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**OGIVRI** 

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## For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

## Trastuzumab for Injection (r-DNA origin)

## 150 mg/440 mg

For I.V. Infusion, single & multiple use vial (Lyophilized powder)

# Ogivri<sup>™</sup> 150/440

le-dose vial of Ogivri™ delivers 440 mg trastuzumab, 337.9 mg D-sorbitol, 6.3 mg L-Histidine, 9.9 mg L-Histidine hydrochloride monohydrate and 98.6 mg Polyethylene glycol 3350/Macrogol on with 20 mL of the appropriate diluent (BWFl or SWFl) yields a solution containing 21 mg/mL trastuzumab that delivers 20 mL (440 mg trastuzumab), at a pH of approximately 6. If Ogivri™ ingle-dose vial of Ogivri™ delivers 150 mg trastuzumab, 115.2 mg D-sorbitol, 2.16 mg L-Histidine, 3.36 mg L-Histidine hydrochloride monohydrate and 33.6 mg Polyethylene glycol 3350/Macrogol 3350.

Cardiomyopathy: Trastuzumab products can result in subclinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue Ogivri™ for cardiomyopathy. Embryo-Fetal Toxicity: Exposure to Ogivri™ during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death. Advise patients of these risks and the need for effective contraception.

The HER2 (or c-erb82) proto-oncogene encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. Trastuzumab products have been shown, in both frastuzumab products are mediators of antibody-dependent cellular cytotoxicity (ADCC). in vitro, trastuzumab product-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer

The effects of trastuzumab on electrocardiographic (ECG) endpoints, including QTc interval duration, were evaluated in patients with HER2 positive solid tumors. Trastuzumab had no clinically relevant effect on the QTc interval duration and there was no apparent relationship between serum trastuzumab concentrations and change in QTcF interval duration in patients with HER2 positive solid tumors. 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.

Although the average trastuzumab exposure was higher following the first cycle in breast cancer patients receiving the three-weekly schedule compared to the weekly schedule of trastuzumab, the average steady state exposure was essentially the same at both dosages. The average trastuzumab exposure following the first cycle and at steady state as well as the time to steady state was higher in breast cancer patients compared to MGC patients at the same dosage; however, the reason for this exposure difference is unknown. Additional predicted trastuzumab exposure and PK parameters following the first trastuzumab cycle and at steady state exposure are described in Tables 1 and 2, respectively.

Schedule Primary tumor type		N				Cmax (μg/mL)		AUC <sub>o-21days</sub> (µg.day/mL)			
6mg/kg q3w		Breast Cancer		1195		29.4 (5.8 to 59.5)		178 (117 to 291)		1373 (736 to	2245)
		мдс		274		23.1 (6.1 to 50.3)		132 (84.2 to 225)		1109 (588 –	1938)
4mg/kg + 2mg/kg qw  Breast Cancer			1195	195 37.7 (12.3 to 70.9)			88.3 (58 to 144)		1066 (586 to	1754)	
able 2: Population I	Predicted Ste	ady State PK Exp	osures (Median	with 5th	to 95th Percentiles) in Br	east Cancer and MGC Pa	atients				
Schedule	Primar tumor		N		Cmin,ss (µg/mL)"	Cmax,ss (μg/mL) <sup>b</sup>	AUC <sub>ο</sub> (μg.da		Time to Steady state (week)		Total CL range at steady- state (L/day)
8mg/kg +	MBC		1195		47.4 (5 - 115)	179 (107 - 309)	1794 (6	673 -3618)	12		0.173 - 0.283
6mg/kg q3w	AGC		274		32.9 (6.1 – 88.9)	131 (72.5 - 251)	1338 (5	557 - 2875)	9		0.189 - 0.337
4mg/kg + 2mg/kg qw	MBC		1195		66.1 (14.9 - 142)	109 (51.0 - 209)	1765 (647 -	3578)	12		0.201 - 0.244

in (n = 264); non-Asian (n = 1324)) and renal impairment (mild (creatinine clearance [CLcr] 60 to 90 mL/min) (n = 636) or moderate (CLcr 30 to 60 mL/min) (n = 133)). The pharmacokinetics of trastuzumab ucts in patients with severe renal impairment, end-stage renal disease with or without hemodialysis, or hepatic impairment is unknown. Drug Interaction Studies: There have been no formal drug interaction studies performed with trastuzumab products in humans. Clinically significant interactions between trastuzumab and concomitant medications Paclitaxel and doxorubicin: Concentrations of paclitaxel and doxorubicin and their major metabolites (i.e., 6-a hydroxyl-paclitaxel [POH], and doxorubicinol [DOL], respectively) were not altered in the presence of rastuzumab when used as combination therapy in clinical trials. Trastuzumab concentrations were not altered as part of this combination therapy.

A fertility study was conducted in female cynomolgus monkeys at doses up to 25 times the weekly recommended human dose of 2 mg/kg of trastuzumab and has revealed no evidence of impaired fertility, as measured

A randomized, double-blind, Phase I study to assess the bioequivalence of Ogivri vs Herceptin® administered as a single intravenous infusion to healthy male volunteers

A total of 120 treatment-emergent adverse events (TEAEs) were reported in 22 subjects during the study, including 47 AEs in 16 subjects after administration with Ogivri (N=19) and 73 AEs in 21 subjects after administration with Herceptin\* (N=2). There were no deaths and no serious AEs. The vast majority of the TEAEs were rated as mild (92%), some as moderate (7.5%), and only 1 (0.5%) as severe (streptococcal pharyngitis after Ogivri). The most frequently reported AE preferred terms for Ogivri were: headache (47%), followed by nasopharyngitis (26%) and CRP increased (21%), while for Herceptin\* were: nasopharyngitis (55%), followed by headache (46%), rhinitis (36%), and CRP increase (32%). Study MYL-Her-1002:

A Single-Center, Randomized, Double-Blind, Three-Arm, Parallel-Group Phase I Study to Compare the Pharmacokinetic Profiles of Ogivri, EU-approved Herceptin® and US-Licensed Herceptin® Administered as a Single Intravenous Infusion to Healthy Male Volunteers. The primary objective of this study was to demonstrate pharmacokinetic similarity of Mylan trastuzumab (Ogivri) versus EU-approved Herceptin\* and US-licensed Herceptin\* and pharmacokinetic similarity of EU-approved Herceptin\* versus US-licensed Herceptin\* after 8 mg/kg as single dose administered as intravenous infusion over 90 minutes in healthy male subjects based on the equivalence criterion that AUCO--->.
AUCO-last, and Cmax least square mean ratios are bounded within the 90% confidence intervals, 80.00% - 125.00% resimilarity assessments were performed, 1) Ogivri vs. EU-approved Herceptin\*, 20 givri vs. US-licensed Herceptin\* and 3 EU-approved Herceptin\*, 20 givri vs. US-licensed Herceptin\* Az, tmax and t1/2 along with assessment of safety (including immunogenicity) and local tolerance.

Mylan's trastuzumab (Ogivri), EU-approved Herceptin<sup>®</sup> and US-licensed Herceptin<sup>®</sup> were well tolerated after 8 mg/kg as single dose administered to healthy male volunteers as intravenous infusion over 90 minutes.

Mylan's trastuzumab (Ogivri), EU-approved Herceptin<sup>®</sup> and US-licensed Herceptin were well tolerated after 8 mg/kg as single dose administered to healthy male volunteers as intravenous infusion over 90 minutes.

Mylan's trastuzumab (Ogivri), EU-approved Herceptin and Valunteers (227) treatment-emergent adverse events (TEAEs) over the course of the study. The TEAEs were emild to moderate in severity, No SAEs were reported. No subjects were withdrawn from the study Local infusions were well tolerated and reactions observed were minimal with all three treatments. There were no instances of either treatment-induced or treatment-boosted ADA-positive subjects in the study. All statistical analyses of these data reveal that the 90% confidence intervals fall within 80%-125% for the test to reference ratio for the natural log transformed parameters, LNAUC0-ast, LNAUC0-and LNCmax, for trastuzumab. This study demonstrates that Mylan trastuzumab (Ogivn) is bioequivalent to both EU-approved Herceptin\* and US-licensed Herceptin\* after 8 mg/kg as single dose administered as intravenous nutsion over 90 minutes in healthy male subjects. In addition, EU-approved Herceptin\* is bioequivalent to US-licensed Herceptin\* after 8 mg/kg as single dose administered as intravenous nutsion over 90 minutes in healthy male subjects. Study MYL-Her-3001:

nulticenter, double-blind, randomized, parallel-group, phase III study to compare the efficacy and safety of Mylan's trastuzumab versus Herceptin® in patients with HER2+ metastatic breast cancer

In Part 2 of the study, after completing a minimum of 8 cycles of treatment in Part 1 of the study, all patients with at least SD continued with the trastuzumab product that they were originally allocated to as a single agent until disease progression, unacceptable toxicity, or death, whichever occurred first. Tumor assessments were conducted every 12 weeks (±3 days). The endpoints for the primary and secondary objectives were to be analyzed at Week 24 in Part 1 and at Week 48 in Part 2. This report summarizes the results from both Part 1 and Part 2 of the study, including the pharmacokinetic (PK) analysis and immunogenicity results through 48 weeks. Study population: 500 Mylan's trastuzumab (n = 250) EU-approved Herceptin®(n=250)

Study population: Study Mylan's trastuzumab (n = 250) EU-approved Herceptin"(n=250)
The efficacy of Mylan's Trastuzumab was confirmed in the pivotal confirmatory, study (MYL-Her-3001) which compared the efficacy and safety between Mylan's Trastuzumab and the EU reference product, Herceptin", when used as primary teatment in patients with newly diagnosed HER2+ MBC. The first part of the study evaluated both treatments in combination with a taxane (docetaxel or pacilitaxel), and the second part of the study evaluated continued treatment with Mylan's Trastuzumab or Herceptin" alone in those patients who had at least stable disease (SD) at 24 week in the first part. The therapeutic equivalence was confirmed by the primary efficacy evaluation of best ORR (according to Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria) at Week 24. All secondary efficacy analyses (TTP, PFS, and OS evaluated at Week 24 and 48) also supported the conclusion of therapeutic equivalence.

In the Mylan's Trastuzumab arm, 189 patients (82.2%) had PFS until Week 24 compared with 180 patients (78.9%) in the Herceptin® arm. According to the log-rank test, the time-to-event curves for both treatment groups were not statistically significantly different (p = 0.303).

Initi Week 48, 128 patients (55.7%) in the Mylan's Trastuzumab group and 126 patients (55.3%) in the Herceptin\* group still did not have progression of the disease. According to the log-rank test, the time-to-event curves for both treatment groups were also not statistically significantly different (p = 0.842). The median PFS (Kaplan-Meier estimate) was 11.1 months in both arms. In the Mylan's Trastuzumab arm, 223 patients (97.0%) survived until Week 24 compared to 218 patients (95.6%) in the Herceptin® arm According to the log-rank test, this difference was not statistically significant (p=0.439).

Until 48 week 205 patients (89.1.0%) survived in the Mylan's Trastuzumab group compared with 194 patients (85.1%) in the Herceptin\* group. According to the log-rank test, this difference was not statistically significant (p=0.131). The median OS was not reached at 48 weeks.

Figure 2 in control (a) the same year or emiciacy of treaturamb in vocree receiving adjuvant chemotherapy for HER2 overexpressing breast cancer were evaluated in an integrated analysis of two parts from the first of MGS vocree in a stratumation in vocree in expectation from the first of MGS vocree in a stratumation of the first of MGS vocree in the first of MGS vocree i A total of 3752 patients were included in the joint efficacy analysis of the primary endpoint of DFS following a median follow-up of 2,0 years in the AC — paclitaxel + trastuzumab arm. The pre-planned final OS analysis from the joint analysis included 4063 patients and was performed when 707 deaths had occurred after a median follow-up of 8.3 years in the AC — paclitaxel + trastuzumab arm. The pre-planned final OS analysis from the joint analysis included 4063 patients and was performed when 707 deaths had occurred after a median follow-up of 8.3 years in the AC — paclitaxel + trastuzumab arm. The data from both arms in Study 1 and two of the three study arms in Study 2 were pooled for efficacy analyses. The patients included in the primary DFS analysis had an median age of 49 years (range, 22 to 80 years; 8% > 65 years), 84% were white, 7% block, 4% Hispannian, and 4% AsianniPacific Islander, Disease characteristics included of 90% inflittrating ductal histology, 38% T1, 91% nodal involvement, 27% intermediate and 66% high grade pathology, and 53% EFI+ and/or PF+ tumors. Similar demographic and baseline characteristics were reported for the efficacy evaluable population, after 8.3 years of median follow-up in the AC — paclitaxel + trastuzumab arm.

Median TTP(mos) In Study 3, breast tumor specimens were required to show HER2 overexpression (3 - by HIC) or gene amplification (by FISH) as determined at a central laboratory. Patients with node-negative disease were required to a Trip primary tumor. Patients with a history of congestive heart failure or LVEF < 55%, uncontrolled arrhythmical and application, clinically significant valvular heart disease, evidence of transmural infarction on EOG, poorly controlled hypertension (systolic > 180 mm Hg or disabloic) > 100 mm Hg were not eligible. Study 3 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). Patients were randomized (1:1:1) upon completion of definitive surgery, and at least four cycles of chemotherapy to receive no additional treatment, or one year of trastuzumab treatment or two years of trastuzumab treatment, Patients undergoing a lumpectomy had also completed standard radiotherapy. Patients with EFF and/or PgR-4 classes received systemic adjuvant hormonal therapy at investigator followed by subsequent doses of 6 mg/kg once every three weeks. The main outcome measure was Disease-Free Survival (DFS), defined as in Studies 1 and 2.

A protocol specified interim efficacy analysis comparing one-year trastuzumab treatment to observation was performed at a median follow-up duration of 12.6 months in the trastuzumab arm and formed the basis for the definitive DFS results from this study. Among the 3386 patients randomized to the observation (n = 1693) and trastuzumab one-year (n = 1693) treatment arms, the median age was 49 years (range 21 to 80)

illeans with at least one of the following high-risk features: ER/PR negative, tumor size > 2 cm, age < 35 years, or histologic and/or nuclear Grade 2 or 3. Patients with a history of CHF, myocardial infarction, Grade 3 or 4 cardiac arrhythmia, angina requiring medication, clinically significant valvular heart disease, poorly controlled hypertension (diastolic > 100 mm Hg), any 14 or N2 or known N3 or M1 breast cancer were not eligible.

Table 3: Efficacy Results from Adjuvant Treatment of Breast Cancer (Studies 1 + 2, Study 3, and Study 4)					
	DFS events	DFS Hazard ratio (95% CI) p-value	Deaths (OS events)	OS Hazard ratio p-value	
Studies 1 + 2*					
AC → TH (n = 1872) <sup>6</sup> (n = 2031) <sup>6</sup>	133°	0.48 <sup>tod</sup> (0.39, 0.59) p < 0.0001°	289°	0.64°.d (0.55, 0.74) p < 0.0001"	
$AC \rightarrow T$ $(n = 1880)^{\circ}$ $(n = 2032)^{\circ}$	261 <sup>b</sup>		418°		
Study 3 <sup>r</sup>					
Chemo → Trastuzumab (n = 1693)	127	0.54 (0.44, 0.67) p < 0.0001°	31	0.75 p = NS <sup>h</sup>	
Chemo → Observation (n = 1693)	219		40		
Study 4					
TCH (n = 1075)	134	0.67 (0.54 to 0.84) p = 0.0006°1	56		
AC → TH (n = 1074)	121	0.60 (0.48 to 0.76) p < 0.0001°	49		

 $^{\circ}$ Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC  $\rightarrow$  T) or paclitaxel plus trastuzumab (AC  $\rightarrow$  TH). Efficacy evaluable population, for the primary DFS analysis, following a median follow-up of 2.0 years in the AC  $\rightarrow$  TH arm.

Hazard ratio estimated by Cox regression stratified by clinical trial, intended paclitaxel schedule, number of positive nodes, and hormone receptor status

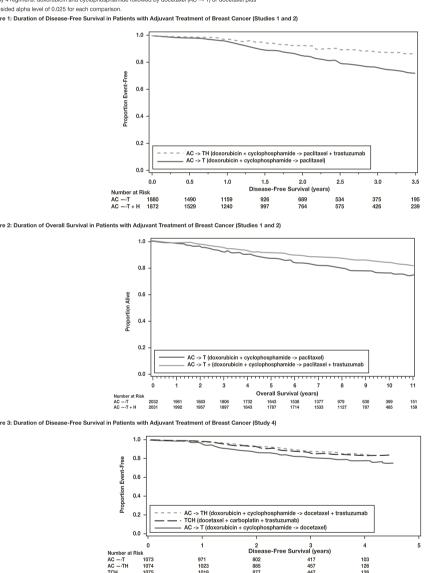


Table 4: Treatment Outcomes in Studies 2 and 3 as a Function of HER2 Overexpression or Amplification

	Stud	ly 2	Stud	y 3°
HER2 Assay Result <sup>a</sup>	Number of Patients	Hazard Ratio DFS (95% CI)	Number of Patients	Hazard Ratio DFS (95% CI)
IHC 3+				
FISH (+)	1170	0.42 (0.27, 0.64)	91	0.56 (0.13, 2.50)
FISH (-)	51	0.71 (0.04, 11.79)	8	_
FISH Unknown	51	0.69 (0.09, 5.14)	2258	0.53 (0.41, 0.69)
IHC < 3+ / FISH (+)	174	1.01 (0.18, 5.65)	299 <sup>b</sup>	0.53 (0.20, 1.42)
IHC unknown / FISH (+)	-	-	724	0.59 (0.38, 0.93)
* IHC by HercenTest_FISH by PathVysion (	(HER2/CEP17 ratio > 2.0) as performed at a	central laboratory		

\*\*\* as greater in the pacilitaxel subgroup.

\*\*Table 5: Study 5: Efficacy Results in First-Line Treatment for Metastatic Breast Cancer

| Combined Results | Pacilitaxel Subgroup | AC 

 Median TTP(mos) b.c
 7.2
 4.5
 6.7
 2.5
 7.6
 5.7

 95% Cl
 7.8
 4.5
 5.10
 2.4
 7.9
 5.7

 Special Warnings and Precautions for Use

 Secondary Endpoints

 Overall Response Rate\*
 45
 29
 38
 15
 50
 38

 95% Cl
 39, 51
 23, 35
 28, 48
 8, 22
 42, 58
 30, 46

Prequiring supplementary oxygen therapy.

Special Warnings and Precautions for Use

Cardiomyopathy

Trastuzumab products can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death *[see Boxed Warning: Cardiomyopathy]*. Trastuzumab products can also cause asymptomatic decline in left ventricular acrdiac dysfunction among patients receiving trastuzumab products as a single agent or in combination therapy compared with those not receiving trastuzumab product is administered with an anthracycline.

Withhold Ogivi¹¹¹º for ≥ 16% absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pre-treatment values or an LVEF value below institution or resumption of Ogivi¹¹¹² nor ≥ 16% absolute decrease in LVEF from pre-treatment values or an LVEF value below institution or resumption of Ogivi¹²² nor ≥ 16% absolute decrease in LVEF from pre-treatment values or an LVEF value below institution or resumption of Ogivi¹²²

Repeat LVEF measurement at 4 week intervals if Ogivri™ is withheld for significant left ventricular cardiac dysfunction [see Dosage and Administration]

Table 9: Incidence of Congestive Heart Failure in Adjuvant Breast Cancer Studies

6 Cardiac Dysfunction<sup>c</sup>

\* Congestive heart failure or significant asymptomatic decrease in LVEF.

<sup>b</sup> Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

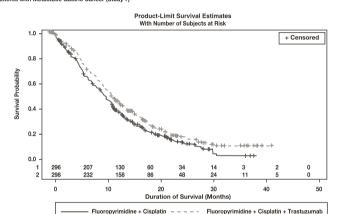
<sup>c</sup>Kaplan-Meier Estimate.

tudy 5 suggest that the beneficial treatment effects were largely limited to patients with the highest level of HER2 protein overexpression (3+) (see Table 6).  atment Effects in Study 5 as a Function of HER2 Overexpression or Amplification					
HER2 Assay Result	Number of Patients (N)	Relative Risk <sup>b</sup> for Time to Disease Progression (95% CI)	Relative Risk <sup>b</sup> for Mortality (95% CI)		
CTA 2+ or 3+	469	0.49 (0.40, 0.61)	0.80 (0.64, 1.00)		
FISH (+) <sup>a</sup>	325	0.44 (0.34, 0.57)	0.70 (0.53, 0.91)		
FISH (-)*	126	0.62 (0.42, 0.94)	1.06 (0.70, 1.63)		
CTA 2+	120	0.76 (0.50, 1.15)	1.26 (0.82, 1.94)		
FISH (+)	32	0.54 (0.21, 1.35)	1.31 (0.53, 3.27)		
FISH (-)	83	0.77 (0.48, 1.25)	1.11 (0.68, 1.82)		
CTA 3+	349	0.42 (0.33, 0.54)	0.70 (0.51, 0.90)		
EIGH (1)	202	0.40 (0.00 0.55)	0.67 (0.64, 0.00)		

Previously Treated Metastatic Breast Cancer (Study 6):

Table 7. Study 7. Sveraii Survivarii 111 Fopulation			
	FC Arm N=296		FC + T Arm N = 298
Definitive (Second Interim) Overall Survival			
No. Deaths (%)	184 (62.2%)		167 (56.0%)
Median	11.0		13.5
95% CI (mos.)	(9.4, 12.5)		(11.7, 15.7)
Hazard Ratio		0.73	
95% CI		(0.60, 0.91)	
p-value*, two-sided		0.0038	
Updated Overall Survival			
No. Deaths (%)	227 (76.7%)		221 (74.2%)
Median	11.7		13.1
95% CI (mos.)	(10.3, 13.0)		(11.9, 15.1)
Hazard Ratio		0.80	
95% CI		(0.67, 0.97)	
	•		

Figure 4: Updated Overall Survival in Patients with Metastatic Gastric Cancer (Study 7)



- Fidotopyrimidine	Cispiatii = = = = Fidoropyiiilid	ille + Oispiatiii + Trastuzumab		
n exploratory analysis of OS in patients based on HER2 gene amplification (FISH) and protein of	overexpression (IHC) testing is summarize	ed in Table 8.		
able 8: Exploratory Analyses by HER2 Status Using Updated Overall Survival Resultsa				_
	FC (N = 296)"		FC + T (N = 298) <sup>6</sup>	
FISH+ / IHC 0, 1+ subgroup (N = 133)				
No. Deaths (%) / n (%)	57/71 (80%)		56/62 (90%)	
Median OS Duration (mos.)	8.8		8.0	
95% CI (mos.)	(6.4, 11.7)		(6.2, 10.7)	
Hazard Ratio (95% CI)		1.33 (0.92, 1.92)		
FISH+ / IHC2+ subgroup (N = 160)				
No. Deaths (%) / n (%)	65/80 (81%)		64/80 (80%)	
Median OS Duration (mos.)	10.8		12.3	
95% CI (mos.)	(6.8, 12.8)		(9.5, 15.7)	
Hazard Ratio (95% CI)		0.78 (0.55, 1.10)		
FISH+ or FISH-/ IHC3+" subgroup (N = 294)				7
No. Deaths (%) / n (%)	104/143 (73%)		96/151 (64%)	
Median OS Duration (mos.)	13.2		18.0	
95% CI (mos.)	(11.5, 15.2)		(15.5, 21.2)	
Hazard Ratio (95% CI)		0.66 (0.50, 0.87)		

 In combination with necadjuvant chemotherapy followed by adjuvant Ogivr™ therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (see section "Warnings and Precautions" and "Pharmacodynamic properties"). givri<sup>nst</sup> should only be used in patients with metastatic or EBC whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay.

indication is based on data from one Phase III trial which studied the use of Herceptin in combination with anastrozole (see Clinical Studies). Experience with other aromatase inhibitors is limited.

Metastatic Gastric Cancer Ogivri in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received prior articancer treatment for their metastatic disease. Ogivri should only be used in patients with metastatic gastric cancer (MGC) whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used (see section "Warnings and Precautions" and "Pharmacodynamic properties") Posology and Method of Administration

Patient Selection Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens [see Indications and Usage and Clinical Studies]. Assessment of HER2 protein overexpression and HER2 gene amplification should be performed using tests specific for breast or gastric cancers by laboratories with demonstrated proficiency. Assessment of HER2 protein overexpression and HER2 gene amplification in metastatic gastric cancer should be performed using tests specifically for gastric cancers due to differences in gastric vs. breast histopathology, including incomplete membrane staining and more frequent heterogeneous expression of HER2 seen in gastric cancers. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

### Do not administer as an intravenous push or bolus. Do not mix Ogivri™ with other drugs. Adjuvant Treatment, Early Breast Cancer

The recommended initial loading dose is 8 mg/kg body weight. The recommended maintenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.

The recommended weekly maintenance dose of trastuzumab is 2 mg/kg body weight, beginning one week after the loading dose. If the prior dose was well tolerated, the dose can be administered as a 30-minute infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see Undesirable effects).

Metastatic Gastric Cancer:

The safety and efficacy of trastuzumab in treatment of women with metastatic breast cancer were studied in a randomized, controlled clinical trial in combination with chemotherapy (Study 5, n = 469 patients) and an open-label single agent clinical trial (Study 6, n = 222 patients). Both trials studied patients with metastatic breast cancer whose tumors overexpress the HER2 protein. Patients were eligible if they had 2 or 3 levels of overexpression (based on a 0 to 3 scale) by immunohistochemical assessment of tumor tissue performed by a central testing lab.

The safety and efficacy of trastuzumab in treatment of women with metastatic breast cancer whose tumors overexpress the HER2 protein. Patients were eligible if they had 2 or 3 levels of overexpression (based on a 0 to 3 scale) by immunohistochemical assessment of tumor tissue performed by a central testing lab.

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The safety and efficacy of trastuzumab in treatment of women with metastatic breast cancer whose tumors overexpress the HER2 protein. Patients were eligible if they had 2 or 3 levels of overexpression (based on a 1 to 3 scale) by immunohistochemical assessment of tumor tissue performed by a central testing lab.

The safety and efficacy of trastuzumab in treatment of women with metastatic breast cancer whose tumors of the weekly schedule: 4 mg/kg; three weekly schedules and the next planned cycle. Subsequent Ogivit<sup>110</sup> maintenance dose should be administered as until the next planned cycle. Subsequent Ogivit<sup>110</sup> maintenance doses should be administered as until the next planned cycle. Subsequent Ogivit<sup>110</sup> maintenance doses should be administered as until the next planned cycle. Subsequent Ogivit<sup>110</sup> maintenance doses should be administer Important Dosing Considerations

Patients who receive anthracycline after stopping Ogivri<sup>TM</sup> may also be at increased risk of cardiac dysfunction [see Drug Interactions and Clinical Pharmacology].

In Study 1, 15% (158/1031) of patients discontinued trastuzumab due to clinical evidence of myocardial dysfunction or significant decline in LVEF after a median follow-up duration of 8.7 years in the AC-TH arm. In Study 3 (one-year trastuzumab treatment), the number of patients who discontinued trastuzumab due to cardiac toxicity at 12.6 months median duration of follow-up was 2.6% (44/1678). In Study 4, a total of 2.9% (31/1056) of patients in the TCH arm (1.5% during the hemotherapy phase and 1.4% during the monotherapy phase) and 5.7% (61/1068) of patients in the AC-TH arm (1.5% during the chemotherapy phase and 4. during the monotherapy phase) discontinued trastuzumab due to cardiac toxicity.

		1		incidence of Chr		1 1 1
Study	Reg	imen	Trastuzumab		Control	Mu
1 & 2*	AC <sup>b</sup> → Paclitax	el + Trastuzumab	3.2% (64/2000)°		1.3% (21/1655)	
3 <sup>rt</sup>	Chemo →	Frastuzumab	2% (30/1678)		0.3% (5/1708)	1
4	AC <sup>b</sup> → Docetax	el + Trastuzumab	2% (20/1068)		0.3% (3/1050)	Nei
4	Docetaxel + Car	bo + Trastuzumab	0.4% (4/1056)		0.3% (3/1050)	1 =
" Median follow-up duration for studies :	1 and 2 combined was 8.3 years in the A	C → TH arm.		•		
b Anthracycline (doxorubicin) and cyclop	hosphamide.					
Includes 1 nations with fatal cardiomyo	pathy and 1 patient with sudden death w	vithout documented etiology				F
	at 12.6 months median duration of follow		h arm			
	nent), at a median follow-up duration of 8			he rate of mild symptomatic and a	symptomatic left ventricular	F
dysfunction was 4.6%.	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	,,	,	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	,-,-	
Table 10: Incidence of Cardiac dysfun	ction <sup>a</sup> in Metastatic Breast Cancer Stu	dies				<u></u> ⊢
			Incir	lence		Re
						-
		NY	HA I-IV	NYH.	A III–IV	1
Study	Event	Trastuzumab	Control	Trastuzumab	Control	ı —
5 (AC) <sup>b</sup>	Cardiac Dysfunction	28%	7%	19%	3%	
5 (paclitaxel)	Cardiac Dysfunction	11%	1%	4%	1%	I —
6	Cardiac Dysfunction <sup>c</sup>	7%	N/A	5%	N/A	
·						∟ ISk

In Study 4, the incidence of NCI-CTC Grade 3/4 cardiac ischemia/infarction was higher in the trastuzumab containing regimens (AC-TH: 0.3% (3/1068) and TCH: 0.2% (2/1056)) as compared to none in AC-T.

Embryo-Fetal Toxicity Trastuzumab products can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of trastuzumab during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Pulmonary Toxicity Tastuzumab product use can result in serious and fatal pulmonary toxicity. Pulmonary toxicity includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, noncardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions [see Warnings and Precautions]. Patients with symptomatic intrinsic lung disease or with exensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have now severe toxicity.

## Embryo-Fetal Toxicity [see Warnings and Precaution]

The most common adverse reactions in patients receiving trastuzumab products in the adjuvant and metastatic breast cancer setting are fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myayilia. Adverse reactions requiring the result of the product treatment include CHF, significant decline in left venticular facilities and the product treatment include CHF, significant decline in left venticular facilities. Clinical Trials Experience

The data below reflect exposure to one-year trastuzumab therapy across three randomized, open-label studies, Studies 1, 2, and 3, with (n = 3678) or without (n = 3363) trastuzumab in the adjuvant treatment of breast cance Table 11: Adverse Reactions for Study 3a, grades<sup>b</sup> Adverse Reaction One year Trastuzumab (n = 1678) Observation (n = 1708)

on	64 (4%)	35 (2%)	thera patie
	60 (4%)	29 (2%)	patie simil
action Decreased	58 (3.5%)	11 (0.6%)	expe
3	48 (3%)	12 (0.7%)	Table
rhythmias°	40 (3%)	17 (1%)	
ilure Congestive	30 (2%)	5 (0.3%)	
ilure	9 (0.5%)	4 (0.2%)	
sorder	5 (0.3%)	0 (0%)	
Dysfunction	4 (0.2%)	0 (0%)	
Thoracic Mediastinal Disorders			
	81 (5%)	34 (2%)	
	70 (4%)	9 (0.5%)	$\vdash$
	57 (3%)	26 (2%)	
	46 (3%)	20 (1%)	
	36 (2%)	6 (0.4%)	
ryngeal Pain	32 (2%)	8 (0.5%)	
•	26 (2%)	5 (0.3%)	" For
	25 (2%)	1 (0.06%)	° Me
Hypertension	4 (0.2%)	0 (0%)	<sup>d</sup> Me
Pneumonitis	4 (0.2%)	0 (0%)	" Stu
stinal Disorders	· (carry	- 1	Figu
ATTENDED	123 (7%)	16 (1%)	
	108 (6%)	19 (1%)	
	58 (3.5%)	10 (0.6%)	
on	33 (2%)	17 (1%)	
···	30 (2%)	9 (0.5%)	
ominal Pain	29 (2%)	15 (1%)	
eletal & Connective Tissue Disorders		, , , , ,	
55541.5.5511.5511.5.11.5.15	137 (8%)	98 (6%)	
	91 (5%)	58 (3%)	
	63 (4%)	17 (1%)	
	49 (3%)	26 (2%)	
asm	46 (3%)	3 (0.2%)	
rstem Disorders		. (	
	162 (10%)	49 (3%)	
ia	29 (2%)	11 (0.6%)	
cutaneous Tissue Disorders		(	
501tan19080 110080 210018019	70 (4%)	10 (0.6%)	Time
ers	43 (2%)	0 (0%)	Figu
013	40 (2%)	10 (0.6%)	
sorders		12 (21277)	
501 UEL 3	100 (6%)	6 (0.4%)	
ipheral	79 (5%)	37 (2%)	
produ	85 (5%)	0 (0%)	
	75 (4.5%)	30 (2%)	
ke Illness	40 (2%)	3 (0.2%)	
ath	1 (0.06%)	0 (0%)	
QUI I	1 (0.0070)	0 (070)	
ngitis	135 (8%)		
- Muro	39 (3%)		
stem Disorders	00 (070)		
tivity	10 (0.6%)	1 (0.06%)	
ne Thyroiditis	4 (0.3%)	0 (0%)	
ne myrodina	4 (0.070)	0 (070)	Time

 $^{\mathrm{b}}$  The incidence of Grade 3 or higher adverse reactions was < 1% in both arms for each listed term.

Study 3, a comparison of 3-weekly trastuzumab treatment for two years versus one year was also performed. The rate of asymptomatic cardiac dysfunction was increased in the 2-year trastuzumab treatment arm 1,1% versus 4.6% in the one-year trastuzumab treatment arm). More patients experienced at least one adverse reaction of Grade 3 or higher in the 2-year trastuzumab treatment arm (20.4%) compared with the one-year trastuzumab treatment arm (30.4%) compared ne safety data from Studies 1 and 2 were obtained from 3655 patients, of whom 2000 received trastuzumab; the median treatment duration was 51 weeks. The median age was 49 years (range: 24 to 80); 84% of attemption to the state of the state In Study 1, only Grade 3 to 5 adverse events, treatment-related Grade 2 events, and Grade 2–5 dyspnea were collected during and for up to 3 months following protocol-specified treatment. The following non-cardiac adverse reactions of Grade 2 to 5 occurred at an incidence of at least 2% greater among patients receiving trastuzumab plus chemotherapy as compared to chemotherapy alone: fatigue (29.5% vs. 22.4%), infection (24.0% vs. 12.8%), hot flastes (71.7% vs. 15.0%), amenia (12.3% vs. 6.7%), dyspened (11.8% vs. 4.6%), rashfurdamiation (10.9% vs. 7.5%), leukspenia (10.5% vs. 8.4%), neutropenia (6.4% vs. 4.3%), hadeache (6.2% vs. 3.8%), pain (5.5% vs. 3.0%), edema (4.7% vs. 2.7%) and insomnia (4.3% vs. 1.5%). The majority of these events were Grade 2 in severity. Safety data from Study 4 reflect exposure to trastuzumab as part of an adjuvant treatment regimen from 2124 patients receiving at least one dose of study treatment (AC-TH: n = 1058; TCH: n = 1056). The overall median treatment duration was 54 weeks in both the AC-TH arm. The median number of infusions was 26 in the AC-TH arm and 30 in the TCH arm, including weekly infusions during the chemotherapy phase and every three week dosing in the monotherapy period. Among these patients, the median age was 49 years (range 22 to 74 years). In Study 4, the toxicity profile was similar to that reported in Studies 1, 2, and 3 with the exception of a low incidence of CHF in the TCH arm.

Among the 352 patients treated in single agent studies (213 patients from Study 6), the median age was 50 years (range 28 to 86 years), 86% were White, 3% were Black, 3% were Asian, and 8% in other racial/ethnic proups. Most of the patients received 4 mg/kg initial dose of trastuzumab followed by 2 mg/kg weekly. The percentages of patients who received trastuzumab treatment for ≥6 months and ≥12 months were 31% and Table 12: Per-Patient Incidence of Adverse Reactions Occurring in ≥5% of Patients in Uncontrolled Studies or at Increased Incidence in the Trastuzumab Arm (Studies 5 and 6)

	n = 352	Paclitaxel n = 91	Alone n = 95	n = 143	AC <sup>b</sup> Alone n = 13
Body as a Whole					
Pain	47%	61%	62%	57%	42%
Asthenia	42%	62%	57%	54%	55%
Fever	36%	49%	23%	56%	34%
Chills	32%	41%	4%	35%	11%
Headache	26%	36%	28%	44%	31%
Abdominal pain	22%	34%	22%	23%	18%
Back pain	22%	34%	30%	27%	15%
Infection	20%	47%	27%	47%	31%
Flu syndrome	10%	12%	5%	12%	6%
Accidental injury	6%	13%	3%	9%	4%
Allergic reaction	3%	8%	2%	4%	2%
Cardiovascular					
Tachycardia	5%	12%	4%	10%	5%
Congestive heart failure	7%	11%	1%	28%	7%

400 26% 41% 22% 43% 29% 
 18%
 38%
 18%
 27%
 17%

 2%
 12%
 3%
 7%
 9%

 2%
 11%
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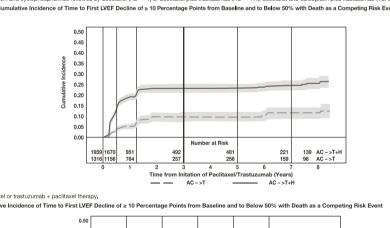
Table 13: Study 7: Per Patient Incidence of Adverse Reactions of All Grades (Incidence ≥ 5% between Arms) or Grade 3/4 (Incidence > 1 % between Arms) and Higher Incidence in Trastuzumab Arm

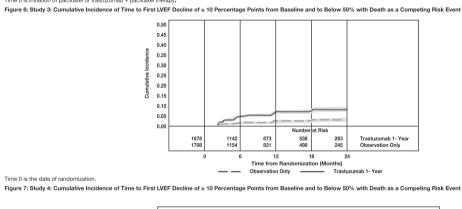
Body System/Adverse Event	(N =	294) N (%)	(N = 290) N (%)		
	All Grades	Grades 3/4	All Grades	Grades	
Investigations					
Neutropenia	230 (78)	101 (34)	212 (73)	83 (2	
Hypokalemia	83 (28)	28 (10)	69 (24)	16 (	
Anemia	81 (28)	36 (12)	61 (21)	30 (*	
Thrombocytopenia	47 (16)	14 (5)	33 (11)	8 (	
Blood and Lymphatic System Disorders					
Febrile Neutropenia		15 (5)		8 (	
Gastrointestinal Disorders					
Diarrhea	109 (37)	27 (9)	80 (28)	11 (	
Stomatitis	72 (24)	2 (1)	43 (15)	6 (	
Dysphagia	19 (6)	7 (2)	10 (3)	1 (≤	
Body as a Whole					
Fatigue	102 (35)	12 (4)	82 (28)	7 (2	
Fever	54 (18)	3 (1)	36 (12)	0 (	
Mucosal Inflammation	37 (13)	6 (2)	18 (6)	2 (	
Chills	23 (8)	1 (≤ 1)	0 (0)	0 (0	
Metabolism and Nutrition Disorders					
Weight Decrease	69 (23)	6 (2)	40 (14)	7 (2	
Infections and Infestations					
Upper Respiratory Tract Infections	56 (19)	0 (0)	29 (10)	0 (	
Nasopharyngitis	37 (13)	0 (0)	17 (6)	0 (0	
Renal and Urinary Disorders					
Renal Failure and Impairment	53 (18)	8 (3)	42 (15)	5 (	
Nervous System Disorders					
Dysgeusia	28 (10)	0 (0)	14 (5)	0 (0	
The following subsections provide additional detail regarding adve	rse reactions observed in clinical trials of adju-	vant breast cancer, metastatic breas	st cancer, metastatic gastric cancer	er, or post-marketin	

	LVEF <50% and Abso	lute Decrease from Baseline		Absolute LVEF Decreas	ве
	LVEF < 50%	≥ 10% decrease	≥ 16% decrease	< 20% and ≥ 10%	≥ 20%
Studies 1 & 2 <sup>h/l</sup>					
$AC \rightarrow TH (n = 1856)$ $AC \rightarrow T (n = 1170)$	23.1% (428) 11.7% (137)	18.5% (344) 7.0% (82)	11.2% (208) 3.0% (35)	37.9% (703) 22.1% (259)	8.9% (166) 3.4% (40)
Study 3 <sup>e</sup>		•	•		
Trastuzumab (n = 1678) Observation (n = 1708)	8.6% (144) 2.7% (46)	7.0% (118) 2.0% (35)	3.8% (64) 1.2% (20)	22.4% (376) 11.9% (204)	3.5% (59) 1.2% (21)
Study 4°			•		
TCH (n = 1056) AC $\rightarrow$ TH (n = 1068) AC $\rightarrow$ T (n = 1050)	8.5% (90) 17% (182) 9.5% (100)	5.9% (62) 13.3% (142) 6.6% (69)	3.3% (35) 9.8% (105) 3.3% (35)	34.5% (364) 44.3% (473) 34% (357)	6.3% (67) 13.2% (141) 5.5% (58)

Median duration of follow-up for Studies 1 and 2 combined was 8.3 years in the AC  $\rightarrow$  TH arm.

gure 5: Studies 1 and 2: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event





In Study 7, 5.0% of patients in the trastuzumab plus chemotherapy arm compared to 1.1% of patients in the chemotherapy alone arm had LVEF value below 50% with a ≥ 10% absolute decrease in LVEF from

Influsion Reactions

During the first infusion with trastuzumab, the symptoms most commonly reported were chills and fever, occurring in approximately 40% of patients in clinical trials. Symptoms were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of trastuzumab infusion); permanent discontinuation of trastuzumab for infusion reactions was required in < 1% of patients. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, elevated blood pressure, rash, and asthenia. Infusion reactions occurred in 21% and 55% of patients, and were severe in 1.4% and 95% of patients, on second or subsequent trastuzumab infusions administered as monotherapy or in combination with chemotherapy, respectively. In the postmarketing setting, severe infusion reactions, including hypersensitivity, anaphylaxis, and angioedema have been reported.

In randomized controlled clinical trials in the adjuvant setting, the incidence of selected NCI-CTG Grade 4 to 5 neutropenia (1.7% vs. 0.8% [Study 2]) and of selected Grade 2 to 5 neutropenia (6.4% vs. 4.3% [Study 1]) were increased in patients receiving trastuzumab and chemotherapy compared with those receiving chemotherapy alone, in a randomized, controlled trial in patients with metastatic breast cancer, the incidences of NCI-CTG Grade 3/4 neutropenia (23% vs. 22%) and of febrile neutropenia (25% vs. 17%) were also increased in patients randomized to trastuzumab in combination with myelosuppressive chemotherapy as compared to chemotherapy alone, in Study 7 (metastatic gastric cancer) on the trastuzumab containing arm as compared to the chemotherapy alone arm, the incidence of NCI-CTG Grade 3/4 neutropenia was 36.8% compared to 28.9%; febrile neutropenia 5.1% compared to 2.8%.

The overall incidences of infection (46% vs. 30% [Study 5]), of selected NCI-CTC Grade 2 to 5 infection/febrile neutropenia (24.3% vs. 13.4% [Study 1]) and of selected Grade 3 to 5 infection/febrile neutropenia (2.9% vs. 1.4%) [Study 2]) were higher in patients receiving trastuzumab and chemotherapy compared with those receiving chemotherapy alone. The most common site of infections in the adjuvant setting involved the upper respiratory tract, skin, and urinary tract. In Study 4, the overall incidence of infection was higher with the addition of trastuzumab to AC-T but not to TCH [44% (AC-TH), 37% (TCH), 38% (AC-T)]. The incidences of NCI-CTC Grade 3 to 4 infection were similar [25% (AC-TH), 21% (TCH), 23% (AC-T)] across the three arms.

In Study 3, there were 4 cases of interstitial pneumonitis in the one-year trastuzumab treatment arm compared to none in the observation arm at a median follow-up duration of 12.6 months.

In the post-marketing setting, rare cases of nephrotic syndrome with pathologic evidence of glomerulopathy have been reported. The time to onset ranged from 4 months to approximately 18 months from initiatic trastuzumab therapy. Pathologic findings included membranous glomerulonephritis, focal glomerulosclerosis, and fibrillary glomerulonephritis. Complications included volume overload and congestive heart failure

Risk Summary

There is no information regarding the presence of trastuzumab products in human milk, the effects on the breastfed infant, or the effects on milk production. Published data suggest human IgG is present in human milk but does not enter the neonatal and infant circulation in substantial amounts. Trastuzumab was present in the milk of lactating Cynomolgus monkeys but not associated with neonatal toxicity. Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for Cigivri<sup>TM</sup> enternet and any potential adverse effects on the breastfed child from Ogivri<sup>TM</sup> or from the underlying maternal condition. This consideration should also take into account the trastuzumab product wash out period of 7 months [see Clinical Pharmacology].

Females and Males of Reproductive Potential Pregnancy Testing fy the pregnancy status of females of reproductive potential prior to the initiation of Ogivri™.

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

440 mg Multiple-dose vial

Store Ogivri™ vials in the refrigerator at 2° to 8°C (36° to 46°F) until time of reconstitution.

Use appropriate aseptic technique when performing the following reconstitution steps:

To prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is Ogivri<sup>TM</sup> (trastuzumab) and not ado-trastuzumab emtansine.

 Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the lyophilized cake of Ogivri™. The stream of diluent should solution for multiple-dose use, containing 21 mg/mL trastuzumab.
 Swirl the vial gently to aid reconstitution. **DO NOT SHAKE.**  Slight foaming of the product may be present upon reconstitution. Allow the vial to stand undisturbed for approximately 5 minutes Store reconstituted Ogivri™ in the refrigerator at 2°C to 8°C (36°F to 46°F); discard unused Ogivri™ after 28 days. If Ogivri™ is reconstituted with SWFI without preservative, use immediately and discard any unused portion. Do not freeze.

 Determine the dose (mg) of Ogivri™ [see Dosage and Administration]. Calculate the volume of the 21 mg/mL reconstituted Ogivri™ solution needed, withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP. DO NOT USE DEXTROSE (5%) SOLUTION. Gently invert the bag to mix the solution. 150 mg Single-dose vial

Reconstitute each 150 mg vial of Ogivri<sup>TM</sup> with 7.2 mL of Sterile Water for Injection (SWFI) (not supplied) to yield a single-dose solution containing 21 mg/mL trastuzumab.

• Using a sterile syringe, slowly inject 7.2 mL of SWFI (not supplied) into the vial containing the lyophilized 150 mg Ogivri™, directing the diluent stream into the lyophilized cake. The reconstituted vial yields a solution for single-dose use, containing 21 mg/mL trastuzumab. Swirl the vial gently to aid reconstitution. DO NOT SHAKE. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Inspect visually for particulates and discoloration. The solution should be free of visible particulates, clear to slightly opalescent and colorless to pale yellow.

Use the Ogivri™ solution immediately following reconstitution with SWFI, as it contains no preservative and is intended for single-dose only. If not used immediately, store the reconstituted Ogivri™ solution for up to 24 hours at 2°C to 8°C (36°F to 46°F), discard any unused Ogivri™ after 24 hours. Do not freeze.

 Determine the dose (mg) of Ogivri™ [see Dosage and Administration]. Withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP. DO NOT USE DEXTROSE (5%) SOLUTION. Gently invert the bag to mix the solution.

440 mg multiple-dose vial Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative.

150 mg multiple-dose vial Ogivri<sup>™</sup> (trastuzumab) for injection 150 mg/vial is supplied in a single-dose vial as a lyophilized sterile powder, under vacuum. Each carton contains one single-dose vial of Ogivri pecial precautions for disposal and other handling Any unused medicinal product should be disposed of in accordance with the local requirements.

Mylan Pharmaceuticals Private Ltd.
Plot No. 1-4/2, MIDC Industrial Estate,
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