OGIVRI®

TRASTUZUMAB (rDNA ORIGIN)
POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION
420 MG/VIAL

NAME OF THE MEDICINAL PRODUCT

Ogivri Trastuzumab (rDNA Origin) Powder for concentrate for solution for infusion 420 mg/vial

Qualitative and Quantitative Composition

Active ingredient: Trastuzumab

420 mg multi-dose vials containing powder for concentrate for solution for intravenous infusion. Reconstituted Ogivri concentrate contains approximately 21 mg/mL of trastuzumab, a humanised IgG1 monoclonal antibody expressed in chinese hamster ovary cell suspension culture and purified by affinity and ion-exchange chromatography including specific viral inactivation and removal procedures.

List of Excipients

L-Histidine, L-Histidine Hydrochloride Monohydrate, Polyethylene glycol 3350/Macrogol 3350, D – Sorbitol.

PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
Ogivri is a white to pale yellow lyophilised powder.

Nature and Contents of Container

Ogivri Trastuzumab 420 mg powder for concentrate for solution for infusion.
Ogivri finished product 420 mg is filled in 50 mL USP type 1 glass vial, closed with a Chlorobutyl rubber stopper and sealed with 20 mm lavender flip – off seal. The 420 mg pack is provided with 20 mL BWFI (containing 1.1% Benzyl alcohol as preservative) for reconstitution.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Antineoplastic Agents, Monoclonal Antibodies, ATC code: L01FD01

Mechanism of Action

Trastuzumab is a recombinant humanised monoclonal antibody that selectively targets the extracellular domain of the human Epidermal Growth Factor Receptor 2 Protein (HER2). The antibody is an IgG1 isotype that contains human framework regions with the complementarity-determining regions of a murine anti-p185 HER2 antibody that binds to human HER2.

The HER2 proto-oncogene or c-erbB2 encodes for a single transmembrane spanning, receptor-like protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. Overexpression of HER2 is observed in 15%-20% of primary breast cancer. The overall rate of HER2 positivity in metastatic gastric cancers as observed during screening for study BO18255 is 15% for IHC3+ and IHC2+/FISH+ or 22.1% when applying the broader definition of IHC3+ or FISH+. 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 protein.

Studies indicate that breast cancer 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 (MBC)

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

Trastuzumab has also been used in clinical trials in combination with paclitaxel or an anthracycline (doxorubicin or epirubicin) plus cyclophosphamide as first line therapy for patients with MBC 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 trastuzumab. Patients could be treated with trastuzumab until progression of disease.

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

The use of trastuzumab in combination with paclitaxel as first-line treatment of women with MBC 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 trastuzumab and paclitaxel is 3.9 months (6.9 months versus 3.0 months). Tumour response and one-year survival rate are also increased for trastuzumab in combination with paclitaxel versus paclitaxel alone.

Trastuzumab has also been studied in a randomised, controlled trial, in combination with docetaxel, as first-line treatment of women with MBC. The combination of trastuzumab and docetaxel significantly increased response rate (61% versus 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 versus 22.7 months).

Combination treatment with trastuzumab and anastrozole

Trastuzumab has been studied in combination with anastrozole for first line treatment of MBC in HER2 overexpressing, hormone-receptor [i.e. oestrogen-receptor (ER) and/or progesterone-receptor (PR)] positive patients. Progression free survival was doubled in the trastuzumab plus anastrozole arm compared to anastrozole (4.8 months versus 2.4 months). For the other parameters the improvements seen for the combination were for overall response (16.5% versus 6.7%); clinical benefit rate (42.7% versus 27.9%); time to progression (4.8 months versus 2.4 months). For time to response and duration of response no difference could be recorded between the arms. The median overall survival was extended by 4.6 months for patients in the combination arm. The difference was not statistically significant, however more than half of the patients in the anastrozole alone arm crossed over to a trastuzumab containing regimen after progression of disease. Fifty two percent of the patients taking trastuzumab plus anastrozole survived for at least 2 years compared to 45% taking anastrozole alone.

Early Breast Cancer (EBC)

In the adjuvant treatment setting, trastuzumab was investigated in 4 large multicentre, randomised phase 3 trials:

- Study BO16348 was designed to compare one and two years of three-weekly trastuzumab treatment versus observation in patients with HER2-positive EBC following surgery, established chemotherapy and radiotherapy (if applicable). In addition, a comparison of two years of trastuzumab treatment versus one year of trastuzumab treatment was performed. Patients assigned to receive trastuzumab were given an initial loading dose of 8 mg/kg, followed by 6 mg/kg every three weeks for either one or two years.
- Studies NSAPB-B31 and NCCTG N9831 that comprise the joint analysis were designed to investigate the clinical utility of combining trastuzumab treatment with paclitaxel following AC chemotherapy; additionally, the NCCTG N9831 study investigated adding trastuzumab sequentially to AC- paclitaxel chemotherapy in patients with HER2-positive EBC following surgery.
- Study BCIRG 006 was designed to investigate combining trastuzumab treatment with docetaxel either following AC chemotherapy or in combination with docetaxel and carboplatin in patients with HER2-positive EBC following surgery.

EBC in the BO16348 study was limited to operable, primary, invasive adenocarcinoma of the breast, with axillary nodes-positive or axillary nodes-negative tumours of at least 1 cm in diameter.

The efficacy results from the BO16348 study are summarized in the following table:

Table 1: Efficacy Results (BO16348 study): Results at 12 months* and 8 years of median follow-up**

	Median follow-up 12 months		**Median follow-up 8 years**	
Parameter	**Observation N=1693**	**Trastuzumab 1 Year N = 1693**	**Observation N= 1697*** **	**Trastuzumab 1 Year N = 1702*** **
Disease-free survival -No. patients with event -No. patients without event P-value versus Observation Hazard Ratio versus Observation	219 (12.9%) 1474 (87.1%) < 0.0001 0.54	127 (7.5%) 1566 (92.5%)	570 (33.6%) 1127 (66.4%) < 0.0001 0.76	471 (27.7%) 1231 (72.3%)
Recurrence-free survival -No. patients with event -No. patients without event P-value versus Observation Hazard Ratio versus Observation	208 (12.3%) 1485 (87.7%) < 0.0001 0.51	113 (6.7%) 1580 (93.3%)	506 (29.8%) 1191 (70.2%) < 0.0001 0.73	399 (23.4%) 1303 (76.6%)
Distant disease-free survival -No. patients with event -No. patients without event P-value versus Observation Hazard Ratio versus Observation	184 (10.9%) 1508 (89.1%) < 0.0001 0.50	99 (5.8%) 1594 (94.6%)	488 (28.8%) 1209 (71.2%) < 0.0001 0.76	399 (23.4%) 1303 (76.6%)
Overall survival (death) -No. patients with event -No. patients without event P-value versus Observation Hazard Ratio versus Observation	40 (2.4%) 1653 (97.6%) 0.24 0.75	31 (1.8%) 1662 (98.2%)	350 (20.6%) 1347 (79.4%) 0.0005 0.76	278 (16.3%) 1424 (83.7%)

* Co-primary endpoint of DFS of 1-year vs observation met the pre-defined statistical boundary

** Final analysis (including crossover of 52% of patients from the observation arm to trastuzumab)

*** There is a discrepancy in the overall sample size due to a small number of patients who were randomized after the cut-off date for the 12-month median follow-up analysis

The efficacy results from the interim efficacy analysis crossed the protocol pre-specified statistical boundary for the comparison of 1-year of trastuzumab vs. observation. After a median follow-up of 12 months, the hazard ratio (HR) for disease free survival (DFS) was 0.54 (95% CI 0.44, 0.67) which translates into an absolute benefit, in terms of a 2-year disease-free survival rate of 7.6 percentage points (85.8% versus 78.2%) in favour of the trastuzumab arm.

A final analysis was performed after a median follow-up of 8 years, which showed that 1 year trastuzumab treatment is associated with a 24% risk reduction compared to observation only (HR=0.76, 95% CI 0.67, 0.86). This translates into an absolute benefit in terms of an 8-year disease free survival rate of 6.4 percentage points in favour of 1 year trastuzumab treatment.

In this final analysis, extending trastuzumab treatment for a duration of two years did not show additional benefit over treatment for 1 year [DFS HR in the intent to treat (ITT) population of 2 years vs 1 year = 0.99 (95% CI: 0.87, 1.13), p- value = 0.90 and OS HR = 0.98 (0.83, 1.15); p-value = 0.78]. The rate of asymptomatic cardiac dysfunction was increased in the 2-year treatment arm (8.1% versus 4.6% in the 1-year treatment arm). More patients experienced at least one grade 3 or 4 adverse event in the 2-year treatment arm (20.4%) compared with the 1-year treatment arm (16.3%).

In the joint analysis of the NSAPB B-31 and NCCTG N9831 studies, EBC was limited to women with operable breast cancer at high risk, defined as HER2-positive and axillary lymph node-positive or HER2-positive and lymph node-negative with high-risk features (tumour size > 1 cm and ER negative or tumour size > 2 cm, regardless of hormonal status). Trastuzumab was administered in combination with paclitaxel, following AC chemotherapy. Paclitaxel was administered as follows:

- Intravenous paclitaxel – 80 mg/m2 as a continuous IV infusion, given every week for 12 weeks, or
- Intravenous paclitaxel – 175 mg/m2 as a continuous IV infusion, given every 3 weeks for 4 cycles (day 1 of each cycle).

Table 2: Summary of Efficacy results from the joint analysis studies NSABP B-31 and NCCTG 9831 at the time of the definitive DFS analysis*

Parameter	AC→P (n=1697)	AC→PH (n=1672)	p-value versus AC→P	Hazard Ratio versus AC→P (95% CI)
Disease-free survival No. patients with event (%)	261 (15.5)	133 (8.0)	< 0.0001	0.48 (0.39, 0.59)
Distant Recurrence No. patients with event (%)	193 (11.5)	96 (5.7)	< 0.0001	0.47 (0.37, 0.60)
Death (OS event): No. patients with event (%)	92 (5.5)	62 (3.7)	0.014**	0.67 (0.48, 0.92)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: trastuzumab

* at median duration of follow up of 1.8 years for the patients in the AC→P arm and 2.0 years for patients in the AC→PH arm

** p value for OS did not cross the pre-specified statistical boundary for comparison of AC→PH vs. AC→P Source: Table 8 Clinical Study Report: Joint Analysis of B-31 and N9831, 04 February 2006, Genentech, Inc.

For the primary endpoint, DFS, the addition of trastuzumab to paclitaxel chemotherapy resulted in a 52% decrease in the risk of disease recurrence. The hazard ratio translates into an absolute benefit, in terms of a 3-year disease-free survival rate of 11.8 percentage points (87.2% versus 75.4%) in favour of the AC→PH (trastuzumab) arm.

The pre-planned final analysis of OS from the joint analysis of studies NSABP B-31 and NCCTG N9831 was performed when 707 deaths had occurred (median follow-up 8.3 years in the AC→PH group). Treatment with AC→PH resulted in a statistically significant improvement in OS compared with AC→P (stratified HR=0.64; 95% CI [0.55, 0.74]; log-rank p value < 0.0001). At 8 years, the

survival rate was estimated to be 86.9% in the AC→PH arm and 79.4% in the AC→P arm, an absolute benefit of 7.4% (95% CI 4.9%, 10.0%).

The final OS results from the joint analysis of studies NSABP B-31 and NCCTG N9831 are summarized in the following table:

Table 3: Final Overall Survival Analysis from the joint analysis of trials NSABP B-31 and NCCTG N9831:

Parameter	AC→P (N=2032)	AC→PH (N=2031)	p-value versus AC→P	Hazard Ratio versus AC→P (95% CI)
Death (OS event): No. patients with event (%)	418 (20.6%)	289 (14.2%)	< 0.0001	0.64 (0.55, 0.74)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: trastuzumab

In the BCIRG 006 study, HER2-positive, EBC was limited to either lymph node-positive or high-risk node- negative patients, defined as negative (pN0) lymph node involvement, and at least 1 of the following factors: tumour size greater than 2 cm, oestrogen receptor and progesterone receptor negative, histologic and/or nuclear grade 2 - 3, or age < 35 years. Trastuzumab was administered either in combination with docetaxel, following AC chemotherapy (AC-DH) or in combination with docetaxel and carboplatin (DCarbH).

Docetaxel was administered as follows:

- Intravenously (100 mg/m2 as an IV infusion over 1 hour) given every 3 weeks for 4 cycles (day 2 of first docetaxel cycle, then day 1 of each subsequent cycle), or
- Intravenously (75 mg/m2 as an IV infusion over 1 hour) given every 3 weeks for 6 cycles (day 2 of cycle 1, then day 1 of each cycle).

Docetaxel therapy was followed by carboplatin (at target AUC = 6 mg/ml/min) administered by IV infusion over 30- 60 minutes repeated every 3 weeks for a total of 6 cycles.

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

Table 4: Overview of Efficacy Analyses AC→D versus AC→DH (BCIRG 006 study)

Parameter	AC→D (N=1073)	AC→DH (N=1074)	p-value versus AC→D (log-rank)	Hazard Ratio versus AC→D (95% CI)
Disease-free survival No. patients with event	195	134	< 0.0001	0.61 (0.49, 0.77)
Distant recurrence No. patients with event	144	95	< 0.0001	0.59 (0.46, 0.77)
Overall Survival (Death) 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 5: Overview of Efficacy Analyses AC→D versus DCarbH (BCIRG 006 study)

Parameter	AC→D (N=1073)	DCarbH (N=1075)	p-value versus AC→D (log-rank)	Hazard Ratio versus AC→D (95% CI)
Disease-free survival No. patients with event	195	145	0.0003	0.67 (0.54, 0.83)
Distant recurrence	144	103	0.0008	0.65 (0.50, 0.84)

Parameter	AC→D (N=1073)	DCarbH (N=1075)	p-value versus AC→D (log-rank)	Hazard Ratio versus AC→D (95% CI)
No. patients with event				
Death (OS event) No. patients with event	80	56	0.0182	0.66 (0.47, 0.93)

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

In the BCIRG 006 study for the primary endpoint, DFS, the hazard ratio translates into an absolute benefit, in terms of a 3-year disease-free survival rate of 5.8 percentage points (86.7% versus 80.9%) in favour of the AC→DH (trastuzumab) arm and 4.6 percentage points (85.5% versus 80.9%) in favour of the DCarbH (trastuzumab) arm compared to AC→D.

For the secondary endpoint overall survival, treatment with AC→DH reduced the risk of death by 42% when compared to AC→D (hazard ratio 0.58 [95% CI: 0.40, 0.83] p = 0.0024, log-rank test) and the risk of death was reduced by 34% for patients treated with DCarbH compared to patients treated with AC→D (hazard ratio 0.66 [95% CI: 0.47, 0.93], p = 0.0182). In the BCIRG 006 study at the second interim analysis, 185 randomized patients had died: 80 patients (7.5%) in the AC→D arm, 49 patients (4.6%) in the AC→DH arm, and 56 patients (5.2%) in the DCarbH arm. The median duration of follow-up was 2.9 years in the AC→D arm and 3.0 years in both the AC→DH and DCarbH arms.

In the neoadjuvant-adjuvant treatment setting, trastuzumab was evaluated in two phase 3 trials:

- Study MO16432 investigated a total of 10 cycles of neoadjuvant chemotherapy [an anthracycline and a taxane (AP+H followed by P+H, followed by CMF+H] concurrently with neoadjuvant-adjuvant trastuzumab, or neoadjuvant chemotherapy alone, followed by adjuvant trastuzumab for up to a total treatment duration of 1 year) in newly diagnosed locally advanced (Stage III) or inflammatory HER2-positive breast cancer patients.

The efficacy results from MO16432 are summarized in the table below. The median duration of follow-up in the trastuzumab arm was 3.8 years.

Table 6: Overview of Efficacy Analyses MO16432

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

* Defined as absence of any invasive cancer both in the breast and axillary nodes

For the primary endpoint, EFS, the addition of trastuzumab to the neoadjuvant chemotherapy followed by adjuvant trastuzumab 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 trastuzumab arm.

Metastatic Gastric Cancer (MGC)

The efficacy results from the BO18255 study are summarized in Table 7. Patients with previously untreated for HER2-positive inoperable locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastro- oesophageal junction not amenable to curative therapy

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

The overall survival was significantly improved in the trastuzumab + capecitabine/5-FU and cisplatin arm compared to the capecitabine/5-FU and cisplatin arm (p = 0.0046, log-rank test). The median survival time was 11.1 months with capecitabine/5-FU and cisplatin and 13.8 months with trastuzumab + capecitabine/5-FU and cisplatin. The risk of death was decreased by 26% (hazard ratio [HR] 0.74 95% CI [0.60-0.91]) for patients in the trastuzumab arm compared to the capecitabine/5-FU arm.

Post-hoc subgroup analyses indicate that targeting tumors with higher levels of HER2 protein (IHC 2+/FISH+ and IHC 3+/regardless of the 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 versus 7.6 months, HR 0.64 (95% CI 0.51-0.79) for capecitabine/5-FU and cisplatin and trastuzumab + capecitabine/5-FU and cisplatin respectively.

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

Table 7: Summary of Efficacy (BO18255 study)

Parameter	FP N=290	H+FP 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
H+ FP: fluoropyrimidine/cisplatin + trastuzumab
a Odds ratio

Pharmacokinetic Properties
A randomised, double-blind, parallel-group, comparative clinical study in patients with HER2-positive MBC showed that the pharmacokinetic profile of Ogivri was similar to that of trastuzumab (Herceptin) after single- and multi-dose intravenous infusions.

As a part of global clinical development, two phase 1 studies 1) Single-center, single-dose, 2-period, randomized, double-blind, cross-over study and 2) Single-center, randomized, double-blind, three-arm, parallel-group study were conducted in normal healthy volunteers. Both studies showed that pharmacokinetic profile of Ogivri was similar to that of trastuzumab (Herceptin). In addition, a multicenter, double-blind, randomized, parallel-group, phase III study showed that pharmacokinetic, efficacy, safety and immunogenicity profiles of Ogivri was similar to trastuzumab (Herceptin) in patients with HER2-positive MBC.

Clinical Efficacy
The clinical efficacy of Ogivri plus docetaxel was assessed in a randomised, double-blind, comparative phase 3 study in patients with HER2-positive MBC without prior chemotherapy. There were no relevant differences between Ogivri and trastuzumab (Herceptin) with regard to overall response rate, clinical benefit rate and progression-free survival rate (at 24 weeks) in MBC.

As a part of global clinical development, the clinical efficacy of Ogivri plus docetaxel/ paclitaxel was assessed in a multicenter, double-blind, randomized, parallel-group, phase III study in MBC

patients. There were no relevant differences between Ogivri and trastuzumab (Herceptin) with regard to overall response rate, progression-free survival and overall survival at 48 weeks.
The pharmacokinetics of Trastuzumab were evaluated in a population pharmacokinetic model analysis using pooled data from 1,582 subjects from 18 Phase I, II and III trials receiving intravenous Trastuzumab. A two-compartment model with parallel linear and non-linear elimination from the central compartment described the Trastuzumab concentration-time profile. Due to the non-linear elimination, total clearance increased with decreasing concentrations. Linear clearance was 0.127 L/day for breast cancer (MBC/EBC) and 0.176 L/day for MGC. The nonlinear elimination parameter values were 8.81 mg/day for the maximum elimination rate (V_{max}) and 8.92 mg/L for the Michaelis-Menten constant (Km). The central compartment volume was 2.62 L for patients with breast cancer and 3.63 L for patients with MGC.

The population predicted PK exposures (with 5^{th} - 95^{th} Percentiles) and PK parameter values at clinically relevant concentrations (C_{max} and C_{min}) for breast cancer and MGC patients treated with the approved q1w and q3w dosing regimens are shown in Table 8 (Cycle 1) and Table 9 (steady-state) below.

Table 8: Population Predicted Cycle 1 PK Exposure Values (with 5^{th} - 95^{th} Percentiles) for IV Regimens in Breast Cancer and MGC Patients

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

Table 9: Population Predicted Steady State PK Exposure Values (with 5th - 95th Percentiles) for Trastuzumab IV Dosing Regimens in Breast Cancer and MGC Patients

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

Trastuzumab washout
Trastuzumab washout time period was assessed following Trastuzumab IV administration using the respective population PK models. The results of these simulations indicate that at least 95% of patients will reach serum Trastuzumab concentrations that are < 1 µg/mL (approximately 3% of the population predicted $C_{min,ss}$, or about 97% washout) by 7 months after the last dose.

Pharmacokinetics in Special Populations
Detailed pharmacokinetic studies in the geriatric population and those with renal or hepatic impairment have not been carried out.

Renal Impairment

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

Geriatric Population
Age has been shown to have no effect on the disposition of trastuzumab ***(see section Dosage and Administration)***

Preclinical Safety Data
Nonclinical studies (conventional toxicity studies) on Ogivri did not indicate any special hazard for humans. During conventional single- and repeat-dose toxicity studies of Ogivri in mice and rabbits, no clinically relevant adverse events were observed at the highest dose levels tested. Local tolerance was also evaluated in these toxicity studies, and no clinically relevant effects were observed.
Two comparative nonclinical studies undertaken in cynomolgus monkeys showed that the pharmacokinetic and toxicokinetic profile of Ogivri was similar to that of trastuzumab (Herceptin).

Carcinogenicity
No carcinogenicity studies have been performed to establish the carcinogenic potential of trastuzumab.

Genotoxicity
No data to report.

Impairment of Fertility
Reproduction studies have been conducted in Cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg trastuzumab (Herceptin) IV and have revealed no evidence of impaired fertility.

Reproductive Toxicity
Reproduction studies have been conducted in Cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg trastuzumab (Herceptin) IV and have revealed no evidence of 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 trastuzumab (Herceptin) IV from days 120 to 150 of pregnancy demonstrated that trastuzumab is secreted in the milk postpartum.

The exposure to trastuzumab in utero and the presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 1 month of age.

CLINICAL PARTICULARS
Therapeutic Indications

Breast Cancer
Metastatic Breast Cancer (MBC)
Ogivri is indicated for the treatment of patients with MBC who have tumours that overexpress HER2:
- As monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease

- In combination with paclitaxel or docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease
- In combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer.

Early Breast Cancer (EBC)
Ogivri is indicated for the treatment of patients with HER2-positive EBC
- Following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).
- Following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.
- In combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- In combination with neoadjuvant chemotherapy followed by adjuvant Ogivri, for locally advanced (including inflammatory) breast cancer or tumours > 2 cm in diameter.

Metastatic Gastric Cancer (MGC)
Ogivri in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Ogivri should only be used in patients with MGC whose tumours have HER2 overexpression as defined by immunohistochemistry (IHC2+) and a confirmatory SISH or FISH (fluorescence in situ hybridization) result, or by an IHC 3+ result. Accurate and validated assay methods should be used.

Dosage and Administration
Metastatic Breast Cancer (MBC) and Early Breast Cancer (EBC)
Weekly schedule:
Loading dose: The recommended initial loading dose is 4 mg/kg body weight Ogivri administered as a 90-minute IV infusion.

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

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

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

Duration of Treatment
Breast Cancer (MBC and EBC) and Gastric Cancer (MGC)
- Patients with MBC should be treated with Ogivri until progression of disease or unmanageable toxicity.
- Patients with EBC should be treated for 1 year or until disease recurrence or unmanageable toxicity, whichever occurs first. Extending treatment in EBC beyond one year is not recommended ***(see section Clinical Efficacy Studies)***.
- Patients with MGC should be treated with Ogivri until progression of disease or unmanageable toxicity

Missed doses
If the patient misses a dose of Ogivri by one week or less, then the usual maintenance dose (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 Ogivri maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg respectively) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

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

Dose modification
If the patient develops an Infusion-Related Reaction (IRR), the infusion rate of Ogivri may be slowed or interrupted ***(see section Special Warnings and Precautions for Use)***.

No reductions in the dose of Ogivri were made during clinical trials. Patients may continue Ogivri 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
Geriatric Use
Data suggest that the disposition of Ogivri is not altered based on age ***(see section Pharmacokinetics in Special Populations)***. In clinical trials, patient's ≥ 65 years of age did not receive reduced doses of Ogivri.

Paediatric Use
The safety and efficacy of Ogivri in paediatric patients < 18 years of age have not been established.

Contraindications
- Hypersensitivity to the active substance, murine proteins, or to any of the excipients listed (***see Section List of Excipients***).
- Severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

Special Warnings and Precautions for Use

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

In order to improve traceability of biological medicinal products, the trade name and batch number of the administered product should be clearly recorded (or stated) in the patient file.

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

Infusion/Administration-Related Reactions (IRRs/ARRs)
IRRs are known to occur with the administration of Ogivri ***(see section Undesirable Effects)***. IRRs/ARRs may be clinically difficult to distinguish from hypersensitivity reactions.
Pre-medication may be used to reduce risk of occurrence of IRRs/ARRs.

Serious IRRs/ARRs to Ogivri including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, supraventricular tachyarrhythmia and urticaria have been reported ***(see section Undesirable Effects)***. Patients should be observed for IRRs/ARRs. Interruption of an IV infusion may help control such symptoms and the infusion may be resumed when symptoms abate. Premedication may be used to reduce risk of occurrence administration-related reaction and these symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists and corticosteroids. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome. Patients who are experiencing dyspnoea at rest due to complications of advanced malignancy or co-morbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with Ogivri.

Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms.

Pulmonary Reactions
Severe pulmonary events have been reported with the use of Ogivri in the post-marketing setting. These events have occasionally resulted in fatal outcome and may occur as part of an IRR or with a delayed onset. In addition, cases of interstitial lung disease including lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported.

Risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy. Patients with dyspnoea at rest due to complications of advanced malignancy and co-morbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with Ogivri.

Cardiac dysfunction
General considerations
Patients treated with Ogivri may be at increased risk of developing congestive heart failure (CHF) (New York Heart Association [NYHA] Class II-IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving Ogivri therapy alone or in combination with taxane following anthracycline (doxorubicin or epirubicin) - containing chemotherapy. This may be moderate to severe and has been associated with death ***(see section Undesirable Effects)***. In addition, caution should be exercised in treating patients with increased cardiac risk e.g. hypertension, documented coronary artery disease, CHF, diastolic dysfunction, older age.

Population pharmacokinetic model simulations indicate that trastuzumab may persist in the circulation for up to 7 months after stopping Ogivri treatment ***(see section Pharmacokinetic Properties)***. Patients who receive anthracycline after stopping Ogivri may also be at increased risk of cardiac dysfunction.

If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping Ogivri. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Candidates for treatment with Ogivri, especially those with prior exposure to an anthracycline, should undergo baseline cardiac assessment including history and physical examination, electrocardiogram (ECG), and echocardiogram or multigated acquisition scanning (MUGA) scan. Monitoring may help to

identify patients who develop cardiac dysfunction, including signs and symptoms of CHF. Cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of Ogivri.

If LVEF percentage drops 10 ejection points from baseline and to below 50%, Ogivri should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further, or if clinical significant CHF has developed, discontinuation of Ogivri should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

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 unless the benefits for the individual patient are deemed to outweigh the risks.

The safety of continuation or resumption of Ogivri in patients who experience cardiac dysfunction has not been prospectively studied. If symptomatic cardiac failure develops during Ogivri therapy, it should be treated with standard medications for heart failure (HF). In the pivotal trials, most patients who developed HF or asymptomatic cardiac dysfunction improved with standard HF treatment consisting of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a β-blocker. The majority of patients with cardiac symptoms and evidence of a clinical benefit of Ogivri treatment continued with Ogivri without additional clinical cardiac events.

Metastatic breast cancer (MBC)
Ogivri and anthracyclines should not be given concurrently in the MBC setting.

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

Patients with history of myocardial infarction (MI), angina pectoris requiring medication, history of or present CHF (NYHA Class II–IV), other cardiomyopathy, cardiac arrhythmia requiring medication, clinically significant cardiac valvular disease, poorly controlled hypertension (hypertension controlled by standard medication eligible), and hemodynamic effective pericardial effusion were excluded from adjuvant breast cancer clinical trials with Ogivri.

Adjuvant treatment
Ogivri and anthracyclines should not be given concurrently in the adjuvant treatment setting.

In patients with EBC an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when Ogivri was administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin. The incidence was more marked when Ogivri was administered concurrently with taxanes than when administered sequentially to taxanes. Regardless of the regimen used, most symptomatic cardiac events occurred within the first 18 months.

Risk factors for a cardiac event identified in four large adjuvant studies included advanced age (> 50 years), low level of baseline and declining LVEF (< 55%), low LVEF prior to or following the initiation of paclitaxel treatment, Ogivri treatment, and prior or concurrent use of anti-hypertensive medications. In patients receiving Ogivri after completion of adjuvant chemotherapy, the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracycline given prior to initiation of Ogivri and a high body mass index (BMI > 25 kg/m^2).

Neoadjuvant-adjuvant treatment
In patients with EBC eligible for neoadjuvant-adjuvant treatment, Ogivri concurrently with anthracyclines should be used with caution and only in chemotherapy-naive patients. The maximum cumulative doses of the low-dose anthracycline regimens should not exceed 180 mg/m^2 (doxorubicin) or 360 mg/m^2 (epirubicin).

If patients have been treated concurrently with low-dose anthracyclines and Ogivri in the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after surgery.

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

Benzyl alcohol
Benzyl alcohol, used as a preservative in Bacteriostatic Water for Injection (BWFI) in the 420 mg multi-dose vial, has been associated with toxicity in neonates and children up to 3 years old. When administering Ogivri to a patient with a known hypersensitivity to benzyl alcohol, Ogivri should be reconstituted with water for injection, and only one dose per Ogivri vial should be used. Any unused portion must be discarded.

Interaction with Other Medicinal Product
There have been no formal drug interaction studies performed with trastuzumab in humans. Clinically significant interactions between trastuzumab and the concomitant medication used in clinical trials have not been observed ***(see section Pharmacokinetics Properties)***.

In studies where trastuzumab was administered in combination with docetaxel, carboplatin, or anastrozole, the pharmacokinetics of these medications was not altered nor was the pharmacokinetics of trastuzumab altered.

Concentrations of paclitaxel and doxorubicin (and their major metabolites 6-α hydroxyl-paclitaxel, POH, and doxorubicinol, DOL) were not altered in the presence of trastuzumab. However, trastuzumab may elevate the overall exposure of one doxorubicin metabolite (7-deoxy-13 dihydro-doxorubicinone, D7D). The bioactivity of D7D and the clinical impact of the elevation of this metabolite is unclear. No changes were observed in trastuzumab concentrations in the presence of paclitaxel and doxorubicin.

The results of a drug interaction sub study evaluating the pharmacokinetics of capecitabine and cisplatin when used with or without trastuzumab suggested that the exposure to the bioactive metabolites (e.g. 5-FU) of capecitabine was not affected by concurrent use of cisplatin or by concurrent use of cisplatin plus trastuzumab. However, capecitabine itself showed higher concentrations and a longer half-life when combined with trastuzumab. The data also suggested that the pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus trastuzumab.

Fertility, Pregnancy and Lactation
Females and Males of Reproductive Potential

Fertility
It is not known whether trastuzumab can affect reproductive capacity. Animal reproduction studies revealed no evidence of impaired fertility or harm to the foetus.

Contraception
Women of childbearing potential should be advised to use effective contraception during treatment with trastuzumab and for 7 months after treatment has concluded ***(see section Pharmacokinetic Properties)***.

Pregnancy
Trastuzumab should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus. In the post-marketing setting, cases of foetal renal growth and/or function

impairment in association with oligohydramnios, some of which resulted in fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving trastuzumab.

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

Labour and Delivery
No data to report.

Lactation
It is not known whether trastuzumab is secreted in human milk. As human immunoglobulin G (IgG) is secreted into human milk, and the potential for harm to the infant is unknown, breast-feeding should be avoided during trastuzumab therapy ***(see section Preclinical Safety Data)***

Paediatric Use
The safety and efficacy of trastuzumab in paediatric patients below the age of 18 have not been established.

Geriatric Use
Data suggest that the disposition of trastuzumab is not altered based on age ***(see section Pharmacokinetics in Special Populations).***

Renal Impairment
In a population pharmacokinetic analysis, renal impairment was shown not to affect trastuzumab disposition.

Hepatic Impairment
No data to report.

Undesirable Effects
Clinical Trials
Table 10 summarizes adverse drug reactions (ADRs) that have been reported in association with the use of trastuzumab alone or in combination with chemotherapy in pivotal clinical trials. All the terms included are based on the highest percentage seen in pivotal clinical trials.

As trastuzumab is commonly used with other chemotherapeutic agents and radiotherapy it is often difficult to ascertain the causal relationship of an adverse event to a particular drug/radiotherapy.

The corresponding frequency category for each adverse drug reaction is based on the following convention: 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 should be presented in order of decreasing seriousness.

Table 10: Summary of adverse drug reactions occurring in patients treated with trastuzumab in clinical trials

System organ class	*Adverse reaction	Frequency
Infections and infestations	Nasopharyngitis	Very common
	Infection	Very common
	Influenza	Common
	Neutropenic sepsis	Common
	Pharyngitis	Common

System organ class	*Adverse reaction	Frequency
	Sinusitis	Common
	Rhinitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
	Cystitis	Common
	Skin infection	Common
Neoplasms benign, malignant and unspecified (incl. Cysts and polyps)	Malignant neoplasm progression	Not known
	Neoplasm progression	Not known
Blood and lymphatic system disorders	Anaemia	Very common
	Thrombocytopenia	Very common
	Febrile Neutropenia	Very common
	White blood cell count decreased/leukopenia	Very common
	Neutropenia	Very common
	Hypoprothrombinaemia	Not Known
	Immune thrombocytopenia	Not Known
Immune system disorders	Hypersensitivity	Common
	[+]Anaphylactic reaction	Rare
	[+]Anaphylactic shock	Rare
Metabolism and nutrition disorders	Weight decreased/ Weight loss	Very common
	Weight increased	Very common
	Decreased appetite	Very common
	Anorexia	Very common
	Tumour lysis syndrome	Not Known
	Hyperkalaemia	Not Known
Psychiatric disorders	Insomnia	Very common
	Depression	Common
	Anxiety	Common
Nervous system disorders	Dizziness	Very common
	Headache	Very common
	Paraesthesia	Very common
	Hypoaesthesia	Very common
	Dysgeusia	Very common
	[1]Tremor	Very common
	Hypertonia	Common
	Peripheral neuropathy	Common
	Somnolence	Common
Eye disorders	Lacrimation increased	Very common
	Conjunctivitis	Very common
	Dry eye	Common
	Papilloedema	Not Known
	Retinal haemorrhage	Not Known
Cardiac disorders	*Ejection fraction decreased	Very common
	[1] Blood pressure decreased	Very common
	[1] Blood pressure increased	Very common
	[+1]Supraventricular tachyarrhythmia	Common
	[+]Cardiac failure (congestive)	Common
	Cardiomyopathy	Common
	[1]Palpitation	Common
	Pericardial effusion	Uncommon
	[1]Heart beat irregular	Very common
	[1]Cardiac flutter	Very common

System organ class	*Adverse reaction	Frequency
	Cardiogenic shock	Not known
	Gallop rhythm present	Not known
Vascular disorders	Lymphoedema	Very common
	Hot flush	Very common
	[+1] Hypotension	Common
	Hypertension	Common
	Vasodilation	Common
Respiratory, thoracic and mediastinal disorders	[+] Dyspnoea	Very common
	Epistaxis	Very common
	Oropharyngeal pain	Very common
	Cough	Very common
	Rhinorrhoea	Very common
	Asthma	Common
	Lung disorder	Common
	[+] Pleural effusion	Common
	[+] Pneumonia	Common
	Pneumonitis	Uncommon
	[+1] Wheezing	Uncommon
	[+] Pulmonary fibrosis	Not known
	[+] Respiratory distress	Not known
	[+] Respiratory failure	Not known
	[+] Lung infiltration	Not known
	[+] Acute pulmonary oedema	Not known
	[+] Acute respiratory distress syndrome	Not known
	[+] Bronchospasm	Not known
	[+] Hypoxia	Not known
	[+] Oxygen saturation decreased	Not known
	[+] Laryngeal oedema	Not known
	[+] Orthopnoea	Not known
	[+] Pulmonary oedema	Not known
	[+] Interstitial lung disease	Not known
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting	Very common
	Nausea	Very common
	Abdominal pain	Very common
	Dyspepsia	Very common
	Constipation	Very common
	Stomatitis	Very common
	[1] Lip swelling	Very common
	Haemorrhoids	Common
	Dry mouth	Common
Skin and subcutaneous tissue disorders	Erythema	Very common
	Rash	Very common
	[1] Swelling face	Very common
	Alopecia	Very common
	Nail disorder	Very common
	Palmar-plantar erythrodysaesthesia syndrome	Very common
	Acne	Common
	Dry skin	Common

System organ class	*Adverse reaction	Frequency
	Hyperhydrosis	Common
	Maculopapular rash	Common
	Pruritus	Common
	Onychoclasis	Common
	Dermatitis	Common
	Ecchymosis	Common
	Urticaria	Uncommon
	Angioedema	Not Known
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	Myalgia	Very common
	Arthritis	Common
	Back pain	Common
	Bone pain	Common
	Muscle spasms	Common
	Neck pain	Common
	Pain in extremity	Common
	Muscle tightness	Very common
Renal and urinary disorders	Renal disorder	Common
	Glomerulonephritis membranous	Not known
	Glomerulonephropathy	Not known
	Renal failure	Not known
Pregnancy, puerperium and perinatal conditions	Oligohydramnios	Not known
	Renal hypoplasia	Not known
	Pulmonary hypoplasia	Not known
Reproductive system and breast disorders	Breast inflammation/mastitis	Common
General disorders and administration site conditions	Asthenia	Very common
	Chest pain	Very common
	Chills	Very common
	Fatigue	Very common
	Influenza-like symptoms	Very common
	Infusion/Administration related reaction	Very common
	Pain	Very common
	Pyrexia	Very common
	Peripheral oedema	Very common
	Mucosal inflammation	Very common
	Oedema	Common
	Injection site pain	Common
	Malaise	Common
Injury, poisoning and procedural complications	Nail toxicity	Very common
	Contusion	Common
Hepatobiliary disorder	Hepatocellular injury	Common
	Jaundice	Rare
	Hepatitis	Common
	Liver Tenderness	Common
Ear and labyrinth disorder	Deafness	Uncommon

* Adverse drug reactions (ADRs) were identified as events that occurred with at least a 2% difference compared to the control arm in at least one of the major randomized clinical trials.
+ 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.

Additional Information for Selected Adverse Drug Reactions

Infusion/Administration-related Reactions (IRRs/ARRs) and Hypersensitivity
IRRs/ARRs reactions such as chills and/or fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress were seen in all trastuzumab clinical trials and formulation ***(see Section Special Warnings and Precautions for Use)***.

IRRs/ARRs may be clinically difficult to distinguish from hypersensitivity reactions.

The rate of IRRs/ARRs of all grades varied between studies depending on the indication, whether trastuzumab was given concurrently with chemotherapy or as monotherapy and data collection methodology.

In MBC, the rate of IRRs ranged from 49% to 54% in the trastuzumab containing arm compared to 36% to 58% in the comparator arm (which may have contained other chemotherapy). Severe (grade 3 and above) ranged from 5% to 7% in the trastuzumab containing arm compared to 5% to 6% in the comparator arm.

In EBC, the rate of IRRs/ARRs ranged from 18% to 54% in the trastuzumab containing arm compared to 6% to 50% in the comparator arm (which may have contained other chemotherapy). Severe (grade 3 and above) ranged from 0.5% to 6% in the trastuzumab containing arm compared to 0.3% to 5% in the comparator arm.

Anaphylactoid reactions were observed in isolated cases.

Cardiac Dysfunction
Congestive heart failure (NYHA Class II-IV) is a common adverse reaction to trastuzumab. It has been associated with fatal outcome. Signs and symptoms of cardiac dysfunction such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S_3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with trastuzumab ***(see Section Special Warnings and Precautions for Use)***.

Metastatic Breast Cancer
Depending on the criteria used to define cardiac dysfunction, the incidence in the pivotal metastatic trials varied between 9% and 12% in the trastuzumab + paclitaxel group, compared with 1% - 4% in the paclitaxel alone group. For trastuzumab monotherapy, the rate was 6% - 9%. The highest rate of cardiac dysfunction was seen in patients receiving concurrent trastuzumab + anthracycline/cyclophosphamide (27%) and was significantly higher than in the anthracycline/cyclophosphamide alone group (7% - 10%). In a subsequent trial with prospective monitoring of cardiac function, the incidence of symptomatic heart failure was 2.2% in patients receiving trastuzumab and docetaxel, compared with 0% in patients receiving docetaxel alone. Most of the patients (79%) who developed cardiac dysfunction in these trials experienced an improvement after receiving standard treatment for CHF.

Early Breast Cancer (Adjuvant Setting)
In three pivotal clinical trials of adjuvant trastuzumab given in combination with chemotherapy the incidence of grade 3/4 cardiac dysfunction (symptomatic CHF) was similar in patients who were administered chemotherapy alone and in patients who were administered trastuzumab sequentially after a taxane (0.3 - 0.4%). The rate was highest in patients who were administered trastuzumab concurrently with a taxane (2.0%). At 3 years, the cardiac event rate in patients receiving AC→P (doxorubicin plus cyclophosphamide followed by paclitaxel) + H (trastuzumab) was estimated at 3.2%, compared with 0.8% in AC→P treated patients. No increase in the cumulative incidence of cardiac events was seen with further follow-up at 5 years.

At 5.5 years, the rates of symptomatic cardiac or LVEF events were 1.0%, 2.3%, and 1.1% in the AC→D (doxorubicin plus cyclophosphamide, followed by docetaxel), AC→DH (doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab), and DCarbH (docetaxel, carboplatin and trastuzumab) treatment arms, respectively. For symptomatic CHF (NCI-CTC Grade 3 - 4), the 5-year rates were 0.6%, 1.9%, and 0.4% in the AC→D, AC→DH, and DCarbH treatment arms, respectively. The overall risk of developing symptomatic cardiac events was low and similar for patients in the AC→D and DCarbH arms; relative to both the AC→D and DCarbH arms there was an increased risk of developing a symptomatic cardiac event for patients in the AC→DH arm, being discernible by a continuous increase in the cumulative rate of symptomatic cardiac or LVEF events up to 2.3% compared to approximately 1% in the two comparator arms (AC→D and DCarbH).

When trastuzumab was administered after completion of adjuvant chemotherapy NYHA class III-IV heart failure was observed in 0.6% of patients in the one-year arm after a median follow-up of 12 month. After a median follow-up of 3.6 years the incidence of severe CHF and left ventricular dysfunction after 1 year trastuzumab therapy remained low at 0.8% and 9.8%, respectively.

In study BO16348, after a median follow-up of 8 years the incidence of severe CHF (NYHA Class III-IV) in the trastuzumab 1 year treatment arm was 0.8%, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6%.

Reversibility of severe CHF (defined as a sequence of at least two consecutive LVEF values ≥50% after the event) was evident for 71.4% of trastuzumab-treated patients. Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 79.5% of patients. Approximately 17% of cardiac dysfunction related events occurred after completion of trastuzumab.

In the joint analysis of studies NSABP B-31 and NCCTG N9831, with a median follow-up of 8.1 years for the AC→PH group (doxorubicin plus cyclophosphamide, followed by paclitaxel plus trastuzumab), the per patient incidence of new onset cardiac dysfunction, as determined by LVEF, remained unchanged compared to the analysis performed at a median follow up of 2.0 years in the AC→PH group: 18.5% of AC→PH patients with an LVEF decrease of ≥ 10% to below 50%. Reversibility of left ventricular dysfunction was reported in 64.5% of patients who experienced a symptomatic CHF in the AC→PH group being asymptomatic at latest follow up, and 90.3% having full or partial LVEF recovery.

Early Breast Cancer (Neoadjuvant-adjuvant Setting)
In the pivotal trial MO16432, trastuzumab was administered concurrently with neoadjuvant chemotherapy containing three cycles of doxorubicin (cumulative dose 180 mg/m^2). The incidence of symptomatic cardiac dysfunction was 1.7% in the trastuzumab arm.

Metastatic Gastric Cancer
In the BO18255 study, at screening, the median LVEF value was 64% (range 48%-90%) in the fluoropyrimidine/cisplatin arm (FP) arm and 65% (range 50%-86%) in the trastuzumab plus fluoropyrimidine/cisplatin arm (H+FP) arm.

The majority of the LVEF decreases noted in BO18255 study were asymptomatic, with the exception of one patient in the trastuzumab-containing arm whose LVEF decrease coincided with cardiac failure.

Table 11: Summary of LVEF Change from baseline (BO18255 study)

LVEF Decrease: Lowest Post-screening Value	**Fluoropyrimidine/Cisplatin (N = 290) (% of patients in each treatment arm)**	**Trastuzumab/Fluoropyrimidine/ Cisplatin (N = 294) (% of patients in each treatment arm)**
*LVEF decrease of ≥ 10% to a value of <50%	1.1%	4.6%
Absolute Value <50%	1.1%	5.9%

LVEF Decrease: Lowest Post-screening Value	Fluoropyrimidine/Cisplatin (N = 290) (% of patients in each treatment arm)	Trastuzumab/Fluoropyrimidine/ Cisplatin (N = 294) (% of patients in each treatment arm)
*LVEF decrease of ≥10% to a value of ≥50%	11.8%	16.5%

*Only includes patients whose method of assessment at that visit is the same as at their initial assessments (FP, n = 187 and H+FP, n = 237)

Table 12: Cardiac Adverse Events (BO18255 study)

	Fluoropyrimidine/Cisplatin (N = 290) (% of patients in each treatment arm)	Trastuzumab/Fluoropyrimidine/ Cisplatin (N = 294) (% of patients in each treatment arm)
Total Cardiac Events	6%	6%
≥Grade 3 NCI CTCAE v3.0	*3%	**1%

* 9 patients experienced 9 Events
** 4 patients experienced 5 Events

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

Haematological Toxicity

Breast Cancer

Haematological toxicity is infrequent following the administration of trastuzumab monotherapy in the metastatic setting, WHO Grade 3 leukopenia, 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 trastuzumab and paclitaxel compared with patients receiving paclitaxel alone (34% versus 21%). Haematological toxicity was also increased in patients receiving trastuzumab and docetaxel, compared with docetaxel alone (32% grade 3/4 neutropenia versus 22%, using NCI-CTC criteria). The incidence of febrile neutropenia/neutropenic sepsis was also increased in patients treated with trastuzumab plus docetaxel (23% versus 17% for patients treated with docetaxel alone).

Using NCI-CTC criteria, in the BO16348 study, 0.4% of trastuzumab -treated patients experienced a shift of 3 or 4 grades from baseline, compared with 0.6% in the observation arm.

Metastatic Gastric Cancer

The most frequently reported AEs, of Grade ≥ 3 occurring with an incidence rate of at least 1% by trial treatment, that were categorised under the Blood and Lymphatic System Disorders SOC are shown below:

Table 13: Frequently reported AEs grade ≥ 3 in blood and lymphatic system disorders SOC

	Fluoropyrimidine/Cisplatin (N = 290) (% of patients in each treatment arm)	Trastuzumab/Fluoropyrimidine/ Cisplatin (N = 294) (% of patients in each treatment arm)
Neutropenia	30%	27%
Anaemia	10%	12%
Febrile neutropenia	3%	5%
Thrombocytopenia	3%	5%

The total percentage of patients who experienced an AE of ≥ grade 3 NCI CTCAE v3.0 that has been 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 Trastuzumab 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 trastuzumab and paclitaxel than among patients receiving paclitaxel alone (7% compared with 15%). No WHO Grade 3 or 4 renal toxicity was observed.

Metastatic Gastric Cancer

In the BO18255 study no significant differences in hepatic and renal toxicity were observed between the two treatment arms.

NCI-CTCAE (version 3.0) grade ≥ 3 renal toxicity was not significantly higher in patients receiving trastuzumab IV than those in the F+P arm (3% and 2% respectively).

NCI-CTCAE (version 3.0) grade ≥ 3 adverse event in the Hepatobiliary Disorders SOC: Hyperbilirubinaemia was the only reported AE and was not significantly higher in patients receiving trastuzumab than those in the F+P arm (1% and < 1% respectively).

Diarrhoea

Breast Cancer

Of patients treated with trastuzumab 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 trastuzumab in combination with paclitaxel compared with patients receiving paclitaxel alone.
In the BO16348 study, 8% of trastuzumab-treated patients experienced diarrhoea during the first year of treatment.

Metastatic Gastric Cancer

In the BO18255 study, 109 patients (37%) participating in the trastuzumab-containing treatment arm versus 80 patients (28%) in the comparator arm experienced any grade diarrhoea. Using NCI-CTCAE v3.0 severity criteria, the percentage of patients experiencing grade ≥ 3 diarrhoea was 4% in the FP arm versus 9% in the FP+H arm.

Infection

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

Post marketing Experience

The adverse drug reactions have been identified from post marketing experience with trastuzumab in the following table:

Table 14: Adverse Reactions reported in the Post marketing Setting

System organ class	Adverse reaction
Blood and lymphatic system disorders	Hypoprothrombinemia Immune thrombocytopenia
Immune system disorders	Anaphylactoid reaction
	Anaphylactic reaction
Metabolism and nutrition disorders	Tumour lysis syndrome

System organ class	Adverse reaction
Eye disorders	Madarosis
Cardiac disorders	Cardiogenic shock
	Tachycardia
Respiratory, thoracic and mediastinal disorders	Bronchospasm
	Oxygen saturation decreased
	Respiratory failure
	Interstitial lung disease
	Lung infiltration
	Acute respiratory distress syndrome
	Respiratory distress
	Pulmonary fibrosis
	Hypoxia
	Laryngeal oedema
Renal and urinary disorders	Glomerulonephropathy
	Renal failure
Pregnancy, puerperium and perinatal conditions	Pulmonary hypoplasia
	Renal hypoplasia
	Oligohydramnios

Adverse Events
Table 15 below indicates adverse events that historically have been reported in patients who have received trastuzumab. As no evidence of a causal association has been found between trastuzumab and these events, these events are not considered expected for the purposes of regulatory reporting.

Table 15: Adverse Events

System organ class	Adverse Event
Infections and infestations	Meningitis
	Bronchitis
Blood and lymphatic system disorders	Leukaemia
Nervous system disorders	Cerebrovascular disorder
	Lethargy
	Coma
Ear and labyrinth disorders	Vertigo
Respiratory, Thoracic and Mediastinal system disorders	Hiccups
	Dyspnoea exertional
Gastrointestinal disorders	Gastritis
	Pancreatitis
Musculoskeletal and connective tissue disorders	Musculoskeletal pain
Renal and urinary system disorders	Dysuria
Reproductive system and breast disorders	Breast pain
General disorders and administration site conditions	Chest discomfort

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

Ability to Drive and Use Machines
Trastuzumab has a minor influence on the ability to drive and use machines. Dizziness and somnolence may occur during treatment with trastuzumab ***(see section Undesirable Effects)***. Patients experiencing

infusion-related symptoms ***(see Section Special Warnings and Precautions for Use)*** should be advised not to drive or use machines until symptoms resolve completely.

PHARMACEUTICAL PARTICULARS

Instructions for Use

Special Instructions for Use, Handling and Disposal

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

Ogivri Trastuzumab (rDNA Origin) Powder for concentrate for solution for infusion 420mg/vial

Each 420 mg vial of Ogivri is reconstituted with 20 mL of BWFI. Use of other reconstitution solvents should be avoided. This yields a 21 mL solution for single-dose use, containing approximately 21 mg/mL trastuzumab, at a pH of approximately 6.0. A volume overage of 4.8 % ensures that the labelled dose of 420 mg can be withdrawn from each vial.

Special Precautions for Disposal and Other Handling

- Appropriate aseptic technique should be used.
- Use of other reconstitution solvents should be avoided.
- Reconstitution details are given in the table below:

Ogivri vial	Reconstitution	Final concentration
420 mg (multi - dose)	20 mL of BWFI (containing 1.1% Benzyl alcohol)	~21 mg/mL

BWFI: Bacteriostatic Water for Injection.

- During reconstitution, handle **Ogivri** carefully. Causing excessive foaming during reconstitution or shaking the reconstitution solution may result in problems with the amount of **Ogivri** that can be withdrawn from the vial.
- Do not freeze the reconstituted solution.

Instructions for Reconstitution 420mg vial (multi-dose vial)

1) Using a sterile syringe, slowly inject the appropriate volume (as noted above) of BWFI in the vial containing the lyophilised Ogivri, directing the stream into the lyophilised cake.
2) Swirl the vial gently to aid reconstitution. DO NOT SHAKE.

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

Instructions for Dilution

Determine the volume of the Ogivri solution required:

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

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

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

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

The appropriate amount of solution should be withdrawn from the vial using a sterile needle and syringe and added to an infusion bag containing 250 mL of sodium chloride 9 mg/mL (0.9 %) solution for injection. Do not use with glucose/dextrose-containing solutions. The bag should be gently inverted to mix the solution in order to avoid foaming. Once the infusion is prepared it should be administered immediately. If diluted aseptically, it may be stored for 24 hours (do not store above 30°C).

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

No incompatibilities between Ogivri and polyvinylchloride or polyethylene bags have been observed.

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

Ogivri has been developed as a similar biological medicinal product to Herceptin.

Incompatibilities
This medicinal product must not be mixed or diluted with other medicinal products except those mentioned in sections Special Instructions for Use, Handling and Disposal.

Glucose solutions must not be used for dilution since these cause aggregation of the protein.

Storage and Handling Information
Store vials at 2°C – 8°C prior to reconstitution.
Store away from light.
Keep out of reach of children.

Vials should not be used beyond the expiration date stamped on the vial. After reconstitution with BWFI, the reconstituted solution is physically and chemically stable for 28 days when stored at 2°C - 8°C.
DO NOT FREEZE DRUG THAT HAS BEEN RECONSTITUTED.

Shelf Life
Refer to Carton/Label.

Shelf-life of the Reconstituted Solution
420 mg Ogivri (Multi-dose vials)
The reconstituted product is physically and chemically stable for 28 days at 2°C – 8°C after dissolving in BWFI (1.1%). Do not freeze the reconstituted solution.

Shelf-life of the Solution for Infusion containing the Reconstituted Product
Infusion solution (0.9% Sodium Chloride) containing the reconstituted drug product is physically and chemically stable for 24 hours at 2°C - 8°C.

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

Manufactured & Released by:
Biocon Biologics Limited
Block No. B1, B2, B3, Q13 of Q1 and W20 & Unit S18,
1st Floor, Block B4, Special Economic Zone,
Plot No. 2, 3, 4 & 5, Phase IV,
Bommasandra-Jigani Link Road,
Bommasandra, Bengaluru 560099, India.

Product Registration Holder:
Biocon Sdn. Bhd.
No. 1, Jalan Bioteknologi 1,
Kawasan Perindustrian SiLC,
79200, Iskandar Puteri, Johor,
Malaysia.

Distributed by:
Duopharma HAPI Sdn. Bhd.
No. 2, Jalan Saudagar U1/16,
Pusat Perindustrian Hicom Glenmarie,
Seksyen U1, 40150 Shah Alam, Selangor,
Malaysia.

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