

FOREWORD TO THE

NINTH EDITION



PHYSICIANS' DESK REFERENCE®

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RX FUJISAWA HEALTHCARE, INC. P. 1302



0.5 mg
1 mg
5 mg



5 mg/mL

Prograf®
(tacrolimus)

RX FUJISAWA HEALTHCARE, INC. P. 1307



0.03%, 30 g
0.03%, 60 g



0.03%, 100 g



0.1%, 30 g



0.1%, 60 g



0.1%, 100 g

Protopic®
(tacrolimus ointment)

GENENTECH, INC.

RX GENENTECH, INC. P. 1332



50 mg
(29 million IU)
Packaged with diluent

100 mg
(58 million IU)
Packaged with diluent and double-sided
sterile, siliconized transfer device

Activase®
(Alteplase)

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400 mg 100 mg

Avastin™
(Bevacizumab)

RX GENENTECH, INC. P. 1337



2 mg

Cathflo® Activase®
(Alteplase)

RX GENENTECH, INC. P. 1337



440 mg
Multi-dose vial

Herceptin®
(Trastuzumab)

RX GENENTECH, INC. P. 1341



5 mg
(approx. 15 IU)
Packaged with 10 mL multi-dose vial of
bacteriostatic water
(benzyl alcohol preserved)

Nutropin®
(somatropin (rDNA origin) for injection)

RX GENENTECH, INC. P. 1348



10 mg
(approx. 30 IU)
Packaged with 10 mL multi-dose vial of
bacteriostatic water
(benzyl alcohol preserved)

Nutropin®
(somatropin (rDNA origin) for injection)

Because tablets and capsules
are shown in this section,
do not infer that these are
the only dosage forms
available. Where a product name
is preceded by the
symbol †, refer to the description
in the Product Information
(White Section) for other forms.

RX GENENTECH, INC. P. 1345



10 mg (5mg/mL)
(approx. 30 IU)

Nutropin AQ®
(somatropin (rDNA origin) injection)

RX GENENTECH, INC. P. 1345



10 mg/2 mL

Nutropin AQ Pen™
(somatropin (rDNA origin) injection)

RX GENENTECH, INC. P. 1357



13.5 mg

Nutropin Depot®
(somatropin (rDNA origin) injection)

RX GENENTECH, INC. P. 1348



2.5 mg/2.5 mL
Each carton contains
30 single-use ampules

Pulmozyme®
(dornase alfa inhalation solution)

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125 mg

Raptiva™
(Efalizumab)

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100 mg (10mg/mL)

Rituxan®
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TNKase™
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75 mg

Xolair®
(Omalizumab)

Designed to help you identify
drugs, this section contains
actual size pills and full color
reproduction of products
selected for inclusion by
participating manufacturers.

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150 mg

Xolair®
(Omalizumab)

RX GENZYME P. 1366



400 mg
800 mg

Renagel® Tablets
(sevelamer HCl)

RX GILEAD SCIENCES, INC. P. 1370



200 mg

Emtriva®
(emtricitabine)

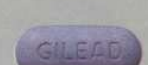
RX GILEAD SCIENCES, INC. P. 1373



10 mg

Hepsera®
(adefovir dipivoxil)

RX GILEAD SCIENCES, INC. P. 1376



200 mg/300 mg

Truvada™
(emtricitabine/tenofovir
disoproxil fumarate)

RX GILEAD SCIENCES, INC. P. 1381



300 mg

Viread®
(tenofovir disoproxil fumarate)

GLAXOSMITHKLINE

RX GLAXOSMITHKLINE P. 1386



0.05%
15 g
0.05%
45 g
Also available in 60 g

Aclovate® Cream
(alclometasone dipropionate cream)

RX GLAXOSMITHKLINE P. 1386



0.05%
15 g
0.05%
45 g
Also available in 60 g

Aclovate® Ointment
(alclometasone dipropionate ointment)

system of non-compressible vessels. In addition, caution should be exercised with patients who have thrombocytopenia or other hematologic defects (including those secondary to liver failure or renal disease), or any condition for which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location, or who are at high risk for embolic complications (e.g., venous thrombosis in the region of the catheter). Death and permanent disability have been reported in patients who have experienced stroke and other serious bleeding episodes when receiving pharmacologic doses of a thrombolytic.

Stroke: serious bleeding in a critical location (e.g., intracranial, gastrointestinal, retroperitoneal, pericardial) occur, treatment with Cathflo Activase should be stopped and the drug should be withdrawn from the catheter.

Infections

Cathflo Activase should be used with caution in the presence of known or suspected infection in the catheter. Using Cathflo Activase in patients with infected catheters may release a localized infection into the systemic circulation (see ADVERSE REACTIONS). As with all catheterization procedures, care should be used to maintain aseptic technique.

Readministration

In clinical trials, patients received up to two 2 mg/2 mL doses (4 mg total) of Alteplase. Additional re-administration of Cathflo Activase has not been studied. Antibody formation in patients receiving one or more doses of Cathflo Activase for restoration of function to CVDs has not been studied.

Drug Interactions

The interaction of Cathflo Activase with other drugs has not been formally studied. Concomitant use of drugs affecting coagulation and/or platelet function has not been studied.

Drug/Laboratory Test Interactions

Minimal interactions between Cathflo Activase and laboratory tests have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies that evaluated tumorigenicity of Alteplase and effect on tumor metastases were negative in rodents. Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure at high concentrations exceeding those expected to be achieved with Cathflo® Activase® (Alteplase).

Pregnancy (Category C)

It is not known whether Cathflo Activase is capable of crossing the placenta. In rabbits, there was an increased postimplantation loss rate in rabbits when administered intravenously at doses approximately 100 times (3 mg/kg) the human dose for restoration of function to occluded CVDs. No maternal or fetal toxicity was evident at 33 times (1 mg/kg) the human dose for restoration of function to occluded CVDs in pregnant rats and rabbits based during the period of organogenesis.

There are no adequate and well-controlled studies in pregnant women. Cathflo Activase should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether Cathflo Activase is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Cathflo Activase is administered to a nursing woman.

Pediatric Use

Cathflo Activase has not been studied in patients who are younger than 2 years of age or who weigh less than 10 kg. In Trials 1 and 2, 126 (11%) of 1135 patients treated were from 1 to 16 years of age. No study drug-related adverse events were observed in these patients. A total of 65 patients (6% of all patients treated in the studies) weighed ≥ 10 kg and < 30 kg. These low body weight patients received up to two doses of Alteplase, with each dose equal to 110% of the internal lumen volume of the catheter (to a maximum dose of 2 mg). The rates of catheter function restoration in these patients were similar to those observed in adult patients. However, there was insufficient enrollment of pediatric patients to draw any conclusions regarding relative efficacy in the pediatric or low weight subgroups, relative efficacy related to catheter types used in these patients, or relative rates of adverse events.

Geriatric Use

In 312 patients enrolled who were age 65 years and over, no incidents of intracranial hemorrhage (ICH), embolic events, or major bleeding events were observed. One hundred three of these patients were age 75 years and over, and 12 were age 85 years and over. The effect of Alteplase on common age-related comorbidities has not been studied. In general, caution should be used in geriatric patients with conditions known to increase the risk of bleeding (see PRECAUTIONS, Bleeding).

ADVERSE REACTIONS

In the clinical trials, the most serious adverse events reported after treatment were sepsis (see PRECAUTIONS, Infections), gastrointestinal bleeding, and venous thrombosis.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the

clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to Cathflo Activase in 1122 patients, of whom 880 received a single dose and 242 received two sequential doses of Cathflo Activase.

In the Cathflo Activase clinical trials, only limited, focused types of serious adverse events were recorded, including death, major hemorrhage, intracranial hemorrhage, pulmonary or arterial emboli, and other serious adverse events not thought to be attributed to underlying disease or concurrent illness. Major hemorrhage was defined as severe blood loss (> 5 mL/kg), blood loss requiring transfusion, or blood loss causing hypotension. Non-serious adverse events and serious events thought to be due to underlying disease or concurrent illness were not recorded. Patients were observed for serious adverse events until catheter function was deemed to be restored or for a maximum of 4 or 6 hours depending on study. For most patients the observation period was 30 minutes to 2 hours. Spontaneously reported deaths and serious adverse events that were not thought to be related to the patient's underlying disease were also recorded during the 30 days following treatment.

Four catheter-related sepsis events occurred from 15 minutes to 1 day after treatment with Alteplase, and a fifth sepsis event occurred on Day 3 after Alteplase treatment. All 5 patients had positive catheter or peripheral blood cultures within 24 hours after symptom onset.

Three patients had a major hemorrhage from a gastrointestinal source from 2 to 3 days after Alteplase treatment. One case of injection site hemorrhage was observed at 4 hours after treatment in a patient with pre-existing thrombocytopenia. These events may have been related to underlying disease and treatments for malignancy, but a contribution to occurrence of the events from Alteplase cannot be ruled out. There were no reports of intracranial hemorrhage. Three cases of subclavian and upper extremity deep venous thrombosis were reported 3 to 7 days after treatment. These events may have been related to underlying disease or to the long-term presence of an indwelling catheter, but a contribution to occurrence of the events from Alteplase treatment cannot be ruled out. There were no reports of pulmonary emboli.

There were no gender-related differences observed in the rates of adverse reactions. Adverse reactions profiles were similar across age subgroups, but there was insufficient enrollment of pediatric patients to draw any conclusions regarding relative adverse event rates (see PRECAUTIONS, Pediatric Use).

Allergic Reactions

No allergic-type reactions were observed in the trials in patients treated with Alteplase. If an anaphylactic reaction occurs, appropriate therapy should be administered.

DOSAGE AND ADMINISTRATION

Cathflo® Activase® (Alteplase) is for instillation into the dysfunctional catheter at a concentration of 1 mg/mL.

• Patients weighing ≥ 30 kg:	2 mg in 2 mL
• Patients weighing ≥ 10 to < 30 kg:	110% of the internal lumen volume of the catheter; not to exceed 2 mg in 2 mL

If catheter function is not restored at 120 minutes after 1 dose of Cathflo Activase, a second dose may be instilled (see Instructions for Administration). There is no efficacy or safety information on dosing in excess of 2 mg per dose for this indication. Studies have not been performed with administration of total doses greater than 4 mg (two 2 mg doses).

Instructions for Administration

Preparation of Solution

Reconstitute Cathflo Activase to a final concentration of 1 mg/mL:

1. Aseptically withdraw 2.2 mL of Sterile Water for Injection, USP (diluent is not provided). Do not use Bacteriostatic Water for Injection.
2. Inject the 2.2 mL of Sterile Water for Injection, USP, into the Cathflo Activase vial, directing the diluent stream into the powder. Slight foaming is not unusual; let the vial stand undisturbed to allow large bubbles to dissipate.
3. Mix by gently swirling until the contents are completely dissolved. Complete dissolution should occur within 3 minutes. **DO NOT SHAKE.** The reconstituted preparation results in a colorless to pale yellow transparent solution containing 1 mg/mL Cathflo Activase at a pH of approximately 7.3.
4. Cathflo Activase contains no antibacterial preservatives and should be reconstituted immediately before use. The solution may be used for intracatheter instillation within 8 hours following reconstitution when stored at 2-30°C (36-86°F).

No other medication should be added to solutions containing Cathflo Activase.

Instillation of Solution into the Catheter

1. Inspect the product prior to administration for foreign matter and discoloration.
2. Withdraw 2.0 mL (2.0 mg) of solution from the reconstituted vial.

3. Instill the appropriate dose of Cathflo Activase (see DOSAGE AND ADMINISTRATION) into the occluded catheter.

4. After 30 minutes of dwell time, assess catheter function by attempting to aspirate blood. If the catheter is functional, go to Step 7. If the catheter is not functional, go to Step 5.

5. After 120 minutes of dwell time, assess catheter function by attempting to aspirate blood and catheter contents. If the catheter is functional, go to Step 7. If the catheter is not functional, go to Step 6.

6. If catheter function is not restored after one dose of Cathflo Activase, a second dose may be instilled. Repeat the procedure beginning with Step 1 under Preparation of Solution.

7. If catheter function has been restored, aspirate 4-5 mL of blood to remove Cathflo Activase and residual clot, and gently irrigate the catheter with 0.9% Sodium Chloride, USP.

Any unused solution should be discarded.

Stability and Storage

Store lyophilized Cathflo Activase at refrigerated temperature (2-8°C/36-46°F). Do not use beyond the expiration date on the vial. Protect the lyophilized material during extended storage from excessive exposure to light.

HOW SUPPLIED

Cathflo Activase is supplied as a sterile, lyophilized powder in 2 mg vials.

Each Cathflo® Activase® carton contains one 2 mg vial of Cathflo® Activase® (Alteplase); NDC 50242-041-64.

Each Novaplus™ Cathflo® Activase® carton contains one 2 mg vial of Novaplus™ Cathflo® Activase® (Alteplase); NDC 50242-041-65.

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Cathflo® Activase® (Alteplase) 7289101
Manufactured by: LB0551

Genentech, Inc. (4821101)
1 DNA Way Revision Date October 2002

South San Francisco, CA 94080-4990
FDA Approval Date September 2001

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Shown in Product Identification Guide, page 313

HERCEPTIN®

[trastuzumab]

(Trastuzumab)

WARNINGS:

CARDIOMYOPATHY

HERCEPTIN administration can result in the development of ventricular dysfunction and congestive heart failure. Left ventricular function should be evaluated in all patients prior to and during treatment with HERCEPTIN. Discontinuation of HERCEPTIN treatment should be strongly considered in patients who develop a clinically significant decrease in left ventricular function. The incidence and severity of cardiac dysfunction was particularly high in patients who received HERCEPTIN in combination with anthracyclines and cyclophosphamide. (See WARNINGS.)

HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS

INFUSION REACTIONS

PULMONARY EVENTS

HERCEPTIN administration can result in severe hypersensitivity reactions (including anaphylaxis), infusion reactions, and pulmonary events. 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

Continued on next page

Herceptin—Cont.

HERCEPTIN treatment should be strongly considered for patients who develop anaphylaxis, angioedema, 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 ($K_d=5\text{ nM}$) to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2.^{1,2} The antibody is an IgG₁ 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 24%–30% of primary breast cancers. HER2 protein overexpression can be determined using immunohistochemistry (IHC) and gene amplification can be determined using fluorescence *in situ* hybridization (FISH) of fixed tumor blocks.² In referenced studies where HERCEPTIN use was not studied,^{2–5} approximately 96%–98% of biopsy specimens that were found to have protein overexpression also had gene amplification and 100% of those with gene amplification also had protein overexpression.^{2–5} The precision of the determination of protein overexpression or gene amplification, however, may vary depending on the sensitivity and specificity of the particular assay and assay procedures used (see PRECAUTIONS). When compared to the referenced studies noted above, the correlation between detectable protein overexpression using IHC and detectable gene amplification using FISH was not as high in the studies of HERCEPTIN clinical trial specimens (see CLINICAL STUDIES: HER2 Detection and HER2 Assay Concordance Studies 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.^{6–8}

Trastuzumab is a mediator of antibody-dependent cellular cytotoxicity (ADCC).^{9,10} *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 1890 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 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 (469 patients) and an open-label single agent clinical trial (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.

A multicenter, randomized, controlled clinical trial was conducted in 469 patients with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease.¹¹ 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/m² 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/m² or epirubicin 75 mg/m² plus 600 mg/m² cyclophosphamide every 21 days for six cycles). Compared with patients in the AC subgroups (n=281), patients in the paclitaxel subgroup (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, myeloblastic chemotherapy, radiotherapy), and a shorter disease-free interval. 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.

Compared with patients randomized to chemotherapy alone, the patients randomized to HERCEPTIN and chemotherapy experienced a significantly longer median time to disease progression, a higher overall response rate (ORR), a longer median duration of response, and a longer median survival (see Table 1). 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).

(See Table 1 below)

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

HER2 Detection

(See PRECAUTIONS: HER2 Testing)

Detection of HER2 protein overexpression is necessary for selection of patients appropriate for HERCEPTIN therapy (see INDICATIONS AND USAGE). Overexpression of HER2 by tumors was an entry criterion of the two clinical studies described above. In those studies, a research-use-only IHC assay (referred to as the Clinical Trial Assay, [CTA]) was used.

The commercial assays described below, HercepTest® (IHC assay) and PathVysion® (FISH assay), are appropriate assays to aid in the selection of patients for HERCEPTIN therapy (see HER2 Detection: HER2 Protein Overexpression Detection Methods and HER2 Gene Amplification Detection Methods). The comparability of either assay with regard to the ability to predict clinical benefit from HERCEPTIN therapy has not been prospectively studied. In addition, the utility of either assay in patients whose tumors would score as 0 or 1+ by the Clinical Trial Assay (CTA) has not been established because patients with tumors that scored as 0 or 1+ were excluded from the clinical studies described.

HER2 Protein Overexpression Detection Methods

HER2 protein overexpression can be established by measuring expressed HER2 protein using IHC methodology. In the clinical trial studies described above, specimens were tested with the 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). Data from the randomized trial suggest that the beneficial treatment effects were largely limited to patients with the highest level of HER2 protein overexpression (3+) (see Table 2). In an exploratory analysis, the relative risk (rr) for time to progression was lower in the patients whose tumors tested as CTA 3+ (rr = 0.42 with 95% CI: 0.33, 0.54) than in those tested as CTA 2+ (rr = 0.76 with 95% CI: 0.50, 1.15). The relative risk represents the risk of progression in the HERCEPTIN plus chemotherapy arm versus the chemotherapy arm. Therefore, a lower ratio represents longer time to progression in the HERCEPTIN arm. In the single-arm study of HERCEPTIN as a single agent, 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%.

HercepTest®, another IHC assay, was assessed for concordance with the CTA (see HER2 Assay: Concordance Studies), but has not been used to assess tumor specimens from the HERCEPTIN clinical studies described above.

HER2 Gene Amplification Detection Methods

As a surrogate for protein overexpression, measurement of the number of HER2 gene copies using FISH to detect gene amplification may be employed. An exploratory, retrospective assessment of known CTA 2+ or 3+ tumor specimens was performed to detect HER2 gene amplification using PathVysion®, a FISH assay. Data from this retrospective analysis involving 660 of 691 (96%) patients enrolled in the clinical studies (all scoring 2+ or 3+ by the CTA) suggested that the beneficial treatment effects were greater in patients whose tumors tested as FISH (+) than in those that were FISH (–); however, time to progression was prolonged for patients on the HERCEPTIN arm, regardless of the FISH result (see Table 2). In the single arm study of HERCEPTIN as a single agent, the overall response rate in patients whose tumors tested as FISH (+) was 20%, while in those tested as FISH (–), there were no responses.

These data are not sufficient to conclude whether FISH testing can distinguish a subpopulation of CTA 2+ patients who would be unlikely to benefit from HERCEPTIN therapy. In addition, there are no data correlating clinical outcome with FISH test results for patients with tumors that scored as 0 or 1+ by CTA; therefore, conclusions regarding the usefulness of FISH in the general population cannot be made.

(See Table 2 at top of next page)

Table 1
Phase III Clinical Efficacy in First-Line Treatment

	Combined Results ^a		Paclitaxel subgroup		AC subgroup	
	HERCEPTIN + 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 (2-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

Information will be superseded by supplements and subsequent editions

HER2 Assay Concordance Studies

(See PRECAUTIONS: HER2 Testing)

Immunohistochemistry: The DAKO HercepTest[®], an IHC test for detecting HER2 protein overexpression, has not been directly studied for its ability to predict HERCEPTIN treatment effect, but has been compared to the CTA on over 500 breast cancer histology specimens obtained from the National Cancer Institute Cooperative Breast Cancer Tissue Resource. Based upon these results, of specimens testing 3+ (strongly positive) on the HercepTest[®], 82% were 3+ (i.e., the reading most associated with clinical benefit), 12% were 2+, and 6% were 0 or 1+ on the CTA. The 6% of HercepTest[®] 3+ specimens that were CTA 0 or 1+ would be expected to represent 2% of the 0 and 1+ population. Of specimens testing 2+ (weakly positive) on the HercepTest[®], 14% were 3+, 20% were 2+, and 66% were 0 or 1+ on the CTA. Of specimens testing 0 or 1+ on the HercepTest[®], 2% were 3+, 6% were 2+, and 92% were 0 or 1+ on the CTA.

Fluorescence in situ Hybridization: The Vysis PathVysion[®] HER2 DNA Probe, a FISH test for detecting HER2 gene amplification, was compared with the CTA on over 500 breast cancer histology specimens originally submitted for potential enrollment in the HERCEPTIN trials. A HER2:CEP17 ratio of ≥ 2 was defined as FISH positive (+). Based on these results, of specimens testing FISH (+) by PathVysion[®], 81% were 3+, 10% were 2+, and 9% were 0 or 1+ on the CTA. The 9% of FISH (+) specimens that were CTA 0 or 1+ would be expected to represent 3% of the total CTA 0 or 1+ population. Of specimens testing FISH (-) by PathVysion[®], 3% were 3+, 10% were 2+, and 87% were 0 or 1+ on the CTA.

INDICATIONS AND USAGE

HERCEPTIN (Trastuzumab) 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. HERCEPTIN should be used in patients whose tumors have been evaluated with an assay validated to predict HER2 protein overexpression (see PRECAUTIONS: HER2 Testing and CLINICAL STUDIES: HER2 Detection).

CONTRAINDICATIONS

None known.

WARNINGS**Cardiotoxicity**

Signs and symptoms of cardiac dysfunction, such as dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, S₃ gallop, or reduced ejection fraction, have been observed in patients treated with HERCEPTIN. Congested heart failure associated with HERCEPTIN therapy may be severe and has been associated with disabling cardiac failure, death, and mural thrombosis leading to stroke (see BOXED WARNINGS: CARDIOMYOPATHY). The clinical status of patients in the trials who developed congestive heart failure 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 3). (See table 3 above)

Candidates for treatment with HERCEPTIN should undergo thorough baseline cardiac assessment including history and physical exam and one or more of the following: EKG, echocardiogram, and MUGA scan. There are no data regarding the most appropriate method of evaluation for the identification of patients at risk for developing cardiotoxicity. Monitoring may not identify all patients who will develop cardiac dysfunction.

Extreme caution should be exercised in treating patients with pre-existing cardiac dysfunction.

Patients receiving HERCEPTIN should undergo frequent monitoring for deteriorating cardiac function.

The probability of cardiac dysfunction was highest in patients who received HERCEPTIN concurrently with anthracyclines. The data suggest that advanced age may increase the probability of cardiac dysfunction.

Pre-existing cardiac disease or prior cardiotoxic therapy (e.g., anthracycline or radiation therapy to the chest) may decrease the ability to tolerate HERCEPTIN therapy; however, the data are not adequate to evaluate the correlation between HERCEPTIN-induced cardiotoxicity and these factors.

Discontinuation of HERCEPTIN therapy should be strongly considered in patients who develop clinically significant congestive heart failure. In the clinical trials, most patients with cardiac dysfunction responded to appropriate medical therapy often including discontinuation of HERCEPTIN. The safety of continuation or resumption of HERCEPTIN in patients who have previously experienced cardiac toxicity has not been studied. There are insufficient data regarding discontinuation of HERCEPTIN therapy in patients with asymptomatic decreases in ejection fraction; such patients should be closely monitored for evidence of clinical deterioration.

Hypersensitivity Reactions Including Anaphylaxis

Severe hypersensitivity reactions have been infrequently reported in patients treated with HERCEPTIN (see BOXED WARNINGS: HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS). Signs and symptoms include

Table 2 1. Slamon D.J., Leyland-Jones B, Shak S., Fuchs H, Paton Treatment Effect versus Level of V. Bajamonde A, et al. Use of chemotherapy plus a Phase III Randomized Trial monoclonal antibody against HER2 for metastatic HERCEPTIN Plus Chemotherapy breast cancer that overexpresses HER2. N Engl J Med. 2001;344:783-92.

HER2 Assay Result	Number of Patients (N)	Progression-free survival (%)	Cardiac development (%)	Nature
CTA 2+ or 3+ FISH (+)*	469	0.49 (0.40, 0.61)	0.44 (0.34, 0.57)	0.70 (0.60, 0.80)
FISH (-)*	126	0.62 (0.42, 0.94)	0.77 (0.48, 1.25)	1.06 (0.70, 1.63)
CTA 2+ FISH (+)	120	0.76 (0.50, 1.15)	0.54 (0.21, 1.35)	1.26 (0.82, 1.94)
FISH (-)	83	0.77 (0.48, 1.25)	0.77 (0.48, 1.25)	1.11 (0.68, 1.82)
CTA 3+ FISH (+)	349	0.42 (0.33, 0.54)	0.42 (0.32, 0.55)	0.70 (0.51, 0.90)
FISH (-)	43	0.43 (0.20, 0.94)	0.43 (0.20, 0.94)	0.67 (0.51, 0.89)
				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.

Table 3
Incidence and Severity of Cardiac Dysfunction

	HERCEPTIN ^a 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.

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

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

There are no data regarding the most appropriate method of identification of patients who may safely be retreated with HERCEPTIN after experiencing a severe hypersensitivity reaction. HERCEPTIN has been readministered to some patients who fully recovered from a 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.

Infusion Reactions

In the postmarketing setting, rare occurrences of severe infusion reactions leading to a fatal outcome have been associated with the use of HERCEPTIN. (See BOXED WARNINGS: 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.)

However, in postmarketing reports, more severe adverse reactions to HERCEPTIN infusion were observed and included bronchospasm, hypoxia, and severe hypotension. These severe reactions were usually associated with the initial infusion of HERCEPTIN and generally occurred during or immediately following the infusion. However, the onset and clinical course were variable. For some patients, symptoms progressively worsened and led to further pulmonary complications. (See WARNINGS: Pulmonary Events.) In other patients with acute onset of signs and symptoms, initial improvement was followed by clinical deterioration. Delayed post-infusion events with rapid clinical deterioration have also been reported. Rarely, severe infusion reactions culminated in death within hours or up to one week following an infusion.

Some severe reactions have been treated successfully with interruption of the HERCEPTIN infusion and supportive therapy including oxygen, intravenous fluids, beta-agonists, and corticosteroids.

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 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. In the postmarketing setting, deaths due to sepsis in patients with severe neutropenia have been reported in patients receiving HERCEPTIN and myelosuppressive chemotherapy, although in controlled clinical trials (pre- and post-marketing), the incidence of septic deaths was not significantly increased. The pathophysiologic basis for exacerbation of neutropenia has not been determined; the effect of HERCEPTIN on the pharmacokinetics of chemotherapeutic agents has not been fully evaluated (see ADVERSE REACTIONS: Anemia and Leukopenia; ADVERSE REACTIONS: Infection).

Pulmonary Events

Severe pulmonary events leading to death have been reported rarely with the use of HERCEPTIN in the post-marketing setting. Signs, symptoms and clinical findings include dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, and acute respiratory distress syndrome. These events may or may not 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, may be at greater risk of severe reactions. Other severe events reported rarely in the postmarketing setting include pneumonitis and pulmonary fibrosis.

PRECAUTIONS**General**

HERCEPTIN therapy should be used with caution in patients with known hypersensitivity to Trastuzumab, Chinese Hamster Ovary cell proteins, or any component of this product.

HER2 Testing

Assessment for HER2 overexpression 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[®] and PathVysion[®] package inserts for full instructions on assay performance (see CLINICAL STUDIES: HER2 Detection).

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.)

Continued on next page

Herceptin—Cont.

HERCEPTIN treatment should be strongly considered for patients who develop anaphylaxis, angioedema, allergic respiratory distress syndrome. (See WARNINGS: Anaphylaxis for Injection.)

DESCRIPTION

HERCEPTIN (Trastuzumab) is a monoclonal antibody. It is a humanized monoclonal antibody. It is a single use.

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/mL 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

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.¹² 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. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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 133 patients who were 65 years of age or over. The risk of cardiac dysfunction may be increased in geriatric patients. The reported clinical experience is not adequate to determine whether older patients respond differently from younger patients.

ADVERSE REACTIONS

The most serious adverse reactions caused by HERCEPTIN include cardiomyopathy, hypersensitivity reactions including anaphylaxis, infusion reactions, pulmonary events, and exacerbation of chemotherapy-induced neutropenia. Please refer to the BOXED WARNINGS and/or WARNINGS sections for detailed descriptions of these reactions. The most common adverse reactions associated with HERCEPTIN use are fever, diarrhea, infections, chills, increased cough, headache, rash, and insomnia.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to 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.

Additional adverse reactions have been identified during post-marketing use of HERCEPTIN. 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.

Where specific percentages are noted, these data are based on clinical studies of HERCEPTIN alone or in combination with chemotherapy in clinical trials. Data in Table 4 are based on the experience with the recommended dosing regimen for HERCEPTIN in a randomized controlled clinical trial of 234 patients who received HERCEPTIN in combination with chemotherapy and four open-label studies of HERCEPTIN as a single agent in 352 patients at doses of 10–500 mg administered weekly. Data regarding serious ad-

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

verse events are based on experience in 958 patients enrolled in all clinical trials of HERCEPTIN conducted prior to marketing approval.

Cardiac Failure/Dysfunction

For a description of cardiac toxicities, see BOXED WARNINGS: CARDIOMYOPATHY and WARNINGS: Cardiotoxicity.

Anemia and Leukopenia

In a randomized, controlled trial (see CLINICAL STUDIES), the per-patient incidences of anemia (30% vs. 21%) and leukopenia (53% vs. 37%) were higher in patients receiving HERCEPTIN in combination with chemotherapy as compared to those receiving chemotherapy alone. The majority of these cytopenic events were mild to moderate in intensity, reversible, and none resulted in discontinuation of therapy with HERCEPTIN.

In a randomized, controlled trial conducted in the post-marketing setting, there were also increased incidences of NCI-CTC Grade 3/4 neutropenia (32% [29/92] vs. 22% [21/94]) and of febrile neutropenia (23% [21/91] vs. 17% [16/94]) in patients randomized to HERCEPTIN in combination with myelosuppressive chemotherapy as compared to chemotherapy alone (see ADVERSE REACTIONS: Infection).

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

In a randomized, controlled trial (see CLINICAL STUDIES), the incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections, was higher (46% vs. 30%) in patients receiving HERCEPTIN in combination with chemotherapy as compared to those receiving chemotherapy alone.

In a randomized, controlled trial conducted in the post-marketing setting, the reported incidence of febrile neutro-

penia was higher (23% [21/92] vs. 17% [16/94]) in patients receiving HERCEPTIN in combination with myelosuppressive chemotherapy as compared to chemotherapy alone.

In the postmarketing setting, there have also been reports of febrile neutropenia and infection with neutropenia culminating in death associated with the use of HERCEPTIN and myelosuppressive chemotherapy (see WARNINGS: Exacerbation of Chemotherapy-Induced Neutropenia).

Infusion Reactions

During the first infusion with HERCEPTIN, a symptom complex most commonly consisting of chills and/or fever was observed in about 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). 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, elevated blood pressure, rash and asthenia. The symptoms occurred infrequently with subsequent HERCEPTIN infusions. (See BOXED WARNINGS: INFUSION REACTIONS and WARNINGS: Infusion Reactions.)

Additional adverse reactions have been identified during postmarketing use of HERCEPTIN. 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.

Hypersensitivity Reactions Including Anaphylaxis**Pulmonary Events**

In the postmarketing setting, severe hypersensitivity reactions (including anaphylaxis), infusion reactions, and pulmonary adverse events have been reported (see BOXED WARNINGS: HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS and WARNINGS: Hypersensitivity Reactions Including Anaphylaxis). These events include anaphylaxis, angioedema, bronchospasm, hypotension, hypoxia, dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema and acute respiratory distress syndrome. For a detailed description, see WARNINGS.

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 glomerulocystitis and fibrillary glomerulonephritis. Complications included volume overload and congestive heart failure.

(See table 4 at top of previous page)

Other Serious Adverse Events

The following other serious adverse events occurred in at least one of the 958 patients treated with HERCEPTIN in clinical studies:

Body as a Whole: cellulitis, anaphylactoid reaction, ascites, hydrocephalus, radiation injury, deafness, amblyopia.
Cardiovascular: vascular thrombosis, pericardial effusion, heart arrest, hypotension, syncope, hemorrhage, shock, arrhythmia

Digestive: hepatic failure, gastroenteritis, hematemesis, ileus, intestinal obstruction, colitis, esophageal ulcer, stomatitis, pancreatitis, hepatitis

Endocrine: hypothyroidism

Hematological: pancytopenia, acute leukemia, coagulation disorder, lymphangitis

Metabolic: hypercalcemia, hypomagnesemia, hyponatremia, hypoglycemia, growth retardation, weight loss

Musculoskeletal: pathological fractures, bone necrosis, myopathy

Nervous: convulsion, ataxia, confusion, manic reaction

Respiratory: apnea, pneumothorax, asthma, hypoxia, laryngitis

Skin: herpes zoster, skin ulceration

Urogenital: hydronephrosis, kidney failure, cervical cancer, hematuria, hemorrhagic cystitis, pyelonephritis

Immunogenicity

Of 903 patients who have been evaluated, human anti-human antibody (HAHA) to Trastuzumab was detected in one patient, who had no allergic manifestations.

The data reflect the percentage of patients whose test results were considered positive for antibodies to HERCEPTIN in the HAHA assay for Trastuzumab, 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.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION**Usual Dose**

The recommended initial loading dose is 4 mg/kg Trastuzumab administered as a 90-minute infusion. The recommended weekly maintenance dose is 2 mg/kg Trastuzumab and can be administered as a 30-minute infusion if the initial loading dose was well tolerated. HERCEPTIN may be administered in an outpatient setting. HERCEPTIN is to be diluted in saline for IV infusion. **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.** (See DOSAGE AND ADMINISTRATION: Administration.)

Preparation for Administration

The diluent provided has been formulated to maintain the stability and sterility of HERCEPTIN for up to 28 days. Other diluents have not been shown to contain effective preservatives for HERCEPTIN. 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. Immediately upon reconstitution with BWFI, the vial of HERCEPTIN must be labeled in the area marked "Do not use after," with the future date that is 28 days from the date of reconstitution.

If the patient has known hypersensitivity to benzyl alcohol, HERCEPTIN must be reconstituted with Sterile Water for Injection. (See PRECAUTIONS.) HERCEPTIN WHICH HAS BEEN RECONSTITUTED WITH SWFI MUST BE USED IMMEDIATELY AND ANY UNUSED PORTION DISCARDED. USE OF OTHER RECONSTITUTION DILUENTS SHOULD BE AVOIDED.

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:

- 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.
- 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.**
- 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.

Determine the number of mg of Trastuzumab needed, based on a loading dose of 4 mg Trastuzumab/kg body weight or a maintenance dose of 2 mg Trastuzumab/kg body weight. Calculate the volume of 21 mg/mL Trastuzumab solution and withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP. **DEXTRIOSE (5%) SOLUTION SHOULD NOT BE USED.** Gently invert the bag to mix the solution. 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.

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

Administration

Treatment may be administered in an outpatient setting by administration of a 4 mg/kg Trastuzumab loading dose by intravenous (IV) infusion over 90 minutes. **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.** Patients should be observed for fever and chills or other infusion-associated symptoms. (See BOXED WARNINGS, WARNINGS, and ADVERSE REACTIONS.) If prior infusions are well tolerated, subsequent weekly doses of 2 mg/kg Trastuzumab may be administered over 30 minutes.

HERCEPTIN should not be mixed or diluted with other drugs. HERCEPTIN infusions should not be administered or mixed with 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), and the solution is preserved for multiple use. Discard any remaining multi-dose reconstituted solution after 28 days. If unpreserved SWFI (not supplied) is used, the reconstituted HERCEPTIN solution should be used immediately and any unused portion must be discarded. **DO NOT FREEZE HERCEPTIN THAT HAS BEEN RECONSTITUTED.** The solution of HERCEPTIN for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP, may be stored at 2–8°C (36–46°F) for up to 24 hours prior to use. Diluted HERCEPTIN has been shown to be stable for up to 24 hours at room temperature (2–25°C). However, because diluted HERCEPTIN contains no effective preservative, the reconstituted and diluted solution should be stored refrigerated (2–8°C).

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.

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HERCEPTIN®

(Trastuzumab)

Manufactured by: Genentech, Inc. 4817405

1 DNA Way Code revision June 2004

South San Francisco, CA 94080-4990

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Shown in Product Identification Guide, page 313

NUTROPIN®

(new-trō-pin)

(somatropin (rDNA origin) for injection)

DESCRIPTION

Nutropin is a human growth hormone (hGH) produced by recombinant DNA technology. Nutropin has 191 amino acid residues and a molecular weight of 22,125 daltons. The amino acid sequence of the product is identical to that of pituitary-derived human growth hormone. The protein is synthesized by a specific laboratory strain of *E. coli* as a precursor consisting of the rhGH molecule preceded by the secretion signal from an *E. coli* protein. This precursor is directed to the plasma membrane of the cell. The signal sequence is removed and the native protein is secreted into the periplasm so that the protein is folded appropriately as it is synthesized.

Nutropin is a highly purified preparation. Biological potency is determined using a cell proliferation bioassay.

Nutropin is a sterile, white, lyophilized powder intended for subcutaneous administration after reconstitution with Bacteriostatic Water for Injection, USP (benzyl alcohol preserved). The reconstituted product is nearly isotonic at a concentration of 5 mg/mL growth hormone (GH) and has a pH of approximately 7.4.

Each 5 mg Nutropin vial contains 5 mg (approximately 15 IU) somatropin, lyophilized with 45 mg mannitol, 1.7 mg sodium phosphates (0.4 mg sodium phosphate monobasic and 1.3 mg sodium phosphate dibasic), and 1.7 mg glycine. Each 10 mg Nutropin vial contains 10 mg (approximately 30 IU) somatropin, lyophilized with 90 mg mannitol, 3.4 mg sodium phosphates (0.8 mg sodium phosphate monobasic and 2.6 mg sodium phosphate dibasic), and 3.4 mg glycine. Bacteriostatic Water for Injection, USP is sterile water containing 0.9 percent benzyl alcohol per mL as an antimicrobial preservative packaged in a multidose vial. The diluent pH is 4.5–7.0.

CLINICAL PHARMACOLOGY**General**

In vitro and *in vivo* preclinical and clinical testing have demonstrated that Nutropin is therapeutically equivalent to pituitary-derived human GH (hGH). Pediatric patients who lack adequate endogenous GH secretion, patients with chronic renal insufficiency, and patients with Turner syndrome that were treated with Nutropin resulted in an increase in growth rate and an increase in insulin-like growth factor-I (IGF-I) levels similar to that seen with pituitary-derived hGH.

Actions that have been demonstrated for Nutropin, somatrem, and/or pituitary-derived hGH include:

A. Tissue Growth

1) **Skeletal Growth:** GH stimulates skeletal growth in pediatric patients with growth failure due to a lack of adequate secretion of endogenous GH or secondary to chronic renal insufficiency and in patients with Turner syndrome. Skeletal growth is accomplished at the epiphyseal plates at the ends of a growing bone. Growth and metabolism of epiphyseal plate cells are directly stimulated by GH and one of its mediators, IGF-I. Serum levels of IGF-I are low in children and adolescents who are GH deficient, but increase during treatment with GH. In pediatric patients, new bone is formed at the epiphyses in response to GH and IGF-I. This results in linear growth until these growth plates fuse at the end of puberty. 2) **Cell Growth:** Treatment with hGH results in an increase in both the number and the size of skeletal muscle cells. 3) **Organ Growth:** GH influences the size of internal organs, including kidneys, and increases red cell mass. Treatment of hypophysectomized or genetic dwarf rats with GH results in organ growth that is proportional to the overall body growth. In normal rats subjected to nephrectomy-induced uremia, GH promoted skeletal and body growth.

B. Protein Metabolism

Linear growth is facilitated in part by GH-stimulated protein synthesis. This is reflected by nitrogen retention as demonstrated by a decline in urinary nitrogen excretion and blood urea nitrogen during GH therapy.

C. Carbohydrate Metabolism

GH is a modulator of carbohydrate metabolism. For example, patients with inadequate secretion of GH some-

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