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 a mean trough and peak concentrations of approximately 79microgram/mL and 123 microgram/mL, respectively.

Detectable concentrations of the circulating extracellular domain of the HER2 receptor (shed antigen) are found in the serum 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. However, with weekly dosing, most patients with elevated shed antigen levels achieved target serum concentrations of Trastuzumab by week 6.

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

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

A multicenter, randomized, controlled clinical trial was conducted in 469patients with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease. 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 2mg/kg. For those who had received prior anthracycline therapy in the adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m^2 over 3hours 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). Compared with patients in the AC subgroups (n = 281), patients in the paclitaxel subgroups (n = 188) were more likely to have had the following: poor prognostic factors (premenopausal status, estrogen or progesterone receptor negative tumors, positive lymph nodes), prior therapy (adjuvant chemotherapy, myeloablative chemotherapy, radiotherapy), and a shorter disease-free interval.

Compared with patients randomized to chemotherapy alone, the patients randomized to HERCEPTIN and chemotherapy experienced a significantly longer time to disease progression, a higher overall response rate (ORR), a longer median duration of response, and a higher one-year survival rate. (See Table1.) 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. The degree of HER2 overexpression was a predictor of treatment effect. (See CLINICAL STUDIES: *HER2 protein overexpression.*)

Table 1
Phase III Clinical Efficacy in First-Line Treatment

	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% quantile	5.5, 14.8	3.9, 8.5	5.1, 11.0	3.7, 7.4	5.8, 14.8	4.5, 8.5
1-Year Survival[c]						
Percent alive	79	68	73	61	83	73
95% confidence interval	74, 84	62, 74	66, 80	51, 71	77, 89	66, 82
p-value (Z-test)	<0.01		0.08		0.04	

[a] AC = anthracycline (doxorubicin or epirubicin) and cyclophosphamide.
[b] Assessed by an independent Response Evaluation Committee.
[c] Kaplan-Meier Estimate

HERCEPTIN was studied as a single agent in a multicenter, open-label, single-arm clinical trial inpatients 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

histochemical detection of HER2 protein overexpression. The
tochemical test for HER2 protein overexpression, has not bee
HERCEPTIN treatment effect, but has been compared to the CT
imens obtained from the National Cancer Institute Cooperativ
upon these results and an expected incidence of 33% of 2+ or 3+ I
with metastatic breast cancer, one can estimate the correlation of
Of specimens testing 3+ (strongly positive) on the HercepTest™
on the CTA (i.e., meeting the study entry criterion) including 8
the CTA (i.e., the reading most associated with clinical benefit).
on the HercepTest™, only 34% would be expected to test at least
be expected to test 3+ on the CTA.

INDICATIONS AND USAGE

HERCEPTIN as a single agent is indicated for the treatment of p
tumors overexpress the HER2 protein and who have received or
metastatic disease. HERCEPTIN in combination with paclitaxe
metastatic breast cancer whose tumors overexpress the H
chemotherapy for their metastatic disease. HERCEPTIN should
HER2 protein overexpression. (See CLINICAL STUDIES: *HE*
tion regarding HER2 protein testing and the relationship betw
treatment effect.)

CONTRAINDICATIONS

None known.

WARNINGS

Cardiotoxicity:

Signs and symptoms of cardiac dysfunction, such as dyspnea, i
pnea, peripheral edema, S_3 gallop, or reduced ejection fraction,
HERCEPTIN. Congestive heart failure associated with HERCI
associated with disabling cardiac failure, death, and mural thron
of patients in the trials who developed congestive heart failure we
Heart Association classification system (I—IV, where IV is t
(SeeTable 3.)

Table 3
Incidence and Severity of Cardiac

	HERCEPTIN[a] alone n = 213	HERCEPTIN+ Paclitaxel[b] n = 91	Paclitaxel[b] n = 95
Any Cardiac Dysfunction	7%	11%	1%
Class III-IV	5%	4%	1%

[a] Open-label, single-agent Phase 2 study (94% received prior ar
[b] Randomized Phase III study comparing chemotherapy plus H
chemotherapy is either anthracycline/cyclophosphamide or pa

Candidates for treatment with HERCEPTIN should undergo th
ing history and physical exam and one or more of the following
There are no data regarding the most appropriate method of e
at risk for developing cardiotoxicity. Monitoring may not ide
dysfunction.

Extreme cautionshould be exercised in treating patients with pr

Patients receiving HERCEPTIN should undergo frequent monit

The probability of cardiac dysfunction was highest in patients wh
anthracyclines. The data suggest that advanced age may increas

Pre-existing cardiac disease or prior cardiotoxic therapy (e.g.
chest) may decrease the ability to tolerate HERCEPTIN therapy;
uate the correlation between HERCEPTIN-induced cardiotoxici

Discontinuation of HERCEPTIN therapy should be strongly co
significant congestive heart failure. In the clinical trials, most p
to appropriate medical therapy often including discontinuation o
or resumption of HERCEPTIN in patients who have previously
studied. There are insufficient data regarding discontinuation
asymptomatic decreases in ejection fraction; such patients sh
clinical deterioration.

PRECAUTIONS

General: HERCEPTIN therapy should be used with caution
Trastuzumab, Chinese Hamster Ovary cell proteins, or any com

Drug Interactions: There have been no formal drug interactio
humans. Administration of paclitaxel in combination with HER
HERCEPTIN clearance in a non-human primate study and in a 1
els in clinical studies (see Pharmacokinetics).

group receiving HERCEPTIN and chemotherapy, especially in the HERCEPTIN and ACsubgroup, compared with the treatment group receiving chemotherapy alone. The majority of these cytopenic events were mild or moderate in intensity, reversible, and none resulted in discontinuation of therapy with HERCEPTIN.

Hematologic toxicity is infrequent following the administration of HERCEPTIN as a single agent, with an incidence of GradeIII toxicities for WBC, platelets, hemoglobin all<1%. No GradeIV toxicities were observed.

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.

Infection: An increased incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections, was observed in patients receiving HERCEPTIN in combination with chemotherapy.

Infusion-Associated Symptoms: During the first infusion with HERCEPTIN, a symptom complex most commonly consisting of chills and/or fever was observed in about 40% of patients. 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). HERCEPTIN discontinuation was infrequent. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, rash, and asthenia. The symptoms occurred infrequently with subsequent HERCEPTIN infusions.

Table 4
Adverse Events Occurring in ≥ 5% of Patients or at
Increased Incidence in the HERCEPTIN Arm of the Randomized Study
(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
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

solution. Parenteral drug products should be inspected visually for p
istration.

No incompatibilities between HERCEPTIN and polyvinylchloride

Administration
Treatment may be administered in an outpatient setting by admi
ing dose by intravenous (IV) infusion over 90 minutes. **DO NO
BOLUS.** Patients should be observed for fever and chills or
ADVERSE REACTIONS). If prior infusions are well tolerat
Trastuzumab may be administered over 30minutes.

**HERCEPTIN should not be mixed or diluted with other drug
administered or mixed with Dextrose solutions.**

Stability and Storage
Vials of HERCEPTIN are stable at 2—8°C (36—46°F) prior to re
ration date stamped on the vial. A vial of HERCEPTIN reconsti
28days after reconstitution when stored refrigerated at 2—8°C (3
multiple use. Discard any remaining multi-dose reconstituted so
(not supplied) is used, the reconstituted HERCEPTIN solution sh
portion must be discarded. DO NOT FREEZE HERCEPTIN TH

The solution of HERCEPTIN for infusion diluted in polyvinyl
0.9% Sodium Chloride for Injection, USP, may be stored at 2—
use. Diluted HERCEPTIN has been shown to be stable for up to
However, since diluted HERCEPTIN contains no effective pr
solution should be stored refrigerated (2—8°C).

HOW SUPPLIED
HERCEPTIN is supplied as a lyophilized, sterile powder containing

Each carton contains one vial of 440mg HERCEPTIN® (Trastuzu
Water for Injection, USP, 1.1% benzyl alcohol. NDC 50242-13-

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