1.14.1.2 Annotated Draft Labeling Text

1.14.1.2.1 Annotated Redlined Draft Package Insert

Herceptin®
Trastuzumab

WARNINGS:

Cardiomyopathy

Herceptin administration can result in left ventricular dysfunction and congestive heart failure (CHF). Left ventricular function should be evaluated in all patients prior to and during treatment with Herceptin.

The incidence and severity of left ventricular cardiac dysfunction/CHF was highest in patients who received Herceptin concurrently with anthracycline-containing chemotherapy regimens. Discontinue Herceptin treatment in patients receiving adjuvant therapy for breast cancer and strongly consider discontinuation of Herceptin in patients with metastatic breast cancer who develop a clinically significant decrease in left ventricular function. (See **WARNINGS: Cardiomyopathy**, See **DOSAGE AND ADMINISTRATION: Dose Modifications**)

Infusion Reactions

Pulmonary Toxicity

Herceptin administration can result in serious infusion reactions and pulmonary toxicity. Rarely, these have been fatal. In most cases, symptoms occurred during or within 24 hours of administration of Herceptin. Herceptin infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of Herceptin should be strongly considered for infusion reactions manifesting as anaphylaxis, angioedema, pneumonitis, or acute respiratory distress syndrome. (See **WARNINGS**.)

DESCRIPTION

Herceptin (Trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity in a cell-based assay (Kd = 5 nM) to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2 (1, 2). The antibody is an IgG_1 kappa that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2.

The humanized antibody against HER2 is produced by a mammalian cell (Chinese Hamster Ovary [CHO]) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Herceptin is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration. The nominal content of each Herceptin vial is 440 mg Trastuzumab, 400 mg α,α-trehalose dihydrate, 9.9 mg L-histidine HCl, 6.4 mg L-histidine, and 1.8 mg polysorbate 20, USP. **Reconstitution with 20 mL of the supplied Bacteriostatic Water for Injection (BWFI),** USP, containing 1.1% benzyl alcohol as a preservative, yields a multi-dose solution containing 21 mg/mL Trastuzumab, at a pH of approximately 6.

CLINICAL PHARMACOLOGY

General

The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the epidermal growth factor receptor (1). HER2 protein overexpression is observed in 25%–30% of primary breast cancers. HER2 protein overexpression can be determined using immunohistochemistry (IHC). The presence of HER2 overexpression may also be inferred when HER2 gene amplification is identified using fluorescence *in situ* hybridization (FISH) on fixed tumor blocks. (2) (see **CLINICAL STUDIES: HER2 Detection** and **PRECAUTIONS: HER2 Testing**).

Trastuzumab has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2 (3).

Trastuzumab is a mediator of antibody-dependent cellular cytotoxicity (ADCC) (4). *In vitro*, Herceptin-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Pharmacokinetics

The pharmacokinetics of Trastuzumab were studied in breast cancer patients with metastatic disease. Short duration intravenous infusions of 10 to 500 mg once weekly demonstrated dose-dependent pharmacokinetics. Mean half-life increased and clearance decreased with increasing dose level. The half-life averaged 1.7 and 12 days at the 10 and 500 mg dose levels, respectively. Trastuzumab's volume of distribution was approximately that of serum volume (44 mL/kg). At the highest weekly dose studied (500 mg), mean peak serum concentrations were 377 μg/mL.

In studies using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg, a mean half-life of 5.8 days (range=1 to 32 days) was observed. Between Weeks 16 and 32, Trastuzumab serum concentrations reached a steady state with mean trough and peak concentrations of approximately 79 μg/mL and 123 μg/mL, respectively.

Detectable concentrations of the circulating extracellular domain of the HER2 receptor (shed antigen) are found in the sera of some patients with HER2 overexpressing tumors. Determination of shed antigen in baseline serum samples revealed that 64% (286/447) of patients had detectable shed antigen, which ranged as high as 1880 ng/mL (median=11 ng/mL). Patients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations.

Data suggest that the disposition of Trastuzumab is not altered based on age or serum creatinine (up to 2.0 mg/dL). No formal interaction studies have been performed.

Mean serum trough concentrations of Trastuzumab, when administered in combination with paclitaxel, were consistently elevated approximately 1.5-fold as compared with serum concentrations of Trastuzumab used in combination with anthracycline plus cyclophosphamide. In primate studies, administration of Trastuzumab with paclitaxel resulted in a reduction in Trastuzumab clearance. Serum levels of Trastuzumab in combination with cisplatin, doxorubicin, or epirubicin plus cyclophosphamide did not suggest any interactions; no formal drug interaction studies were performed.

CLINICAL STUDIES

Adjuvant Breast Cancer

The safety and efficacy of Herceptin in combination with chemotherapy for the adjuvant treatment of HER2 overexpressing breast cancer were studied in two randomized, open-label, clinical trials with a total of 3752 patients who were randomized in the studies prior to a pre-specified interim analysis. The data from both arms in Study 1 and two of the three study arms in Study 2 were pooled for efficacy analyses. Breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH). Patients with a history of active cardiac disease based on symptoms, abnormal electrocardiographic, radiologic, or left ventricular ejection fraction findings or uncontrolled hypertension (diastolic > 100 mmHg or systolic > 200 mmHg) were not eligible. HER2 testing was verified by a central laboratory prior to randomization (Study 2) or was required to be performed at a reference laboratory (Study 1).

Patients were randomized (1:1) to receive doxorubicin and cyclophosphamide followed by paclitaxel (AC→paclitaxel) alone or paclitaxel plus Herceptin (AC→paclitaxel + Herceptin). In both trials,

patients received four 21-day cycles of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2. Paclitaxel was administered either weekly (80 mg/m^2) or every 3 weeks (175 mg/m^2) for a total of 12 weeks in Study 1; paclitaxel was administered only by the weekly schedule in Study 2. Herceptin was administered at 4 mg/kg on the day of initiation of paclitaxel and then at a dose of 2 mg/kg weekly for a total of 52 weeks. Herceptin treatment was permanently discontinued in patients who developed congestive heart failure, or persistent/recurrent LVEF decline. (See **DOSAGE AND ADMINISTRATION**). Radiation therapy, if administered, was initiated after the completion of chemotherapy. Patients with ER+ and/or PR+ tumors received hormonal therapy. Disease-free survival (DFS), defined as the time from randomization to recurrence, occurrence of contralateral breast cancer, other second primary cancer, or death, was the primary endpoint of the combined efficacy analysis. There were 401 patients without follow up assessment for DFS at the time of interim analysis who were censored at study day 1.

A total of 3752 patients were included in the efficacy analyses. Of these patients, the median age was 49 years (range, 22–80 years; 6%>65 years), 84% were white, 7% black, 4% Hispanic, and 4% Asian/Pacific Islander. Disease characteristics included 90% infiltrating ductal histology, 38% T1, 91% nodal involvement, 27% intermediate and 66% high grade pathology, and 53% ER+ and/or PR+ tumors. At the time of randomization 53% of the population were to receive paclitaxel on a weekly regimen, and the remainder were to receive a q3 week schedule of paclitaxel.

Efficacy results for DFS are presented in Table 1 and Figure 1. Exploratory analyses for the risk of recurrence, second primary malignancy, or death within patient subgroups were generally consistent with the overall treatment effects. There were insufficient numbers of patients within each of the following subgroups to determine if the treatment effect was different from that of the overall patient population: patients with node negative disease, patients with low tumor grade, and

patients within specific ethnic/racial subgroups (Black, Hispanic and Asian/Pacific Islander patients).

Table 1

Efficacy Results from Adjuvant Breast Cancer Clinical Studies

	AC→Paclitaxel n = 1880 No. with Event	AC→Paclitaxel + Herceptin n = 1872 No. with Event	Hazard Ratio[a] (95% CI)	p-value[b]
Disease-free survival	261	133	0.48 (0.39–0.59)	< 0.0001
Overall survival	92	62	0.67	NS[c]

CI=confidence interval.

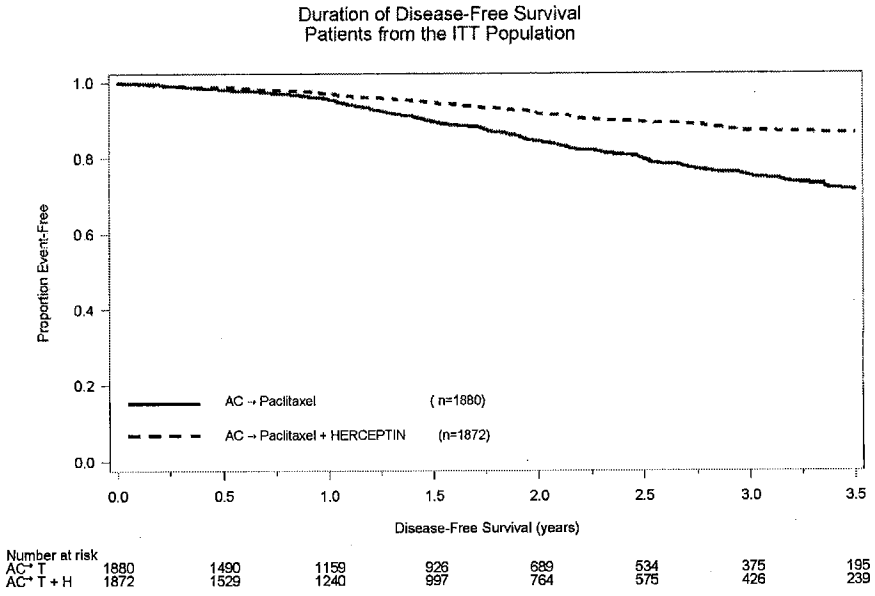
[a] Hazard ratio estimated by Cox regression stratified by clinical trial, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.

[b] log-rank test stratified by clinical trial, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.

[c] Nonsignificant at an interim analysis.

Figure 1

Duration of Disease-Free Survival in Patients from the Adjuvant Breast Cancer Clinical Studies



Exploratory analyses of DFS as a function of HER2 overexpression or gene amplification were conducted for patients in study 2, where central laboratory testing data were available. The results are shown in Table 2. The number of events were small with the exception of the IHC 3+/FISH+ subgroup, which constituted 81% of those with data. Definitive conclusions cannot be drawn regarding efficacy within other subgroups due to the small number of events.

Table 2
Treatment Outcomes in Study 2 as a Function of HER2 Overexpression or Amplification

HER2 Assay Result*	Number of Patients	Hazard Ratio for DFS** (95% CI)
IHC 3+		
FISH (+)	1170	0.42 (0.27, 0.64)
FISH (–)	51	0.71 (0.04, 11.79)
FISH Unknown	51	0.69 (0.09, 5.14)
IHC 0, 1+, or 2+		
FISH (+)	174	1.01 (0.18, 5.65)

* IHC by Herceptest, FISH by PathVysion as performed at a central laboratory.

** The hazard ratio represents the risk of recurrence, second primary malignancy, or death in the Herceptin plus chemotherapy arm versus the chemotherapy arm. Hazard ratio was estimated by Cox regression stratified by number of positive nodes and hormone receptor status.

Metastatic Breast Cancer

The safety and efficacy of Herceptin in the treatment of women with metastatic breast cancer were studied in a randomized, controlled clinical trial in combination with chemotherapy (Study 3, n=469 patients) and an open-label single agent clinical trial (Study 4, n=222 patients). Both trials studied patients with metastatic breast cancer whose tumors overexpressed 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.

First Line Treatment of Metastatic Breast Cancer

Study 3 was a multicenter, randomized, open-label clinical trial conducted in 469 women with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease (5). Tumor specimens were tested by IHC (Clinical Trial Assay, CTA) and scored as 0, 1+, 2+, or 3+, with 3+ indicating the strongest positivity. Only patients with 2+ or 3+ positive tumors were eligible (about 33% of those screened). Patients were randomized to receive chemotherapy alone or in combination with Herceptin given intravenously as a 4 mg/kg loading dose followed by weekly doses of Herceptin at 2 mg/kg. For those who had received prior anthracycline therapy in the adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m^2 over 3 hours every 21 days for at least six cycles); for all other patients, chemotherapy consisted of anthracycline plus cyclophosphamide (AC: doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2 plus 600 mg/m^2 cyclophosphamide every 21 days for six cycles). Sixty-five percent of patients randomized to receive chemotherapy alone in this study received Herceptin at the time of disease progression as part of a separate extension study.

Based upon the determination by an independent response evaluation committee the patients randomized to Herceptin and chemotherapy experienced a significantly longer median time to disease progression, a higher overall response rate (ORR), and a longer median duration of response, as compared with patients randomized to chemotherapy alone. Patients randomized to Herceptin and chemotherapy also had a longer median survival (see Table 3). These treatment effects were observed both in patients who received Herceptin plus paclitaxel and in those who received Herceptin plus AC; however the magnitude of the effects was greater in the paclitaxel subgroup (see **CLINICAL STUDIES: HER2 Detection**).

Table 3

Study 3: Efficacy Results in
First-Line Treatment for Metastatic Breast Cancer

	Combined Results		Paclitaxel Subgroup		AC Subgroup	
	Herceptin + All Chemotherapy (n=235)	All Chemotherapy (n=234)	Herceptin + Paclitaxel (n=92)	Paclitaxel (n=96)	Herceptin + AC[a] (n=143)	AC (n=138)
Primary Endpoint						
Time to Progression[b,c]						
Median (months)	7.2	4.5	6.7	2.5	7.6	5.7
95% confidence interval	6.9, 8.2	4.3, 4.9	5.2, 9.9	2.0, 4.3	7.2, 9.1	4.6, 7.1
p-value (log rank)	<0.0001		<0.0001		0.002	
Secondary Endpoints						
Overall Response Rate[b]						
Rate (percent)	45	29	38	15	50	38
95% confidence interval	39, 51	23, 35	28, 48	8, 22	42, 58	30, 46
p-value (χ2-test)	<0.001		<0.001		0.10	
Duration of Response[b,c]						
Median (months)	8.3	5.8	8.3	4.3	8.4	6.4
25%, 75% quartile	5.5, 14.8	3.9, 8.5	5.1, 11.0	3.7, 7.4	5.8, 14.8	4.5, 8.5
Survival Time[c]						
Median Survival (months)	25.1	20.3	22.1	18.4	26.8	21.4
95% confidence interval	22.2, 29.5	16.8, 24.2	16.9, 28.6	12.7, 24.4	23.3, 32.9	18.3, 26.6
p-value (log rank)	0.05		0.17		0.16	

[a] AC=Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

[b] Assessed by an independent Response Evaluation Committee.

[c] Kaplan-Meier Estimate.

Data from Study 3 suggest that the beneficial treatment effects were largely limited to patients with the highest level of HER2 protein overexpression (3+) (see Table 4).

Table 4
Treatment Effects in Study 3 as a Function of HER2 Overexpression or Amplification

HER2 Assay Result	Number of Patients (N)	Relative Risk** for Time to Disease Progression (95% CI)	Relative Risk** for Mortality (95% CI)
CTA 2+ or 3+	469	0.49 (0.40, 0.61)	0.80 (0.64, 1.00)
FISH (+)*	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)
FISH (+)	293	0.42 (0.32, 0.55)	0.67 (0.51, 0.89)
FISH (–)	43	0.43 (0.20, 0.94)	0.88 (0.39, 1.98)

* FISH testing results were available for 451 of the 469 patients enrolled on study.

** The relative risk represents the risk of progression or death in the Herceptin plus chemotherapy arm versus the chemotherapy arm.

Second or Third Line Treatment of Metastatic Breast Cancer

Herceptin was studied as a single agent in a multicenter, open-label, single-arm clinical trial (Study 4) in patients with HER2 overexpressing metastatic breast cancer who had relapsed following one or two prior chemotherapy regimens for metastatic disease. Of 222 patients enrolled, 66% had received prior adjuvant chemotherapy, 68% had received two prior chemotherapy regimens for metastatic disease, and 25% had received prior myeloablative treatment with hematopoietic rescue. Patients were treated with a loading dose of 4 mg/kg IV followed by weekly doses of Herceptin at 2 mg/kg IV.

The ORR (complete response+partial response), as determined by an independent Response Evaluation Committee, was 14%, with a 2% complete response rate and a 12% partial response rate. Complete responses were observed only in patients with disease limited to skin and lymph nodes (see **CLINICAL STUDIES: HER2 Detection**).

The overall response rate in patients whose tumors tested as CTA 3+ was 18% while in those that tested as CTA 2+, it was 6%.

HER2 Detection

(See **PRECAUTIONS: HER2 Testing**)

Detection of HER2 protein overexpression, either directly through IHC or indirectly through gene amplification, is necessary for selection of patients appropriate for Herceptin therapy (see **INDICATIONS AND USAGE**). Assessment for HER2 expression or gene amplification should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Several FDA-approved commercial assays are available to aid in the selection of patients for Herceptin therapy (see **HER2 Protein Overexpression Detection Methods** and **HER2 Gene Amplification Detection Methods**). These include HercepTest® and [Ventana's approved assay] (IHC assays) and PathVysion® and [Dako's approved assay] (FISH assays). Users should refer to the package inserts of specific assay kits for information on the validation and performance of each assay.

Limitations in assay precision (particularly for the IHC method) and in the direct linkage between assay result and overexpression of the Herceptin target (for the FISH method) make it inadvisable to rely on a single method to rule out potential Herceptin benefit. A negative FISH result does not rule out HER2 overexpression and potential benefit from Herceptin (see Tables 2 and 4).

HER2 Protein Overexpression Detection Methods

HER2 protein overexpression can be established by measuring HER2 protein using an IHC method. HercepTest®, one test approved for this use, was assessed for concordance with the CTA, using tumor specimens collected and stored independently from those obtained in Herceptin clinical studies in women with metastatic breast cancer. Data are provided in the package insert for HerceptTest®.

Due to limitations in assay precision, assessment for HER2 protein overexpression should be performed by laboratories with demonstrated proficiency and in accordance with the package insert for the assay kit. In adjuvant breast cancer (Study 2), tumor testing for protein overexpression by IHC, when performed, was conducted with HercepTest®. There were 1153 women in Study 2 for whom HER2 protein overexpression was determined at a local laboratory and for whom central laboratory testing was also performed. Analyses of breast tumor specimens identified as IHC 3+ at a local laboratory yielded concordant results in 979 (85%) samples and discordant results in 174 (15%) samples when retested at a central laboratory. (See **PRECAUTIONS: HER2 Testing)**

Treatment outcomes for metastatic breast cancer (Study 3), as a function of IHC and FISH testing are provided in Table 4. Treatment outcomes for adjuvant breast cancer (Studies 1 and 2), as a function of IHC and FISH testing are provided in Table 2.

HER2 Gene Amplification Detection Methods

The presence of HER2 protein overexpression and gene amplification are highly correlated, therefore the use of FISH to detect gene amplification may be employed for selection of patients appropriate for Herceptin therapy. PathVysion®, one test approved for this use was evaluated in an exploratory, retrospective assessment of available CTA 2+ or 3+ tumor specimens collected as part of patient screening for clinical studies in metastatic breast cancer (Studies 3 and 4). Data are provided in the package insert for PathVysion®.

Assessment for HER2 gene amplification should be performed by laboratories with demonstrated proficiency and in accordance with the package insert for the assay kit. In adjuvant breast cancer (Study 2), tumor testing for gene amplification by FISH, when performed, was conducted with PathVysion®. There were 414 women in Study 2 for whom HER2 gene amplification was determined at a local laboratory and

for whom central laboratory testing was also performed. Analyses of breast tumor specimens identified as gene amplified at a local laboratory yielded concordant results in 391 (94.4%) samples for FISH amplification and discordant results in 23 (5.6%) samples, i.e., non-amplified when re-tested at a central laboratory. (See **PRECAUTIONS: HER2 Testing**)

Treatment outcomes for metastatic breast cancer (Study 3), as a function of IHC and FISH testing are provided in Table 4. Treatment outcomes for adjuvant breast cancer (Studies 1 and 2), as a function of IHC and FISH testing are provided in Table 2.

There are limitations in the direct linkage between gene amplification and overexpression of the Herceptin target which make it inadvisable to rely on a single method to rule out potential benefit from Herceptin. There is insufficient information to conclude whether patients without 3+ protein overexpression by IHC but with gene amplification by FISH may benefit from Herceptin therapy in the adjuvant breast cancer setting. There is insufficient information to determine whether FISH testing can distinguish a subpopulation of CTA 2+ patients with metastatic breast cancer who would benefit from Herceptin therapy.

INDICATIONS AND USAGE

Herceptin (Trastuzumab), as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel, is indicated for the adjuvant treatment of patients with HER2-overexpressing, node-positive breast cancer. (See **CLINICAL STUDIES** and **DOSAGE AND ADMINISTRATION**)

Herceptin as a single agent is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease.

Herceptin in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the

HER2 protein and who have not received chemotherapy for their metastatic disease. (See **PRECAUTIONS: HER2 Testing** and **CLINICAL STUDIES: HER2 Detection**).

CONTRAINDICATIONS

None.

WARNINGS

Cardiomyopathy

Herceptin can cause left ventricular cardiac dysfunction. Cardiac dysfunction in patients receiving Herceptin therapy can be serious with disabling cardiac failure, death, and mural thrombosis leading to stroke (see **BOXED WARNINGS: Cardiomyopathy**).

Among women receiving adjuvant therapy for breast cancer in Study 1, 16% (136/844) of patients discontinued Herceptin therapy due to clinical evidence of myocardial dysfunction or significant decline in LVEF (see **DOSAGE AND ADMINISTRATION: Dose Modifications**). There was one death due to cardiomyopathy among patients receiving Herceptin. If Herceptin therapy is discontinued for left ventricular cardiac dysfunction, patients should be closely monitored for evidence of clinical deterioration and further decline in left ventricular function.

Among 32 patients receiving adjuvant chemotherapy (Studies 1 and 2) with clinical cardiac events as determined by ACREC, one patient died of cardiomyopathy and all other patients were receiving cardiac medication at last follow-up. Approximately half of the surviving patients had recovery to a normal LVEF (defined as $\geq 50\%$) on continuing medical management at the time of last follow-up. The safety of continuation or resumption of Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been studied.

In the adjuvant setting, among patients who completed AC chemotherapy and received at least one dose of paclitaxel, 2% [32/1677] of patients in the Herceptin arm and 0.4% [7/1600] of patients in the control arm

experienced clinically symptomatic, laboratory-confirmed cardiomyopathy as determined by an external review committee (ACREC).

Among patients with metastatic breast cancer, the incidence of CHF was 11% versus 1% in patients receiving paclitaxel with or without Herceptin and 28% versus 7% in patients receiving AC chemotherapy with or without Herceptin, respectively. The incidence of CHF in patients with metastatic breast cancer receiving Herceptin monotherapy was 7%.

An exploratory analysis for risk factors for symptomatic cardiomyopathy was conducted in patients receiving adjuvant treatment for breast cancer. The analysis is limited by the number and type of variables collected and how they were defined. Declining LVEF to below the lower limit of normal after completion of AC chemotherapy or during Herceptin treatment, a reported history of prior or concurrent use of anti-hypertensive medications, and increasing age were associated with an increased risk of Herceptin-induced symptomatic cardiomyopathy. Similar limited analyses in patients receiving chemotherapy for metastatic breast cancer identified prior cardiotoxic therapy (e.g., anthracycline or radiation therapy to the chest) and increasing age as potentially associated with an increased risk of Herceptin-induced CHF.

Candidates for treatment with Herceptin should undergo a thorough baseline cardiac assessment, including history, physical examination, and an assessment of LVEF by echocardiogram or MUGA scan. Patients receiving Herceptin should undergo frequent monitoring for deteriorating left ventricular function. The following recommended schedule is consistent with that used in Studies 1 and 2: at baseline prior to AC chemotherapy, immediately prior to initiation of Herceptin, 3 months after initiation of Herceptin with paclitaxel, 3 months after initiation of Herceptin monotherapy, and 3 months after completion of Herceptin monotherapy. More frequent monitoring should be employed in patients

with preexisting cardiac dysfunction. Monitoring will not identify all patients who will develop cardiac dysfunction.

Infusion Reactions

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

However, in postmarketing reports, serious and fatal infusion reactions were reported infrequently. Severe reactions which include bronchospasm, hypoxia, and severe hypotension, were usually reported during or immediately following the initial infusion. However, the onset and clinical course were variable including progressive worsening, initial improvement followed by clinical deterioration, or delayed post-infusion events with rapid clinical deterioration. For fatal events, death occurred within hours to days following a serious infusion reaction.

Herceptin infusion should be interrupted in all patients experiencing dyspnea or clinically significant hypotension and medical therapy administered, which may include epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be strongly considered in all patients with severe infusion reactions.

There are no data regarding the most appropriate method of identification of patients who may safely be retreated with Herceptin after experiencing a severe infusion reaction. Herceptin has been readministered to some patients who fully recovered from the previous severe reaction. Prior to readministration of Herceptin, the majority of these patients were prophylactically treated with pre-medications including antihistamines

and/or corticosteroids. While some of these patients tolerated retreatment, others had severe reactions again despite the use of prophylactic pre-medications.

Exacerbation of Chemotherapy-Induced Neutropenia

In randomized, controlled clinical trials in women with metastatic breast cancer designed to assess the impact of the addition of Herceptin on chemotherapy, the per-patient incidences of moderate to severe neutropenia and of febrile neutropenia were higher in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. Deaths due to sepsis in patients with severe neutropenia have been reported in patients receiving Herceptin and myelosuppressive chemotherapy, although in controlled clinical trials, the incidence of septic death was not significantly increased. (See **ADVERSE REACTIONS: Neutropenia** and **Infection**).

Pulmonary Toxicity

Herceptin use can result in serious and fatal pulmonary toxicity. Pulmonary toxicity includes dyspnea, pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions (see **WARNINGS: Infusion Reactions**). Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity.

PRECAUTIONS

HER2 Testing

Detection of HER2 protein overexpression is necessary for selection of patients appropriate for Herceptin therapy because these are the only patients studied and for whom benefit has been shown (see **INDICATIONS AND USAGE**). Patients enrolled in metastatic breast cancer clinical studies were required to have immunohistochemical

evidence of HER2 protein overexpression. In trials of adjuvant therapy, patients were required to have evidence of HER2 protein overexpression and/or HER2 gene amplification. Assessment for HER2 overexpression and of HER2 gene amplication should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. 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. Refer to the HercepTest®, the PathVysion®, or any other FDA-approved test kit package inserts for full instructions on assay performance (see **CLINICAL STUDIES: HER2 Detection: HER2 Protein Overexpression Detection Methods** and **HER2 Gene Amplification Detection Methods**).

Drug Interactions

There have been no formal drug interaction studies performed with Herceptin in humans. Administration of paclitaxel in combination with Herceptin resulted in a two-fold decrease in Herceptin clearance in a non-human primate study and in a 1.5-fold increase in Herceptin serum levels in clinical studies (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Herceptin has not been tested for its carcinogenic potential.

Mutagenesis

No evidence of mutagenic activity was observed in Ames tests using six different test strains of bacteria, with and without metabolic activation, at concentrations of up to 5000 μg/mL Trastuzumab. Human peripheral blood lymphocytes treated *in vitro* at concentrations of up to 5000 μg/plate Trastuzumab, with and without metabolic activation, revealed no evidence of mutagenic potential. In an *in vivo* mutagenic assay (the micronucleus assay), no evidence of chromosomal damage to mouse bone marrow cells

was observed following bolus intravenous doses of up to 118 mg/kg Trastuzumab.

Impairment of Fertility

A fertility study has been conducted in female cynomolgus monkeys at doses up to 25 times the weekly human maintenance dose of 2 mg/kg Herceptin and has revealed no evidence of impaired fertility.

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Herceptin should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In the postmarketing setting, oligohydramnios has been reported in women who received Herceptin during pregnancy, either in combination with chemotherapy or as a single agent. Given the limited number of reported cases, the high background rate of occurrence of oligohydramnios, the lack of clear temporal relationships between drug use and clinical findings, and the lack of supportive findings in animal studies, an association between Herceptin and oligohydramnios has not been established.

Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 times the weekly human maintenance dose of 2 mg/kg Herceptin and have revealed no evidence of impaired fertility or harm to the fetus. However, HER2 protein expression is high in many embryonic tissues including cardiac and neural tissues; in mutant mice lacking HER2, embryos died in early gestation (6). Placental transfer of Herceptin during the early (Days 20–50 of gestation) and late (Days 120–150 of gestation) fetal development period was observed in monkeys.

Nursing Mothers

A study conducted in lactating cynomolgus monkeys at doses 25 times the weekly human maintenance dose of 2 mg/kg Herceptin demonstrated that

Trastuzumab is secreted in the milk. The presence of Trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 3 months of age. It is not known whether Herceptin is secreted in human milk. Because human IgG is secreted in human milk, and the potential for absorption and harm to the infant is unknown, women should be advised to discontinue nursing during Herceptin therapy and for 6 months after the last dose of Herceptin.

Pediatric Use

The safety and effectiveness of Herceptin in pediatric patients have not been established.

Geriatric Use

Herceptin has been administered to 257 patients who were 65 years of age or over (124 in the adjuvant treatment and 133 in metastatic breast cancer treatment settings). The risk of cardiac dysfunction was increased in geriatric patients as compared to younger patients in both those receiving treatment for metastatic disease or adjuvant therapy. Aside from cardiac dysfunction, limitations in data collection and differences in study design of the 2 studies of Herceptin in adjuvant treatment of breast cancer preclude a determination of whether the toxicity profile of Herceptin in older patients is different from younger patients. The reported clinical experience is not adequate to determine whether the efficacy improvements (ORR, TTP, OS, DFS) of Herceptin treatment in older patients is different from that observed in patients <65 years of age for metastatic disease and adjuvant treatment.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for

identifying the adverse events that appear to be related to drug use and for approximating rates.

The most serious toxicities of Herceptin are:

- Cardiomyopathy
- Pulmonary toxicity (respiratory failure, pneumonitis, pulmonary infiltrates)
- Infusion reactions
- Febrile neutropenia/exacerbation of chemotherapy-induced neutropenia

Please refer to the **BOXED WARNINGS** and/or **WARNINGS** sections for detailed descriptions of these serious adverse reactions.

The most common adverse reactions in patients receiving Herceptin are fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia. Adverse reactions requiring interruption or discontinuation of Herceptin treatment include severe infusion reactions, CHF, and significant decline in left ventricular cardiac function. (See **DOSAGE AND ADMINISTRATION: Dose Modifications**)

Where specific percentages are noted, these data are based on clinical studies of Herceptin alone or in combination with chemotherapy in women with metastatic breast cancer or in combination with and following chemotherapy in women receiving adjuvant treatment for breast cancer.

Additional adverse reactions have been identified during post-marketing use of Herceptin in the metastatic breast cancer population. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Herceptin exposure. Decisions to include these reactions in labeling are typically based on one or more of the following

factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to Herceptin.

Cardiomyopathy

See **BOXED WARNINGS: Cardiomyopathy** and **WARNINGS: Cardiomyopathy**.

Herceptin can cause left ventricular myocardial dysfunction, characterized by signs and symptoms of congestive heart failure and a decline in LVEF. Cardiac dysfunction due to Herceptin therapy can be serious with disabling cardiac failure, death, and mural thrombosis leading to stroke (see **BOXED WARNINGS: Cardiomyopathy**). Herceptin can also cause asymptomatic decline in LVEF.

Serial measurement of cardiac function (LVEF) was obtained only in clinical trials in the adjuvant treatment of breast cancer. There were 6% of patients who were unable to receive Herceptin following completion of AC chemotherapy due to cardiac dysfunction (LVEF $<50\%$ or ≥ 15 point decline in LVEF from baseline to end of AC). Following initiation of Herceptin therapy, the incidence of new-onset dose-limiting myocardial dysfunction was higher among patients receiving Herceptin and paclitaxel as compared to those receiving paclitaxel alone (see Table 5).

Table 5

Per Patient Incidence* of New Onset Myocardial Dysfunction (LVEF Decline Below 50%) by Time Period Following the Initiation of Paclitaxel +/- Herceptin

Timepoint following initiation of chemotherapy	**AC→T**	**AC→TH**
Paclitaxel +/- Herceptin Treatment (Month 3–6)	5.0 % (66/1330)	11.6 % (171/1469)
During Herceptin Monotherapy / Observation (Month 6–9)	4.1 % (46/1125)	8.8 % (96/1090)

* Incidence is proportion of patients with LVEF < 50% during the time period in patients with a normal LVEF at the start of that time period.

Among patients receiving adjuvant therapy for breast cancer (Studies 1 and 2), investigator-identified cases of cardiac adverse events underwent a secondary review by subcommittees each of which used different criteria for classification of a cardiac event. The per-patient incidence of clinical cardiac adverse events, as determined either by a central study committee or by an external safety committee (ACREC) that was blinded to treatment assignment, was increased among those receiving Herceptin. The results are presented in Table 6.

Table 6

Incidence of Clinical Cardiac Events in Adjuvant Breast Cancer

	Study 1		Study 2	
	AC→T (n = 876)	AC→T+H (n = 920)	AC→T (n = 724)	AC→T+H (n = 757)
ACREC	6 0.68%	19 2.07%	1 0.14%	13 1.72%
Study-specific subcommittee	10 1.14%	31 3.37%	0 0.00%	20 2.64%

Approximately half of the clinical cardiac events among patients in the Herceptin arm were identified by the end of paclitaxel therapy (month 6) and approximately 90% were identified by one year following completion of paclitaxel (month 15).

The incidence of treatment emergent congestive heart failure among patients in the metastatic breast cancer trials was classified for severity using the New York Heart Association classification system (I–IV, where IV is the most severe level of cardiac failure) (see Table 7).

Table 7
Incidence and Severity of
Cardiac Dysfunction in Metastatic Breast Cancer

	Herceptin[a] Alone n = 213	Herceptin + Paclitaxel[b] n = 91	Paclitaxel[b] n = 95	Herceptin + Anthracycline + Cyclophosphamide[b] n = 143	Anthracycline + Cyclophosphamide[b] n = 135
Any Cardiac Dysfunction	7%	11%	1%	28%	7%
Class III–IV	5%	4%	1%	19%	3%

[a] Open-label, single-agent Phase II study (94% received prior anthracyclines).

[b] Randomized Phase III study comparing chemotherapy plus Herceptin to chemotherapy alone, where chemotherapy is either anthracycline/cyclophosphamide or paclitaxel.

In the metastatic breast cancer trials the probability of cardiac dysfunction was highest in patients who received Herceptin concurrently with anthracyclines.

Infusion Reactions

During the first infusion with Herceptin, a symptom complex most commonly consisting of chills and/or fever was observed in approximately 40% of patients in clinical trials. The symptoms were usually mild to moderate in severity and were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of Herceptin infusion); permanent discontinuation of Herceptin for infusional toxicity 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. Infusional toxicity occurred in 21% and 35% of patients, and was severe in 1.4% and 9% of patients, on second or subsequent Herceptin infusions administered as monotherapy or in combination with

chemotherapy, respectively. (See **BOXED WARNINGS: Infusion Reactions** and **WARNINGS: Infusion Reactions**).

Anemia

In randomized controlled clinical trials, the overall incidence of anemia (30% vs. 21% [Study 3]), of selected NCI CTC Grade 2–5 anemia (12.5% vs. 6.6% [Study 1]), and of anemia requiring transfusions (0.1% vs. 0 patients [Study 2]) were increased in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone.

Neutropenia

In randomized controlled clinical trials in the adjuvant setting, the incidence of selected NCI CTC Grade 4–5 neutropenia (2% vs. 0.7% [Study 2]) and of selected Grade 2–5 neutropenia (7.1% vs. 4.5 % [Study 1]) were increased in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. In a randomized, controlled trial in patients with metastatic breast cancer, the incidences of NCI-CTC Grade 3/4 neutropenia (32% vs. 22%) and of febrile neutropenia (23% vs. 17%) were also increased in patients randomized to Herceptin in combination with myelosuppressive chemotherapy as compared to chemotherapy alone (see **ADVERSE REACTIONS: Infection**).

Following the administration of Herceptin as a single agent (Study 4), the incidences of NCI-CTC Grade 3 leukopenia, thrombocytopenia, and anemia were all <1%. No Grade 4 hematologic toxicities were observed.

Infection

The overall incidences of infection (46% vs. 30% [Study 3]), of selected NCI-CTC Grade 2–5 infection/febrile neutropenia (22% vs. 14% [Study 1]) and of selected Grade 3–5 infection/febrile neutropenia (3.3% vs. 1.4%) [Study 2]), were higher in patients receiving Herceptin 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 a randomized, controlled trial in treatment of metastatic breast cancer, the reported incidence of febrile neutropenia was higher (23% vs. 17%) in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to chemotherapy alone (see **WARNINGS: Exacerbation of Chemotherapy-Induced Neutropenia**).

Pulmonary Toxicity

Among women receiving adjuvant therapy for breast cancer, the incidence of selected NCI-CTC Grade 2–5 pulmonary toxicity (14% vs. 5% [Study 1]) and of selected NCI-CTC Grade 3–5 pulmonary toxicity and spontaneously reported Grade 2 dyspnea (3.4 % vs. 1% [Study 2]) was higher in patients receiving Herceptin and chemotherapy compared with chemotherapy alone. The most common pulmonary toxicity was dyspnea (NCI-CTC Grade 2–5: 12% vs. 4% [Study 1]; NCI-CTC Grade 2–5: 2.5% vs. 0.1% [Study 2]). Pneumonitis/pulmonary infiltrates occurred in 0.7% of patients receiving Herceptin compared with 0.3% of those receiving chemotherapy alone. Fatal respiratory failure occurred in 3 patients receiving Herceptin, one as a component of multi-organ system failure, as compared to 1 patient receiving chemotherapy alone.

Among women receiving Herceptin for treatment of metastatic breast cancer, the incidence of pulmonary toxicity was also increased. Pulmonary adverse events have been reported in the post-marketing experience as part of the symptom complex of infusion reactions (see **BOXED WARNINGS: Infusion Reactions; Pulmonary Toxicity** and **WARNINGS: Infusion Reactions**). Pulmonary events include bronchospasm, hypoxia, dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, and acute respiratory distress syndrome. For a detailed description, see **WARNINGS**.

Thrombosis/Embolism

In three randomized, controlled clinical trials, the incidence of thrombotic adverse events was higher in patients receiving Herceptin and chemotherapy compared to chemotherapy alone in two studies (3.0 vs. 1.3% [Study 1] and 2.1% vs. 0% [Study 3]).

Diarrhea

Of patients treated with Herceptin as a single agent, 25% experienced diarrhea. An increased incidence of diarrhea, primarily mild to moderate in severity, was observed in patients receiving Herceptin in combination with chemotherapy for treatment of metastatic breast cancer. Among women receiving adjuvant therapy for breast cancer, the incidence of treatment-related NCI-CTC Grade 2 and all Grade 3–5 diarrhea (6.2% vs. 4.8% [Study 1]) and of treatment-related NCI-CTC Grade 3–5 diarrhea (1.6% vs. 0% [Study 2]) were higher in patients receiving Herceptin and chemotherapy compared with chemotherapy alone.

Glomerulopathy

In the postmarketing 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 initiation of Herceptin therapy. Pathologic findings included membranous glomerulonephritis, focal glomerulosclerosis, and fibrillary glomerulonephritis. Complications included volume overload and congestive heart failure.

Immunogenicity

Among 903 women with metastatic breast cancer, human anti-human antibody (HAHA) to Trastuzumab was detected in one patient using an enzyme-linked immunoabsorbant assay (ELISA). This patient did not experience an allergic reaction. Samples for assessment of HAHA were not collected in studies of adjuvant breast cancer.

The data reflect the percentage of patients whose test results were considered positive for antibodies to Herceptin in ELISA assay, and are

highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Herceptin with the incidence of antibodies to other products may be misleading.

Adjuvant Breast Cancer

Safety data for Herceptin in the adjuvant breast cancer setting are based on two randomized, controlled clinical trials [Study 1 and Study 2] in which 1635 women received at least one dose of Herceptin in combination with paclitaxel adjuvant therapy for breast cancer and 1571 women in the control arms who received at least one dose of paclitaxel chemotherapy and for whom any follow-up safety data were recorded.

Because the initial treatment was similar in both study arms (4 cycles of AC chemotherapy), comparisons of adverse events are limited to the post-AC period. Data collection was limited in both studies.

The data in Table 8 were obtained from 1772 patients enrolled in Study 1. Among these patients, the median age was 49 years (range 22 to 78 years); 83% of patients were White, 8% were Black, 4% were Hispanic, and 4% were Asian/Pacific Islander. The data in Study 2 were obtained from 1434 patients enrolled, of which 732 received Herceptin. The median age was 49 years (range 24 to 80 years); 86% of patients were White, 6% were Black, 3% were Hispanic, and 4% were Asian/Pacific Islander. Herceptin was administered at a loading dose of 4 mg/kg followed by 2 mg/kg weekly, for a maximum of 52 weeks.

Table 8

Study 1: Selected Non-Cardiac Adverse Events with Higher Incidence (≥2%) in the Herceptin + Chemotherapy Arm*

NCI-CTC (v.2.0) Toxicity Term	AC→Paclitaxel + Herceptin (n=903)		AC→Paclitaxel (n=869)	
	Grade 2–5	Gr. 3–5	Grade 2–5	Gr. 3–5
Arthralgia	31%	6%	28%	6%
Fatigue	28%	2%	22%	3%
Infection	22%	6%	14%	4%
Hot Flashes	17%	0%	15%	0.2%
Anemia	13%	1%	7%	1%
Dyspnea	12%	2%	4%	1%
Rash/ desquamation	11%	1%	7%	1%
Neutropenia	7%	4%	5%	3%
Headache	6%	1%	4%	1%
Insomnia	3.7%	0.4%	1.5%	0%

* Only Grade 3–5 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.

In Study 2, data collection was limited to the following investigator-attributed treatment-related adverse reactions NCI-CTC Grade 4 and 5 hematologic toxicities, Grade 3–5 non-hematologic toxicities, selected Grade 2–5 toxicities associated with taxanes (myalgia, arthralgias, nail changes, motor neuropathy, sensory neuropathy) and Grade 1–5 cardiac toxicities occurring during chemotherapy and/or Herceptin treatment. The following non-cardiac adverse reactions of Grade 2–5 toxicities occurred at an incidence of at least 2% greater among patients randomized to Herceptin plus chemotherapy as compared to chemotherapy alone: arthralgia (11% vs. 8.4%), myalgia (10% vs. 8%), nail changes (9% vs. 7%), and dyspnea (2.5% vs. 0.1%). The majority of these events were grade 2 in severity.

Metastatic Breast Cancer

Where specific percentages are noted these data are based on clinical studies of Herceptin alone or in combination with chemotherapy for the treatment of metastatic breast cancer. Data in Table 9 are based on the experience for Herceptin in a randomized controlled trial in which 464 patients were treated with chemotherapy alone (n=230), Herceptin in combination with chemotherapy (n=234), and four open-label studies of Herceptin as a single agent which enrolled 352 patients. Data regarding serious adverse events are based on experience in 958 patients (including some with other cancer diagnoses) enrolled in clinical trials of Herceptin conducted prior to marketing.

Among the 464 patients treated in Study 3, the median age was 52 years (range: 25–77 years). Eighty-nine percent were White, 5% Black, 1% Asian and 5% other racial/ethnic groups. All patients received 4 mg/kg initial dose of Herceptin following by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for ≥6 months and ≥12 months were 58% and 9%, respectively.

Among the 352 patients treated in single agent studies (213 patients from Study 4), the median age was 50 years (range 28–86 years), 100% had breast cancer, 86% were White, 3% were Black, 3% were Asian, and 8% in other racial/ethnic groups. Most of patients received 4 mg/kg initial dose of Herceptin following by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for ≥6 months and ≥12 months were 31% and 16%, respectively.

Table 9

Per-Patient Incidence of Adverse Events Occurring in ≥5% of Patients in Uncontrolled Studies or at Increased Incidence in the Herceptin Arm (Study 3)

(Percent of Patients)

	Single Agent n=352	Herceptin + Paclitaxel n=91	Paclitaxel Alone n=95	Herceptin + AC n=143	AC Alone n=135
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
Digestive					
Nausea	33	51	9	76	77
Diarrhea	25	45	29	45	26
Vomiting	23	37	28	53	49
Nausea and vomiting	8	14	11	18	9
Anorexia	14	24	16	31	26
Heme & Lymphatic					
Anemia	4	14	9	36	26
Leukopenia	3	24	17	52	34
Metabolic					
Peripheral edema	10	22	20	20	17
Edema	8	10	8	11	5
Musculoskeletal					
Bone pain	7	24	18	7	7
Arthralgia	6	37	21	8	9

Table 9 (cont'd)

Per-Patient Incidence of Adverse Events Occurring in ≥5% of Patients in Uncontrolled Studies or at Increased Incidence in the Herceptin Arm (Study 3)

(Percent of Patients)

	Single Agent n=352	Herceptin + Paclitaxel n=91	Paclitaxel Alone n=95	Herceptin + AC n=143	AC Alone n=135
Nervous					
Insomnia	14	25	13	29	15
Dizziness	13	22	24	24	18
Paresthesia	9	48	39	17	11
Depression	6	12	13	20	12
Peripheral neuritis	2	23	16	2	2
Neuropathy	1	13	5	4	4
Respiratory					
Cough increased	26	41	22	43	29
Dyspnea	22	27	26	42	25
Rhinitis	14	22	5	22	16
Pharyngitis	12	22	14	30	18
Sinusitis	9	21	7	13	6
Skin					
Rash	18	38	18	27	17
Herpes simplex	2	12	3	7	9
Acne	2	11	3	3	<1
Urogenital					
Urinary tract infection	5	18	14	13	7

OVERDOSAGE

There is no experience with overdosage in human clinical trials. Single doses higher than 500 mg have not been tested.

DOSAGE AND ADMINISTRATION

See **BOXED WARNING**

Recommended Dose

Trastuzumab is administered as an intravenous infusion once every 7 days. The recommended dose of Trastuzumab for the first infusion is 4 mg/kg administered as a 90-minute intravenous infusion. **Do not administer as an IV push or bolus.** The recommended subsequent weekly dose of 2 mg/kg can be administered as a 30-minute intravenous infusion if the first infusion was well tolerated (see **Dose Modifications: Infusion Reactions**).

Metastatic Breast Cancer

Trastuzumab is administered until tumor progression.

Adjuvant Treatment of Breast Cancer

Do not administer concurrently with doxorubicin and cyclophosphamide. Following completion of doxorubicin and cyclophosphamide, Trastuzumab is administered weekly for 52 weeks. During the first 12 weeks, Herceptin is administered concurrently with paclitaxel.

Dose Modifications

Infusion Reactions (See **BOXED WARNINGS: Infusion Reactions** and **WARNINGS: Infusion Reactions**) During Adjuvant Treatment or Treatment of Metastatic Disease

- Decrease the rate of infusion for mild or moderate infusion reactions
- Interrupt the infusion in patients with dyspnea or clinically significant hypotension
- Strongly consider permanent discontinuation of Trastuzumab for severe and life-threatening infusion reactions.

Cardiomyopathy (See **BOXED WARNINGS: Cardiomyopathy** and **WARNINGS: Cardiomyopathy**) in Patients Receiving Adjuvant Therapy

Left ventricular ejection fraction (LVEF) should be assessed prior to initiation of Trastuzumab and frequently during treatment.

- Withhold Trastuzumab dosing for at least 4 weeks and repeat LVEF assessment every 4 weeks for either of the following
  - ≥16% absolute decrease in LVEF from pre-treatment values
  - LVEF below institutional limits of normal and ≥10% absolute decrease in LVEF from pretreatment values.
- Trastuzumab may be resumed if, within 4–8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is ≤15%.
- Permanently discontinue Trastuzumab for a persistent (>8 weeks) LVEF decline or for suspension of Trastuzumab dosing on more than 3 occasions for cardiomyopathy.

Preparation for Administration

Reconstitution

Each vial of Herceptin should be reconstituted with 20 mL of BWFI, USP, 1.1% benzyl alcohol preserved, as supplied, to yield a multi-dose solution containing 21 mg/mL Trastuzumab. The reconstituted preparation results in a colorless to pale yellow transparent solution. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration. Reconstituted Herceptin must be discarded after 28 days.

Use of diluents other than BWFI should be avoided unless contraindicated. For patients with known hypersensitivity to benzyl alcohol, Herceptin must be reconstituted with Sterile Water for Injection; discard any unused portion.

Shaking the reconstituted Herceptin or causing excessive foaming during the addition of diluent may result in problems with dissolution and the amount of Herceptin that can be withdrawn from the vial.

Use appropriate aseptic technique when performing the following reconstitution steps:

a. Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the lyophilized cake of Trastuzumab. The stream of diluent should be directed into the lyophilized cake.

b. Swirl the vial gently to aid reconstitution. Trastuzumab may be sensitive to shear-induced stress, e.g., agitation or rapid expulsion from a syringe. **DO NOT SHAKE.**

c. Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The solution should be essentially free of visible particulates, clear to slightly opalescent and colorless to pale yellow.

Dilution

Determine the number of mg of Trastuzumab needed, based on an initial dose of 4 mg Trastuzumab/kg body weight or subsequent dose of 2 mg Trastuzumab/kg body weight. Calculate the volume of the 21 mg/mL reconstituted Trastuzumab 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. **DEXTROSE (5%) SOLUTION SHOULD NOT BE USED.** Gently invert the bag to mix the solution. No incompatibilities between Herceptin and polyvinylchloride or polyethylene bags have been observed.

Herceptin should not be mixed or diluted with other drugs. Herceptin infusions should not be administered through an IV line containing dextrose solutions.

Stability and Storage

Vials of Herceptin are stable at 2–8°C (36–46°F) prior to reconstitution. Do not use beyond the expiration date stamped on the vial.

A vial of Herceptin reconstituted with BWFI, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2–8°C (36–46°F). Discard any remaining multi-dose reconstituted solution after 28 days. A vial of Herceptin reconstituted with unpreserved SWFI (not supplied) should be used immediately and any unused portion discarded. DO NOT FREEZE Herceptin following reconstitution or dilution.

The solution of Herceptin for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP,

should be stored at 2–8°C (36–46°F) for no more than 24 hours prior to use.

HOW SUPPLIED

Herceptin (Trastuzumab) is supplied as a lyophilized, sterile powder nominally containing 440 mg Trastuzumab per vial under vacuum.

Each carton contains one vial of 440 mg Herceptin®(Trastuzumab) and one vial containing 20 mL of Bacteriostatic Water for Injection, USP, 1.1% benzyl alcohol. NDC 50242-134-68.

REFERENCES

1. Coussens L, Yang-Feng TL, Liao Y-C, Chen E, Gray A, McGrath J, et al. Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene. *Science* 1985;230:1132–9.

2. Press MF, Pike MC, Chazin VR, Hung G, Udove JA, Markowicz M, et al. Her-2/*neu* expression in node-negative breast cancer: direct tissue quantitation by computerized image analysis and association of overexpression with increased risk of recurrent disease. *Cancer Res* 1993;53:4960–4970.

3. Baselga J, Norton L, Albanell J, Kim Y-M, Mendelsohn J. Recombinant humanized anti-HER2 antibody (Herceptin™) enhances the antitumor activity of paclitaxel and doxorubicin against HER2/*neu* overexpressing human breast cancer xenografts. *Cancer Res* 1998;58:2825–2831.

4. Pegram MD, Baly D, Wirth C, Gilkerson E, Slamon DJ, Sliwkowski MX, et al. Antibody dependent cell-mediated cytotoxicity in breast cancer patients in Phase III clinical trials of a humanized anti-HER2 antibody [abstract]. *Proc Am Assoc Cancer Res* 1997;38:602. Abstract 4044.

5. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344:783–792.

6. Lee KS, Simon H, Chen H, Bates B, Hung MC, Hauser C. Requirement for neuroregulin receptor, erbB2, in neural and cardiac development. *Nature* 1995;378:394–396.

7. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Davidson NE, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2 positive breast cancer. *N Engl J Med* 2005;353:1673–1684.

8. Tan-Chiu E, Yothers G, Romond E, Geyer CE, Ewer M, Keefe D, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without Trastuzumab as adjuvant therapy in node positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol* 2005; 23:7811-7819.

Herceptin®

[Trastuzumab]

Manufactured by:
Genentech, Inc.
1 DNA Way
South San Francisco, CA
94080-4990

4817406
Initial US Approval September 1998
Revision Date November 2006

903