer 6 mg/kg body weight every 3 weeks as an intravenous infusion over approximately 90 minutes. If the loading dose was well tolerated, the subsequent doses can be administered as a 30 minute infusion.

Weekly regimen (B-31/N9831/BCIRG 006 trials)
In the B-31, N9831 and BCIRG 006 studies, treatment with HERCEPTIN was commenced following surgery and completion of 4 cycles (12 weeks) of doxorubicin and cyclophosphamide (AC) chemotherapy. In B-31 and N9831, HERCEPTIN was then administered with paclitaxel (weekly or 3-weekly schedule) for 12 weeks, then as a single agent for a further 40 weeks. In the BCIRG 006 study, HERCEPTIN was then administered with docetaxel or docetaxel and carboplatin (3-weekly schedule) for 6 cycles (18 weeks), then as a single agent during treatment with chemotherapy. HERCEPTIN was administered on a 3-weekly schedule following completion of chemotherapy treatment.

Loading dose: an initial dose of 4 mg/kg body weight administered as a 90 minute intravenous infusion.

Subsequent doses: 1 week after the loading dose administer 2 mg/kg body weight at weekly intervals. If the loading dose was well tolerated, the subsequent doses can be administered as a 30 minute infusion.

Locally Advanced Breast Cancer

In the NOAH study, treatment with HERCEPTIN was commenced with neoadjuvant doxorubicin and paclitaxel, and was given throughout chemotherapy until surgery. Following surgery, HERCEPTIN was continued as a single agent. Patients were treated with HERCEPTIN in total for 1 year.

Loading Dose: an initial loading dose of 8 mg/kg body weight administered as an intravenous infusion over approximately 90 minutes.

Subsequent Doses: 3 weeks after the loading dose administer 6 mg/kg body weight every 3 weeks as an intravenous infusion over approximately 90 minutes. If the loading dose was well tolerated, the subsequent doses can be administered as a 30 minute infusion.

Metastatic Breast Cancer

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

Subsequent Doses: The recommended weekly dose of HERCEPTIN is 2 mg/kg body weight given at weekly intervals. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30 minute infusion.

In clinical trials, patients with metastatic breast cancer were treated with HERCEPTIN until progression of disease.

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 the **CLINICAL TRIALS, Advanced Gastric Cancer** section 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; 3-weekly: 6 mg/kg) should be given as soon as possible (do not wait until the next planned cycle). Subsequent maintenance doses (weekly regimen: 2 mg/kg; 3-weekly: 6 mg/kg) 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; 3-weekly: 8 mg/kg). Subsequent maintenance doses (weekly regimen: 2 mg/kg; 3-weekly: 6 mg/kg) should then be given according to the previous schedule.

Detection of HER2 Protein Overexpression or HER2 Gene Amplification

HERCEPTIN should only be used in patients whose tumours have HER2 protein overexpression or HER2 gene amplification.

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

HER2 protein overexpression should be detected using an immunohistochemistry (IHC)-based assessment of fixed tumour blocks. HER2 gene amplification should be detected using in situ hybridization (ISH) of fixed tumour blocks. Examples of ISH include fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH) and silver in situ hybridization (SISH).

For any other method to be used for the assessment of HER2 protein or gene expression, the test method must be precise and accurate enough to demonstrate overexpression of HER2 (it must be able to distinguish between moderate (congruent with 2+) and strong (congruent with 3+) HER2 overexpression).

For full instructions on the use of these assays and interpretation of the results please refer to the package inserts of validated FISH, CISH and SISH assays. Official recommendations on HER2 testing may also apply.

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.

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.

Bright-field ISH technology is recommended for advanced gastric cancer samples to enable evaluation of tumor histology and morphology in parallel. Either FISH or SISH are recommended for detecting HER2 gene amplification in advanced gastric cancer tissue.

Preparation for Administration

Reconstituting the Powder

Appropriate aseptic technique should be used.

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.

Each 60 mg vial should be reconstituted with 3.0 mL of sterile water for injections as the solvent. The use of other solvents should be avoided. The resultant solution is 3.1 mL of approximately 21 mg/mL trastuzumab. A 7.5% overage is included to ensure withdrawal of the labelled dose of 60 mg.

Each 150 mg vial should be reconstituted with 7.2 mL of sterile water for injections as the solvent. The use of other solvents should be avoided. The resultant solution is 7.4 mL of approximately 21 mg/mL trastuzumab. A 4% overage is included to ensure withdrawal of the labelled dose of 150 mg.

Instructions for Reconstitution

1) Using a sterile syringe, slowly inject 7.2 mL of sterile water for injections in the vial containing the lyophilized HERCEPTIN, directing the stream into the lyophilized cake.
2) Swirl vial gently to aid reconstitution. HERCEPTIN may be sensitive to shear-induced stress, e.g. agitation or rapid expulsion from a syringe. 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 and should be essentially free of visible particulates.

Instructions for Dilution

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

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

Three-Weekly Regimen: Determine the volume of the reconstituted solution required based on a loading dose of trastuzumab 8 mg/kg body weight, or subsequent every 3 weeks dose of 6 mg/kg body weight:

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

Preparation and Stability of the Admixture

The appropriate amount of the 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 since it causes aggregation of the protein. HERCEPTIN SHOULD NOT BE MIXED OR DILUTED WITH OTHER MEDICINES. No incompatibilities

between HERCEPTIN and polyvinylchloride, polyethylene or polypropylene bags have been observed.

The infusion bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.

From a microbiological point of view, the HERCEPTIN infusion solution should be used immediately. If diluted aseptically, it may be stored for 24 hours when refrigerated at 2 to 8°C.

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 carefully monitored for complications of neutropenia during this time. The specific instructions to reduce or hold the dose of chemotherapy should be followed.

Detailed pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. The data from Study H0649g suggest that the disposition of trastuzumab is not altered by patient characteristics such as age or serum creatinine. The population pharmacokinetic analysis also shows that the estimated creatinine clearance (Cockcroft and Gault) does not correlate with the pharmacokinetics of trastuzumab.

Use in Elderly: Age has been shown to have no effect on the disposition of trastuzumab (see **DOSAGE AND ADMINISTRATION**).

Data suggest that the disposition of HERCEPTIN is not altered based on age or serum creatinine (see **Pharmacokinetics**). In clinical trials, elderly patients did not receive reduced doses of HERCEPTIN.

OVERDOSAGE

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

Treatment of overdose should consist of general supportive measures.

Contact the Poisons Information Centre for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

HERCEPTIN is available as:

- 60 mg pack containing one single-dose vial
- 150 mg pack containing one single-dose vial

The contents of the sterile vial appear as a lyophilized, white to pale yellow powder. The reconstituted HERCEPTIN solution contains approximately 21 mg/mL of trastuzumab.

Storage

Store HERCEPTIN vials at 2 to 8°C. Refrigerate. Do not freeze. Do not use beyond the expiration date stamped on the vial.

Reconstituted Solution
A vial of HERCEPTIN reconstituted with sterile water for injections without preservative should be used immediately and any unused portion must be discarded. Do not freeze the reconstituted solution.

Diluted Solution for Infusion
From a microbiological point of view, the HERCEPTIN infusion solution should be diluted and used immediately. The product is not intended to be stored after dilution. Solutions of HERCEPTIN for infusion are physically and chemically stable in polyvinylchloride, polyethylene or polypropylene bags containing 0.9% sodium chloride at 2 to 8°C for 24 hours. Diluted HERCEPTIN has been shown to be stable for up to 24 hours at temperatures up to 30°C.

Disposal of Medicines

The release of medicines into the environment should be minimized. 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.

NAME AND ADDRESS OF THE SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
4–10 Inman Road
Dee Why NSW 2099

Customer Enquiries: 1800 233 950

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):

60 mg (171014): 3 December 2010
150 mg (73229): 14 September 2000

DATE OF MOST RECENT AMENDMENT:

13 August 2012