PDR®

58 EDITION

2004

PHYSICIANS' DESK REFERENCE®

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ISBN: 1-56363-471-6

Gengraf—Cont.

Patients generally show some improvement in the clinical manifestations of psoriasis in 2 weeks. Satisfactory control and stabilization of the disease may take 12–16 weeks to achieve. Results of a dose-titration clinical trial with Gengraf® indicate that an improvement of psoriasis by 75% or more (based on PASI) was achieved in 51% of the patients after 8 weeks and in 79% of the patients after 16 weeks. Treatment should be discontinued if satisfactory response cannot be achieved after 6 weeks at 4 mg/kg/day or the patient's maximum tolerated dose. Once a patient is adequately controlled and appears stable the dose of Gengraf® should be lowered, and the patient treated with the lowest dose that maintains an adequate response (this should not necessarily be total clearing of the patient). In clinical trials, cyclosporine doses at the lower end of the recommended dosage range were effective in maintaining a satisfactory response in 60% of the patients. Doses below 2.5 mg/kg/day may also be equally effective.

Upon stopping treatment with cyclosporine, relapse will occur in approximately six weeks (50% of the patients) to 16 weeks (75% of the patients). In the majority of patients rebound does not occur after cessation of treatment with cyclosporine. Thirteen cases of transformation of chronic plaque psoriasis to more severe forms of psoriasis have been reported. There were 9 cases of pustular and 4 cases of erythrodermic psoriasis. Long term experience with Gengraf® in psoriasis patients is limited and continuous treatment for extended periods greater than one year is not recommended. Alternation with other forms of treatment should be considered in the long term management of patients with this life long disease.

Blood Concentration Monitoring in Transplant Patients: Transplant centers have found blood concentration monitoring of cyclosporine to be an essential component of patient management. Of importance to blood concentration analysis are the type of assay used, the transplanted organ, and other immunosuppressant agents being administered. While no fixed relationship has been established, blood concentration monitoring may assist in the clinical evaluation of rejection and toxicity, dose adjustments, and the assessment of compliance.

Various assays have been used to measure blood concentrations of cyclosporine. Older studies using a non-specific assay often cited concentrations that were roughly twice those of the specific assays. Therefore, comparison between concentrations in the published literature and an individual patient concentration using current assays must be made with detailed knowledge of the assay methods employed. Current assay results are also not interchangeable and their use should be guided by their approved labeling. A discussion of the different assay methods is contained in *Annals of Clinical Biochemistry* 1994;31:420-446. While several assays and assay matrices are available, there is a consensus that parent-compound-specific assays correlate best with clinical events. Of these, HPLC is the standard reference, but the monoclonal antibody RIAs and the monoclonal antibody FPIA offer sensitivity, reproducibility, and convenience. Most clinicians base their monitoring on trough cyclosporine concentrations. *Applied Pharmacokinetics, Principles of Therapeutic Drug Monitoring* (1992) contains a broad discussion of cyclosporine pharmacokinetics and drug monitoring techniques. Blood concentration monitoring is not a replacement for renal function monitoring or tissue biopsies.

HOW SUPPLIED

Gengraf® Capsules (cyclosporine capsules, USP [MODIFIED])

25 mg

Oval, white imprinted in blue, the corporate logo ⊐, 25 mg, and the Abbo-Code OR.

Packages of 30 unit-dose blisters. (NDC 0074-6463-32).

100 mg

Oval, white, with two blue stripes, imprinted in blue, the corporate logo ⊐, 100 mg, and Abbo-Code OT.

Packages of 30 unit-dose blisters. (NDC 0074-6479-32).

Store and Dispense: In the original unit-dose container at controlled room temperature 15°–30°C (59°–86°F). (See USP).

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*Sandimmune® is a registered trademark of Novartis Pharmaceuticals Corporation.

Manufactured by: Abbott Laboratories North Chicago, IL 60064, U.S.A.

Distributed by: SangStat Medical Corporation Fremont, CA 94555, U.S.A.

03-5242-R4

Revised: January, 2003

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NORTH CHICAGO, IL 60064, U.S.A.
SANGSTAT
The Transplant Company®
Fremont, CA 94555, U.S.A.

Shown in Product Identification Guide, page 303

HUMIRA™ (adalimumab)

℞

Rx only

WARNING
RISK OF INFECTIONS
Cases of tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) have been observed in patients receiving HUMIRA.
Patients should be evaluated for latent tuberculosis infection with a tuberculin skin test. Treatment of latent tuberculosis infection should be initiated prior to therapy with HUMIRA.

DESCRIPTION

HUMIRA (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). HUMIRA was created using phage display technology resulting in an antibody with human derived heavy and light chain variable regions and human IgG1:κ constant regions. HUMIRA is produced by recombinant DNA technology in a mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons.

HUMIRA is supplied in single-use, 1 mL pre-filled glass syringes as a sterile, preservative-free solution for subcutaneous administration. The solution of HUMIRA is clear and colorless, with a pH of about 5.2. Each syringe delivers 0.8 mL (40 mg) of drug product. Each 0.8 mL HUMIRA contains 40 mg adalimumab, 4.93 mg sodium chloride, 0.69 mg monobasic sodium phosphate dihydrate, 1.22 mg dibasic sodium phosphate dihydrate, 0.24 mg sodium citrate, 1.04 mg citric acid monohydrate, 9.6 mg mannitol, 0.8 mg polysorbate 80 and Water for Injection, USP. Sodium hydroxide added as necessary to adjust pH.

CLINICAL PHARMACOLOGY

General

Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells *in vitro* in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of rheumatoid arthritis patients and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of rheumatoid arthritis.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of $1–2 \times 10^{-10}$M).

Pharmacodynamics

After treatment with HUMIRA, a rapid decrease in levels of acute phase reactants of inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) and serum cytokines (IL-6) was observed compared to baseline in patients with rheumatoid arthritis. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after HUMIRA administration.

Pharmacokinetics

The maximum serum concentration (C_{max}) and the time to reach the maximum concentration (T_{max}) were 4.7 ± 1.6 µg/mL and 131 ± 56 hours respectively, following a single 40 mg subcutaneous administration of HUMIRA to healthy adult subjects. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. The pharmacokinetics of adalimumab were linear over the dose range of 0.5 to 10.0 mg/kg following a single intravenous dose.

The single dose pharmacokinetics of adalimumab were determined in several studies with intravenous doses ranging from 0.25 to 10 mg/kg. The distribution volume (V_{ss}) ranged from 4.7 to 6.0 L. The systemic clearance of adalimumab is approximately 12 mL/hr. The mean terminal half-life was approximately 2 weeks, ranging from 10 to 20 days across studies. Adalimumab concentrations in the synovial fluid from five rheumatoid arthritis patients ranged from 31–96% of those in serum.

Adalimumab mean steady-state trough concentrations of approximately 5 µg/mL and 8 to 9 µg/mL, were observed without and with methotrexate (MTX) respectively. The serum adalimumab trough levels at steady increased approximately proportionally with dose following 20, 40 and 80 mg every other week and every week subcutaneous dosing. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time.

Population pharmacokinetic analyses revealed that there was a trend toward higher apparent clearance of adalimumab in the presence of anti-adalimumab antibodies, and lower clearance with increasing age in patients aged 40 to >75 years.

Minor increases in apparent clearance were also predicted in patients receiving doses lower than the recommended dose and in patients with high rheumatoid factor or CRP concentrations. These increases are not likely to be clinically important.

No gender-related pharmacokinetic differences were observed after correction for a patient's body weight. Healthy volunteers and patients with rheumatoid arthritis displayed similar adalimumab pharmacokinetics.

No pharmacokinetic data are available in patients with hepatic or renal impairment

HUMIRA has not been studied in children.

Drug Interactions

MTX reduced adalimumab apparent clearance after single and multiple dosing by 29% and 44% respectively.

CLINICAL STUDIES

The efficacy and safety of HUMIRA were assessed in four randomized, double-blind studies in patients ≥ age 18 with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 6 swollen and 9 tender joints. HUMIRA was administered subcutaneously in combination with MTX (12.5 to 25 mg, Studies I and III) or as monotherapy (Study II) or with other disease-modifying anti-rheumatic drugs (DMARDs) (Study IV).

Study I evaluated 271 patients who had failed therapy with at least one but no more than four DMARDs and had inadequate response to MTX. Doses of 20, 40 or 80 mg of HUMIRA or placebo were given every other week for 24 weeks.

Study II evaluated 544 patients who had failed therapy with at least one DMARD. Doses of placebo, 20 or 40 mg of HUMIRA were given as monotherapy every other week or weekly for 26 weeks.

Study III evaluated 619 patients who had an inadequate response to MTX. Patients received placebo, 40 mg of HUMIRA every other week with placebo injections on alternate weeks, or 20 mg of HUMIRA weekly for up to 52 weeks. Study III had an additional primary endpoint at 52 weeks of inhibition of disease progression (as detected by X-ray results).

Study IV assessed safety in 636 patients who were either DMARD-naive or were permitted to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. Patients were randomized to 40 mg of HUMIRA or placebo every other week for 24 weeks.

The percent of HUMIRA treated patients achieving ACR 20, 50 and 70 responses in Studies II and III are shown in Table 1.

[See table 1 at top of next page]

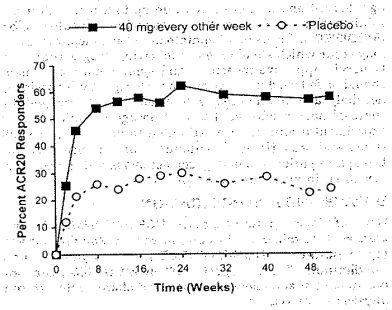
The results of Study I were similar to Study III; patients receiving HUMIRA 40 mg every other week in Study I also achieved ACR 20, 50 and 70 response rates of 65%, 52% and 24%, respectively, compared to placebo responses of 13%, 7% and 3% respectively, at 6 months ($p<0.01$).

The results of the components of the ACR response criteria for Studies II and III are shown in Table 2. Improvement was seen in all components and was maintained to week 52.

[See table 2 at top of next page]

The time course of ACR 20 response for Study III is shown in Figure 1. In Study III, 85% of patients with ACR 20 responses at week 24 maintained the response at 52 weeks. The time course of ACR 20 response for Study I and Study II were similar.

Figure 1: Study III ACR 20 Responses over 52 Weeks



In Study IV, 53% of patients treated with HUMIRA 40 mg every other week plus standard of care had an ACR 20 response at week 24 compared to 35% on placebo plus standard of care ($p<0.001$). No unique adverse reactions related to the combination of HUMIRA and other DMARDs were observed.

In all four studies, HUMIRA showed significantly greater improvement than placebo in the disability index of Health Assessment Questionnaire (HAQ) from baseline to the end of study, and significantly greater improvement than placebo in the health-outcomes as assessed by The Short Form Health Survey (SF 36). Improvement was seen in both the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

Radiographic Response

In Study III, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score, at month 12 compared to baseline. At baseline, the median TSS was approximately 55 in the

placebo and 40 mg every other week groups. The results are shown in Table 3. HUMIRA/MTX treated patients demonstrated less radiographic progression than patients receiving MTX alone.
[See table 3 above]

INDICATIONS AND USAGE

HUMIRA is indicated for reducing signs and symptoms and inhibiting the progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more DMARDs. HUMIRA can be used alone or in combination with MTX or other DMARDs.

CONTRAINDICATIONS

HUMIRA should not be administered to patients with known hypersensitivity to HUMIRA or any of its components.

WARNINGS

SERIOUS INFECTIONS AND SEPSIS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF TNF BLOCKING AGENTS INCLUDING HUMIRA. MANY OF THE SERIOUS INFECTIONS HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR RHEUMATOID ARTHRITIS, COULD PREDISPOSE THEM TO INFECTIONS. TUBERCULOSIS AND INVASIVE OPPORTUNISTIC FUNGAL INFECTIONS HAVE BEEN OBSERVED IN PATIENTS TREATED WITH TNF BLOCKING AGENTS INCLUDING HUMIRA. TREATMENT WITH HUMIRA SHOULD NOT BE INITIATED IN PATIENTS WITH ACTIVE INFECTIONS INCLUDING CHRONIC OR LOCALIZED INFECTIONS. PATIENTS WHO DEVELOP A NEW INFECTION WHILE UNDERGOING TREATMENT WITH HUMIRA SHOULD BE MONITORED CLOSELY. ADMINISTRATION OF HUMIRA SHOULD BE DISCONTINUED IF A PATIENT DEVEVLOPS A SERIOUS INFECTION. PHYSICIANS SHOULD EXERCISE CAUTION WHEN CONSIDERING THE USE OF HUMIRA IN PATIENTS WITH A HISTORY OF RECURRENT INFECTION OR UNDERLYING CONDITIONS WHICH MAY PREDISPOSE THEM TO INFECTIONS, OR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE TUBERCULOSIS AND HISTOPLASMOSIS ARE ENDEMIC (see PRECAUTIONS - Tuberculosis and ADVERSE REACTIONS - Infections). THE BENEFITS AND RISKS OF HUMIRA TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF HUMIRA THERAPY.

Neurologic Events

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease. Prescribers should exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central nervous system demyelinating disorders.

Malignancies

Lymphomas have been observed in patients treated with TNF blocking agents including HUMIRA. In clinical trials, patients treated with HUMIRA had a higher incidence of lymphoma than the expected rate in the general population (see **ADVERSE REACTIONS-Malignancies**). While patients with rheumatoid arthritis, particularly those with highly active disease, may be at a higher risk (up to several fold) for the development of lymphoma, the role of TNF blockers in the development of malignancy is not known.[4,5]

PRECAUTIONS

General

Allergic reactions have been observed in approximately 1% of patients receiving HUMIRA. If an anaphylactic reaction or other serious allergic reaction occurs, administration of HUMIRA should be discontinued immediately and appropriate therapy initiated.

Information to Patients

The first injection should be performed under the supervision of a qualified health care professional. If a patient or caregiver is to administer HUMIRA, he/she should be instructed in injection techniques and their ability to inject subcutaneously should be assessed to ensure the proper administration of HUMIRA (see **HUMIRA, PATIENT INFORMATION LEAFLET**). A puncture-resistant container for disposal of needles and syringes should be used. Patients or caregivers should be instructed in the technique as well as proper syringe and needle disposal, and be cautioned against reuse of these items.

Tuberculosis

As observed with other TNF blocking agents, tuberculosis associated with the administration of HUMIRA in clinical trials has been reported (see **WARNINGS**). While cases were observed at all doses, the incidence of tuberculosis reactivations was particularly increased at doses of HUMIRA that were higher than the recommended dose. All patients recovered after standard antimicrobial therapy. No deaths due to tuberculosis occurred during the clinical trials.

Before initiation of therapy with HUMIRA, patients should be evaluated for active or latent tuberculosis infection with a tuberculin skin test. If latent infection is diagnosed, appropriate prophylaxis in accordance with the Centers for Disease Control and Prevention guidelines[6] should be instituted. Patients should be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur.

Immunosuppression

The possibility exists for TNF blocking agents, including HUMIRA, to affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 64 patients with rheumatoid arthritis treated with HUMIRA, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T- and B-cells and NK-cells, monocyte/macrophages, and neutrophils. The impact of treatment with HUMIRA on the development and course of malignancies, as well as active and/or chronic infections is not fully understood (see **WARNINGS, ADVERSE REACTIONS, Infections and Malignancies**). The safety and efficacy of HUMIRA in patients with immunosuppression have not been evaluated.

Immunizations

No data are available on the effects of vaccination in patients receiving HUMIRA. Live vaccines should not be given concurrently with HUMIRA. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

Autoimmunity

Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, treatment should be discontinued (see **ADVERSE REACTIONS, Autoantibodies**).

Drug Interactions

HUMIRA has been studied in rheumatoid arthritis patients taking concomitant MTX (see **CLINICAL PHARMACOLOGY, Drug Interactions**). The data do not suggest the need for dose adjustment of either HUMIRA or MTX.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility. No clastogenic or mutagenic effects of HUMIRA were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.

Pregnancy

Pregnancy Category B—An embryo-fetal perinatal development toxicity study has been performed in cynomolgus monkeys at dosages up to 100 mg/kg (266 times human AUC when given 40 mg subcutaneous with MTX every week or 373 times human AUC when given 40 mg subcutaneous without MTX) and has revealed no evidence of harm to the fetuses due to adalimumab. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, HUMIRA (adalimumab) should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether adalimumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from HUMIRA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of HUMIRA in pediatric patients have not been established.

Geriatric Use

A total of 519 patients 65 years of age and older, including 107 patients 75 years and older, received HUMIRA in clin-

Continued on next page

Table 1: ACR Responses in Placebo-Controlled Trials (Percent of Patients)

	Study II Monotherapy (26 weeks)			Study III Methotrexate Combination (24 and 52 weeks)	
Response	Placebo N=110	HUMIRA 40 mg every other week N=113	HUMIRA 40 mg weekly N=103	Placebo/MTX N=200	HUMIRA/MTX 40 mg every other week N=207
ACR20					
Month 6	19%	46%*	53%*	30%	63%*
Month 12	NA	NA	NA	24%	59%*
ACR50					
Month 6	8%	22%*	35%*	10%	39%*
Month 12	NA	NA	NA	10%	42%*
ACR70					
Month 6	2%	12%*	18%*	3%	21%*
Month 12	NA	NA	NA	5%	23%*

*p<0.01, HUMIRA vs. placebo

Table 2: Components of ACR Response in Studies II and III

Parameter (median)	Study II				Study III			
	Placebo N=110		HUMIRA[a] N=113		Placebo/MTX N=200		HUMIRA[a]/MTX N=207	
	Baseline	Wk 26	Baseline	Wk 26	Baseline	Wk 24	Baseline	Wk 24
Number of tender joints (0–68)	35	26	31	16*	26	15	24	8*
Number of swollen joints (0–66)	19	16	18	10*	17	11	18	5*
Physician global assessment[b]	7.0	6.1	6.6	3.7*	6.3	3.5	6.5	2.0*
Patient global assessment[b]	7.5	6.3	7.5	4.5*	5.4	3.9	5.2	2.0*
Pain[b]	7.3	6.1	7.3	4.1*	6.0	3.8	5.8	2.1*
Disability index (HAQ)[c]	2.0	1.9	1.9	1.5*	1.5	1.3	1.5	0.8*
CRP (mg/dL)	3.9	4.3	4.6	1.8*	1.0	0.9	1.0	0.4*

[a] 40 mg HUMIRA administered every other week
[b] Visual analogue scale; 0 = best, 10 = worst
[c] Disability Index of the Health Assessment Questionnaire[2]; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity
* p<0.001, HUMIRA vs. placebo, based on mean change from baseline

Table 3: Radiographic Mean Changes Over 12 Months in Study III

	Placebo/MTX	HUMIRA/MTX 40 mg every other week	Placebo/MTX-HUMIRA/MTX (95% Confidence Interval*)	P-value**
Total Sharp score	2.7	0.1	2.6 (1.4, 3.8)	<0.001
Erosion score	1.6	0.0	1.6 (0.9, 2.2)	<0.001
JSN score	1.0	0.1	0.9 (0.3, 1.4)	0.002

*95% confidence intervals for the differences in change scores between MTX and HUMIRA.
**Based on rank analysis

Humira—Cont.

ical studies. No overall difference in effectiveness was observed between these subjects and younger subjects. The frequency of serious infection and malignancy among HUMIRA treated subjects over age 65 was higher than for those under age 65. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

ADVERSE REACTIONS

General

The most serious adverse reactions were (see **WARNINGS**):

- Serious Infections
- Neurologic Events
- Malignancies

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse events during the double-blind, placebo-controlled portion of Studies I, II, III and IV was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse events leading to discontinuation of HUMIRA were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in a broader patient population in clinical practice.

Infections

In placebo-controlled trials, the rate of infection was 1 per patient year in the HUMIRA treated patients and 0.9 per patient year in the placebo-treated patients. The infections consisted primarily of upper respiratory tract infections, bronchitis and urinary tract infections. Most patients continued on HUMIRA after the infection resolved. The incidence of serious infections was 0.04 per patient year in HUMIRA treated patients and 0.02 per patient year in placebo-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis (see **WARNINGS**).

Thirteen cases of tuberculosis, including miliary, lymphatic, peritoneal, and pulmonary were reported in clinical trials. Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. Six cases of invasive opportunistic infections caused by histoplasma, aspergillus, and nocardia were also reported in clinical trials (see **WARNINGS**).

Malignancies

Among 2468 rheumatoid arthritis patients treated in clinical trials with HUMIRA for a median of 24 months, 48 malignancies of various types were observed, including 10 patients with lymphoma. The Standardized Incidence Ratio (SIR) (ratio of observed rate to age-adjusted expected frequency in the general population) for malignancies was 1.0 (95% CI, 0.7, 1.3) and for lymphomas was 5.4 (95% CI, 2.6, 10.0). An increase of up to several fold in the rate of lymphomas has been reported in the rheumatoid arthritis patient population[4], and may be further increased in patients with more severe disease activity[5] (see **WARNINGS-Malignancies**). The other malignancies observed during use of HUMIRA were breast, colon-rectum, uterine-cervical, prostate, melanoma, gallbladder-bile ducts, and other carcinomas.

Autoantibodies

In the controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. One patient out of 2334 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patient improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Immunogenicity

Patients in Studies I, II, and III were tested at multiple time points for antibodies to adalimumab during the 6 to 12 month period. Approximately 5% (58 of 1,062) of adult rheumatoid arthritis patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant MTX had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse events was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab in an 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 adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

The data described below reflect exposure to HUMIRA in 2334 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies I, II, III, and IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week.

Table 4 summarizes events reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. Adverse event rates in patients treated with HUMIRA 40 mg weekly were similar to rates in patients treated with HUMIRA 40 mg every other week.

Table 4: Adverse Events Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Rheumatoid Arthritis Studies

	HUMIRA 40 mg subcutaneous Every Other Week (N=705)	Placebo (N=690)
Adverse Event (Preferred Term)	Percentage	Percentage
Respiratory		
Upper respiratory infection	17	13
Sinusitis	11	9
Flu syndrome	7	6
Gastrointestinal		
Nausea	9	8
Abdominal pain	7	4
Laboratory Tests*		
Laboratory test abnormal	8	7
Hypercholesterolemia	6	4
Hyperlipidemia	7	5
Hematuria	5	4
Alkaline phosphatase increased	5	3
Other		
Injection site pain	12	12
Headache	12	8
Rash	12	6
Accidental injury	10	8
Injection site reaction**	8	1
Back pain	6	4
Urinary tract infection	8	5
Hypertension	5	3

* Laboratory test abnormalities were reported as adverse events in European trials

** Does not include erythema and/or itching, hemorrhage, pain or swelling

Other Adverse Events

Other infrequent serious adverse events occurring at an incidence of less than 5% in patients treated with HUMIRA were:

Body As A Whole: Fever, infection, pain in extremity, pelvic pain, sepsis, surgery, thorax pain, tuberculosis reactivated

Cardiovascular System: Arrhythmia, atrial fibrillation, cardiovascular disorder, chest pain, congestive heart failure, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis, syncope, tachycardia, vascular disorder

Collagen Disorder: Lupus erythematosus syndrome

Digestive System: Cholecystitis, cholelithiasis, esophagitis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, hepatic necrosis, vomiting

Endocrine System: Parathyroid disorder

Hemic And Lymphatic System: Agranulocytosis, granulocytopenia, leukopenia, lymphoma like reaction, pancytopenia, polycythemia

Metabolic And Nutritional Disorders: Dehydration, healing abnormal, ketosis, paraproteinemia, peripheral edema

Musculo—Skeletal System: Arthritis, bone disorder, bone fracture (not spontaneous), bone necrosis, joint disorder, muscle cramps, myasthenia, pyogenic arthritis, synovitis, tendon disorder

Neoplasia: Adenoma, carcinomas such as breast, gastrointestinal, skin, urogenital, and others; lymphoma, and melanoma.

Nervous System: Confusion, multiple sclerosis, paresthesia, subdural hematoma, tremor

Respiratory System: Asthma, bronchospasm, dyspnea, lung disorder, lung function decreased, pleural effusion, pneumonia

Skin And Appendages: Cellulitis, erysipelas, herpes zoster

Special Senses: Cataract

Thrombosis: Thrombosis leg

Urogenital System: Cystitis, kidney calculus, menstrual disorder, pyelonephritis

OVERDOSAGE

The maximum tolerated dose of HUMIRA has not been established in humans. Multiple doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

DOSAGE AND ADMINISTRATION

The recommended dose of HUMIRA for adult patients with rheumatoid arthritis is 40 mg administered every other week as a subcutaneous injection. MTX, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics or other DMARDs may be continued during treatment with HUMIRA. Some patients not taking concomitant MTX may derive additional benefit from increasing the dosing frequency of HUMIRA to 40 mg every week.

HUMIRA is intended for use under the guidance and supervision of a physician. Patients may self-inject HUMIRA if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in injection technique.

The solution in the syringe should be carefully inspected visually for particulate matter and discoloration prior to subcutaneous administration. If particulates and discolorations are noted, the product should not be used. HUMIRA does not contain preservatives; therefore, unused portions of drug remaining from the syringe should be discarded. NOTE: The needle cover of the syringe contains dry rubber (latex), which should not be handled by persons sensitive to this substance.

Patients using the pre-filled syringes should be instructed to inject the full amount in the syringe (0.8 mL), which provides 40 mg of HUMIRA, according to the directions provided in the Patient Information Leaflet.

Injection sites should be rotated and injections should never be given into areas where the skin is tender, bruised, red or hard (see **PATIENT INFORMATION LEAFLET**).

Instructions For Activating the Needle Stick Device: Cartons for institutional use contain a syringe and needle with a needle protection device (see **HOW SUPPLIED**). To activate the needle stick protection device after injection, hold the syringe in one hand and, with the other hand, slide the outer protective shield over the exposed needle until it locks into place.

Storage and Stability

Do not use beyond the expiration date on the container. HUMIRA must be refrigerated at 2–8° C (36–46° F). DO NOT FREEZE. Protect the pre-filled syringe from exposure to light. Store in original carton until time of administration.

HOW SUPPLIED

HUMIRA™ (adalimumab) is supplied in pre-filled syringes as a preservative-free, sterile solution for subcutaneous administration. The following packaging configurations are available:

Patient Use Syringe Carton

HUMIRA is dispensed in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use, 1 mL pre-filled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg (0.8 mL) of HUMIRA. **The NDC number is 0074-3799-02.**

Institutional Use Syringe Carton

Each carton contains two alcohol preps and one tray. Each dose tray consists of a single use, 1 mL pre-filled glass syringe with a fixed 27 gauge ½ inch needle (with a needle stick protection device) providing 40 mg (0.8 mL) of HUMIRA. **The NDC number is 0074-3799-01.**

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Revised: January, 2003
ABBOTT LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.
U.S. Govt. Lic. No. 0043

HUMIRA™ (adalimumab) Patient Information

Read this leaflet carefully before you start taking HUMIRA (**hu-mare-ah**). You should also read this leaflet each time you get your prescription refilled, in case something has changed. The information in this leaflet does not take the placebo of talking with your doctor before you start taking this medicine and at check ups. Talk to your doctor if you have any questions about your treatment with HUMIRA.

What is HUMIRA?

HUMIRA is a medicine that is used in people with moderate to severe rheumatoid arthritis (RA). RA is an inflammatory disease of the joints. People with RA are usually given other medicines for their disease before they are given HUMIRA. HUMIRA is for people with RA who have not responded well enough to these other medicines.

How does HUMIRA work?

HUMIRA is a medicine called a *TNF blocker*, that is a type of protein that blocks the action of a substance your body makes called TNF-alpha. TNF-alpha (tumor necrosis factor alpha) is made by your body's immune system. People with RA have too much of it in their bodies. The extra TNF-alpha in your body can attack normal healthy body tissues and cause inflammation especially in the tissues in your bones, cartilage, and joints. HUMIRA helps reduce the signs and symptoms of RA (such as pain and swollen joints) and may help prevent further damage to your bones and joints.

HUMIRA can block the damage that too much TNF-alpha can cause, and it can also lower your body's ability to fight infections. Taking HUMIRA can make your more prone to getting infections or make any infection you have worse.

Who should not take HUMIRA?

You should not take HUMIRA if you have an allergy to any of the ingredients in HUMIRA (sodium phosphate, sodium citrate, citric acid, mannitol, and polysorbate 80). The needle cover on the pre-filled syringe contains dry natural rubber. Tell your doctor if you have any allergies to rubber or latex.

Before you start taking HUMIRA you should tell your doctor if you have or have had any of the following:

- Any kind of infection including an infection that is in only one place in your body (such as an open cut or sore), or an infection that is in your whole body (such as the flu). Having an infection could put you at risk for serious side effects from HUMIRA. If you are unsure, please ask your doctor.
- A history of infections that keep coming back or other conditions that might increase your risk of infections.
- If you have ever had tuberculosis (TB), or if you have been in close contact with someone who has had tuberculosis. If you develop any of the symptoms of tuberculosis (a dry cough that doesn't go away, weight loss, fever, night sweats) call your doctor right away. Your doctor will need to examine you for TB and perform a skin test.
- If you experience any numbness or tingling or have or have ever had a disease that affects your nervous system like multiple sclerosis.
- If you are scheduled to have major surgery.
- If you are scheduled to be vaccinated for anything.

If you are not sure or have any questions about any of this information, ask your doctor.

What important information do I need to know about side effects with HUMIRA?

Any medicine can have side effects. Like all medicines that affect your immune system, HUMIRA can cause serious side effects. The possible serious side effects include:

Serious infections: There have been rare cases where patients taking HUMIRA or other TNF-blocking agents have developed serious infections, including tuberculosis (TB) and infections caused by bacteria or fungi. Some patients have died when the bacteria that cause infections have spread throughout their body (sepsis).

Nervous system diseases: There have been rare cases of disorders that affect the nervous system of people taking HUMIRA or other TNF blockers. Signs that you could be experiencing a problem affecting your nervous system include: numbness or tingling, problems with your vision, weakness in your legs and dizziness.

Malignancies: There have been very rare cases of certain kinds of cancer in patients taking HUMIRA or other TNF blockers. People with more serious RA that have had the disease for a long time may have a higher than average risk of getting a kind of cancer that affects the lymph system, called lymphoma. If you take HUMIRA or other TNF blockers, your risk may increase.

Lupus-like symptoms: Some patients have developed lupus-like symptoms that got better after their treatment was stopped. If you have chest pains that do not go away, shortness of breath, joint pain or a rash on your cheeks or arms that is sensitive to the sun, call your doctor right away. Your doctor may decide to stop your treatment.

Allergic reactions: If you develop a severe rash, swollen face or difficulty breathing while taking HUMIRA, call your doctor right away.

What are the other more common side effects with HUMIRA?

Many patients experience a reaction where the injection was given. These reactions are usually mild and include redness, rash, swelling, itching or bruising. Usually, the rash will go away within a few days. If the skin around the area where you injected HUMIRA still hurts or is swollen, try using a towel soaked with cold water on the injection site. If you have pain, redness or swelling around the injection site that doesn't go away within a few days or gets worse, call your doctor right away. Other side effects are upper respiratory infections (sinus infections), headache and nausea.

Can I take HUMIRA if I am pregnant or breast-feeding?

HUMIRA has not been studied in pregnant women or nursing mothers, so we don't know what the effects are on pregnant women or nursing babies. You should tell your doctor if you are pregnant, become pregnant or are thinking about becoming pregnant.

Can I take HUMIRA if I am taking other medicines for my RA or other conditions?

Yes, you can take other medicines provided your doctor has prescribed them, or has told you it is ok to take them while you are taking HUMIRA. It is important that you tell your doctor about any other medicines you are taking for other conditions (for example, high blood pressure medicine) before you start taking HUMIRA.

You should also tell your doctor about any over-the-counter drugs, herbal medicines and vitamin and mineral supplements you are taking.

You should not take HUMIRA with other TNF blockers. If you have questions, ask your doctor.

How do I take HUMIRA?

You take HUMIRA by giving yourself an injection under the skin once every other week, or more frequently (every week) if your doctor tells you to. If you accidentally take more HUMIRA than you were told to take, you should call your doctor. Make sure you have been shown how to inject HUMIRA before you do it yourself. You can call your doctor or the HUMIRA Patient Resource Center at 1-800 4HUMIRA (448-6472) if you have any questions about giving yourself an injection. Someone you know can also help you with your injection. Remember to take this medicine just as your doctor has told you and do not miss any doses.

What should I do if I miss a dose of HUMIRA?

If you forgot to take HUMIRA when you are supposed to, inject the next dose right away. Then, take your next dose when your next scheduled dose is due. This will put you back on schedule.

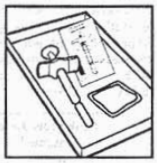
Is one time better than another for taking HUMIRA?

Always follow your doctor's instructions about when and how often to take HUMIRA. To help you remember when to take HUMIRA, you can mark your calendar ahead of time with the stickers provided in the back of the patient information booklet. For other information and ideas you can enroll in a patient support program by calling the HUMIRA Patient Resource Center at 1-800-4HUMIRA (448-6472).

What do I need to do to prepare and give an injection of HUMIRA?

1) Setting up for an injection

- Find a clean flat working surface.
- Remove one dose tray containing a pre-filled syringe of HUMIRA from the refrigerator. Do not use a pre-filled syringe that is frozen or if it has been left in direct sunlight. You will need the following items for each dose:
  - A dose tray containing a pre-filled syringe of HUMIRA with a fixed needle
  - 1 alcohol prep
  - The card with the drawing of the pre-filled syringe



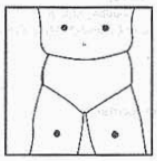
If you do not have all of the pieces you need to give yourself an injection, call your pharmacist. Use only the items provided in the box your HUMIRA comes in.

- Check and make sure the name HUMIRA appears on the dose tray and pre-filled syringe label.
- Check the expiration date on the dose tray label and pre-filled syringe to make sure the date has not passed. Do not use a pre-filled syringe if the date has passed.
- Make sure the liquid in the pre-filled syringe is clear and colorless. Do not use a pre-filled syringe if the liquid is cloudy or discolored or has flakes or particles in it.
- Have a puncture proof container nearby for disposing of used needles and syringes.

FOR YOUR PROTECTION, IT IS IMPORTANT THAT YOU FOLLOW THESE INSTRUCTIONS.

2) Choosing and preparing an injection site

- Wash your hands thoroughly
- Choose a site on the front of your thighs or your abdomen. If you choose your abdomen, you should avoid the area 2 inches around your navel.
- Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before. Do **NOT** inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks.
- You may find it helpful to keep notes on the location of previous injections.



- Wipe the site where HUMIRA is to be injected with an alcohol prep, using a circular motion. Do NOT touch this area again until you are ready to inject.

3) How to prepare your HUMIRA dose for injection with a Pre-filled Syringe

- Hold the syringe upright with the needle facing down. Take the card with the drawing of the syringe and hold it next to the real syringe so the drawing and the real syringe are side-by-side. Check to make sure that the amount of liquid in the syringe is the same or very close to the 0.8 mL arrow shown on the card with the drawing of the pre-filled syringe. The top of the liquid may be curved as shown in the drawing. The 0.8 mL arrow should point near the middle of the curved liquid. If the real syringe does not have the correct amount of liquid, DO NOT USE THAT SYRINGE. Call your pharmacist.
- Remove the needle cover taking care not to touch the needle with your fingers or allow it to touch any surface.
- Turn the syringe so the needle is facing up and slowly push the plunger in to push the air in the syringe out through the needle. If a small drop of liquid comes out of the needle that is ok.

4) Injecting HUMIRA

- With your other hand, gently pinch the cleaned area of skin and hold it firmly. Hold the syringe like a pencil at about a 45° angle to the skin.

- With a quick, short, "dart-like" motion, push the needle into the skin.
- After the needle is in, let go of the skin. Pull back slightly on the plunger, if blood appears in the syringe it means that you have entered a blood vessel. Do not inject HUMIRA. Withdraw the needle and repeat the steps to choose and clean a new injection site. DO NOT use the same syringe; discard it in your puncture proof container. If no blood appears, slowly push the plunger all the way in until all of the HUMIRA is injected.
- When the syringe is empty, remove the needle from the skin keeping it at the same angle it was when it was inserted.
- Press a cotton ball over the injection site and hold it for 10 seconds. Do **NOT** rub the injection site. If you have slight bleeding, do not be alarmed.
- Dispose of the syringe immediately.

5) Disposing of syringes and needles

You should always check with your healthcare provider for instructions on how to properly dispose of used needles and syringes. You should follow any special state or local laws regarding the proper disposal of needles and syringes. **DO NOT throw the needle or syringe in the household trash or recycle.**

- Place the used needles and syringes in a container made specially for disposing of used syringes and needles (called a "Sharps" container), or a hard plastic container with a screw-on cap or metal container with a plastic lid labeled *"Used Syringes"*. Do not use glass or clear plastic containers.
- Always keep the container out of the reach of children.
- When the container is about two-thirds full, tape the cap or lid down so it does not come off and dispose of it as instructed by your doctor, nurse or pharmacist. DO NOT THROW THE CONTAINER IN THE HOUSEHOLD TRASH OR RECYCLE.
- Used preps may be placed in the trash, unless otherwise instructed by your doctor, nurse or pharmacist. The dose tray and cover may be recycled.

HOW DO I STORE HUMIRA?

Store at 2°C–8°C/36–46°F (in a refrigerator) in the original container until it is used. Protect from light. DO NOT FREEZE HUMIRA. Refrigerated HUMIRA remains stable until the expiration date printed on the pre-filled syringe. If you need to take it with you, such as when traveling, store it in a cool carrier with an ice pack and protect it from light.

Continued on next page

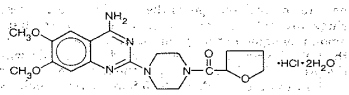
Keep HUMIRA, injection supplies, and all other medicines out of the reach of children.
Revised: January, 2003
Ref: 03-5236-R2
ABBOTT LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.
Shown in Product Identification Guide, page 303

HYTRIN®
(terazosin hydrochloride)
Capsules

℞

DESCRIPTION

HYTRIN (terazosin hydrochloride), an alpha-1-selective adrenoceptor blocking agent, is a quinazoline derivative represented by the following chemical name and structural formula: (RS)-Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetra-hydro-2-furanyl)carbonyl]-, monohydrochloride, dihydrate.



Terazosin hydrochloride is a white, crystalline substance, freely soluble in water and isotonic saline and has a molecular weight of 459.93. HYTRIN capsules (terazosin hydrochloride capsules) for oral ingestion are supplied in four dosage strengths containing terazosin hydrochloride equivalent to 1 mg, 2 mg, 5 mg, or 10 mg of terazosin.

Inactive Ingredients:
1 mg capsules: gelatin, glycerin, iron oxide, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin.
2 mg capsules: D&C yellow No. 10, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin.
5 mg capsules: D&C red No. 28, FD&C red No. 40, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin.
10 mg capsules: FD&C blue No. 1, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin.

CLINICAL PHARMACOLOGY

Pharmacodynamics:

A. Benign Prostatic Hyperplasia (BPH)

The symptoms associated with BPH are related to bladder outlet obstruction, which is comprised of two underlying components: a static component and a dynamic component. The static component is a consequence of an increase in prostate size. Over time, the prostate will continue to enlarge. However, clinical studies have demonstrated that the size of the prostate does not correlate with the severity of BPH symptoms or the degree of urinary obstruction. The dynamic component is a function of an increase in smooth muscle tone in the prostate and bladder neck, leading to constriction of the bladder outlet. Smooth muscle tone is mediated by sympathetic nervous stimulation of alpha-1 adrenoceptors, which are abundant in the prostate, prostatic capsule and bladder neck. The reduction in symptoms and improvement in urine flow rates following administration of terazosin is related to relaxation of smooth muscle produced by blockade of alpha-1 adrenoceptors in the bladder neck and prostate. Because there are relatively few alpha-1 adrenoceptors in the bladder body, terazosin is able to reduce the bladder outlet obstruction without affecting bladder contractility.

Terazosin has been studied in 1222 men with symptomatic BPH. In three placebo-controlled studies, symptom evaluation and uroflowmetric measurements were performed approximately 24 hours following dosing. Symptoms were quantified using the Boyarsky Index. The questionnaire evaluated both obstructive (hesitancy, intermittency, terminal dribbling, impairment of size and force of stream, sensation of incomplete bladder emptying) and irritative (nocturia, daytime frequency, urgency, dysuria) symptoms by rating each of the 9 symptoms from 0-3, for a total score of 27 points. Results from these studies indicated that terazosin statistically significantly improved symptoms and peak urine flow rates over placebo as follows:

[See table below]

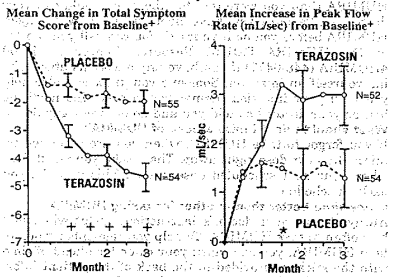
In all three studies, both symptom scores and peak urine flow rates showed statistically significant improvement from baseline in patients treated with terazosin from week 2 (or the first clinic visit) and throughout the study duration.

Analysis of the effect of terazosin on individual urinary symptoms demonstrated that compared to placebo, terazosin significantly improved the symptoms of hesitancy, intermittency, impairment in size and force of urinary stream, sensation of incomplete emptying, terminal dribbling, daytime frequency and nocturia.

Global assessments of overall urinary function and symptoms were also performed by investigators who were blinded to patient treatment assignment. In studies 1 and 3, patients treated with terazosin had a significantly ($p \leq 0.001$) greater overall improvement compared to placebo treated patients.

In a short term study (Study 1), patients were randomized to either 2, 5 or 10 mg of terazosin or placebo. Patients randomized to the 10 mg group achieved a statistically significant response in both symptoms and peak flow rate compared to placebo (Figure 1).

Figure 1
Study 1



+ for baseline values see above table
* $p \leq 0.05$, compared to placebo group

In a long-term, open-label, non-placebo controlled clinical trial, 181 men were followed for 2 years and 58 of these men were followed for 30 months. The effect of terazosin on urinary symptom scores and peak flow rates was maintained throughout the study duration (Figures 2 and 3):

[See figure 2 at top of next column]

[See figure 3 at top of next column]

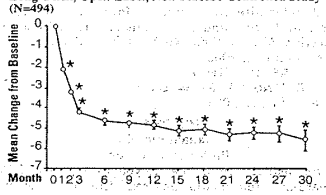
In this long-term trial, both symptom scores and peak urinary flow rates showed statistically significant improvement suggesting a relaxation of smooth muscle cells.

Although blockade of alpha-1 adrenoceptors also lowers blood pressure in hypertensive patients with increased peripheral vascular resistance, terazosin treatment of normotensive men with BPH did not result in a clinically significant blood pressure lowering effect.

	Symptom Score (Range 0-27)			Peak Flow Rate (mL/sec)		
	N	Mean Baseline	Mean Change (%)	N	Mean Baseline	Mean Change (%)
Study 1 (10 mg)[a]						
Titration to fixed dose (12 wks)						
Placebo	55	9.7	-2.3 (24)	54	10.1	+1.0 (10)
Terazosin	54	10.1	-4.5 (45)*	52	8.8	+3.0 (34)*
Study 2 (2, 5, 10, 20 mg)[b]						
Titration to response (24 wks)						
Placebo	89	12.5	-3.8 (30)	88	8.8	+1.4 (16)
Terazosin	85	12.2	-5.3 (43)*	84	8.4	+2.9 (35)*
Study 3 (1, 2, 5, 10 mg)[c]						
Titration to response (24 wks)						
Placebo	74	10.4	-1.1 (11)	74	8.8	+1.2 (14)
Terazosin	73	10.9	-4.6 (42)*	73	8.6	+2.6 (30)*

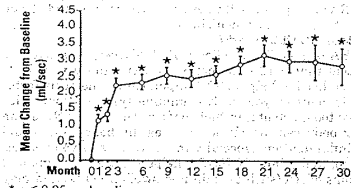
[a] Highest dose 10 mg shown.
[b] 23% of patients on 10 mg, 41% of patients on 20 mg.
[c] 67% of patients on 10 mg.
* Significantly ($p \leq 0.05$) more improvement than placebo.

Figure 2
Mean Change in Total Symptom Score from Baseline
Long-Term, Open-Label, Non-Placebo Controlled Study
(N=494)



* $p \leq 0.05$ vs. baseline
mean baseline = 10.7

Figure 3
Mean Change in Peak Flow Rate from Baseline
Long-Term, Open-Label, Non-Placebo Controlled Study
(N=494)



* $p \leq 0.05$ vs. baseline
mean baseline = 9.9

Mean Changes in Blood Pressure from Baseline to Final Visit in all Double-Blind, Placebo-Controlled Studies

		Normotensive Patients DBP ≤ 90 mm Hg		Hypertensive Patients DBP > 90 mm Hg	
	Group	N	Mean Change	N	Mean Change
SBP (mm Hg)	Placebo	293	-0.1	45	-5.8
	Terazosin	519	-3.3*	65	-14.4*
DBP (mm Hg)	Placebo	293	+0.4	45	-7.1
	Terazosin	519	-2.2*	65	-15.1*

* $p \leq 0.05$ vs. placebo

B. Hypertension

In animals, terazosin causes a decrease in blood pressure by decreasing total peripheral vascular resistance. The vasodilatory hypotensive action of terazosin appears to be produced mainly by blockade of alpha-1 adrenoceptors. Terazosin decreases blood pressure gradually within 15 minutes following oral administration.

Patients in clinical trials of terazosin were administered once daily (the great majority) and twice daily regimens with total doses usually in the range of 5-20 mg/day, and had mild (about 77%, diastolic pressure 95-105 mmHg) or moderate (23%, diastolic pressure 105-115 mmHg) hypertension. Because terazosin, like all alpha antagonists, can cause unusually large falls in blood pressure after the first dose or first few doses, the initial dose was 1 mg in virtually all trials, with subsequent titration to a specified fixed dose or titration to some specified blood pressure end point (usually a supine diastolic pressure of 90 mmHg).

Blood pressure responses were measured at the end of the dosing interval (usually 24 hours) and effects were shown to persist throughout the interval, with the usual supine responses 5-10 mmHg systolic and 3.5-8 mmHg diastolic greater than placebo. The responses in the standing position tended to be somewhat larger, by 1-3 mmHg, although this was not true in all studies. The magnitude of the blood pressure responses was similar to prazosin and less than hydrochlorothiazide (in a single study of hypertensive patients). In measurements 24 hours after dosing, heart rate was unchanged.

Limited measurements of peak response (2-3 hours after dosing) during chronic terazosin administration indicate that it is greater than about twice the trough (24 hour) response, suggesting some attenuation of response at 24 hours, presumably due to a fall in blood terazosin concentrations at the end of the dose interval. This explanation is not established with certainty, however, and is not consistent with the similarity of blood pressure response to once daily and twice daily dosing and with the absence of an observed dose-response relationship over a range of 5-20 mg, i.e., if blood concentrations had fallen to the point of providing less than full effect at 24 hours, a shorter dosing interval or larger dose should have led to increased response.

Further dose response and dose duration studies are being carried out. Blood pressure should be measured at the end

the patient's condition, sodium intake, and responsiveness. A decision to change the daily dose should be based on the results of thorough clinical and laboratory evaluations. If antihypertensive drugs or diuretics are given concurrently with ZAROXOLYN, more careful dosage adjustment may be necessary. For patients who tend to experience paroxysmal nocturnal dyspnea, it may be advisable to employ a larger dose to ensure prolongation of diuresis and saluresis for a full 24-hour period.

Treatment of Hypertension: The time interval required for the initial dosage regimen to show effect may vary from three or four days to three to six weeks in the treatment of elevated blood pressure. Doses should be adjusted at appropriate intervals to achieve maximum therapeutic effect.

HOW SUPPLIED

ZAROXOLYN Tablets (metolazone tablets, USP) are shallow biconvex, round tablets, and are available in three strengths:

2½ mg, pink, debossed "ZAROXOLYN" on one side, and "2½" on reverse side.

NDC 53014-975-71 Bottle of 100's
NDC 53014-975-90 Bottle of 1000's
NDC 53014-975-72 Carton of 100's, unit dose

5 mg, blue, debossed "ZAROXOLYN" on one side, and "5" on reverse side.

NDC 53014-850-71 Bottle of 100's
NDC 53014-850-90 Bottle of 1000's
NDC 53014-850-72 Carton of 100's, unit dose

10 mg, yellow, debossed "ZAROXOLYN" on one side, and "10" on reverse side.

NDC 53014-835-71 Bottle of 100's
NDC 53014-835-90 Bottle of 1000's
NDC 53014-835-72 Carton of 100's, unit dose

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature]. Protect from light. Keep out of the reach of children.

Celltech Pharmaceuticals, Inc.
Rochester, NY 14623 USA
® Celltech Manufacturing, Inc. Rev. 2/03

EDUCATIONAL MATERIAL

For educational information, please write to Celltech Pharmaceuticals, Inc., PO Box 31766, Rochester, NY 14603.

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Medical Emergency Contact:
Ph: 1-(800)-457-6399

For Medical Information/Adverse Experience Reporting Contact:
Medical Information
Ph: (800) 457-6399

REMICADE®

[rĕm-ĭ-kăd]
(infliximab)
for IV injection

WARNING
RISK OF INFECTIONS
TUBERCULOSIS (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL (SEE WARNINGS).
PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION WITH A TUBERCULIN SKIN TEST.[1] TREATMENT OF LATENT TUBERCULOSIS INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE.

DESCRIPTION

REMICADE is a chimeric IgG1κ monoclonal antibody with an approximate molecular weight of 149,100 daltons. It is composed of human constant and murine variable regions. Infliximab binds specifically to human tumor necrosis factor alpha (TNFα) with an association constant of 10^{10} M^{-1}. Infliximab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses. REMICADE is supplied as a sterile, white, lyophilized

Table 1
PERCENTAGE OF PATIENTS WHO ACHIEVED AN ACR RESPONSE AT WEEKS 30 AND 54

Response	Placebo + MTX (n=88)	REMICADE + MTX 3 mg/kg[a] q 8 wks (n=86)	REMICADE + MTX 3 mg/kg[a] q 4 wks (n=86)	REMICADE + MTX 10 mg/kg[a] q 8 wks (n=87)	REMICADE + MTX 10 mg/kg[a] q 4 wks (n=81)
ACR 20					
Week 30	20%	50%	50%	52%	58%
Week 54	17%	42%	48%	59%	59%
ACR 50					
Week 30	5%	27%	29%	31%	26%
Week 54	9%	21%	34%	40%	38%
ACR 70					
Week 30	0%	8%	11%	18%	11%
Week 54	2%	11%	18%	26%	19%

[a] $p<0.05$ for each outcome compared to placebo

Table 2
COMPONENTS OF ACR 20 AT BASELINE AND 54 WEEKS

Parameter (medians)	Placebo + MTX (n=88) Baseline	Placebo + MTX (n=88) Week 54	REMICADE + MTX[a] (n=340) Baseline	REMICADE + MTX[a] (n=340) Week 54
No. of Tender Joints	24	16	32	8
No. of Swollen Joints	19	13	20	7
Pain[b]	6.7	6.1	6.8	3.3
Physician's Global Assessment[b]	6.5	5.2	6.2	2.1
Patient's Global Assessment[b]	6.2	6.2	6.3	3.2
Disability Index (HAQ)[c]	1.8	1.5	1.8	1.3
CRP (mg/dL)	3.0	2.3	2.4	0.6

[a] All doses/schedules of REMICADE + MTX
[b] Visual Analog Scale (0=best, 10=worst)
[c] Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3=worst)

Table 3
RADIOGRAPHIC CHANGE FROM BASELINE TO WEEK 54

Median (10, 90 percentiles)	Placebo + MTX (n=64)	REMICADE + MTX 3 mg/kg q 8 wks (n=71)	REMICADE + MTX 3 mg/kg q 4 wks (n=71)	REMICADE + MTX 10 mg/kg q 8 wks (n=77)	REMICADE + MTX 10 mg/kg q 4 wks (n=66)	p-value[a]
Total Score						
Baseline	55 (14, 188)	57 (15, 187)	45 (8, 162)	56 (6, 143)	43 (7, 178)	
Change from baseline	4.0 (-1.0, 19.0)	0.5 (-3.0, 5.5)	0.1 (-5.2, 9.0)	0.5 (-4.8, 5.0)	-0.5 (-5.7, 4.0)	p<0.001
Erosion Score						
Baseline	25 (8, 110)	29 (9, 100)	22 (3, 91)	22 (3, 80)	26 (4, 104)	
Change from baseline	2.0 (-1.0, 9.7)	0.0 (-3.0, 4.3)	-0.3 (-3.1, 2.5)	0.5 (-3.0, 2.5)	-0.5 (-2.7, 2.5)	p<0.001
JSN Score						
Baseline	26 (3, 88)	29 (4, 80)	20 (3, 83)	24 (1, 79)	2[F] (3, 77)	
Change from baseline	1.5 (-0.8, 8.0)	0.0 (-2.5, 4.5)	0.0 (-3.4, 5.0)	0.0 (-3.0, 2.5)	0.0 (-3.0, 3.5)	p<0.001

[a] For comparisons of each dose against placebo

with 10 mL of Sterile Water for Injection, USP, the resulting pH is approximately 7.2. Each single-use vial contains 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate, monohydrate, and 6.1 mg dibasic sodium phosphate, dihydrate. No preservatives are present.

CLINICAL PHARMACOLOGY

General

Infliximab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors.[2,3] Infliximab does not neutralize TNFβ (lymphotoxin α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab can be lysed *in vitro*[3] or *in vivo*.[4] Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes and epithelial cells. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab prevents disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allows eroded joints to heal.

Pharmacodynamics

Elevated concentrations of TNFα have been found in the joints of rheumatoid arthritis patients and the stools of Crohn's disease patients and correlate with elevated disease activity. In rheumatoid arthritis, treatment with REMICADE reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion [E-selectin, intercellular molecule-1 (VCAM-1)], chemoattraction [IL-8 and monocyte chemotactic protein (MCP-1)] and tissue degradation [matrix metalloproteinase (MMP) 1 and 3]. In Crohn's disease, treatment with REMICADE reduced infiltration of inflammatory cells and TNFα production in inflamed areas of the intestine, and reduced the proportion of mononuclear cells from the lamina propria able to express TNFα and interferon. After treatment with REMICADE, patients with rheumatoid arthritis or Crohn's disease exhibited decreased levels of serum IL-6 and C-reactive protein (CRP) compared to baseline. Peripheral blood lymphocytes from REMICADE-treated patients showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared to cells from untreated patients.

Pharmacokinetics

Single intravenous (IV) infusions of 3 mg/kg to 20 mg/kg showed a linear relationship between the dose administered and the maximum serum concentration. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment. Median pharmacokinetic results for doses of 3 mg/kg to 10 mg/kg in rheumatoid arthritis and 5 mg/kg in Crohn's disease indicate that the terminal half-life of infliximab is 8.0 to 9.5 days.

Following an initial dose of REMICADE, repeated infusions at 2 and 6 weeks resulted in predictable concentration-time profiles following each treatment. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 8-week intervals. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight, or gender. It is not known if there are differences in clearance or volume of distribution in patients with marked impairment of hepatic or renal function.

A pediatric Crohn's disease pharmacokinetic study was conducted in 21 patients aged 11 to 17 years old. No notable differences in single-dose pharmacokinetic parameters were observed between pediatric and adult Crohn's disease patients (see *PRECAUTIONS, Pediatric Use*).

Remicade—Cont.

CLINICAL STUDIES

Rheumatoid Arthritis

The safety and efficacy of REMICADE when given in conjunction with methotrexate (MTX) were assessed in a multicenter, randomized, double-blind, placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with MTX (the Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy or ATTRACT). Patients enrolled had a median age of 54 years, median disease duration of 8.4 years, median swollen and tender joint count of 20 and 31 respectively, and were on a median dose of 15 mg/wk of MTX. Patients received either placebo + MTX or one of 4 doses/schedules of REMICADE + MTX: 3 mg/kg or 10 mg/kg of REMICADE by IV infusion at weeks 0, 2 and 6 followed by additional infusions every 4 or 8 weeks in combination with MTX. Concurrent use of stable doses of folic acid, oral corticosteroids (≤10 mg/day) and/or nonsteroidal anti-inflammatory drugs was also permitted.

Data on use of REMICADE without concurrent MTX are limited (see *ADVERSE REACTIONS, Immunogenicity*).[5,6]

Clinical response

All doses/schedules of REMICADE + MTX resulted in improvement in signs and symptoms as measured by the American College of Rheumatology response criteria (ACR 20) with a higher percentage of patients achieving an ACR 20, 50 and 70 compared to placebo + MTX (Table 1). This improvement was observed at week 2 and maintained through week 102. Greater effects on each component of the ACR 20 were observed in all patients treated with REMICADE + MTX compared to placebo + MTX (Table 2).

Approximately 10% of patients treated with REMICADE achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period compared to 0% of placebo-treated patients (p≤0.018).

[See table 1 at top of previous page]

[See table 2 at top of previous page]

Radiographic response

Structural damage in both hands and feet was assessed radiographically at week 54 by the change from baseline in the van der Heijde-modified Sharp score, a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet.[7] Approximately 80% of patients had paired x-ray data at 54 weeks and approximately 70% at 102 weeks. The inhibition of progression of structural damage was observed at 54 weeks (Table 3) and maintained through 102 weeks.

[See table 3 at top of previous page]

Physical function response

Physical function and disability were assessed using the Health Assessment Questionnaire (HAQ) and the general health-related quality of life questionnaire SF-36. All doses/schedules of REMICADE + MTX showed significantly greater improvement from baseline in HAQ and SF-36 physical component summary score averaged over time through week 54 compared to placebo + MTX, and no worsening in the SF-36 mental component summary score.

The median (interquartile range) improvement from baseline to week 54 in HAQ was 0.1 (−0.1, 0.5) for the placebo + MTX group and 0.4 (0.1, 0.9) for REMICADE + MTX (p<0.001). Both HAQ and SF-36 effects were maintained through week 102. Approximately 80% of patients in all doses/schedules of REMICADE + MTX remained in the trial through 102 weeks.

Active Crohn's Disease

The safety and efficacy of single and multiple doses of REMICADE were assessed in two randomized, double-blind, placebo-controlled clinical studies in 653 patients with moderate to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] ≥220 and ≤400) with an inadequate response to prior conventional therapies. Concomitant stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents were permitted and 92% of patients continued to receive at least one of these medications.

In the single-dose trial[8] of 108 patients, 16% (4/25) of placebo patients achieved a clinical response (decrease in CDAI ≥70 points) at week 4 vs. 81% (22/27) of patients receiving 5 mg/kg REMICADE (p<0.001, two-sided, Fisher's Exact test). Additionally, 4% (1/25) of placebo patients and 48% (13/27) of patients receiving 5 mg/kg REMICADE achieved clinical remission (CDAI <150) at week 4.

In a multidose trial (ACCENT I),[9] 545 patients received 5 mg/kg at week 0 and were then randomized to one of three treatment groups; the placebo maintenance group received placebo at weeks 2 and 6, and then every 8 weeks; the 5 mg/kg maintenance group received 5 mg/kg at weeks 2 and 6, and then every 8 weeks; and the 10 mg/kg maintenance group received 5 mg/kg at weeks 2 and 6, and then 10 mg/kg every 8 weeks. Patients in response at week 2 were randomized and analyzed separately from those not in response at week 2. Corticosteroid taper was permitted after week 6.

At week 2, 57% (311/545) of patients were in clinical response. At week 30, a significantly greater proportion of these patients in the 5 mg/kg and 10 mg/kg maintenance groups achieved clinical remission compared to patients in the placebo maintenance group (Table 4).

Additionally, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg infliximab maintenance groups were in clinical remission and were able to discontinue corticosteroid use compared to patients in the placebo maintenance group at week 54 (Table 4).

[See table 4 below]

Patients in the infliximab maintenance groups (5 mg/kg and 10 mg/kg) had a longer time to loss of response than patients in the placebo maintenance group (Figure 1). At weeks 30 and 54, significant improvement from baseline was seen among the 5 mg/kg and 10 mg/kg infliximab-treated groups compared to the placebo group in the disease specific inflammatory bowel disease questionnaire (IBDQ), particularly the bowel and systemic components, and in the physical component summary score of the general health-related quality of life questionnaire SF-36.

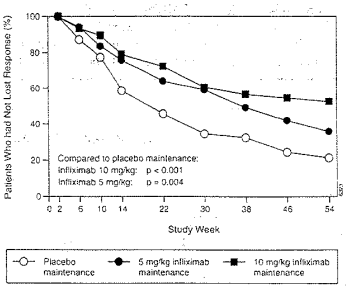

Figure 1
Kaplan-Meier estimate of the proportion of patients who had not lost response through week 54

In a subset of 78 patients who had mucosal ulceration at baseline and who participated in an endoscopic substudy, 13 of 43 patients in the infliximab maintenance group had endoscopic evidence of mucosal healing compared to 1 of 28 patients in the placebo group at week 10. Of the infliximab-treated patients showing mucosal healing at week 10, 9 of 12 patients also showed mucosal healing at week 54.

Patients who achieved a response and subsequently lost response were eligible to receive infliximab on an episodic basis at a dose that was 5 mg/kg higher than the dose to which they were randomized. The majority of such patients responded to the higher dose. Among patients who were not in response at week 2, 59% (92/157) of infliximab maintenance patients responded by week 14 compared to 51% (39/77) of placebo maintenance patients. Among patients who did not respond by week 14, additional therapy did not result in significantly more responses (see *DOSAGE AND ADMINISTRATION*).

Fistulizing Crohn's Disease

The safety and efficacy of REMICADE were assessed in 2 randomized, double-blind, placebo-controlled studies in patients with fistulizing Crohn's disease with fistula(s) that were of at least 3 months duration. Concurrent use of stable doses of corticosteroids, 5-ASA, antibiotics, MTX, 6-MP and/or AZA was permitted.

In the first trial,[10] 94 patients received three doses of either placebo or REMICADE at weeks 0, 2 and 6. Fistula response (≥50% reduction in number of enterocutaneous fistulas draining upon gentle compression on at least two consecutive visits without an increase in medication or surgery for Crohn's disease) was seen in 68% (21/31) of patients in the 5 mg/kg REMICADE group (p=0.002) and 56% (18/32) of patients in the 10 mg/kg REMICADE group (p=0.021) vs. 26% (8/31) of patients in the placebo arm. The median time to onset of response and median duration of response in REMICADE-treated patients was 2 and 12 weeks, respectively. Closure of all fistula was achieved in 52% of REMICADE-treated patients compared with 13% of placebo-treated patients (p<0.001).

In the second trial (ACCENT II), patients who were enrolled had to have at least one draining enterocutaneous (perianal, abdominal) fistula. All patients received 5 mg/kg REMICADE at weeks 0, 2 and 6. Patients were randomized to placebo or 5 mg/kg REMICADE maintenance at week 14. Patients received maintenance doses at week 14 and then every eight weeks through week 46. Patients who were in fistula response (fistula response was defined the same as in the first trial) at both weeks 10 and 14 were randomized separately from those not in response. The primary endpoint was time from randomization to loss of response among those patients who were in fistula response.

Among the randomized patients (273 of the 296 initially enrolled), 87% had perianal fistulas and 14% had abdominal fistulas. Eight percent also had rectovaginal fistulas. Greater than 90% of the patients had received previous immunosuppressive and antibiotic therapy.

At week 14, 65% (177/273) of patients were in fistula response. Patients randomized to REMICADE maintenance had a longer time to loss of fistula response compared to the placebo maintenance group (Figure 2). At week 54, 38% (33/87) of REMICADE-treated patients had no draining fistulas compared with 22% (20/90) of placebo-treated patients (p=0.02). Compared to placebo maintenance, patients on REMICADE maintenance had a trend toward fewer hospitalizations.

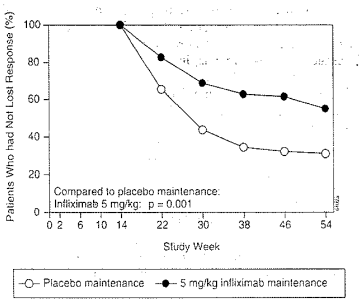

Figure 2
Life table estimates of the proportion of patients who had lost fistula response through week 54

Patients who achieved a fistula response and subsequently lost response were eligible to receive REMICADE maintenance therapy at a dose that was 5 mg/kg higher than the dose to which they were randomized. Of the placebo maintenance patients, 66% (25/38) responded to 5 mg/kg REMICADE, and 57% (12/21) of REMICADE maintenance patients responded to 10 mg/kg.

Patients who had not achieved a response by week 14 were unlikely to respond to additional doses of REMICADE.

Similar proportions of patients in either group developed new fistulas (17% overall) and similar numbers developed abscesses (15% overall).

Table 4
CLINICAL REMISSION AND STEROID WITHDRAWAL

	Single 5 mg/kg Dose[a]	Three Dose Induction[b] REMICADE Maintenance q 8 wks	
	Placebo Maintenance	5 mg/kg	10 mg/kg
Week 30	25/102	41/104	48/105
Clinical remission	25%	39%	46%
p-value[c]		0.022	0.001
Week 54			
Patients in remission able to discontinue corticosteroid use[d]	6/54 11%	14/56 25%	18/53 34%
p-value[c]		0.059	0.005

[a] REMICADE at week 0
[b] REMICADE 5 mg/kg administered at weeks 0, 2 and 6
[c] p-values represent pairwise comparisons to placebo

INDICATIONS AND USAGE

Rheumatoid Arthritis

REMICADE, in combination with methotrexate, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate.

Crohn's Disease

REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.

REMICADE is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in patients with fistulizing Crohn's disease.

CONTRAINDICATIONS

REMICADE is contraindicated in patients with moderate or severe (NYHA Class III/IV) congestive heart failure (see *WARNINGS, Congestive Heart Failure*).

REMICADE should not be administered to patients with known hypersensitivity to any murine proteins or other component of the product.

WARNINGS

RISK OF INFECTIONS

(See boxed WARNING)

SERIOUS INFECTIONS, INCLUDING SEPSIS HAVE BEEN REPORTED IN PATIENTS RECEIVING TNF-BLOCKING AGENTS. SOME OF THESE INFECTIONS HAVE BEEN FATAL. MANY OF THE SERIOUS INFECTIONS IN PATIENTS TREATED WITH REMICADE HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR CROHN'S DISEASE OR RHEUMATOID ARTHRITIS, COULD PREDISPOSE THEM TO

REMICADE SHOULD NOT BE GIVEN TO PATIENTS WITH A CLINCALLY IMPORTANT, ACTIVE INFECTION. CAUTION SHOULD BE EXERCISED WHEN CONSIDERING THE USE OF REMICADE IN PATIENTS WITH A CHRONIC INFECTION OR A HISTORY OF RECURRENT INFECTION. PATIENTS SHOULD BE MONITORED FOR SIGNS AND SYMPTOMS OF INFECTION WHILE ON OR AFTER TREATMENT WITH REMICADE. NEW INFECTIONS SHOULD BE CLOSELY MONITORED. IF A PATIENT DEVELOPS A SERIOUS INFECTION, REMICADE THERAPY SHOULD BE DISCONTINUED (see *ADVERSE REACTIONS, Infections*).

CASES OF HISTOPLASMOSIS, COCCIDIOIDOMYCOSIS, LISTERIOSIS, PNEUMOCYSTOSIS, TUBERCULOSIS, OTHER BACTERIAL, MYCOBACTERIAL AND FUNGAL INFECTIONS HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. FOR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE HISTOPLASMOSIS OR COCCIDIOIDOMYCOSIS IS ENDEMIC, THE BENEFITS AND RISKS OF REMICADE TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF REMICADE THERAPY.

Congestive Heart Failure

Doses greater than 5 mg/kg should not be administered to patients with congestive heart failure (CHF). REMICADE should be used with caution in patients with mild heart failure (NYHA Class I/II). Patients should be closely monitored, and REMICADE must not be continued in patients who develop new or worsening symptoms of heart failure (see *CONTRAINDICATIONS* and *ADVERSE REACTIONS, Congestive Heart Failure*).

Hypersensitivity

REMICADE has been associated with hypersensitivity reactions that vary in their time of onset. Most hypersensitivity reactions, which include urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of REMICADE infusion. However, in some cases, serum sickness-like reactions have been observed in Crohn's disease patients 3 to 12 days after REMICADE therapy was reinstituted following an extended period without REMICADE treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia. These reactions were associated with marked increase in antibodies to infliximab, loss of detectable serum concentrations of infliximab, and possible loss of drug efficacy. REMICADE should be discontinued for severe reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a reaction (see *ADVERSE REACTIONS, Infusion-related Reactions*).

Neurologic Events

Infliximab and other agents that inhibit TNF have been associated in rare cases with optic neuritis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis. Prescribers should exercise caution in considering the use of REMICADE in patients with pre-existing or recent onset of central nervous system demyelinating or seizure disorders.

PRECAUTIONS

Autoimmunity

Treatment with REMICADE may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with REMICADE, treatment should be discontinued (see *ADVERSE REACTIONS, Autoantibodies/Lupus-like Syndrome*).

Malignancy

Patients with long duration of Crohn's disease or rheumatoid arthritis and chronic exposure to immunosuppressant therapies are more prone to develop lymphomas (see *ADVERSE REACTIONS, Malignancies/Lymphoproliferative Disease*). The impact of treatment with REMICADE on these phenomena is unknown.

Vaccinations

No data are available on the response to vaccination or on the secondary transmission of infection by live vaccines in patients receiving anti-TNF therapy. It is recommended that live vaccines not be given concurrently.

Information for Patients

Patients should be provided the REMICADE Patient Information Sheet and provided an opportunity to read it prior to each treatment infusion session. Because caution should be exercised in administering REMICADE to patients with clinically important active infections, it is important that the patient's overall health be assessed at each treatment visit and any questions resulting from the patient's reading of the Patient Information Sheet be discussed.

Drug Interactions

Specific drug interaction studies, including interactions with MTX, have not been conducted. The majority of patients in rheumatoid arthritis or Crohn's disease clinical studies received one or more concomitant medications. In rheumatoid arthritis, concomitant medications besides MTX were nonsteroidal anti-inflammatory agents, folic acid, corticosteroids and/or narcotics. Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids, 6-MP/AZA and aminosalicylates. Patients with Crohn's disease who received immunosuppressants tended to experience fewer infusion reactions compared to patients on no immunosuppressants (see *ADVERSE REACTIONS, Immunogenicity*). Serum infliximab concentrations appeared to be unaffected by baseline use of medications for the treatment of Crohn's disease including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and aminosalicylates.

Carcinogenesis, Mutagenesis and Impairment of Fertility

A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNFα to evaluate tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNFα in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. The significance of these findings for human risk is unknown. It is not known whether infliximab can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study.

Pregnancy Category B

Since infliximab does not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with REMICADE. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies. It is not known whether REMICADE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. REMICADE should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether infliximab is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from REMICADE, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of REMICADE in patients with juvenile rheumatoid arthritis and in pediatric patients with Crohn's disease have not been established.

Geriatric Use

In the ATTRACT study, no overall differences were observed in effectiveness or safety in 72 patients aged 65 or older compared to younger patients. In Crohn's disease studies, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly (see *ADVERSE REACTIONS, Infections*).

ADVERSE REACTIONS

The data described herein reflect exposure to REMICADE in 1678 patients, including 842 patients exposed beyond 30 weeks and 295 exposed beyond one year. The most common reason for discontinuation of treatment was infusion-related reactions (e.g. dyspnea, flushing, headache and rash). Adverse events have been reported in a higher proportion of rheumatoid arthritis patients receiving the 10 mg/kg dose than the 3 mg/kg dose, however, no differences were observed in the frequency of adverse events between the 5 mg/kg dose and 10 mg/kg dose in patients with Crohn's disease.

Infusion-related Reactions

Acute infusion reactions

An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 to 2 hours after an infusion. Approximately 20% of REMICADE-treated patients in all clinical studies experienced an infusion reaction compared to approximately 10% of placebo-treated patients. Among all REMICADE infusions, 3% were accompanied by nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension or dyspnea), and <1% were accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Serious infusion reactions occurred in <1% of patients and included anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patients discontinued REMICADE because of infusion reactions, and all patients recovered with treatment and/or discontinuation of the infusion. REMICADE infusions beyond the initial infusion were not associated with a higher incidence of reactions.

Patients who became positive for antibodies to infliximab were more likely (approximately 2- to 3-fold) to have an infusion reaction than were those who were negative. Use of concomitant immunosuppressant agents appeared to reduce the frequency of antibodies to infliximab and infusion reactions (see *ADVERSE REACTIONS, Immunogenicity* and In post-marketing experience, cases of anaphylactic-like reactions, including laryngeal/pharyngeal edema and severe bronchospasm, and seizure have been associated with REMICADE administration.

Reactions following readministration

In a study where 37 of 41 patients with Crohn's disease were retreated with infliximab following a 2 to 4 year period without infliximab treatment, 10 patients experienced adverse events manifesting 3 to 12 days following infusion of which 6 were considered serious. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients also experiencing pruritus, facial, hand or lip edema, dysphagia, urticaria, sore throat, and headache. Patients experiencing these adverse events had not experienced infusion-related adverse events associated with their initial infliximab therapy. These adverse events occurred in 39% (9/23) of patients who had received liquid formulation which is no longer in use and 7% (1/14) of patients who received lyophilized formulation. The clinical data are not adequate to determine if occurrence of these reactions is due to differences in formulation. Patients' signs and symptoms improved substantially or resolved with treatment in all cases. There are insufficient data on the incidence of these events after drug-free intervals of 1 to 2 years. These events have been observed only infrequently in clinical studies and post-marketing surveillance with retreatment intervals up to 1 year.

Infections

In REMICADE clinical studies, treated infections were reported in 35% of REMICADE-treated patients (average of 53 weeks of follow-up) and in 26% of placebo-treated patients (average of 41 weeks of follow-up). When longer observation of patients on REMICADE was accounted for, the event rate was similar for both groups. The infections most frequently reported were respiratory tract infections (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. No increased risk of serious infections or sepsis was observed with REMICADE compared with placebo in clinical studies. Among REMICADE-treated patients, serious infections included pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection. Three opportunistic infections were reported: coccidioidomycosis (which resulted in death), nocardiosis and cytomegalovirus. Tuberculosis was reported in two patients, one of whom died due to miliary tuberculosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported post-marketing. Most of the cases of tuberculosis occurred within the first two months after initiation of therapy with infliximab and may reflect recrudescence of latent disease (see *WARNINGS, RISK OF INFECTIONS*). During the 54 week ACCENT II trial, 15% of patients with fistulizing Crohn's disease developed a new fistula-related abscess.

In post-marketing experience, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving REMICADE alone or in combination with immunosuppressive agents.

Autoantibodies/Lupus-like Syndrome

Approximately 52% of 1261 infliximab-treated patients in clinical trials who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial compared with approximately 19% of 129 placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately 17% of 1507 infliximab-treated patients compared with 0% of 162 placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon.

Malignancies/Lymphoproliferative Disease

In completed clinical studies of REMICADE for up to 102 weeks, 18 of 1678 patients developed 19 new or recurrent malignancies of various types, such as non-Hodgkin's B-cell lymphoma, breast, melanoma, squamous, rectal and basal cell. There are insufficient data to determine whether REMICADE contributed to the development of these malignancies. The observed rates and incidences were similar to those expected for the populations studied[11,12] (see *PRECAUTIONS, Malignancy*).

Immunogenicity

Treatment with REMICADE can be associated with the development of antibodies to infliximab. The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed by maintenance dosing was approximately 10% as assessed through one to two years of REMICADE treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease patients receiving REMICADE after drug free intervals >16 weeks. The majority of antibody-positive patients had low titers. Patients who were antibody-positive were more likely to experience an infusion reaction (see *ADVERSE REACTIONS, Infusion-related Reactions*). Antibody development was lower among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX.

The data reflect the percentage of patients whose test results were positive for antibodies to infliximab in an 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 medication, and underlying disease. For

Remicade—Cont.

these reasons, comparison of the incidence of antibodies to infliximab with the incidence of antibodies to other products may be misleading.

Congestive Heart Failure

In a phase II study evaluating REMICADE in NYHA Class III/IV CHF patients (left ventricular ejection fraction ≤35%), higher incidences of mortality and hospitalization due to worsening heart failure were seen in REMICADE-treated patients, especially those treated with 10 mg/kg. One hundred and fifty patients were treated with 3 infusions of REMICADE 5 mg/kg, 10 mg/kg, or placebo over 6 weeks. At 28 weeks, 4 of 101 patients treated with REMICADE (1 at 5 mg/kg and 3 at 10 mg/kg) died compared with no deaths among the 49 placebo-treated patients. In follow-up, at 38 weeks, 9 patients treated with REMICADE (2 at 5 mg/kg and 7 at 10 mg/kg) died compared with one death among the placebo-treated patients. At 28 weeks, 14 of 101 patients treated with REMICADE (3 at 5 mg/kg and 11 at 10 mg/kg) were hospitalized for worsening CHF compared with 5 of the 49 placebo-treated patients (see *CONTRAINDICATIONS* and *WARNINGS, Congestive Heart Failure*).

Other Adverse Reactions

Safety data are available from 1678 REMICADE-treated patients, including 555 with rheumatoid arthritis, 1106 with Crohn's disease and 17 with conditions other than rheumatoid arthritis or Crohn's disease. Adverse events reported in ≥5% of all patients with rheumatoid arthritis receiving 4 or more infusions are in Table 5. The types and frequencies of adverse reactions observed were similar in REMICADE-treated rheumatoid arthritis and Crohn's disease patients except for abdominal pain which occurred in 26% of REMICADE-treated patients with Crohn's disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-up for patients who never received REMICADE to provide meaningful comparisons.

Table 5
ADVERSE EVENTS OCCURRING IN 5% OR MORE OF PATIENTS RECEIVING 4 OR MORE INFUSIONS FOR RHEUMATOID ARTHRITIS

	Placebo (n=81)	REMICADE (n=430)
Average weeks of follow-up	73	82
Gastrointestinal		
Abdominal pain	12%	17%
Nausea	23%	24%
Diarrhea	19%	19%
Dyspepsia	9%	10%
Respiratory		
Upper respiratory tract infection	35%	40%
Pharyngitis	12%	17%
Sinusitis	7%	20%
Coughing	9%	18%
Rhinitis	14%	14%
Dyspnea	2%	6%
Skin and appendage disorders		
Rash	7%	18%
Pruritis	2%	9%
Body as a whole–general disorders		
Fatigue	9%	13%
Chest pain	6%	7%
Resistance mechanism disorders		
Fever	11%	13%
Abscess	5%	6%
Moniliasis	2%	8%
Central and peripheral nervous system disorders		
Headache	21%	29%
Musculoskeletal system disorders		
Arthralgia	7%	13%
Back pain	5%	13%
Psychiatric disorders		
Insomnia	4%	6%
Depression	2%	8%
Urinary system disorders		
Urinary tract infection	12%	14%
Cardiovascular disorders, general		
Hypertension	6%	10%

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not predict the rates observed in broader patient populations in clinical practice.

The most common serious adverse events observed in clinical trials were infections (see *ADVERSE REACTIONS, Infections*). Other serious, medically relevant adverse events ≥0.2% or clinically significant adverse events by body system were as follows:

Body as a whole: allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequela
Blood: pancytopenia
Cardiovascular: circulatory failure, hypotension, syncope
Gastrointestinal: constipation, gastrointestinal hemorrhage, ileus, intestinal obstruction, intestinal perforation, intestinal stenosis, pancreatitis, peritonitis, proctalgia
Central & Peripheral Nervous: meningitis, neuritis, peripheral neuropathy, dizziness
Heart Rate and Rhythm: arrhythmia, bradycardia, cardiac
Liver and Biliary: biliary pain, cholecystitis, cholelithiasis, hepatitis
Metabolic and Nutritional: dehydration
Musculoskeletal: intervertebral disk herniation, tendon disorder
Myo-, Endo-, Pericardial and Coronary Valve: myocardial infarction
Platelet, Bleeding and Clotting: thrombocytopenia
Neoplasms: basal cell, breast, lymphoma
Psychiatric: confusion, suicide attempt
Red Blood Cell: anemia, hemolytic anemia
Reproductive: menstrual irregularity
Resistance Mechanism: cellulitis, sepsis, serum sickness
Respiratory: adult respiratory distress syndrome, lower respiratory tract infection, pleural effusion, pleurisy, pulmonary edema, respiratory insufficiency
Skin and Appendages: increased sweating, ulceration
Urinary: renal calculus, renal failure
Vascular (Extracardiac): brain infarction, pulmonary embolism, thrombophlebitis
White Cell and Reticuloendothelial: leukopenia, lymphadenopathy

A greater proportion of patients enrolled into the ATTRACT study who received REMICADE + MTX experienced transient mild (<2 times the upper limit of normal) or moderate (≥2 but <3 times the upper limit of normal) elevations in AST or ALT (49% and 47%, respectively) compared to patients treated with placebo + MTX (27% and 35%, respectively). Six (1.8%) patients treated with REMICADE + MTX experienced more prolonged elevations in their ALT.

The following adverse events have been reported during post-approval use of REMICADE: demyelinating disorders (see *WARNINGS, Neurologic Events*) (such as multiple sclerosis and optic neuritis), Guillain-Barré syndrome, hemolytic anemia, idiopathic thrombocytic purpura, interstitial pneumonitis/fibrosis, neuropathies, thrombotic thrombocytopenic purpura, and transverse myelitis. Because these events 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 REMICADE exposure.

OVERDOSAGE

Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

DOSAGE AND ADMINISTRATION

Rheumatoid Arthritis

The recommended dose of REMICADE is 3 mg/kg given as an intravenous infusion followed with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. REMICADE should be given in combination with methotrexate. For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or treating as often as every 4 weeks.

Crohn's Disease or Fistulizing Crohn's Disease

The recommended dose of REMICADE is 5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active Crohn's disease or fistulizing disease. For patients who respond and then lose their response, consideration may be given to treatment with 10 mg/kg. Patients who do not respond by week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue REMICADE in these patients.

Preparation and administration instructions

Use aseptic technique.

REMICADE vials do not contain antibacterial preservatives. Therefore, the vials after reconstitution should be used immediately, not re-entered or stored. The diluent to be used for reconstitution is 10 mL of Sterile Water for Injection, USP. The total dose of the reconstituted product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection, USP. The infusion concentration should range between 0.4 mg/mL and 4 mg/mL. The REMICADE infusion should begin within 3 hours of preparation.

1. Calculate the dose and the number of REMICADE vials needed. Each REMICADE vial contains 100 mg of infliximab. Calculate the total volume of reconstituted REMICADE solution required.
2. Reconstitute each REMICADE vial with 10 mL of Sterile Water for Injection, USP, using a syringe equipped with a 21-gauge or smaller needle. Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Do not use the vial if the vacuum is not present. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to light yellow and opalescent, and the solution may develop a few translucent particles as infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign particles are present.
3. Dilute the total volume of the reconstituted REMICADE solution dose to 250 mL with 0.9% Sodium Chloride Injection, USP, by withdrawing a volume of 0.9% Sodium tuted REMICADE from the 0.9% Sodium Chloride Injection, USP, 250 mL bottle or bag. Slowly add the total volume of reconstituted REMICADE solution to the 250 mL infusion bottle or bag. Gently mix.
4. The infusion solution must be administered over a period of not less than 2 hours and must use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 µm or less). Any unused portion of the infusion solution should not be stored for reuse.
5. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of REMICADE with other agents. REMICADE should not be infused concomitantly in the same intravenous line with other agents.
6. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particulates are observed, the solution should not be used.

Storage

Store the lyophilized product under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze. Do not use beyond the expiration date. This product contains no preservative.

HOW SUPPLIED

REMICADE lyophilized concentrate for IV injection is supplied in individually-boxed single-use vials in the following strength:

NDC 57894-030-01 100 mg infliximab in a 20 mL vial

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IN03175

Shown in Product Identification Guide, page 312

RETAVASE®

(reteplase)
recombinant

℞

DESCRIPTION

Retavase® (Reteplase) is a non-glycosylated deletion mutein of tissue plasminogen activator (tPA), containing the kringle 2 and the protease domains of human tPA. Retavase® contains 355 of the 527 amino acids of native tPA (amino acids 1–3 and 176–527). Retavase® is produced by recombinant DNA technology in E. coli. The protein is isolated as inactive inclusion bodies from E. coli, converted into its active form by an in vitro folding process and purified by chromatographic separation. The molecular weight of Reteplase is 39,571 daltons.

Potency is expressed in units (U) using a reference standard which is specific for Retavase® and is not comparable with units used for other thrombolytic agents.

Retavase® is a sterile, white, lyophilized powder for intravenous bolus injection after reconstitution with Sterile Wa-

ing moderate to severe cough (24/65, 37% as compared to 6/33, 18%). Other events tended to be of mild to moderate severity. The number of patients reporting rhinitis was higher in the younger age group as compared to the older age group (23/65, 35% compared to 9/33, 27%) as was the number reporting rash (4/65, 6% as compared to 0/33). The nature of adverse events was similar to that seen in the larger trials of Pulmozyme® (dornase alfa) Inhalation Solution.

Allergic Reactions

There have been no reports of anaphylaxis attributed to the administration of Pulmozyme to date. Urticaria, mild to moderate, and mild skin rash have been observed and have been transient. Within all of the studies, a small percentage (average of 2-4%) of patients treated with Pulmozyme developed serum antibodies to Pulmozyme. None of these patients developed anaphylaxis, and the clinical significance of serum antibodies to Pulmozyme is unknown.

OVERDOSAGE

Single-dose inhalation studies in rats and monkeys at doses up to 180-times higher than doses routinely used in clinical studies are well tolerated. Single dose oral administration of Pulmozyme in doses up to 200 mg/kg are also well tolerated by rats.

Cystic fibrosis patients have received up to 20 mg BID for up to 6 days and 10 mg BID intermittently (2 weeks on/2 weeks off drug) for 168 days. These doses were well tolerated.

DOSAGE AND ADMINISTRATION

The recommended dose for use in most cystic fibrosis patients is one 2.5 mg single-use ampule inhaled once daily using a recommended nebulizer. Some patients may benefit from twice daily administraton (see Clinical Experience, Table 1). Clinical trial results and laboratory information are only available to support use of the following nebulizer/compressor systems (see Table 3).

Table 3
Recommended Nebulizer/Compressor Systems

Jet Nebulizer	Compressor
Hudson T Up-draft II® with	Pulmo-Aide®
Marquest Acorn II® with	Pulmo-Aide®
PARI LC Jet+ with	PARI PRONEB®
*PARI BABY™ with	PARI PRONEB®
Durable Sidestream® with	MOBILAIRE™
Durable Sidestream® with	Porta-Neb®

*Patients who are unable to inhale or exhale orally throughout the entire nebulization period may use the PARI BABY™ nebulizer.

Patients who use the Sidestream® Nebulizer with the MOBILAIRE™ compressor should turn the compressor control knob fully to the right and then turn on the compressor. At this setting, the needle on the pressure gauge should vibrate between 35 and 45 pounds per square inch (highest pressure output).

No data are currently available that support the administration of Pulmozyme with other nebulizer systems. The patient should follow the manufacturer's instructions on the use and maintenance of the equipment.

Pulmozyme should not be diluted or mixed with other drugs in the nebulizer. Mixing of Pulmozyme with other drugs could lead to adverse physicochemical and/or functional changes in Pulmozyme or the admixed compound. Patients should be advised to squeeze each ampule prior to use in order to check for leaks.

HOW SUPPLIED

Pulmozyme® (dornase alfa) Inhalation Solution is supplied in single-use ampules. Each ampule delivers 2.5 mL of a sterile, clear, colorless, aqueous solution containing 1.0 mg/mL dornase alfa, 0.15 mg/mL calcium chloride dihydrate and 8.77 mg/mL sodium chloride with no preservative. The nominal pH of the solution is 6.3.

Pulmozyme is supplied in:

• 30 unit cartons containing 5 foil pouches of 6 single-use ampules: NDC 50242-100-40.

Storage

Pulmozyme® (dornase alfa) Inhalation Solution should be stored under refrigeration (2–8°C/36–46°F). Ampules should be protected from strong light. Do not use beyond the expiration date stamped on the ampule. Unused ampules should be stored in their protective foil pouch under refrigeration.

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Pulmozyme® 4812405
(dornase alfa) Revised January 2001

INHALATION SOLUTION
Manufactured by
GENENTECH, Inc.
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Shown in Product Identification Guide, page 315

RITUXAN® ℞
(Rituximab)

> **WARNINGS**
>
> **Fatal Infusion Reactions:** Deaths within 24 hours of RITUXAN infusion have been reported. These fatal reactions followed an infusion reaction complex which included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. (See WARNINGS and ADVERSE REACTIONS.)
>
> Patients who develop severe infusion reactions should have RITUXAN infusion discontinued and receive medical treatment.
>
> **Tumor Lysis Syndrome (TLS):** Acute renal failure requiring dialysis with instances of fatal outcome has been reported in the setting of TLS following treatment with RITUXAN. (See WARNINGS.)
>
> **Severe Mucocutaneous Reactions:** Severe mucocutaneous reactions, some with fatal outcome, have been reported in association with RITUXAN treatment. (See WARNINGS and ADVERSE REACTIONS.)

DESCRIPTION

The RITUXAN® (Rituximab) antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody is an IgG_1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.

The chimeric anti-CD20 antibody is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. The anti-CD20 antibody is purified by affinity and ion exchange chromatography. The purification process includes specific viral inactivation and removal procedures. Rituximab drug product is manufactured from either bulk drug substance manufactured by Genentech, Inc. (US License No. 1048) or utilizing formulated bulk Rituximab supplied by IDEC Pharmaceuticals Corporation (US License No. 1235) under a shared manufacturing arrangement.

RITUXAN is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration. RITUXAN is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for IV administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Sterile Water for Injection. The pH is adjusted to 6.5.

CLINICAL PHARMACOLOGY

General

Rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted differentiation antigen, Bp35), a hydrophobic transmembrane protein with a molecular weight of approximately 35 kD located on pre-B and mature B lymphocytes.[1,2] The antigen is also expressed on > 90% of B-cell non-Hodgkin's lymphomas (NHL),[3] but is not found on hematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissues.[4] CD20 regulates an early step(s) in the activation process for cell cycle initiation and differentiation,[4] and possibly functions as a calcium ion channel.[5] CD20 is not shed from the cell surface and does ...

Preclinical Pharmacology and Toxicology

Mechanism of Action: The Fab domain of Rituximab binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions to mediate B-cell lysis *in vitro*. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC)[7] and antibody-dependent cell mediated cytotoxicity (ADCC). The antibody has been shown to induce apoptosis in the DHL-4 human B-cell lymphoma line.[8]

Normal Tissue Cross-reactivity: Rituximab binding was observed on lymphoid cells in the thymus, the white pulp of the spleen, and a majority of B lymphocytes in peripheral blood and lymph nodes. Little or no binding was observed in the non-lymphoid tissues examined.

Human Pharmacokinetics/Pharmacodynamics

In patients given single doses at 10, 50, 100, 250 or 500 mg/m² as an IV infusion, serum levels and the half-life of Rituximab were proportional to dose.[9] In 14 patients given 375 mg/m² as an IV infusion for 4 weekly doses, the mean serum half-life was 76.3 hours (range, 31.5 to 152.6 hours) after the first infusion and 205.8 hours (range, 83.9 to 407.0 hours) after the fourth infusion.[10,11,12] The wide range of half-lives may reflect the variable tumor burden among patients and the changes in CD20-positive (normal and malignant) B-cell populations upon repeated administrations.

RITUXAN at a dose of 375 mg/m² was administered as an IV infusion at weekly intervals for 4 doses to 203 patients naive to RITUXAN. The mean C_{max} following the fourth infusion was 486 µg/mL (range, 77.5 to 996.6 µg/mL). The peak and trough serum levels of Rituximab were inversely correlated with baseline values for the number of circulating CD20 positive B cells and measures of disease burden. Median steady-state serum levels were higher for responders compared with nonresponders; however, no difference was found in the rate of elimination as measured by serum half-life. Serum levels were higher in patients with International Working Formulation (IWF) subtypes B, C, and D as compared with those with subtype A. Rituximab was detectable in the serum of patients 3 to 6 months after completion of treatment.

RITUXAN at a dose of 375 mg/m² was administered as an IV infusion at weekly intervals for 8 doses to 37 patients. The mean C_{max} after 8 infusions was 550 µg/mL (range, 171 to 1177 µg/mL). The mean C_{max} increased with each successive infusion through the eighth infusion (Table 1).

Table 1
Rituximab C_{max} Values

Infusion Number	Mean C_{max} µg/mL	Range µg/mL
1	242.6	16.1–581.9
2	357.5	106.8–948.6
3	381.3	110.5–731.2
4	460.0	138.0–835.8
5	475.3	156.0–929.1
6	515.4	152.7–865.2
7	544.6	187.0–936.8
8	550.0	170.6–1177.0

The pharmacokinetic profile of RITUXAN when administered as 6 infusions of 375 mg/m² in combination with 6 cycles of CHOP chemotherapy was similar to that seen with RITUXAN alone.

Administration of RITUXAN resulted in a rapid and sustained depletion of circulating and tissue-based B cells. Lymph node biopsies performed 14 days after therapy showed a decrease in the percentage of B cells in seven of eight patients who had received single doses of Rituximab ≥100 mg/m².[9] Among the 166 patients in the pivotal study, circulating B cells (measured as CD19-positive cells) were depleted within the first three doses with sustained depletion for up to 6 to 9 months post-treatment in 83% of patients. Of the responding patients assessed (n = 80), 1% failed to show significant depletion of CD19-positive cells after the third infusion of Rituximab as compared to 19% of the nonresponding patients. B-cell recovery began at approximately 6 months following completion of treatment. Median B-cell levels returned to normal by 12 months following completion of treatment.

There were sustained and statistically significant reductions in both IgM and IgG serum levels observed from 5 through 11 months following Rituximab administration. However, only 14% of patients had reductions in IgM and/or IgG serum levels, resulting in values below the normal range.

CLINICAL STUDIES

Studies with a collective enrollment of 296 patients having relapsed or refractory low-grade or follicular B-cell NHL are described below (Table 2). RITUXAN regimens tested include treatment weekly for 4 doses and treatment weekly for 8 doses. Clinical settings studied were initial treatment, initial treatment of bulky disease, and retreatment.

[See table 2 at top of next page]

Initial Treatment, Weekly for 4 doses

A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or refractory low-grade or follicular B-cell NHL who received 375 mg/m² of RITUXAN given as an IV infusion weekly for 4 doses.[13] Patients with

Rituxan—Cont.

tumor masses >10 cm or with >5,000 lymphocytes/μL in the peripheral blood were excluded from the study. The overall response rate (ORR) was 48% with 6% complete response (CR) and 42% partial response (PR) rates. The median time to onset of response was 50 days and the median duration of response was 11.2 months (range, 1.9 to 42.1+). Disease-related signs and symptoms (including B-symptoms) were present in 23% (39/166) of patients at study entry and resolved in 64% (25/39) of those patients.

In a multivariate analysis, the ORR was higher in patients with IWF B, C, and D histologic subtypes as compared to IWF subtype A (58% vs. 12%), higher in patients whose largest lesion was <5 cm vs. >7 cm (maximum, 21 cm) in greatest diameter (53% vs. 38%), and higher in patients with chemosensitive relapse as compared with chemoresistant (defined as duration of response <3 months) relapse (53% vs. 36%). ORR in patients previously treated with autologous bone marrow transplant was 78% (18/23). The following adverse prognostic factors were *not* associated with a lower response rate: age ≥60 years, extranodal disease, prior anthracycline therapy, and bone marrow involvement.

Initial Treatment, Weekly for 8 Doses

In a multicenter, single-arm study, 37 patients with relapsed or refractory, low-grade NHL received 375 mg/m^2 of RITUXAN weekly for 8 doses. The ORR was 57% (CR 14%, PR 43%) with a projected median duration of response of 13.4 months (range, 2.5 to 36.5+).[14] (For information on the higher incidence of Grade 3 and 4 adverse events, see ADVERSE REACTIONS, Risk Factors Associated with Increased Rates of Adverse Events.)

Initial Treatment, Bulky Disease, Weekly for 4 Doses

In pooled data from multiple studies of RITUXAN, 39 patients with relapsed or refractory, bulky disease (single lesion >10 cm in diameter), low-grade NHL received 375 mg/m^2 of RITUXAN weekly for 4 doses. The ORR was 36% (CR 3%, PR 33%) with a median duration of response of 6.9 months (range 2.8 to 25.0+). (For information on the higher incidence of Grade 3 and 4 adverse events, see ADVERSE REACTIONS, Risk Factors Associated with Increased Rates of Adverse Events.)

Retreatment, Weekly for 4 Doses

In a multi-center, single-arm study, 60 patients received 375 mg/m^2 of RITUXAN weekly for 4 doses.[15] All patients had relapsed or refractory, low-grade or follicular B-cell NHL and had achieved an objective clinical response to a prior course of RITUXAN. Of these 60 patients, 55 received their second course of RITUXAN, 3 patients received their third course and 2 patients received their second and third courses of RITUXAN in this study. The ORR was 38% (10% CR and 28% PR) with a projected median duration of response of 15 months (range, 3.0 to 25.1+ months).

Table 2
Summary of RITUXAN Efficacy Data by Schedule and Clinical Setting (See ADVERSE REACTIONS for Risk Factors Associated with Increased Rates of Adverse Events.)

	Initial, Weekly × 4 N = 166	Initial, Weekly × 8 N = 37	Initial, Bulky, Weekly × 4 N = 39[1]	Retreatment, Weekly × 4 N = 60
Overall Response Rate	48%	57%	36%	38%
Complete Response Rate	6%	14%	3%	10%
Median Duration of Response[2,3,4] (Months) [Range]	11.2 [1.9 to 42.1+]	13.4 [2.5 to 36.5+]	6.9 [2.8 to 25.0+]	15.0 [3.0 to 25.1+]

[1]Six of these patients are included in the first column. Thus, data from 296 intent to treat patients are provided in this table.
[2]Kaplan-Meier projected with observed range.
[3]"+" indicates an ongoing response.
[4]Duration of response: interval from the onset of response to disease progression.

INDICATIONS AND USAGE

RITUXAN is indicated for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma.

CONTRAINDICATIONS

RITUXAN is contraindicated in patients with known anaphylaxis or IgE-mediated hypersensitivity to murine proteins or to any component of this product. (See WARNINGS.)

WARNINGS (See BOXED WARNINGS.)

Severe Infusion Reactions (See BOXED WARNINGS, ADVERSE REACTIONS and Hypersensitivity Reactions): RITUXAN has caused severe infusion reactions. In some cases, these reactions were fatal. These severe reactions typically occurred during the first infusion with time to onset of 30 to 120 minutes. Signs and symptoms of severe infusion reactions may include hypotension, angioedema, hypoxia or bronchospasm, and may require interruption of RITUXAN administration. The most severe manifestations and sequelae include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. In the reported cases, the following factors were more frequently associated with fatal outcomes: female gender, pulmonary infiltrates, and chronic lymphocytic leukemia or mantle cell lymphoma.

Management of severe infusion reactions: The RITUXAN infusion should be interrupted for severe reactions and supportive care measures instituted as medically indicated (e.g., intravenous fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen). In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Patients requiring close monitoring during first and all subsequent infusions include those with pre-existing cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary adverse events and those with high numbers of circulating malignant cells (≥ 25,000/mm^3) with or without evidence of high tumor burden.

Tumor Lysis Syndrome [TLS] (See BOXED WARNINGS and ADVERSE REACTIONS):

Rapid reduction in tumor volume followed by acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatasemia, have been reported within 12 to 24 hours after the first RITUXAN infusion. Rare instances of fatal outcome have been reported in the setting of TLS following treatment with RITUXAN. The risks of TLS are lating malignant cells (≥25,000/mm^3) or high tumor burden. Prophylaxis for TLS should be considered for patients at high risk. Correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care, including dialysis, should be initiated as indicated. Following complete resolution of the complications of TLS, RITUXAN has been tolerated when re-administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

Hypersensitivity Reactions:

RITUXAN has been associated with hypersensitivity reactions (non-IgE-mediated reactions) which may respond to adjustments in the infusion rate and in medical management. Hypotension, bronchospasm, and angioedema have occurred in association with RITUXAN infusion (see Severe Infusion Reactions). RITUXAN infusion should be interrupted for severe hypersensitivity reactions and can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Treatment of these symptoms with diphenhydramine and acetaminophen is recommended; additional treatment with bronchodilators or IV saline may be indicated. In most cases, patients who have experienced non-life-threatening hypersensitivity reactions have been able to complete the full course of therapy. (See DOSAGE and ADMINISTRATION.) Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines and corticosteroids, should be available for immediate use in the event of a reaction during administration.

Cardiovascular:

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of RITUXAN. Patients with pre-existing cardiac conditions including arrhythmias and angina have had recurrences of these events during RITUXAN therapy and should be monitored throughout the infusion and immediate post-infusion period.

Renal:

RITUXAN administration has been associated with severe renal toxicity including acute renal failure requiring dialysis and in some cases, has led to a fatal outcome. Renal toxicity has occurred in patients with high numbers of circulating malignant cells (>25,000/mm^3) or high tumor burden who experience tumor lysis syndrome (see Tumor Lysis Syndrome) and in patients administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and RITUXAN is not an approved treatment regimen. If this combination is used in clinical trials *extreme caution* should be exercised; patients should be monitored closely for signs of renal failure. Discontinuation of RITUXAN should be considered for those with rising serum creatinine or oliguria.

Severe Mucocutaneous Reactions (See BOXED WARNINGS and ADVERSE REACTIONS.):

Mucocutaneous reactions, some with fatal outcome, have been reported in patients treated with RITUXAN. These reports include paraneoplastic pemphigus (an uncommon disorder which is a manifestation of the patient's underlying malignancy),[16] Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of the reaction in the reported cases has varied from 1 to 13 weeks following RITUXAN exposure. Patients experiencing a severe mucocutaneous reaction should not receive any further infusions and seek prompt medical evaluation. Skin biopsy may help to distinguish among different mucocutaneous reactions and guide subsequent treatment. The safety of readministration of RITUXAN to patients with any of these mucocutaneous reactions has not been determined.

PRECAUTIONS

Laboratory Monitoring: Because RITUXAN targets all CD20-positive B lymphocytes, malignant and nonmalignant, complete blood counts (CBC) and platelet counts should be obtained at regular intervals during RITUXAN therapy and more frequently in patients who develop cytopenias (see ADVERSE REACTIONS). The duration of cytopenias caused by RITUXAN can extend well beyond the treatment period.

Drug/Laboratory Interactions: There have been no formal drug interaction studies performed with RITUXAN. How-

HACA Formation: Human antichimeric antibody (HACA) was detected in 4 of 356 patients and 3 had an objective clinical response. The data reflect the percentage of patients whose test results were considered positive for antibodies to RITUXAN using an enzyme-linked immunosorbant assay (limit of detection = 7 ng/mL). The observed incidence of antibody positivity in an assay is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to RITUXAN with the incidence of antibodies to other products may be misleading.

Immunization: The safety of immunization with live viral vaccines following RITUXAN therapy has not been studied. The ability to generate a primary or anamnestic humoral response to vaccination is currently being studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of RITUXAN, or to determine its effects on fertility in males or females. Individuals of childbearing potential should use effective contraceptive methods during treatment and for up to 12 months following RITUXAN therapy.

Pregnancy Category C: Animal reproduction studies have not been conducted with RITUXAN. It is not known whether RITUXAN can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. Human IgG is known to pass the placental barrier, and thus may potentially cause fetal B-cell depletion; therefore, RITUXAN should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether RITUXAN is excreted in human milk. Because human IgG is excreted in human milk and the potential for absorption and immunosuppression in the infant is unknown, women should be advised to discontinue nursing until circulating drug levels are no longer detectable. (See CLINICAL PHARMACOLOGY.)

Pediatric Use: The safety and effectiveness of RITUXAN in pediatric patients have not been established.

Geriatric Use: Among the 331 patients enrolled in clinical studies of single agent RITUXAN, 24% were 65 to 75 years old and 5% were 75 years old and older. The overall response rates were higher in older (age ≥ 65 years) vs. younger (age < 65 years) patients (52% vs. 44%, respectively). However, the median duration of response, based on Kaplan-Meier estimates, was shorter in older vs. younger patients: 10.1 months (range, 1.9 to 36.5+) vs. 11.4 months (range, 2.1 to 42.1+), respectively. This shorter duration of response was not statistically significant. Adverse reactions, including incidence, severity and type of adverse reaction were similar between older and younger patients.

ADVERSE REACTIONS

The most serious adverse reactions caused by RITUXAN include infusion reactions, tumor lysis syndrome, mucocutaneous reactions, hypersensitivity reactions, cardiac arrhythmias and angina, and renal failure. Please refer to the BOXED WARNINGS and WARNINGS sections for detailed descriptions of these reactions. Infusion reactions and lymphopenia are the most commonly occurring 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 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 postmarketing use of RITUXAN. 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 RITUXAN 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 RITUXAN.

Where specific percentages are noted, these data are based on 356 patients treated in nonrandomized, single-arm studies of RITUXAN administered as a single agent. Most pa-

≥10 cm) and 60 patients who received more than 1 course of RITUXAN. Thirty-seven patients received 375 mg/m² for 8 doses and 25 patients received doses other than 375 mg/m² for 4 doses and up to 500 mg/m² single dose in the Phase 1 setting. Adverse events of greater severity are referred to as "Grade 3 and 4 events" defined by the commonly used National Cancer Institute Common Toxicity Criteria.[17]

Table 3
Incidence of Adverse Events ≥ 5% of Patients in Clinical Trials (N = 356) (Adverse Events were followed for a period of 12 months following RITUXAN therapy.)

	All Grades (%)	Grade 3 and 4 (%)
Any Adverse Events	**99**	**57**
Body as a Whole	**86**	**10**
Fever	53	1
Chills	33	3
Infection	31	4
Asthenia	26	1
Headache	19	1
Abdominal Pain	14	1
Pain	12	1
Back Pain	10	1
Throat Irritation	9	0
Flushing	5	0
Cardiovascular System	**25**	**3**
Hypotension	10	1
Hypertension	6	1
Digestive System	**37**	**2**
Nausea	23	1
Diarrhea	10	1
Vomiting	10	1
Hemic and Lymphatic System	**67**	**48**
Lymphopenia	48	40
Leukopenia	14	4
Neutropenia	14	6
Thrombocytopenia	12	2
Anemia	8	3
Metabolic and Nutritional Disorders	**38**	**3**
Angioedema	11	1
Hyperglycemia	9	1
Peripheral Edema	8	0
LDH Increase	7	0
Musculoskeletal System	**26**	**3**
Myalgia	10	1
Arthralgia	10	1
Nervous System	**32**	**1**
Dizziness	10	1
Anxiety	5	1
Respiratory System	**38**	**4**
Increased Cough	13	1
Rhinitis	12	1
Bronchospasm	8	1
Dyspnea	7	1
Sinusitis	6	0
Skin and Appendages	**44**	**2**
Night Sweats	15	1
Rash	15	1
Pruritus	14	1
Urticaria	8	1

Risk Factors Associated with Increased Rates of Adverse Events:
Administration of RITUXAN weekly for 8 doses resulted in higher rates of Grade 3 and 4 adverse events[17] overall (70%) compared with administration weekly for 4 doses (57%). The incidence of Grade 3 or 4 adverse events was similar in patients retreated with RITUXAN compared with initial treatment (58% and 57%, respectively). The incidence of the following clinically significant adverse events was higher in patients with bulky disease (lesions ≥10 cm) (N = 39) versus patients with lesions < 10 cm (N = 195): abdominal pain, anemia, dyspnea, hypotension, and neutropenia.

Infusion Reactions (See BOXED WARNINGS and WARNINGS): Mild to moderate infusion reactions consisting of fever and chills/rigors occurred in the majority of patients during the first RITUXAN infusion. Other frequent infusion reaction symptoms included nausea, pruritus, angioedema, asthenia, hypotension, headache, bronchospasm, throat irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and hypertension. These reactions generally occurred within 30 to 120 minutes of beginning the first infusion, and resolved with slowing or interruption of the RITUXAN infusion and with supportive care (diphenhydramine, acetaminophen, IV saline, and vasopressors). In an analysis of data from 356 patients with relapsed or refractory, low-grade NHL who received 4 (N = 319) or 8 (N = 37) weekly infusions of RITUXAN, the incidence of infusion reactions was highest during the first infusion (77%) and decreased with each subsequent infusion (30% with fourth infusion and 14% with eighth infusion).

Infectious Events: RITUXAN induced B-cell depletion in 70% to 80% of patients and was associated with decreased serum immunoglobulins in a minority of patients; the lymphopenia lasted a median of 14 days (range, 1 to 588 days). Infectious events occurred in 31% of patients: 19% of patients had fungal infections, and 6% were unknown infections. Incidence is not additive because a single patient may have had more than one type of infection. Serious infectious events (Grade 3 or 4),[17] including sepsis occurred in 2% of patients.

Hematologic Events: Grade 3 and 4 cytopenias[17] were reported in 12% of patients treated with RITUXAN; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following RITUXAN therapy were reported. In addition, there have been rare postmarketing reports of prolonged pancytopenia and marrow hypoplasia.

Cardiac Events (See BOXED WARNINGS): Grade 3 or 4 cardiac-related events include hypotension. Rare, fatal cardiac failure with symptomatic onset weeks after RITUXAN has also been reported. Patients who develop clinically significant cardiopulmonary events should have RITUXAN infusion discontinued.

Pulmonary Events (See BOXED WARNINGS): 135 patients (38%) experienced pulmonary events. The most common respiratory system adverse events experienced were increased cough, rhinitis, bronchospasm, dyspnea, and sinusitis. Three pulmonary events have been reported in temporal association with RITUXAN infusion as a single agent: acute bronchospasm, acute pneumonitis presenting 1–4 weeks post-RITUXAN infusion, and bronchiolitis obliterans. One case of bronchiolitis obliterans was associated with progressive pulmonary symptoms and culminated in death several months following the last RITUXAN infusion. The safety of resumption or continued administration of RITUXAN in patients with pneumonitis or bronchiolitis obliterans is unknown.

Immune/Autoimmune Events: Immune/autoimmune events have been reported, including uveitis, optic neuritis in a patient with systemic vasculitis, pleuritis in a patient with a lupus-like syndrome, serum sickness with polyarticular arthritis, and vasculitis with rash.

Less Commonly Observed Events: In clinical trials, < 5% and > 1% of the patients experienced the following events regardless of causality assessment: agitation, anorexia, arthritis, conjunctivitis, depression, dyspepsia, edema, hyperkinesia, hypertonia, hypesthesia, hypoglycemia, injection site pain, insomnia, lacrimation disorder, malaise, nervousness, neuritis, neuropathy, paresthesia, somnolence, vertigo, weight decrease.

OVERDOSAGE

There has been no experience with overdosage in human clinical trials. Single doses of up to 500 mg/m² have been given in controlled clinical trials.[10]

DOSAGE AND ADMINISTRATION

Initial Therapy:
RITUXAN is given at 375 mg/m² IV infusion once weekly for 4 or 8 doses.

Retreatment Therapy:
Patients who subsequently develop progressive disease may be safely retreated with RITUXAN 375 mg/m² IV infusion once weekly for 4 doses. Currently there are limited data concerning more than 2 courses.

RITUXAN as a Component of Zevalin™ (Ibritumomab Tiuxetan) Therapeutic Regimen:
As a required component of the Zevalin therapeutic regimen, RITUXAN 250 mg/m² should be infused within 4 hours prior to the administration of Indium-111-(In-111-) Zevalin and within 4 hours prior to the administration of Yttrium-90-(Y-90-) Zevalin. Administration of RITUXAN and In-111-Zevalin should precede RITUXAN and Y-90-Zevalin by 7–9 days. Refer to the Zevalin package insert for full prescribing information regarding the Zevalin therapeutic regimen.

RITUXAN may be administered in an outpatient setting. **DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. (See Administration.)**

Instructions for Administration

Preparation for Administration: Use appropriate aseptic technique. Withdraw the necessary amount of RITUXAN and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

RITUXAN solutions for infusion may be stored at 2–8°C (36–46°F) for 24 hours. RITUXAN solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since RITUXAN solutions do not contain a preservative, diluted solutions should be stored refrigerated (2–8°C). No incompatibilities between RITUXAN and polyvinylchloride or polyethylene bags have been observed.

Administration: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.
Infusion and hypersensitivity reactions may occur (see BOXED WARNINGS, WARNINGS, and ADVERSE REACTIONS). Premedication consisting of acetaminophen and diphenhydramine should be considered before each infusion of RITUXAN. Premedication may attenuate infusion reactions. Since transient hypotension may occur during RITUXAN infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to RITUXAN infusion.

First Infusion: The RITUXAN solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. RITUXAN should not be mixed or diluted with other drugs. If hypersensitivity or infusion reactions do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If a hypersensitivity (non-IgE-mediated) or an infusion reaction develops, the infusion should be temporarily slowed or interrupted (see BOXED WARNINGS and WARNINGS). The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

Subsequent Infusions: If the patient tolerated the first infusion well, subsequent RITUXAN infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr as tolerated. If the patient did not tolerate the first infusion well, follow the guidelines under First Infusion.

Stability and Storage: RITUXAN vials are stable at 2–8°C (36–46°F). Do not use beyond expiration date stamped on carton. RITUXAN vials should be protected from direct sunlight. Refer to the "Preparation and Administration" section for information on the stability and storage of solutions of RITUXAN diluted for infusion.

HOW SUPPLIED

RITUXAN is supplied as 100 mg and 500 mg of sterile, preservative-free, single-use vials.
Single unit 100 mg carton: Contains one 10 mL vial of RITUXAN (10 mg/mL).
NDC 50242-051-21
Single unit 500 mg carton: Contains one 50 mL vial of RITUXAN (10 mg/mL).
NDC 50242-053-06

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(4809705 Revised February 2002)

Shown in Product Identification Guide, page 315

TNKase™ (Tenecteplase) Full Prescribing Information

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DESCRIPTION

Tenecteplase is a tissue plasminogen activator (tPA) produced by recombinant DNA technology using an established mammalian cell line (Chinese Hamster Ovary cells). Tenecteplase is a 527 amino acid glycoprotein developed by introducing the following modifications to the complementary DNA (cDNA) for natural human tPA: a substitution of threonine 103 with asparagine, and a substitution of asparagine 117 with glutamine, both within the kringle 1 domain, and a tetra-alanine substitution at amino acids 296–299 in the protease domain. Cell culture is carried out in nutrient medium containing the antibiotic gentamicin (65 mg/L). However, the presence of the antibiotic is not detectable in the final product (limit of detection is 0.67 pg/vial). TNKase is a sterile, white to off-white, lyophilized powder for single intravenous (IV) bolus administration after reconstitution with Sterile Water for Injection (SWFI), USP. Each vial of TNKase nominally contains 52.5 mg Tenecteplase, 0.55 g L-arginine, 0.17 g phosphoric acid, and 4.3 mg polysorbate 20, which includes a 5% overfill. Each vial will deliver 50 mg of Tenecteplase.

CLINICAL PHARMACOLOGY

General

Tenecteplase is a modified form of human tissue plasminogen activator (tPA) that binds to fibrin and converts plasminogen to plasmin. In the presence of fibrin, *in vitro* studies demonstrate that Tenecteplase conversion of plasminogen to plasmin is increased relative to its conversion in the absence of fibrin. This fibrin specificity decreases systemic activation of plasminogen and the resulting degradation of circulating fibrinogen as compared to a molecule lacking this property. Following administration of 30, 40, or 50 mg of TNKase, there are decreases in circulating fibrinogen (4%–15%) and plasminogen (11%–24%). The clinical significance of fibrin-specificity on safety (e.g., bleeding) or efficacy has not been established. Biological potency is determined by an *in vitro* clot lysis assay and is expressed in Tenecteplase-specific units. The specific activity of Tenecteplase has been defined as 200 units/mg.

Pharmacokinetics

In patients with acute myocardial infarction (AMI), TNKase administered as a single bolus exhibits a biphasic disposition from the plasma. Tenecteplase was cleared from the plasma with an initial half-life of 20 to 24 minutes. The terminal phase half-life of Tenecteplase was 90 to 130 minutes. In 99 of 104 patients treated with Tenecteplase, mean plasma clearance ranged from 99 to 119 mL/min.

The initial volume of distribution is weight related and approximates plasma volume. Liver metabolism is the major clearance mechanism for Tenecteplase.

CLINICAL STUDIES

ASSENT-2 was an international, randomized, double-blind trial that compared 30-day mortality rates in 16,949 patients assigned to receive an IV bolus dose of TNKase or an accelerated infusion of Activase® (Alteplase, recombinant).[1] Eligibility criteria included onset of chest pain within 6 hours of randomization and ST-segment elevation or left bundle branch block on electrocardiogram (ECG). Patients were to be excluded from the trial if they received GP IIb/IIIa inhibitors within the previous 12 hours. TNKase was dosed using actual or estimated weight in a weight-tiered fashion as described in DOSAGE AND ADMINISTRATION. All patients were to receive 150–325 mg of aspirin administered as soon as possible, followed by 150–325 mg daily. Intervention was to be administered as soon as possible

Table 1
ASSENT-2
Mortality, Stroke, and Combined Outcome of Death or Stroke Measured at Thirty Days

30-day Events	TNKase (N=8461)	Accelerated Activase (N=8488)	Relative Risk TNKase/Activase (95% CI)
Mortality	6.2%	6.2%	1.00 (0.89, 1.12)
Intracranial Hemorrhage (ICH)	0.9%	0.9%	0.99 (0.73, 1.35)
Any Stroke	1.8%	1.7%	1.07 (0.86, 1.35)
Death or Nonfatal Stroke	7.1%	7.0%	1.01 (0.91, 1.13)

Table 2
TIMI 10B Patency Rates
TIMI Grade Flow at 90 Minutes

	Activase ≤ 100 mg (n=311)	TNKase 30 mg (n=302)	TNKase 40 mg (n=148)	TNKase 50 mg (n=76)
TIMI Grade 3 Flow	63%	54%	63%	66%
TIMI Grade 2/3 Flow	82%	77%	79%	88%
95% CI (TIMI 2/3 Flow)	(77%, 86%)	(72%, 81%)	(72%, 85%)	(79%, 94%)

administered as a 4000 unit IV bolus followed by infusion at 800 U/hr; for patients weighing > 67 kg, heparin was administered as a 5000 unit IV bolus followed by infusion at 1000 U/hr. Heparin was continued for 48 to 72 hours with infusion adjusted to maintain aPTT at 50–75 seconds. The use of GP IIb/IIIa inhibitors was discouraged for the first 24 hours following randomization. The results of the primary endpoint (30-day mortality rates with non-parametric adjustment for the covariates of age, Killip class, heart rate, systolic blood pressure and infarct location) along with selected other 30-day endpoints are shown in Table 1.

[See table 1 above]

Rates of mortality and the combined endpoint of death or stroke among pre-specified subgroups, including age, gender, time to treatment, infarct location, and history of previous myocardial infarction, demonstrate consistent relative risks across these subgroups. There was insufficient enrollment of non-Caucasian patients to draw any conclusions regarding relative efficacy in racial subsets.

Rates of in-hospital procedures, including percutaneous transluminal coronary angioplasty (PTCA), stent placement, intra-aortic balloon pump (IABP) use, and coronary artery bypass graft (CABG) surgery, were similar between the TNKase and Activase groups.

TIMI 10B was an open-label, controlled, randomized, dose-ranging, angiography study which utilized a blinded core laboratory for review of coronary arteriograms.[2] Patients (n = 837) presenting within 12 hours of symptom onset were treated with fixed doses of 30, 40, or 50 mg of TNKase or the accelerated infusion of Activase and underwent coronary arteriography at 90 minutes. The results showed that the 40 mg and 50 mg doses were similar to accelerated infusion of Activase in restoring patency. TIMI grade 3 flow and TIMI grade 2/3 flow at 90 minutes are shown in Table 2. The exact relationship between coronary artery patency and clinical activity has not been established.

[See table 2 above]

The angiographic results from TIMI 10B and the safety data from ASSENT-1, an additional uncontrolled safety study of 3,235 TNKase-treated patients, provided the framework to develop a weight-tiered TNKase dose regimen.[3] Exploratory analyses suggested that a weight-adjusted dose of 0.5 mg/kg to 0.6 mg/kg of TNKase resulted in a better patency to bleeding relationship than fixed doses of TNKase across a broad range of patient weights.

INDICATIONS AND USAGE

TNKase is indicated for use in the reduction of mortality associated with acute myocardial infarction (AMI). Treatment should be initiated as soon as possible after the onset of AMI symptoms (see CLINICAL STUDIES).

CONTRAINDICATIONS

TNKase therapy in patients with acute myocardial infarction is contraindicated in the following situations because of an increased risk of bleeding (see WARNINGS):

- **Active internal bleeding**
- **History of cerebrovascular accident**
- **Intracranial or intraspinal surgery or trauma within 2 months**
- **Intracranial neoplasm, arteriovenous malformation, or aneurysm**
- **Known bleeding diathesis**
- **Severe uncontrolled hypertension**

WARNINGS

Bleeding

The most common complication encountered during TNKase therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories:

- Internal bleeding, involving intracranial and retroperitoneal sites, or the gastrointestinal, genitourinary, or respiratory tracts.
- Superficial or surface bleeding, observed mainly at vascular puncture and access sites (e.g., venous cutdowns, arterial punctures) or sites of recent surgical intervention.

Should serious bleeding (not controlled by local pressure) occur, any concomitant heparin or antiplatelet agents should be discontinued immediately.

In clinical studies of TNKase, patients were treated with both aspirin and heparin. Heparin may contribute to the bleeding risks associated with TNKase. The safety of the use of TNKase with other antiplatelet agents has not been adequately studied (see PRECAUTIONS: Drug Interactions). Intramuscular injections and nonessential handling of the patient should be avoided for the first few hours following treatment with TNKase. Venipunctures should be performed and monitored carefully.

Should an arterial puncture be necessary during the first few hours following TNKase therapy, it is preferable to use an upper extremity vessel that is accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding.

Each patient being considered for therapy with TNKase should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy. In the following conditions, the risk of TNKase therapy may be increased and should be weighed against the anticipated benefits:

- Recent major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels
- Cerebrovascular disease
- Recent gastrointestinal or genitourinary bleeding
- Recent trauma
- Hypertension: systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg
- High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- Acute pericarditis
- Subacute bacterial endocarditis
- Hemostatic defects, including those secondary to severe hepatic or renal disease
- Severe hepatic dysfunction
- Pregnancy
- Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions
- Septic thrombophlebitis or occluded AV cannula at seriously infected site
- Advanced age (see PRECAUTIONS: Geriatric Use)
- Patients currently receiving oral anticoagulants, e.g., warfarin sodium
- Recent administration of GP IIb/IIIa inhibitors
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

Cholesterol Embolization

Cholesterol embolism has been reported rarely in patients treated with all types of thrombolytic agents; the true incidence is unknown. This serious condition, which can be lethal, is also associated with invasive vascular procedures (e.g., cardiac catheterization, angiography, vascular surgery) and/or anticoagulant therapy. Clinical features of cholesterol embolism may include livedo reticularis, "purple toe" syndrome, acute renal failure, gangrenous digits, hypertension, pancreatitis, myocardial infarction, cerebral infarction, spinal cord infarction, retinal artery occlusion

Rituxan—Cont.

tions. Since transient hypotension may occur during RITUXAN infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to RITUXAN infusion.

First Infusion: The RITUXAN solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. RITUXAN should not be mixed or diluted with other drugs. If hypersensitivity or infusion reactions do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If a hypersensitivity (non-IgE-mediated) or an infusion reaction develops, the infusion should be temporarily slowed or interrupted (see BOXED WARNINGS and WARNINGS). The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

Subsequent Infusions: If the patient tolerated the first infusion well, subsequent RITUXAN infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr as tolerated. If the patient did not tolerate the first infusion well, follow the guidelines under First Infusion.

Stability and Storage: RITUXAN vials are stable at 2–8°C (36–46°F). Do not use beyond expiration date stamped on carton. RITUXAN vials should be protected from direct sunlight. Refer to the "Preparation and Administration" section for information on the stability and storage of solutions of RITUXAN diluted for infusion.

HOW SUPPLIED

RITUXAN is supplied as 100 mg and 500 mg of sterile, preservative-free, single-use vials.

Single unit 100 mg carton: Contains one 10 mL vial of RITUXAN (10 mg/mL).
NDC 50242-051-21

Single unit 500 mg carton: Contains one 50 mL vial of RITUXAN (10 mg/mL).
NDC 50242-053-06

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(4809705 Revised February 2002)

Shown in Product Identification Guide, page 321

ZEVALIN®

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[zē-vă-lĭn]

(Ibritumomab Tiuxetan)

For intravenous use only as part of Zevalin Therapeutic Regimen

Kits for the Preparation of Indium-111 (In-111) Ibritumomab Tiuxetan (In-111 ZEVALIN) and Yttrium-90 (Y-90) Ibritumomab Tiuxetan (Y-90 ZEVALIN)

In-111 Ibritumomab Tiuxetan and Y-90 Ibritumomab Tiuxetan are components of the ZEVALIN therapeutic regimen (See **Description**).

WARNINGS

Fatal Infusion Reactions: Deaths have occurred within 24 hours of Rituximab infusion, an essential component of the ZEVALIN therapeutic regimen. These fatalities were associated with an infusion reaction symptom complex that included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred in association with the first Rituximab infusion (See **WARNINGS** and **ADVERSE REACTIONS**). Patients who develop severe infusion reactions should have Rituximab, In-111 ZEVALIN, and Y-90 ZEVALIN infusions discontinued and receive medical treatment.

Prolonged and Severe Cytopenias: Y-90 ZEVALIN administration results in severe and prolonged cytopenias in most patients. The ZEVALIN therapeutic regimen should not be administered to patients with ≥ 25% lymphoma marrow involvement and/or impaired bone marrow reserve (See **WARNINGS** and **ADVERSE REACTIONS**).

Dosing

* The prescribed, measured, and administered dose of Y-90 ZEVALIN should not exceed the absolute maximum allowable dose of 32.0 mCi (1184 MBq).
* Y-90 ZEVALIN should not be administered to patients with altered biodistribution as determined by imaging with In-111 ZEVALIN.

In-111 ZEVALIN and Y-90 ZEVALIN are radiopharmaceuticals and should be used only by physicians and other professionals qualified by training and experienced in the safe use and handling of radionuclides.

DESCRIPTION

ZEVALIN®

ZEVALIN (Ibritumomab Tiuxetan) is the immunoconjugate resulting from a stable thiourea covalent bond between the monoclonal antibody Ibritumomab and the linker-chelator tiuxetan [N-[2-bis(carboxymethyl)amino]-3-(p-isothiocyanatophenyl)-propyl]-[N-[2-bis(carboxymethyl)amino]-2-(methyl)-ethyl]glycine. This linker-chelator provides a high affinity, conformationally restricted chelation site for Indium-111 or Yttrium-90. The approximate molecular weight of Ibritumomab Tiuxetan is 148 kD.

The antibody moiety of ZEVALIN is Ibritumomab, a murine IgG1 kappa monoclonal antibody directed against the CD20 antigen, which is found on the surface of normal and malignant B lymphocytes. Ibritumomab is produced in Chinese hamster ovary cells and is composed of two murine gamma 1 heavy chains of 445 amino acids each and two kappa light chains of 213 amino acids each.

ZEVALIN Therapeutic Regimen

The ZEVALIN therapeutic regimen is administered in two

ZEVALIN is supplied as two separate and distinctly labeled kits that contain all of the non-radioactive ingredients necessary to produce a single dose of In-111 ZEVALIN and a single dose of Y-90 ZEVALIN, both essential components of the ZEVALIN therapeutic regimen. Indium-111 chloride and Rituximab must be ordered separately from the ZEVALIN kit. Yttrium-90 chloride sterile solution is supplied by MDS Nordion when the Y-90 ZEVALIN kit is ordered.

ZEVALIN Kits

Each of the two ZEVALIN kits contains four vials that are used to produce a single dose of either In-111 ZEVALIN or Y-90 ZEVALIN, as indicated on the outer container label:

(1) One (1) ZEVALIN Vial containing 3.2 mg of Ibritumomab Tiuxetan in 2 mL of 0.9% sodium chloride solution; a sterile, pyrogen-free, clear, colorless solution that may contain translucent particles; no preservative present.

(2) One (1) 50 mM Sodium Acetate Vial containing 13.6 mg of sodium acetate trihydrate in 2 mL of Water for Injection; a sterile, pyrogen-free, clear, colorless solution; no preservative present.

(3) One (1) Formulation Buffer Vial containing 750 mg of Albumin (Human), 76 mg of sodium chloride, 28 mg of sodium phosphate dibasic dodecahydrate, 4 mg of pentetic acid, 2 mg of potassium phosphate monobasic and 2 mg of potassium chloride in 10 mL of Water for Injection adjusted to pH 7.1 with either sodium hydroxide or hydrochloric acid; a sterile, pyrogen-free, clear yellow to amber colored solution; no preservative present.

(4) One (1) empty Reaction Vial, sterile, pyrogen-free.

Physical/Radiochemical Characteristics of In-111

Indium-111 decays by electron capture, with a physical half-life of 67.3 hours (2.81 days)[1]. The product of radioactive decay is nonradioactive cadmium-111. Radiation emission data for In-111 are summarized in Table 1.

Table 1.
Principal In-111 Radiation Emission Data

Radiation	Mean % per Disintegration	Mean Energy (keV)
Gamma-2	90.2	171.3
Gamma-3	94.0	245.4

External Radiation

The exposure rate constant for 37 MBq (1 mCi) of In-111 is 8.3×10^{-4} C/kg/hr (3.2 R/hr) at 1 cm. Adequate shielding should be used with this gamma-emitter, in accordance with institutional good radiation safety practices.

To allow correction for physical decay of In-111, the fractions that remain at selected intervals before and after the time of calibration are shown in Table 2.

Table 2.
Physical Decay Chart: In-111
Half-life 2.81 Days (67.3 Hours)

Calibration Time (Hrs.)	Fraction Remaining
-48	1.64
-42	1.54
-36	1.45
-24	1.28
-12	1.13
-6	1.06
0	1.00
6	0.94
12	0.88
24	0.78
36	0.69
42	0.65
48	0.61

Physical/Radiochemical Characteristics of Y-90

Yttrium-90 decays by emission of beta particles, with a physical half-life of 64.1 hours (2.67 days)[1]. The product of radioactive decay is non-radioactive zirconium-90. The range of beta particles in soft tissue (X_{90}) is 5 mm. Radiation emission data for Y-90 are summarized in Table 3.

Table 3.
Principal Y-90 Radiation Emission Data

Radiation	Mean % per Disintegration	Mean Energy (keV)
Beta minus	100	750-935

External Radiation

The exposure rate for 37 MBq (1 mCi) of Y-90 is 8.3×10^{-3} C/kg/hr (32 R/hr) at the mouth of an open Y-90 vial. Adequate shielding should be used with this beta-emitter, in ac-

tion should not receive any further infusions and seek prompt medical evaluation. Skin biopsy may help to distinguish among different mucocutaneous reactions and guide subsequent treatment. The safety of readministration of RITUXAN to patients with any of these mucocutaneous reactions has not been determined.

PRECAUTIONS

Laboratory Monitoring: Because RITUXAN targets all CD20-positive B lymphocytes, malignant and nonmalignant, complete blood counts (CBC) and platelet counts should be obtained at regular intervals during RITUXAN therapy and more frequently in patients who develop cytopenias (see ADVERSE REACTIONS). The duration of cytopenias caused by RITUXAN can extend well beyond the treatment period.

Drug/Laboratory Interactions: There have been no formal drug interaction studies performed with RITUXAN. However, renal toxicity was seen with this drug in combination with cisplatin in clinical trials. (See WARNINGS, Renal.)

HACA Formation: Human antichimeric antibody (HACA) was detected in 4 of 356 patients and 3 had an objective clinical response. The data reflect the percentage of patients whose test results were considered positive for antibodies to RITUXAN using an enzyme-linked immunosorbant assay (limit of detection = 7 ng/mL). The observed incidence of antibody positivity in an assay is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to RITUXAN with the incidence of antibodies to other products may be misleading.

Immunization: The safety of immunization with live viral vaccines following RITUXAN therapy has not been studied. The ability to generate a primary or anamnestic humoral response to vaccination is currently being studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of RITUXAN, or to determine its effects on fertility in males or females. Individuals of childbearing potential should use effective contraceptive methods during treatment and for up to 12 months following RITUXAN therapy.

Pregnancy Category C: Animal reproduction studies have not been conducted with RITUXAN. It is not known whether RITUXAN can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. Human IgG is known to pass the placental barrier, and thus may potentially cause fetal B-cell depletion; therefore, RITUXAN should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether RITUXAN is excreted in human milk. Because human IgG is excreted in human milk and the potential for absorption and immunosuppression in the infant is unknown, women should be advised to discontinue nursing until circulating drug levels are no longer detectable. (See CLINICAL PHARMACOLOGY.)

Pediatric Use: The safety and effectiveness of RITUXAN in pediatric patients have not been established.

Geriatric Use: Among the 331 patients enrolled in clinical studies of single agent RITUXAN, 24% were 65 to 75 years old and 5% were 75 years old and older. The overall response rates were higher in older (age ≥ 65 years) vs. younger (age < 65 years) patients (52% vs. 44%, respectively). However, the median duration of response, based on Kaplan-Meier estimates, was shorter in older vs. younger patients: 10.1 months (range, 1.9 to 36.5+) vs. 11.4 months (range, 2.1 to 42.1+), respectively. This shorter duration of response was not statistically significant. Adverse reactions, including incidence, severity and type of adverse reaction were similar between older and younger patients.

ADVERSE REACTIONS

The most serious adverse reactions caused by RITUXAN include infusion reactions, tumor lysis syndrome, mucocutaneous reactions, hypersensitivity reactions, cardiac arrhythmias and angina, and renal failure. Please refer to the BOXED WARNINGS and WARNINGS sections for detailed descriptions of these reactions. Infusion reactions and lymphopenia are the most commonly occurring 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 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 postmarketing use of RITUXAN. 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 RITUXAN 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 RITUXAN.

Where specific percentages are noted, these data are based on 356 patients treated in nonrandomized, single-arm studies of RITUXAN administered as a single agent. Most patients received RITUXAN 375 mg/m^2 weekly for 4 doses (≥10 cm) and 60 patients who received more than 1 course of RITUXAN. Thirty-seven patients received 375 mg/m^2 for 8 doses and 25 patients received doses other than 375 mg/m^2 for 4 doses and up to 500 mg/m^2 single dose in the Phase 1 setting. Adverse events of greater severity are referred to as "Grade 3 and 4 events" defined by the commonly used National Cancer Institute Common Toxicity Criteria.[17]

Table 3
Incidence of Adverse Events ≥ 5% of Patients in Clinical Trials (N = 356) (Adverse Events were followed for a period of 12 months following RITUXAN therapy.)

	All Grades (%)	Grade 3 and 4 (%)
Any Adverse Events	**99**	**57**
Body as a Whole	**86**	**10**
Fever	53	1
Chills	33	3
Infection	31	4
Asthenia	26	1
Headache	19	1
Abdominal Pain	14	1
Pain	12	1
Back Pain	10	1
Throat Irritation	9	0
Flushing	5	0
Cardiovascular System	**25**	**3**
Hypotension	10	1
Hypertension	6	1
Digestive System	**37**	**2**
Nausea	23	1
Diarrhea	10	1
Vomiting	10	1
Hemic and Lymphatic System	**67**	**48**
Lymphopenia	48	40
Leukopenia	14	4
Neutropenia	14	6
Thrombocytopenia	12	2
Anemia	8	3
Metabolic and Nutritional Disorders	**38**	**3**
Angioedema	11	1
Hyperglycemia	9	1
Peripheral Edema	8	0
LDH Increase	7	0
Musculoskeletal System	**26**	**3**
Myalgia	10	1
Arthralgia	10	1
Nervous System	**32**	**1**
Dizziness	10	1
Anxiety	5	1
Respiratory System	**38**	**4**
Increased Cough	13	1
Rhinitis	12	1
Bronchospasm	8	1
Dyspnea	7	1
Sinusitis	6	0
Skin and Appendages	**44**	**2**
Night Sweats	15	1
Rash	15	1
Pruritus	14	1
Urticaria	8	1

Risk Factors Associated with Increased Rates of Adverse Events:

Administration of RITUXAN weekly for 8 doses resulted in higher rates of Grade 3 and 4 adverse events[17] overall (70%) compared with administration weekly for 4 doses (57%). The incidence of Grade 3 or 4 adverse events was similar in patients retreated with RITUXAN compared with initial treatment (58% and 57%, respectively). The incidence of the following clinically significant adverse events was higher in patients with bulky disease (lesions ≥10 cm) (N = 39) versus patients with lesions < 10 cm (N = 195): abdominal pain, anemia, dyspnea, hypotension, and neutropenia.

Infusion Reactions (See BOXED WARNINGS and WARNINGS): Mild to moderate infusion reactions consisting of fever and chills/rigors occurred in the majority of patients during the first RITUXAN infusion. Other frequent infusion reaction symptoms included nausea, pruritus, angioedema, asthenia, hypotension, headache, bronchospasm, throat irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and hypertension. These reactions generally occurred within 30 to 120 minutes of beginning the first infusion, and resolved with slowing or interruption of the RITUXAN infusion and with supportive care (diphenhydramine, acetaminophen, IV saline, and vasopressors). In an analysis of data from 356 patients with relapsed or refractory, low-grade NHL who received 4 (N = 319) or 8 (N = 37) weekly infusions of RITUXAN, the incidence of infusion reactions was highest during the first infusion (77%) and decreased with each subsequent infusion (30% with fourth infusion and 14% with eighth infusion).

Infectious Events: RITUXAN induced B-cell depletion in 70% to 80% of patients and was associated with decreased serum immunoglobulins in a minority of patients; the lymphopenia lasted a median of 14 days (range, 1 to 588 days). Infectious events occurred in 31% of patients: 19% of patients had fungal infections, and 6% were unknown infections. Incidence is not additive because a single patient may have had more than one type of infection. Serious infectious events (Grade 3 or 4),[17] including sepsis occurred in 2% of patients.

Hematologic Events: Grade 3 and 4 cytopenias[17] were reported in 12% of patients treated with RITUXAN; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following RITUXAN therapy were reported. In addition, there have been rare postmarketing reports of prolonged pancytopenia and marrow hypoplasia.

Cardiac Events (See BOXED WARNINGS): Grade 3 or 4 cardiac-related events include hypotension. Rare, fatal cardiac failure with symptomatic onset weeks after RITUXAN has also been reported. Patients who develop clinically significant cardiopulmonary events should have RITUXAN infusion discontinued.

Pulmonary Events (See BOXED WARNINGS): 135 patients (38%) experienced pulmonary events. The most common respiratory system adverse events experienced were increased cough, rhinitis, bronchospasm, dyspnea, and sinusitis. Three pulmonary events have been reported in temporal association with RITUXAN infusion as a single agent: acute bronchospasm, acute pneumonitis presenting 1–4 weeks post-RITUXAN infusion, and bronchiolitis obliterans. One case of bronchiolitis obliterans was associated with progressive pulmonary symptoms and culminated in death several months following the last RITUXAN infusion. The safety of resumption or continued administration of RITUXAN in patients with pneumonitis or bronchiolitis obliterans is unknown.

Immune/Autoimmune Events: Immune/autoimmune events have been reported, including uveitis, optic neuritis in a patient with systemic vasculitis, pleuritis in a patient with a lupus-like syndrome, serum sickness with polyarticular arthritis, and vasculitis with rash.

Less Commonly Observed Events: In clinical trials, < 5% and > 1% of the patients experienced the following events regardless of causality assessment: agitation, anorexia, arthritis, conjunctivitis, depression, dyspepsia, edema, hyperkinesia, hypertonia, hypesthesia, hypoglycemia, injection site pain, insomnia, lacrimation disorder, malaise, nervousness, neuritis, neuropathy, paresthesia, somnolence, vertigo, weight decrease.

OVERDOSAGE

There has been no experience with overdosage in human clinical trials. Single doses of up to 500 mg/m^2 have been given in controlled clinical trials.[10]

DOSAGE AND ADMINISTRATION

Initial Therapy:

RITUXAN is given at 375 mg/m^2 IV infusion once weekly for 4 or 8 doses.

Retreatment Therapy:

Patients who subsequently develop progressive disease may be safely retreated with RITUXAN 375 mg/m^2 IV infusion once weekly for 4 doses. Currently there are limited data concerning more than 2 courses.

RITUXAN as a Component of Zevalin™ (Ibritumomab Tiuxetan) Therapeutic Regimen:

As a required component of the Zevalin therapeutic regimen, RITUXAN 250 mg/m^2 should be infused within 4 hours prior to the administration of Indium-111-(In-111-) Zevalin and within 4 hours prior to the administration of Yttrium-90-(Y-90-) Zevalin. Administration of RITUXAN and In-111-Zevalin should precede RITUXAN and Y-90-Zevalin by 7–9 days. Refer to the Zevalin package insert for full prescribing information regarding the Zevalin therapeutic regimen.

RITUXAN may be administered in an outpatient setting. **DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. (See Administration.)**

Instructions for Administration

Preparation for Administration: Use appropriate aseptic technique. Withdraw the necessary amount of RITUXAN and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

RITUXAN solutions for infusion may be stored at 2–8°C (36–46°F) for 24 hours. RITUXAN solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since RITUXAN solutions do not contain a preservative, diluted solutions should be stored refrigerated (2–8°C). No incompatibilities between RITUXAN and polyvinylchloride or polyethylene bags have been observed.

Administration: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

Infusion and hypersensitivity reactions may occur (see BOXED WARNINGS, WARNINGS, and ADVERSE REACTIONS). Premedication consisting of acetaminophen and diphenhydramine should be considered before each infusion of RITUXAN. Premedication may attenuate infusion reac-

Table 4.
Physical Decay Chart: Y-90
Half-life 2.67 Days (64.1 Hours)

Calibration Time (Hrs.)	Fraction Remaining	Calibration Time (Hrs.)	Fraction Remaining
-36	1.48	0	1.00
-24	1.30	1	0.99
-12	1.14	2	0.98
-8	1.09	3	0.97
-7	1.08	4	0.96
-6	1.07	5	0.95
-5	1.06	6	0.94
-4	1.04	7	0.93
-3	1.03	8	0.92
-2	1.02	12	0.88
-1	1.01	24	0.77
0	1.00	36	0.68

CLINICAL PHARMACOLOGY

General Pharmacology

Ibritumomab Tiuxetan binds specifically to the CD20 antigen (human B-lymphocyte-restricted differentiation antigen, Bp35)[2, 3]. The apparent affinity (K_D) of Ibritumomab Tiuxetan for the CD20 antigen ranges between approximately 14 to 18 nM. The CD20 antigen is expressed on pre-B and mature B lymphocytes and on > 90% of B-cell non-Hodgkin's lymphomas (NHL)[4, 5]. The CD20 antigen is not shed from the cell surface and does not internalize upon antibody binding[6].

Mechanism of Action: The complementarity-determining regions of Ibritumomab bind to the CD20 antigen on B lymphocytes. Ibritumomab, like Rituximab, induces apoptosis in CD20+ B-cell lines in vitro[6]. The chelate tiuxetan, which tightly binds In-111 or Y-90, is covalently linked to the amino groups of exposed lysines and arginines contained within the antibody. The beta emission from Y-90 induces cellular damage by the formation of free radicals in the target and neighboring cells[7].

Normal Human Tissue Cross-Reactivity: Ibritumomab Tiuxetan binding was observed in vitro on lymphoid cells of the bone marrow, lymph node, thymus, red and white pulp of the spleen, and lymphoid follicles of the tonsil, as well as lymphoid nodules of other organs such as the large and small intestines. Binding was not observed on the nonlymphoid tissues or gonadal tissues (see **CLINICAL PHARMACOLOGY, Radiation Dosimetry**)

Pharmacokinetics / Pharmacodynamics

Pharmacokinetic and biodistribution studies were performed using In-111 ZEVALIN (5 mCi [185 MBq] In-111, 1.6 mg Ibritumomab Tiuxetan). In an early study designed to assess the need for pre-administration of unlabeled antibody, only 18% of known sites of disease were imaged when In-111 ZEVALIN was administered without unlabeled Ibritumomab. When preceded by unlabeled Ibritumomab (1.0 mg/kg or 2.5 mg/kg), In-111 ZEVALIN detected 56% and 92% of known disease sites, respectively. These studies were conducted with a Zevalin therapeutic regimen that included unlabeled Ibritumomab.

In pharmacokinetic studies of patients receiving the ZEVALIN therapeutic regimen, the mean effective half-life for Y-90 activity in blood was 30 hours, and the mean area under the fraction of injected activity (FIA) vs. time curve in blood was 39 hours. Over 7 days, a median of 7.2% of the injected activity was excreted in urine.

In clinical studies, administration of the ZEVALIN therapeutic regimen resulted in sustained depletion of circulating B cells. At four weeks, the median number of circulating B cells was zero (range, 0-1084 cell/mm^3). B-cell recovery began at approximately 12 weeks following treatment, and the median level of B cells was within the normal range (32 to 341 cells/mm^3) by 9 months after treatment. Median serum levels of IgG and IgA remained within the normal range throughout the period of B-cell depletion. Median IgM serum levels dropped below normal (median 49 mg/dL, range 13-3990 mg/dL) after treatment and recovered to normal values by 6 month post therapy.

Radiation Dosimetry

Estimations of radiation-absorbed doses for In-111 ZEVALIN and Y-90 ZEVALIN were performed using sequential whole body images and the MIRDOSE 3 software program[8, 9]. The estimated radiation absorbed doses to organs and marrow from a course of the ZEVALIN therapeutic regimen are summarized in Table 5. Absorbed dose estimates for the lower large intestine, upper large intestine, and small intestine have been modified from the standard MIRDOSE 3 output to account for the assumption that activity is within the intestine wall rather than the intestine contents.

[See table 5 above]

CLINICAL STUDIES

The safety and efficacy of the ZEVALIN therapeutic regimen were evaluated in two multi-center trials enrolling a total of 197 subjects. The ZEVALIN therapeutic regimen was administered in two steps (see **DOSAGE** and **ADMINISTRATION**). The activity and toxicity of a variation of the ZEVALIN therapeutic regimen employing a reduced dose of Y-90 ZEVALIN was further defined in a third study enrolling a total of 30 patients who had mild thrombocytopenia

Table 5.
Estimated Radiation Absorbed Doses From Y-90 ZEVALIN and In-111 ZEVALIN

Organ	Y-90 ZEVALIN mGy/MBq Median	Y-90 ZEVALIN mGy/MBq Range	In-111 ZEVALIN mGy/MBq Median	In-111 ZEVALIN mGy/MBq Range
Spleen[1]	9.4	1.8-14.4	0.9	0.2-1.2
Testes[1]	9.1	5.4-11.4	0.6	0.4-0.8
Liver[1]	4.8	2.3-8.1	0.7	0.3-1.1
Lower Large Intestinal Wall[1]	4.8	3.1-8.2	0.4	0.2-0.6
Upper Large Intestinal Wall[1]	3.6	2.0-6.7	0.3	0.2-0.6
Heart Wall[1]	2.8	1.5-3.2	0.4	0.2-0.5
Lungs[1]	2.0	1.2-3.4	0.2	0.1-0.4
Small Intestine[1]	1.4	0.8-2.1	0.2	0.1-0.3
Red Marrow[2]	1.3	0.7-1.8	0.2	0.1-0.2
Urinary Bladder Wall[3]	0.9	0.7-2.1	0.2	0.1-0.2
Bone Surfaces[2]	0.9	0.5-1.2	0.2	0.1-0.2
Ovaries[3]	0.4	0.3-0.5	0.2	0.2-0.2
Uterus[3]	0.4	0.3-0.5	0.2	0.1-0.2
Adrenals[3]	0.3	0.0-0.5	0.2	0.1-0.3
Brain[3]	0.3	0.0-0.5	0.1	0.0-0.1
Breasts[3]	0.3	0.0-0.5	0.1	0.0-0.1
Gallbladder Wall[3]	0.3	0.0-0.5	0.3	0.1-0.4
Muscle[3]	0.3	0.0-0.5	0.1	0.0-0.1
Pancreas[3]	0.3	0.0-0.5	0.2	0.1-0.3
Skin[3]	0.3	0.0-0.5	0.1	0.0-0.1
Stomach[3]	0.3	0.0-0.5	0.1	0.1-0.2
Thymus[3]	0.3	0.0-0.5	0.1	0.1-0.2
Thyroid[3]	0.3	0.0-0.5	0.1	0.0-0.1
Kidneys[1]	0.1	0.0-0.2	0.2	0.1-0.2
Total Body[3]	0.5	0.2-0.7	0.1	0.1-0.2

[1] Organ region of interest
[2] Sacrum region of interest[10]
[3] Whole body region of interest

Table 6.
Summary of Efficacy Data[1]

	Study 1	Study 2	
	ZEVALIN therapeutic regimen N = 54	ZEVALIN therapeutic regimen N = 73	Rituximab N = 70
Overall Response Rate (%)	74	80	56
Complete Response Rate (%)	15	30	16
CRu Rate[2] (%)	0	4	4
Median DR[3,4] (Months) [Range[5]]	6.4 [0.5-24.9+]	13.9 [1.0-30.1+]	11.8 [1.2-24.5]
Median TTP[3,6] (Months) [Range[5]]	6.8 [1.1-25.9+]	11.2 [0.8-31.5+]	10.1 [0.7-26.1]

[1]IWRC: International Workshop response criteria
[2]CRu: Unconfirmed complete response
[3]Estimated with observed range.
[4]Duration of response: interval from the onset of response to disease progression.
[5]"+" indicates an ongoing response.
[6]Time to Disease Progression: interval from the first infusion to disease progression.

Study 1 was a single arm study of 54 patients with relapsed follicular lymphoma refractory to Rituximab treatment. Patients were considered refractory if their last prior treatment with Rituximab did not result in a complete or partial response, or if time to disease progression (TTP) was < 6 months[11]. The primary efficacy endpoint of the study was the overall response rate (ORR) using the International Workshop Response Criteria (IWRC)[12]. Secondary efficacy endpoints included time to disease progression (TTP) and duration of response (DR). In a secondary analysis comparing objective response to the ZEVALIN therapeutic regimen with that observed with the most recent treatment with Rituximab, the median duration of response following the ZEVALIN therapeutic regimen was 6 vs. 4 months. Table 6 summarizes efficacy data from this study.

Study 2 was a randomized, controlled, multicenter study comparing the ZEVALIN therapeutic regimen to treatment with Rituximab. The trial was conducted in 143 patients with relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma (NHL), or transformed B-cell NHL. A total of 73 patients received the ZEVALIN therapeutic regimen, and 70 patients received Rituximab given as an IV infusion at 375 mg/m^2 weekly times 4 doses. The primary efficacy endpoint of the study was to determine the ORR using the IWRC[12] (see Table 6). The ORR was significantly higher (80% vs. 56%, p = 0.002)[13] for patients treated with the ZEVALIN therapeutic regimen. The secondary endpoints, duration of response and time to progression, were not significantly different between the two treatment arms.

[See table 6 above]

Study 3 was a single arm study of 30 patients with relapsed or refractory low-grade, follicular, or transformed B-cell NHL who had mild thrombocytopenia (platelet count 100,000 to 149,000 cells/mm^3). Excluded from the study were patients with ≥ 25% lymphoma marrow involvement and/or impaired bone marrow reserve. Patients were considered to have impaired bone marrow reserve if they had any of the following: prior myeloablative therapy with stem

tive marrow; a platelet count <100,000 cells/mm^3; or neutrophil count < 1,500 cells/mm^3. In this study, a modification of the ZEVALIN therapeutic regimen with a lower specific activity Y-90 ZEVALIN dose [(Y-90 ZEVALIN at 0.3 mCi/kg (11.1 MBq/kg)] was used. Objective, durable clinical responses were observed [67% ORR (95% CI: 48-85%)[14], 11.8 months median DR (range: 4-17 months)] and resulted in a greater incidence of hematologic toxicity (see **ADVERSE REACTIONS**) than in Studies 1 and 2.

INDICATIONS AND USAGE

ZEVALIN, as part of the ZEVALIN therapeutic regimen (see **DOSAGE AND ADMINISTRATION**), is indicated for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma, including patients with Rituximab refractory follicular non-Hodgkin's lymphoma. Determination of the effectiveness of the ZEVALIN therapeutic regimen in a relapsed or refractory patient population is based on overall response rates (see **CLINICAL STUDIES**). The effects of the ZEVALIN therapeutic regimen on survival are not known.

CONTRAINDICATIONS

The ZEVALIN therapeutic regimen is contraindicated in patients with known Type I hypersensitivity or anaphylactic reactions to murine proteins or to any component of this product, including Rituximab, yttrium chloride, and indium chloride.

WARNINGS (SEE BOXED WARNING)

Altered Biodistribution: Y-90 ZEVALIN should not be administered to patients with altered biodistribution of In-111 ZEVALIN. The expected biodistribution of In-111 ZEVALIN includes easily detectable uptake in the blood pool areas on the first day image, with less activity in the blood pool areas on the second or third day image; moderately high to high uptake in normal liver and spleen during the first day and the second or third day image; and moderately low or very low uptake in normal kidneys, urinary bladder, and normal bowel on the first day image and the second or third day

Zevalin—Cont.

image. Altered biodistribution of In-111 ZEVALIN can be characterized by diffuse uptake in normal lung more intense than the cardiac blood pool on the first day image or more intense than the liver on the second or third day image; kidneys with greater intensity than the liver on the posterior view of the second or third day image; or intense areas of uptake throughout the normal bowel comparable to uptake by the liver on the second or third day images.

Severe Infusion Reactions (See PRECAUTIONS, Hypersensitivity):

The ZEVALIN therapeutic regimen may cause severe, and potentially fatal, infusion reactions. These severe reactions typically occur during the first Rituximab infusion with time to onset of 30 to 120 minutes. Signs and symptoms of severe infusion reaction may include hypotension, angioedema, hypoxia, or bronchospasm, and may require interruption of Rituximab, In-111 ZEVALIN, or Y-90 ZEVALIN administration. The most severe manifestations and sequelae may include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. **Because the ZEVALIN therapeutic regimen includes the use of Rituximab, see also prescribing information for RITUXAN (Rituximab).**

Cytopenias (See ADVERSE REACTIONS, Hematologic Events):

The most common severe adverse events reported with the ZEVALIN therapeutic regimen were thrombocytopenia (61% of patients with platelet counts <50,000 cells/mm^3) and neutropenia (57% of patients with absolute neutrophil count (ANC) <1,000 cells/mm^3) in patients with ≥150,000 platelets/mm^3 prior to treatment. Both incidences of severe thrombocytopenia and neutropenia increase to 78% and 74% for patients with mild thrombocytopenia at baseline (platelet count of 100,000 to 149,000 cells/mm^3). For all patients, the median time to nadir was 7-9 weeks and the median duration of cytopenias was 22-35 days. In <5% of cases, patients experienced severe cytopenia that extended beyond the prospectively defined protocol treatment period of 12 weeks following administration of the ZEVALIN therapeutic regimen. Some of these patients eventually recovered from cytopenia, while others experienced progressive disease, received further anti-cancer therapy, or died of their lymphoma without having recovered from cytopenia. The cytopenias may have influenced subsequent treatment decisions.

Hemorrhage, including fatal cerebral hemorrhage, and severe infections have occurred in a minority of patients in clinical studies. Careful monitoring for and management of cytopenias and their complications (e.g., febrile neutropenia, hemorrhage) for up to 3 months after use of the ZEVALIN therapeutic regimen are necessary. Caution should be exercised in treating patients with drugs that interfere with platelet function or coagulation following the ZEVALIN therapeutic regimen and patients receiving such agents should be closely monitored.

The ZEVALIN therapeutic regimen should not be administered to patients with ≥ 25% lymphoma marrow involvement and/or impaired bone marrow reserve, e.g., prior myeloablative therapies; platelet count < 100,000 cells/mm^3; neutrophil count < 1,500 cells/mm^3; hypocellular bone marrow (≤ 15% cellularity or marked reduction in bone marrow precursors); or to patients with a history of failed stem cell collection.

Secondary Malignancies: Out of 349 patients treated with the ZEVALIN therapeutic regimen, three cases of acute myelogenous leukemia and two cases of myelodysplastic syndrome have been reported following the ZEVALIN therapeutic regimen (see **ADVERSE REACTIONS**).

Pregnancy Category D: Y-90 ZEVALIN can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Creutzfeldt-Jakob disease (CJD): This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS

The ZEVALIN therapeutic regimen is intended as a single course treatment. The safety and toxicity profile from multiple courses of the ZEVALIN therapeutic regimen or of other forms of therapeutic irradiation preceding, following, or in combination with the ZEVALIN therapeutic regimen have not been established.

to minimize radiation exposure to patients and to medical personnel, consistent with institutional good radiation safety practices and patient management procedures.

Hypersensitivity: Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines and corticosteroids, should be available for immediate use in the event of an allergic reaction during administration of ZEVALIN. Patients who have received murine proteins should be screened for human anti-mouse antibodies (HAMA). Patients with evidence of HAMA have not been studied and may be at increased risk of allergic or serious hypersensitivity reactions during ZEVALIN therapeutic regimen administrations.

Immunization: The safety of immunization with live viral vaccines following the ZEVALIN therapeutic regimen has not been studied. Also, the ability of patients who received the ZEVALIN therapeutic regimen to generate a primary or anamnestic humoral response to any vaccine has not been studied.

Laboratory Monitoring: Complete blood counts (CBC) and platelet counts should be obtained weekly following the ZEVALIN therapeutic regimen and should continue until levels recover. CBC and platelet counts should be monitored more frequently in patients who develop severe cytopenia, or as clinically indicated.

Drug Interactions: No formal drug interaction studies have been performed with ZEVALIN. Due to the frequent occurrence of severe and prolonged thrombocytopenia, the potential benefits of medications which interfere with platelet function and/or anticoagulation should be weighed against the potential increased risks of bleeding and hemorrhage. Patients receiving medications that interfere with platelet function or coagulation should have more frequent laboratory monitoring for thrombocytopenia. In addition, the transfusion practices for such patients may need to be modified given the increased risk of bleeding.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of the ZEVALIN therapeutic regimen, or to determine its effects on fertility in males or females. However, radiation is a potential carcinogen and mutagen. The ZEVALIN therapeutic regimen results in a significant radiation dose to the testes. The radiation dose to the ovaries has not been established. There have been no studies to evaluate whether the ZEVALIN therapeutic regimen causes hypogonadism, premature menopause, azoospermia and/or mutagenic alterations to germ cells. There is a potential risk that the ZEVALIN therapeutic regimen could cause toxic effects on the male and female gonads. Effective contraceptive methods should be used during treatment and for up to 12 months following the ZEVALIN therapeutic regimen.

Pregnancy Category D: SEE WARNINGS.

Nursing Mothers: It is not known whether ZEVALIN is excreted in human milk. Because human IgG is excreted in human milk and the potential for ZEVALIN exposure in the infant is unknown, women should be advised to discontinue nursing and formula feeding should be substituted for breast feedings (see **CLINICAL PHARMACOLOGY**).

Geriatric Use: Of 349 patients treated with the ZEVALIN therapeutic regimen in clinical studies, 38% (132 patients) were age 65 years and over, while 12% (41 patients) were age 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pediatric Use: The safety and effectiveness of the ZEVALIN therapeutic regimen in children have not been established.

ADVERSE REACTIONS

Safety data, except where indicated, are based upon 349 patients treated in 5 clinical studies with the ZEVALIN therapeutic regimen (see **DOSAGE AND ADMINISTRATION**). Because the ZEVALIN therapeutic regimen includes the use of Rituximab, also see prescribing information for RITUXAN (Rituximab).

The most serious adverse reactions caused by the ZEVALIN therapeutic regimen include infections (predominantly bacterial in origin), allergic reactions (bronchospasm and angioedema), and hemorrhage while thrombocytopenic (resulting in deaths). In addition, patients who have received the ZEVALIN therapeutic regimen have developed myeloid malignancies and dysplasias. Fatal infusion reactions have occurred following the infusion of Rituximab. Please refer to the **BOXED WARNINGS** and **WARNINGS** sections for detailed descriptions of these reactions.

The most common toxicities reported were neutropenia, thrombocytopenia, anemia, gastrointestinal symptoms (nausea, vomiting, abdominal pain, and diarrhea), increased cough, dyspnea, dizziness, arthralgia, anorexia, anxiety, and ecchymosis. Hematologic toxicity was often severe and prolonged, whereas most non-hematologic toxicity was mild in severity. Table 7 lists adverse events that occurred in ≥ 5% of patients. A more detailed description of

Table 7.
Incidence of Adverse Events in ≥ 5% of Patients Receiving the ZEVALIN Therapeutic Regimen† (N = 349)

	All Grades %	Grade 3/4 %
Any Adverse Event	**99**	**89**
Body as a Whole	**80**	**12**
Asthenia	43	3
Infection	29	5
Chills	24	<1
Fever	17	1
Abdominal Pain	16	3
Pain	13	1
Headache	12	1
Throat Irritation	10	0
Back Pain	8	1
Flushing	6	0
Cardiovascular System	**17**	**3**
Hypotension	6	1
Digestive System	**48**	**3**
Nausea	31	1
Vomiting	12	0
Diarrhea	9	<1
Anorexia	8	0
Abdominal enlargement	5	0
Constipation	5	0
Hemic and Lymphatic System	**98**	**86**
Thrombocytopenia	95	63
Neutropenia	77	60
Anemia	61	17
Ecchymosis	7	<1
Metabolic and Nutritional Disorders	**23**	**3**
Peripheral Edema	8	1
Angioedema	5	<1
Musculoskeletal System	**18**	**1**
Arthralgia	7	1
Myalgia	7	<1
Nervous System	**27**	**2**
Dizziness	10	<1
Insomnia	5	0
Respiratory System	**36**	**3**
Dyspnea	14	2
Increased Cough	10	0
Rhinitis	6	0
Bronchospasm	5	0
Skin and Appendages	**28**	**1**
Pruritus	9	<1
Rash	8	<1
Special Senses	**7**	**<1**
Urogenital System	**6**	**<1**

† Adverse events were followed for a period of 12 weeks following the first Rituximab infusion of the ZEVALIN therapeutic regimen

Note: All adverse events are included, regardless of relationship.

The following adverse events (except for those noted in Table 7) occurred in between 1 and 4% of patients during the treatment period: urticaria (4%), anxiety (4%), dyspepsia (4%), sweats (4%), petechia (3%), epistaxis (3%), allergic reaction (2%), and melena (2%).

Severe or life-threatening adverse events occurring in 1-5% of patients (except for those noted in Table 7) consisted of pancytopenia (2%), allergic reaction (1%), gastrointestinal hemorrhage (1%), melena (1%), tumor pain (1%), and apnea (1%). The following severe or life threatening events occurred in <1% of patients: angioedema, tachycardia, urticaria, arthritis, lung edema, pulmonary embolus, encephalopathy, hematemesis, subdural hematoma, and vaginal hemorrhage.

Hematologic Events: Hematologic toxicity was the most frequently observed adverse event in clinical trials. Table 8 presents the incidence and duration of severe hematologic toxicity for patients with normal baseline platelet count (≥ 150,000 cells/mm^3) treated with the ZEVALIN therapeutic regimen and patients with mild thrombocytopenia (platelet count 100,000 to 149,000 cells/mm^3) at baseline who were treated with a modified ZEVALIN therapeutic regimen that included a lower Y-90 ZEVALIN dose at 0.3 mCi/kg (11.1 MBq/kg)

mation on growth factor use and platelet transfusions is based on 211 patients for whom data were collected. Filgrastim was given to 13% of patients and erythropoietin to 8%. Platelet transfusions were given to 22% of patients and red blood cell transfusions to 20%.

Infectious Events: During the first 3 months after initiating the ZEVALIN therapeutic regimen, 29% of patients developed infections. Three percent of patients developed serious infections comprising urinary tract infection, febrile neutropenia, sepsis, pneumonia, cellulitis, colitis, diarrhea, osteomyelitis, and upper respiratory tract infection. Life threatening infections were reported for 2% of patients that included sepsis, empyema, pneumonia, febrile neutropenia, fever, and biliary stent-associated cholangitis. During follow-up from 3 months to 4 years after the start of treatment with ZEVALIN, 6% of patients developed infections. Two percent of patients had serious infections comprising urinary tract infection, bacterial or viral pneumonia, febrile neutropenia, perihilar infiltrate, pericarditis, and intravenous drug-associated viral hepatitis. One percent of patients had life threatening infections that included bacterial pneumonia, respiratory disease, and sepsis.

Secondary Malignancies: A total of 2% of patients developed secondary malignancies following the ZEVALIN therapeutic regimen. One patient developed a Grade 1 meningioma, three developed acute myelogenous leukemia, and two developed a myelodysplastic syndrome. The onset of a second cancer was 8-34 months following the ZEVALIN therapeutic regimen and 4 to 14 years following the patients' diagnosis of NHL.

Immunogenicity: Of 211 patients who received the ZEVALIN therapeutic regimen in clinical trials and who were followed for 90 days, there were eight (3.8%) patients with evidence of human anti-mouse antibody (HAMA) (n=5) or human anti-chimeric antibody (HACA) (n=4) at any time during the course of the study. Two patients had low titers of HAMA prior to initiation of the ZEVALIN therapeutic regimen; one remained positive without an increase in titer while the other had a negative titer post-treatment. Three patients had evidence of HACA responses prior to initiation of the ZEVALIN therapeutic regimen; one had a marked increase in HACA titer while the other two had negative titers post-treatment. Of the three patients who had negative HAMA or HACA titers prior to the ZEVALIN therapeutic regimen, two developed HAMA in absence of HACA titers, and one had both HAMA and HACA positive titers post-treatment. Evidence of immunogenicity may be masked in patients who are lymphopenic. There has not been adequate evaluation of HAMA and HACA at delayed timepoints, concurrent with the recovery from lymphopenia at 6-12 months, to establish whether masking of the immunogenicity at early timepoints occurs. The data reflect the percentage of patients whose test results were considered positive for antibodies to Ibritumomab or Rituximab using kinetic enzyme immunoassays to Ibritumomab and Rituximab. The observed incidence of antibody positivity in an assay is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors including sample handling and concomitant medications. Comparisons of the incidence of HAMA/HACA to the ZEVALIN therapeutic regimen with the incidence of antibodies to other products may be misleading.

OVERDOSAGE

Doses as high as 0.52 mCi/kg (19.2 MBq/kg) of Y-90 ZEVALIN were administered in ZEVALIN therapeutic regimen clinical trials and severe hematological toxicities were observed. No fatalities or second organ injury resulting from overdosage administrations were documented. However, single doses up to 50 mCi (1850 MBq) of Y-90 ZEVALIN, and multiple doses of 20 mCi (740 MBq) followed by 40 mCi (1480 MBq) of Y-90 ZEVALIN were studied in a limited number of subjects. In these trials, some patients required autologous stem cell support to manage hematological toxicity.

DOSAGE AND ADMINISTRATION

The ZEVALIN therapeutic regimen is administered in two steps: Step 1 includes a single infusion of 250 mg/m^2 Rituximab (not included in the ZEVALIN kits) preceding a fixed dose of 5.0 mCi (1.6 mg total antibody dose) of In-111 ZEVALIN administered as a 10 minute IV push. Step 2 follows step 1 by seven to nine days and consists of a second infusion of 250 mg/m^2 of Rituximab prior to 0.4 mCi/kg of Y-90 ZEVALIN administered as a 10 minute IV push.

Rituximab Administration: NOTE THAT THE DOSE OF RITUXIMAB IS LOWER WHEN USED AS PART OF THE ZEVALIN THERAPEUTIC REGIMEN, AS COMPARED TO THE DOSE OF RITUXIMAB WHEN USED AS A SINGLE AGENT. DO NOT ADMINISTER RITUXIMAB AS AN INTRAVENOUS PUSH OR BOLUS. Hypersensitivity reactions may occur (see **WARNINGS**). Premedication, consisting of acetaminophen and diphenhydramine, should be considered before each infusion of Rituximab.

ZEVALIN Therapeutic Regimen Dose Modification in Patients with Mild Thrombocytopenia: The Y-90 ZEVALIN dose should be reduced to 0.3 mCi/kg (11.1 MBq/kg) for patients with a baseline platelet count between 100,000 and 149,000 cells/mm^3.

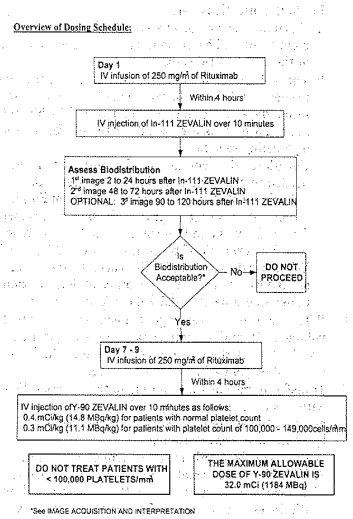
Two separate and distinctly-labeled kits are ordered for the preparation of a single dose each of In-111 ZEVALIN and Y-90 ZEVALIN. In-111 ZEVALIN and Y-90 ZEVALIN are radiopharmaceuticals and should be used only by physicians enced in the safe use and handling of radionuclides. **Changing the ratio of any of the reactants in the radiolabeling process may adversely impact therapeutic results. In-111 ZEVALIN and Y-90 ZEVALIN should not be used in the absence of the Rituximab pre-dose.**

Table 8.
Severe Hematologic Toxicity

	ZEVALIN therapeutic regimen using 0.4 mCi/kg Y-90 Dose (14.8 MBq/kg)	Modified ZEVALIN therapeutic regimen using 0.3 mCi/kg Y-90 dose (11.1 MBq/kg)
ANC		
Median nadir (cells/mm^3)	800	600
Per Patient Incidence ANC <1000 cells/mm^3	57%	74%
Per Patient Incidence ANC <500 cells/mm^3	30%	35%
Median Duration (Days)* ANC <1000 cells/mm^3	22	29
Platelets		
Median nadir (cells/mm^3)	41,000	24,000
Per Patient Incidence Platelets <50,000 cells/mm^3	61%	78%
Per Patient Incidence Platelets <10,000 cells/mm^3	10%	14%
Median Duration (Days)# Platelets <50,000 cells/mm^3	24	35

*Median duration of neutropenia for patients with ANC <1000 cells/mm^3 (Date from last laboratory value showing ANC ≥1000 cells/mm^3 to date of first laboratory value following nadir showing ANC ≥1000 cells/mm^3, censored at initiation of next treatment or death)

#Median duration of thrombocytopenia for patients with platelets <50,000 cells/mm^3 (Date from last laboratory value showing platelet count ≥50,000 cells/mm^3 to date of first laboratory value following nadir showing platelet count ≥50,000 cells/mm^3, censored at initiation of next treatment or death)



ZEVALIN Therapeutic Regimen Administration

Step 1:

First Rituximab Infusion: Rituximab at a dose of 250 mg/m^2 should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If hypersensitivity or an infusion-related event develops, the infusion should be temporarily slowed or interrupted (see **WARNINGS**). The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

In-111 ZEVALIN Injection: Within 4 hours following completion of the Rituximab dose, 5.0 mCi (1.6 mg total antibody dose) of In-111 ZEVALIN is injected intravenously (I.V.) over a period of 10 minutes. A 0.22 micrometer low-protein-binding filter should be in-line between the syringe and the infusion port prior to injection of In-111 ZEVALIN. After injection, the line should be flushed with at least 10 mL of normal saline.

Step 2:

Step 2 of the ZEVALIN therapeutic regimen is initiated seven to nine days following Step 1 administrations.

Second Rituximab Infusion: Rituximab at a dose of 250 mg/m^2 is administered I.V. at an initial rate of 100 mg/hr (50 mg/hr if infusion related events were documented during the first Rituximab administration) and increased by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr, as tolerated.

Y-90 ZEVALIN Injection:

Within 4 hours following completion of the Rituximab dose, Y-90 ZEVALIN at a dose of 0.4 mCi/kg (14.8 MBq/kg) actual body weight for patients with a platelet count ≥150,000 cells/mm^3 and 0.3 mCi/kg (11.1 MBq/kg) actual body weight mm^3 is injected intravenously (I.V.) over a period of 10 minutes. A 0.22 micrometer low-protein-binding filter should be in-line between the syringe and the infusion port prior to injection of In-111 ZEVALIN. After injection, the line should be flushed with at least 10 mL of normal saline. Precautions should be taken to avoid extravasation. A free flowing I.V. line should be established prior to Y-90 ZEVALIN injection. Close monitoring for evidence of extravasation during the injection of Y-90 ZEVALIN is required. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. **The prescribed, measured, and administered dose of Y-90 ZEVALIN must not exceed the absolute maximum allowable dose of 32.0 mCi (1184 MBq), regardless of the patient's body weight. Do not give Y-90 ZEVALIN to patients with a platelet count <100,000/mm^3 (see WARNINGS).**

DIRECTIONS FOR PREPARATION OF RADIOLABELED ZEVALIN

A. PREPARATION OF THE IN-111 ZEVALIN DOSE

GENERAL:

Read all directions thoroughly and assemble all materials before starting the radiolabeling procedure. Important, significant differences exist in the preparation of the In-111 ZEVALIN dose and the Y-90 ZEVALIN dose.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration. The dose calibrator must be operated in accordance with the manufacturer's specifications and quality control for the measurement of In-111.

Proper aseptic technique and precautions for handling radioactive materials should be employed. Waterproof gloves should be utilized in the preparation and during the determination of radiochemical purity of In-111 ZEVALIN. Appropriate shielding should be used during radiolabeling, and use of a syringe shield is recommended during administration to the patient. The radiolabeling of ZEVALIN shall be done according to the following directions.

Required materials not supplied in the kit:

A. Indium-111 Chloride Sterile Solution (In-111 Chloride) from Amersham Health, Inc. or Mallinckrodt, Inc.
B. Three sterile 1 mL syringes
C. One sterile 3 mL syringe
D. Two sterile 10 mL syringes with 18-20 G needles
E. Instant thin-layer chromatographic silica gel strips
F. 0.9% sodium chloride aqueous solution for the chromatography solvent
G. Developing chamber for chromatography
H. Suitable radioactivity counting apparatus
I. Filter, 0.22 micrometer, low-protein-binding (see DOSAGE AND ADMINISTRATION, Zevalin Therapeutic Regimen Administration)
J. Vial and syringe shield

Method:

1. Sterile, pyrogen-free In-111 chloride must be used for the preparation of In-111 ZEVALIN. The use of high purity In-111 chloride manufactured by Amersham Health, Inc. or Mallinckrodt, Inc. is required.
2. Before radiolabeling, allow contents of the refrigerated carton to reach room temperature. Note: The ZEVALIN vial contains a protein solution that may develop translucent particulates. These particulates will be removed by filtration prior to administration.
3. Clean the rubber stoppers of all of the vials in the kit and the In-111 chloride vial with a suitable alcohol swab and allow to air dry.
4. Place the empty Reaction Vial in a suitable dispensing shield (pre-warmed to room temperature). To

Zevalin—Cont.

avoid the buildup of excessive pressure during the procedure, use a 10 mL syringe to withdraw 10 mL of air from the Reaction Vial.

5. Prior to initiating the radiolabeling reaction, determine the amount of each component needed according to the directions below:
   a. Calculate the volume of In-111 chloride that is equivalent to 5.5 mCi based on the activity concentration of the In-111 chloride stock.
   b. The volume of 50 mM sodium acetate solution needed is 1.2 times the volume of In-111 chloride solution determined in step 5.a., above. (The 50 mM sodium acetate is used to adjust the pH for the radiolabeling reaction.)
   c. Calculate the volume of Formulation Buffer needed to bring the Reaction Vial contents to a final volume of 10 mL. This is the volume of Formulation Buffer needed to protect the labeled product from radiolysis and to terminate the labeling reaction. For example, if volumes of 0.5 mL of In-111 chloride, 0.6 mL of sodium acetate and 1.0 mL of ZEVALIN were used, then the amount of formulation buffer would be 10 - (0.5 + 0.6 + 1.0) = 7.9 mL.
6. With a sterile 1 mL syringe, transfer the calculated volume of 50 mM of sodium acetate to the empty Reaction Vial. Coat the entire inner surface of the Reaction Vial by gentle inversion or rolling.
7. Transfer 5.5 mCi of In-111 chloride to the Reaction Vial with a sterile 1 mL syringe. Mix the two solutions and coat the entire inner surface of the Reaction Vial by gentle inversion or rolling.
8. With a sterile 3 mL syringe, transfer 1.0 mL of ZEVALIN (Ibritumomab Tiuxetan) to the Reaction Vial. Coat the entire surface of the Reaction Vial by gentle inversion or rolling. **Do not shake or agitate the vial contents, since this will cause foaming and denaturation of the protein.**
9. Allow the labeling reaction to proceed at room temperature for 30 minutes. Allowing the labeling reaction to proceed for a longer or shorter time may result in inadequate labeling.
10. **Immediately** after the 30-minute incubation period, using a sterile 10 mL syringe with a large bore needle (18 G - 20 G), transfer the calculated volume of Formulation Buffer from step 5.c. to the Reaction Vial. Gently add the Formulation Buffer down the side of the Reaction Vial. If necessary, to normalize air pressure, withdraw an equal volume of air. Coat the entire inner surface of the Reaction Vial by gentle inversion or rolling. Do not shake or agitate the vial contents. Avoid foaming.
11. Using the supplied labels, record the patient identification, the date and time of preparation, the total activity and volume, and the date and time of expiration, and affix these labels to the reaction vial and shielded reaction vial container.
12. Calculate the volume required for an In-111 ZEVALIN dose of 5 mCi. Withdraw the required volume from the Reaction Vial contents into a sterile 10 mL syringe with a large bore needle (18 G - 20 G). Assay the syringe and contents in a dose calibrator. The syringe should contain the dose of In-111 ZEVALIN to be administered to the patient. Using the supplied labels, record the patient identification, the date and time of preparation, the total activity and volume added, and the date and time of expiration, and affix these labels to the syringe and shielded unit dose container.
13. Determine Radiochemical purity. See Section C: Procedure for Determining Radiochemical Purity Section that follows DIRECTIONS FOR PREPARATION OF THE Y-90 ZEVALIN DOSE.
14. Indium-111 ZEVALIN should be stored at 2 - 8°C (36 - 46°F) until use and administered within 12 hours of radiolabeling.
15. See DOSAGE AND ADMINISTRATION: ZEVALIN Therapeutic Regimen Administration: Step 1
16. Discard vials, needles and syringes in accordance with local, state, and federal regulations governing radioactive and biohazardous waste.

B. PREPARATION OF THE Y-90 ZEVALIN DOSE

GENERAL:

Read all directions thoroughly and assemble all materials before starting the radiolabeling procedure. Important, significant differences exist in the preparation of the In-111 ZEVALIN dose and the Y-90 ZEVALIN dose.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration. The dose calibrator must be operated in accordance with the manufacturer's specifications and quality control for the measurement of Y-90.

Proper aseptic technique and precautions for handling radioactive materials should be employed. Waterproof gloves should be utilized in the preparation and during the determination of radiochemical purity of Y-90 ZEVALIN. Appropriate shielding should be used during radiolabeling, and use of a syringe shield is recommended during administration to the patient. The radiolabeling of ZEVALIN shall be

Required materials not supplied in the kit:

A. Yttrium-90 Chloride Sterile Solution from MDS Nordion (shipped directly from MDS Nordion upon placement of an order for the Y-90 ZEVALIN kit)
B. Three sterile 1 mL syringes
C. One sterile 3 mL syringe
D. Two sterile 10 mL syringes with 18-20 G needles
E. Instant thin-layer chromatographic silica gel strips (ITLC-SG)
F. 0.9% sodium chloride aqueous solution for the chromatography solvent
G. Suitable radioactivity counting apparatus
H. Developing chamber for chromatography
I. Filter, 0.22 micrometer, low-protein-binding (see DOSAGE AND ADMINISTRATION, Zevalin Therapeutic Regimen Administration)
J. Vial and syringe shield

Method:

1. Sterile, pyrogen-free Y-90 chloride must be used for the preparation of Y-90 ZEVALIN. The use of high purity Y-90 chloride manufactured by MDS Nordion is required.
2. Before radiolabeling, allow the contents of the refrigerated carton to reach room temperature. Note: The ZEVALIN vial contains a protein solution that may develop translucent particulates. These particulates will be removed by filtration prior to administration.
3. Clean the rubber stoppers of all of the vials in the kit and the Y-90 chloride vial with a suitable alcohol swab and allow to air dry.
4. Place the empty Reaction Vial in a suitable dispensing shield (pre-warmed to room temperature). To avoid the buildup of excessive pressure during the procedure, use a 10 mL syringe to withdraw 10 mL of air from the Reaction Vial.
5. Prior to initiating the radiolabeling reaction, determine the amount of each component needed according to the directions below:
   a. Calculate the volume of Y-90 chloride that is equivalent to 40 mCi based on the activity concentration of the Y-90 chloride stock.
   b. The volume of 50 mM sodium acetate solution needed is 1.2 times the volume of Y-90 chloride solution determined in step 5.a., above. (The 50 mM sodium acetate is used to adjust the pH for the radiolabeling reaction.)
   c. Calculate the volume of Formulation Buffer needed to bring the Reaction Vial contents to a final volume of 10 mL. This is the volume of Formulation Buffer needed to protect the labeled product from radiolysis and to terminate the labeling reaction. For example if the volumes were 0.5 mL of Y-90 chloride, 0.6 mL of sodium acetate and 1.3 mL of ZEVALIN, then the amount of formulation buffer would be 10 - (0.5 + 0.6 + 1.3) = 7.6 mL.
6. With a sterile 1 mL syringe, transfer the calculated volume of 50 mM sodium acetate to the empty Reaction Vial. Coat the entire inner surface of the Reaction Vial by gentle inversion or rolling.
7. Transfer 40 mCi of Y-90 chloride to the Reaction Vial with a sterile 1 mL syringe. Mix the two solutions and coat the entire inner surface of the Reaction Vial by gentle inversion or rolling.
8. With a sterile 3 mL syringe, transfer 1.3 mL of ZEVALIN (Ibritumomab Tiuxetan) to the Reaction Vial. Coat the entire surface of the Reaction Vial by gentle inversion or rolling. **Do not shake or agitate the vial contents, since this will cause foaming and denaturation of the protein.**
9. Allow the labeling reaction to proceed at room temperature for 5 minutes. Allowing the labeling reaction to proceed for a longer or shorter time may result in inadequate labeling.
10. **Immediately** after the 5-minute incubation period, using a sterile 10 mL syringe with a large bore needle (18 G - 20 G), transfer the calculated volume of Formulation Buffer from step 5.c. to the Reaction Vial, terminating incubation. Gently add the Formulation Buffer down the side of the Reaction Vial. If necessary to normalize air pressure, withdraw an equal volume of air. Coat the entire inner surface of the Reaction Vial by gentle inversion or rolling. Do not shake or agitate the vial contents. Avoid foaming.
11. Using the supplied labels, record the patient identification, the date and time of preparation, the total activity and volume, and the date and time of expiration and affix these labels to the reaction vial and shielded reaction vial container.
12. Calculate the volume required for a Y-90 ZEVALIN dose of 0.4 mCi/kg (14.8 MBq/kg) actual body weight for patients with normal platelet count, and 0.3 mCi/kg (11.1 MBq/kg) actual body weight for patients with platelet count of 100,000 - 149,000 cells/mm^3. **The prescribed, measured, and administered dose of Y-90 ZEVALIN must not exceed the absolute maximum allowable dose of 32.0 mCi (1184 MBq), regardless of the patient's body weight.** Withdraw the required volume from the Reaction Vial contents into a sterile 10 mL syringe with a large bore needle (18 G - 20 G). Assay the syringe and contents in a dose calibrator. The dose calibrator must be operated in accordance with the manufacturer's specifications

syringe should contain the dose of Y-90 ZEVALIN to be administered to the patient, and should be within 10% of the actual prescribed dose of Y-90 ZEVALIN, not to exceed a maximum dose of 32.0 mCi. Do not exceed ± 10% of the prescribed dose. Using the supplied labels, record the patient identification, the date and time of preparation, the total activity and volume added, and the date and time of expiration and affix these labels to the syringe and shielded unit dose container.
13. Determine Radiochemical Purity. See Section C: Procedure for Determining Radiochemical Purity Section that follows these DIRECTIONS FOR PREPARATION OF THE Y-90 ZEVALIN DOSE.
14. Yttrium-90 ZEVALIN should be stored at 2 - 8°C (36 - 46°F) until use and administered within 8 hours of radiolabeling.
15. See DOSAGE AND ADMINISTRATION: ZEVALIN Therapeutic Regimen Administration: Step 2.
16. Discard vials, needles and syringes in accordance with local, state, and federal regulations governing radioactive and biohazardous waste.

Yttrium-90 ZEVALIN is suitable for administration on an outpatient basis. Beyond the use of vial and syringe shields for preparation and injection, no special shielding is necessary.

C. PROCEDURE FOR DETERMINING RADIOCHEMICAL PURITY (RCP)

The following procedure should be used for both In-111 ZEVALIN and Y-90 ZEVALIN:

A. At room temperature, place a small drop of either In-111 ZEVALIN or Y-90 ZEVALIN at the origin of an ITLC-SG strip.
B. Place the ITLC-SG strip into a chromatography chamber with the origin at the bottom and the solvent front at the top. Allow the solvent (0.9% NaCl) to migrate at least 5 cm from the bottom of the strip. Remove the strip from the chamber and cut the strip in half. Count each half of the ITLC-SG strip for one minute (CPM) with a suitable counting apparatus.
C. Calculate the percent RCP as follows:

$$\% \text{ RCP} = \frac{\text{CPM bottom half}}{\text{CPM bottom half + CPM top half}} \times 100$$

D. If the radiochemical purity is <95%, the ITLC procedure should be repeated. If repeat testing confirms that radiochemical purity is < 95%, the preparation should not be administered.

IMAGE ACQUISITION AND INTERPRETATION

The biodistribution of In-111 ZEVALIN should be assessed by a visual evaluation of whole body planar view anterior and posterior gamma images at 2 - 24 hours and 48 - 72 hours after injection. To resolve ambiguities, a third image at 90 - 120 hours may be necessary. Images should be acquired using a large field of view gamma camera equipped with a medium energy collimator. Whole body anterior/posterior planar images should be acquired using a large field-of-view gamma camera and medium energy collimators. Suggested gamma camera settings: 256 × 1024 matrix; dual energy photopeaks set at 172 and 247 keV; 15% symmetric window; scan speed of 10 cm/min for the 2-24 hour scan, 7-10 cm/min for the 48-72 hour scan and 5 cm/min for the optional 90-120 hour scan.

The radiopharmaceutical is expected to be easily detectable in the blood pool areas at the first time point, with less activity in the blood pool on later images. Moderately high to high uptake is seen in the normal liver and spleen, with low uptake in the lungs, kidneys, and urinary bladder. Localization to lymphoid aggregates in the bowel wall has been reported. Tumor uptake may be visualized in soft tissue as areas of increased intensity, and tumor-bearing areas in normal organs may be seen as areas of increased or decreased intensity.

If a visual inspection of the gamma images reveals an altered biodistribution, the patient should not proceed to the Y-90 ZEVALIN dose. The patient may be considered to have an altered biodistribution if the blood pool is not visualized on the first image indicating rapid clearance of the radiopharmaceutical by the reticuloendothelial system to the liver, spleen, and/or marrow. Other potential examples of altered biodistribution may include diffuse uptake in the normal lungs or kidneys more intense than the liver on the second or third image.

During ZEVALIN clinical development, individual tumor radiation absorbed dose estimates as high as 778 cGy/mCi have been reported. Although solid organ toxicity has not been directly attributed to radiation from adjacent tumors, careful consideration should be applied before proceeding with treatment in patients with very high tumor uptake next to critical organs or structures.

HOW SUPPLIED

The In-111 ZEVALIN kit provides for the radiolabeling of Ibritumomab Tiuxetan with In-111. The Y-90 ZEVALIN kit provides for the radiolabeling of Ibritumomab Tiuxetan with Y-90.

The kit for the preparation of a single dose of In-111 ZEVALIN includes four vials: one ZEVALIN vial containing 3.2 mg of Ibritumomab Tiuxetan in 2 mL of 0.9% sodium

mulation Buffer vial; one empty Reaction vial and four identification labels.
The kit for the preparation of a single dose of Y-90 ZEVALIN includes four vials: one ZEVALIN vial containing 3.2 mg of Ibritumomab Tiuxetan in 2 mL of 0.9% sodium chloride solution; one 50 mM Sodium Acetate vial; one Formulation Buffer vial; one empty Reaction vial and four identification labels.
The contents of all vials are sterile, pyrogen-free and contain no preservatives.
The Indium-111 Chloride Sterile Solution (In-111 Chloride) must be ordered separately from either Amersham Health, Inc. or Mallinckrodt, Inc. at the time the In-111 ZEVALIN kit is ordered. The Yttrium-90 chloride sterile solution will be shipped directly from MDS Nordion upon placement of an order for the Y-90 ZEVALIN kit.

Storage
Store at 2 - 8°C (36 - 46°F). Do not freeze.

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Rx Only
In-111 ZEVALIN kit, NDC 64406-104-04
Y-90 ZEVALIN kit, NDC 64406-103-03

3030 Callan Road
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U.S. License Number 1235
Protected by one or more U.S. Patents.

3-665-1820

Issue Date: January 2003

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IMMUNOCAL® OTC

2003
NUTRACEUTICAL
(Bonded cysteine supplement)
Powder Sachets

DESCRIPTION and CLINICAL PHARMACOLOGY

IMMUNOCAL® is a U.S. patented natural food protein concentrate in the FDA category of GRAS (generally recognized as safe) which assists the body in maintaining optimal concentrations of glutathione (GSH) by supplying the precursors required for intracellular glutathione synthesis. It is clinically proven to raise glutathione values (Lands et al, 1999).
Glutathione is a tripeptide made intracellularly from its constituent amino acids L-glutamate, L-cysteine and glycine. The sulfhydryl (thiol) group (SH) of cysteine serves as a proton donor and is responsible for the biological activity of glutathione. Provision of this amino acid is the rate-limiting factor in glutathione synthesis by the cells since cysteine is relatively rare in foodstuffs and furthermore, if released as the free amino acid, is toxic and spontaneously catabolized in the gastrointestinal tract and blood plasma. Immunocal® is a bovine whey protein isolate specially prepared so as to provide a rich source of bioavailable cysteine. Following digestion, the cysteine remains as the stable form cystine (2 molecules of cysteine linked by disulfide bond) and glutamylcystine. After absorption, these dipeptides travel safely in the blood stream and readily enter the cells to release free cysteine for intracellular glutathione synthesis. Immunocal® can thus be viewed as a cysteine delivery system.
The disulphide bond in cystine is pepsin and trypsin resistant but may be split by heat, low pH or mechanical stress releasing free cysteine. When subject to heat or shearing forces (inherent in most extraction processes), the fragile disulfide bonds within the peptides are broken and the bioavailability of cysteine is greatly diminished.
Glutathione is a tightly regulated intracellular constituent and is limited in its production by negative feedback inhibition of its own synthesis through the enzyme gamma-glutamylcysteine synthetase, thus greatly minimizing any possibility of overdosage.
Glutathione has multiple functions:
1. It is the major endogenous antioxidant produced by the cells, participating directly in the neutralization of free radicals and reactive oxygen compounds, as well as maintaining exogenous antioxidants such as vitamins C and E in their reduced (active) forms.
2. Through direct conjugation, it detoxifies many xenobiotics (foreign compounds) and carcinogens, both organic and inorganic.
3. It is essential for the immune system to exert its full potential, e.g. (1) modulating antigen presentation to lymphocytes, thereby influencing cytokine production and type of response (cellular or humoral) that develops, (2) enhancing proliferation of lymphocytes thereby increasing magnitude of response, (3) enhancing killing activity of cytotoxic T cells and NK cells, and (4) regulating apoptosis, thereby maintaining control of the immune response.
4. It plays a fundamental role in numerous metabolic and biochemical reactions such as DNA synthesis and repair, protein synthesis, prostaglandin synthesis, amino acid transport and enzyme activation. Thus, every system in the body can be affected by the state of the glutathione system, especially the immune system, the nervous system, the gastrointestinal system and the lungs.

INDICATIONS AND USAGE

IMMUNOCAL® is a natural food supplement and as such is limited from stating medical claims per se. Statements have not been evaluated by the FDA. As such, this product is thus not intended to diagnose, cure, prevent or treat any disease. Glutathione augmentation is a strategy developed to address states of glutathione deficiency, high oxidative stress, immune deficiency, and xenobiotic overload in which glutathione plays a part in the detoxification of the xenobiotic in question. Glutathione deficiency states include, but are not limited to: HIV/AIDS, chemical and infectious hepatitis, prostate and other cancers, cataracts, Alzheimer's, Parkinsons, chronic obstructive pulmonary disease, asthma, radiation poisoning, malnutritive states, arduous physical stress, aging, and has been associated with suboptimal immune response. Many clinical pathologies are associated with oxidative stress and are elaborated upon in numerous medical references.
Low glutathione is also strongly implicated in wasting and negative nitrogen balance (Droge and Holm, 1997), notably as seen in cancer, AIDS, sepsis, trauma, burns and even athletic overtraining. Glutathione supplementation can oppose this process and in AIDS, for example, result in im-

CONTRAINDICATIONS

IMMUNOCAL® is contraindicated in individuals who develop or have known hypersensitivity to specific milk proteins.

PRECAUTIONS

Each sachet of IMMUNOCAL® contains nine grams of protein. Patients on a protein-restricted diet need to take this into account when calculating their daily protein load. Although a bovine milk derivative, IMMUNOCAL® contains less than 1% lactose and therefore is generally well tolerated by lactose-intolerant individuals.

WARNINGS

Patients undergoing immunosuppressive therapy should discuss the use of this product with their health professional.

ADVERSE REACTIONS

Gastrointestinal bloating and cramps if not sufficiently rehydrated. Transient urticarial-like rash in rare individuals undergoing severe detoxification reaction. Rash abates when product intake stopped or reduced.

OVERDOSAGE

Overdosing on IMMUNOCAL® has not been reported.

DOSAGE AND ADMINISTRATION

For mild to moderate health challenges, 20 grams per day is recommended. Clinical trials in patients with AIDS, COPD, cancer and chronic fatigue syndrome have used 30–40 grams per day without ill effect. IMMUNOCAL® is best administered on an empty stomach or with a light meal. Concomitant intake of another high protein load may adversely affect absorption.

RECONSTITUTION
IMMUNOCAL® is a dehydrated powdered protein isolate. It must be appropriately rehydrated before use. Remains bioactive up to 12 hours after mixing. DO NOT heat or use a hot liquid to rehydrate the product. DO NOT use a high-speed blender for reconstitution. These methods will decrease the activity of the product.
Proper mixing is imperative. Consult instructions included in packaging.

HOW SUPPLIED

10 grams of bovine milk protein isolate powder per sachet. 30 sachets per box.

STORAGE
Store in a cool dry environment. Refrigeration is not necessary.
Patent no.'s: 5,230,902 - 5,290,571 - 5,456,924 - 5,451,412 - 5,888,552

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fined as those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

Body as a Whole—*Frequent:* chest pain, chills; *Infrequent:* chills and fever, face edema, intentional overdose, malaise, pelvic pain, suicide attempt; *Rare:* abdominal syndrome acute, hypothermia, intentional injury, neuroleptic malignant syndrome[1], photosensitivity reaction.

Cardiovascular System—*Frequent:* hemorrhage, hypertension, palpitation; *Infrequent:* angina pectoris, arrhythmia, congestive heart failure, hypotension, migraine, myocardial infarct, postural hypotension, syncope, tachycardia, vascular headache; *Rare:* atrial fibrillation, bradycardia, cerebral embolism, cerebral ischemia, cerebrovascular accident, extrasystoles, heart arrest, heart block, pallor, peripheral vascular disorder, phlebitis, shock, thrombophlebitis, thrombosis, vasospasm, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation.

Digestive System—*Frequent:* increased appetite, nausea and vomiting; *Infrequent:* aphthous stomatitis, cholelithiasis, colitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, glossitis, gum hemorrhage, hyperchlorhydria, increased salivation, liver function tests abnormal, melena, mouth ulceration, nausea/vomiting/diarrhea, stomach ulcer, stomatitis, thirst; *Rare:* biliary pain, bloody diarrhea, cholecystitis, duodenal ulcer, enteritis, esophageal ulcer, fecal incontinence, gastrointestinal hemorrhage, hematemesis, hemorrhage of colon, hepatitis, intestinal obstruction, liver fatty deposit, pancreatitis, peptic ulcer, rectal hemorrhage, salivary gland enlargement, stomach ulcer hemorrhage, tongue edema.

Endocrine System—*Infrequent:* hypothyroidism; *Rare:* diabetic acidosis, diabetes mellitus.

Hemic and Lymphatic System—*Infrequent:* anemia, ecchymosis; *Rare:* blood dyscrasia, hypochromic anemia, leukopenia, lymphedema, lymphocytosis, petechia, purpura, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional—*Frequent:* weight gain; *Infrequent:* dehydration, generalized edema, gout, hypercholesteremia, hyperlipemia, hypokalemia, peripheral edema; *Rare:* alcohol intolerance, alkaline phosphatase increased, BUN increased, creatine phosphokinase increased, hyperkalemia, hyperuricemia, hypocalcemia, iron deficiency anemia, SGPT increased.

Musculoskeletal System—*Infrequent:* arthritis, bone pain, bursitis, leg cramps, tenosynovitis; *Rare:* arthrosis, chondrodystrophy, myasthenia, myopathy, myositis, osteomyelitis, osteoporosis, rheumatoid arthritis.

Nervous System—*Frequent:* agitation, amnesia, confusion, emotional lability, sleep disorder; *Infrequent:* abnormal gait, acute brain syndrome, akathisia, apathy, ataxia, buccoglossal syndrome, CNS depression, CNS stimulation, depersonalization, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, hypesthesia, incoordination, libido increased, myoclonus, neuralgia, neuropathy, neurosis, paranoid reaction, personality disorder[2], psychosis, vertigo; *Rare:* abnormal electroencephalogram, antisocial reaction, circumoral paresthesia, coma, delusions, dysarthria, dystonia, extrapyramidal syndrome, foot drop, hyperesthesia, neuritis, paralysis, reflexes decreased, reflexes increased, stupor.

Respiratory System—*Infrequent:* asthma, epistaxis, hiccup, hyperventilation; *Rare:* apnea, atelectasis, cough decreased, emphysema, hemoptysis, hypoventilation, hypoxia, larynx edema, lung edema, pneumothorax, stridor.

Skin and Appendages—*Infrequent:* acne, alopecia, contact dermatitis, eczema, maculopapular rash, skin discoloration, skin ulcer, vesiculobullous rash; *Rare:* furunculosis, herpes zoster, hirsutism, petechial rash, psoriasis, purpuric rash, pustular rash, seborrhea.

Special Senses—*Frequent:* ear pain, taste perversion, tinnitus; *Infrequent:* conjunctivitis, dry eyes, mydriasis, photophobia; *Rare:* blepharitis, deafness, diplopia, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, iritis, parosmia, scleritis, strabismus, taste loss, visual field defect.

Urogenital System—*Frequent:* urinary frequency; *Infrequent:* abortion[3], albuminuria, amenorrhea[3], anorgasmia, breast enlargement, breast pain, cystitis, dysuria, female lactation[3], fibrocystic breast[3], hematuria, leukorrhea[3], menorrhagia[3], metrorrhagia[3], nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage[3]; *Rare:* breast engorgement, glycosuria, hypomenorrhea[3], kidney pain, oliguria, priapism[3], uterine hemorrhage[3], uterine fibroids enlarged[3].

[1] Neuroleptic malignant syndrome is the COSTART term which best captures serotonin syndrome.

[2] Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.

[3] Adjusted for gender.

Postintroduction Reports

Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction and that may have no causal relationship with the drug include the following: aplastic anemia, atrial fibrillation, cataract, cerebral vascular accident, cholestatic jaundice, confusion, dyskinesia (including, for example, a case of buccal-lingual-masticatory syndrome with involuntary tongue protrusion reported to develop in a 77-year-old female after 5 weeks of fluoxetine therapy and which completely resolved over the next few months following drug discontinuation), eosinophilic pneumonia, epidermal necrolysis, erythema nodosum, exfoliative dermatitis, gynecomastia, hypoglycemia, immune-related hemolytic anemia, kidney failure, misuse/abuse, movement disorders developing in patients with risk factors including drugs associated with such events and worsening of preexisting movement disorders, neuroleptic malignant syndrome-like events, optic neuritis, pancreatitis, pancytopenia, priapism, pulmonary embolism, pulmonary hypertension, QT prolongation, serotonin syndrome (a range of signs and symptoms that can rarely, in its most severe form, resemble neuroleptic malignant syndrome), Stevens-Johnson syndrome, sudden unexpected death, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, ventricular tachycardia (including torsades de pointes-type arrhythmias), and violent behaviors.

DRUG ABUSE AND DEPENDENCE

Controlled substance class—Prozac is not a controlled substance.

Physical and psychological dependence—Prozac has not been systematically studied in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the premarketing clinical experience with Prozac did not reveal any tendency for a withdrawal syndrome or any drug seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Prozac (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Worldwide exposure to fluoxetine hydrochloride is estimated to be over 38 million patients (circa 1999). Of the 1578 cases of overdose involving fluoxetine hydrochloride, alone or with other drugs, reported from this population, there were 195 deaths.

Among 633 adult patients who overdosed on fluoxetine hydrochloride alone, 34 resulted in a fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after overdosage, including abnormal accommodation, abnormal gait, confusion, unresponsiveness, nervousness, pulmonary dysfunction, vertigo, tremor, elevated blood pressure, impotence, movement disorder, and hypomania. The remaining 206 patients had an unknown outcome. The most common signs and symptoms associated with non-fatal overdosage were seizures, somnolence, nausea, tachycardia, and vomiting. The largest known ingestion of fluoxetine hydrochloride in adult patients was 8 grams in a patient who took fluoxetine alone and who subsequently recovered. However, in an adult patient who took fluoxetine alone, an ingestion as low as 520 mg has been associated with lethal outcome, but causality has not been established.

Among pediatric patients (ages 3 months to 17 years), there were 156 cases of overdose involving fluoxetine alone or in combination with other drugs. Six patients died, 127 patients completely recovered, 1 patient experienced renal failure, and 22 patients had an unknown outcome. One of the six fatalities was a 9-year-old boy who had a history of OCD, Tourette's syndrome with tics, attention deficit disorder, and fetal alcohol syndrome. He had been receiving 100 mg of fluoxetine daily for 6 months in addition to clonidine, methylphenidate, and promethazine. Mixed-drug ingestion or other methods of suicide complicated all 6 overdoses in children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams which was nonlethal.

Other important adverse events reported with fluoxetine overdose (single or multiple drugs) include coma, delirium, ECG abnormalities (such as QT interval prolongation and ventricular tachycardia, including torsades de pointes-type arrhythmias), hypotension, mania, neuroleptic malignant syndrome-like events, pyrexia, stupor, and syncope.

Animal Experience

Studies in animals do not provide precise or necessarily valid information about the treatment of human overdose. However, animal experiments can provide useful insights into possible treatment strategies.

The oral median lethal dose in rats and mice was found to be 452 and 248 mg/kg, respectively. Acute high oral doses produced hyperirritability and convulsions in several animal species.

Among 6 dogs purposely overdosed with oral fluoxetine, 5 experienced grand mal seizures. Seizures stopped immediately upon the bolus intravenous administration of a standard veterinary dose of diazepam. In this short-term study, the lowest plasma concentration at which a seizure occurred was only twice the maximum plasma concentration seen in humans taking 80 mg/day, chronically.

In a separate single-dose study, the ECG of dogs given high doses did not reveal prolongation of the PR, QRS, or QT intervals. Tachycardia and an increase in blood pressure were observed. Consequently, the value of the ECG in predicting cardiac toxicity is unknown. Nonetheless, the ECG should ordinarily be monitored in cases of human overdose (*see* Management of Overdose).

Management of Overdose

Treatment should consist of those general measures employed in the management of overdosage with any drug effective in the treatment of major depressive disorder.

Ensure an adequate airway, oxygenation and ventilation and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for fluoxetine are known.

A specific caution involves patients who are taking or have recently taken fluoxetine and might ingest excessive quantities of a TCA. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (*see* Other drugs effective in the treatment of major depressive disorder *under* PRECAUTIONS).

Based on experience in animals, which may not be relevant to humans, fluoxetine-induced seizures that fail to remit spontaneously may respond to diazepam.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (*PDR*).

DOSAGE AND ADMINISTRATION

Major Depressive Disorder

Initial Treatment

Adult—In controlled trials used to support the efficacy of fluoxetine, patients were administered morning doses ranging from 20 to 80 mg/day. Studies comparing fluoxetine 20, 40, and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory response in major depressive disorder in most cases. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose.

A dose increase may be considered after several weeks if insufficient clinical improvement is observed. Doses above 20 mg/day may be administered on a once-a-day (morning) or BID schedule (i.e., morning and noon) and should not exceed a maximum dose of 80 mg/day.

Pediatric (children and adolescents)—In the short-term (8 to 9 week) controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of major depressive disorder, patients were administered fluoxetine doses of 10 to 20 mg/day (*see* CLINICAL TRIALS). Treatment should be initiated with a dose of 10 or 20 mg/day. After 1 week at 10 mg/day, the dose should be increased to 20 mg/day.

However, due to higher plasma levels in lower weight children, the starting and target dose in this group may be 10 mg/day. A dose increase to 20 mg/day may be considered after several weeks if insufficient clinical improvement is observed.

All patients—As with other drugs effective in the treatment of major depressive disorder, the full effect may be delayed until 4 weeks of treatment or longer.

As with many other medications, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (*see* Liver disease *and* Renal disease *under* CLINICAL PHARMACOLOGY, *and* Use in patients with concomitant illness *under* PRECAUTIONS).

Maintenance/Continuation/Extended Treatment

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Daily Dosing

Systematic evaluation of Prozac in adult patients has shown that its efficacy in major depressive disorder is maintained for periods of up to 38 weeks following 12 weeks of open-label acute treatment (50 weeks total) at a dose of 20 mg/day (*see* CLINICAL TRIALS).

Weekly Dosing

Systematic evaluation of Prozac Weekly in adult patients has shown that its efficacy in major depressive disorder is maintained for periods of up to 25 weeks with once-weekly dosing following 13 weeks of open-label treatment with Prozac 20 mg once daily. However, therapeutic equivalence of Prozac Weekly given on a once-weekly basis with Prozac 20 mg given daily for delaying time to relapse has not been established (*see* CLINICAL TRIALS).

Weekly dosing with Prozac Weekly capsules is recommended to be initiated 7 days after the last daily dose of Prozac 20 mg (*see* Weekly dosing *under* CLINICAL PHARMACOLOGY).

Continued on next page

* Identi-Code® symbol. This product information was prepared in June 2002. Current information on these and other products of Eli Lilly and Company may be obtained by direct inquiry to Lilly Research Laboratories, Lilly Corporate Center,

Prozac—Cont.

If satisfactory response is not maintained with Prozac Weekly, consider reestablishing a daily dosing regimen (*see* CLINICAL TRIALS).

Switching Patients to a Tricyclic Antidepressant (TCA)

Dosage of a TCA may need to be reduced, and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (*see* Other drugs effective in the treatment of major depressive disorder *under* Drug Interactions).

Switching Patients to or from a Monoamine Oxidase Inhibitor (MAOI)

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Prozac. In addition, at least 5 weeks, perhaps longer, should be allowed after stopping Prozac before starting an MAOI (*see* CONTRAINDICATIONS *and* PRECAUTIONS).

Obsessive-Compulsive Disorder

Initial Treatment

Adult—In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of OCD, patients were administered fixed daily doses of 20, 40, or 60 mg of fluoxetine or placebo (*see* CLINICAL TRIALS). In 1 of these studies, no dose-response relationship for effectiveness was demonstrated. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose. Since there was a suggestion of a possible dose-response relationship for effectiveness in the second study, a dose increase may be considered after several weeks if insufficient clinical improvement is observed. The full therapeutic effect may be delayed until 5 weeks of treatment or longer.

Doses above 20 mg/day may be administered on a once-a-day (i.e., morning) or BID schedule (i.e., morning and noon). A dose range of 20 to 60 mg/day is recommended; however, doses of up to 80 mg/day have been well tolerated in open studies of OCD. The maximum fluoxetine dose should not exceed 80 mg/day.

Pediatric (children and adolescents)—In the controlled clinical trial of fluoxetine supporting its effectiveness in the treatment of OCD, patients were administered fluoxetine doses in the range of 10 to 60 mg/day (*see* CLINICAL TRIALS).

In adolescents and higher weight children, treatment should be initiated with a dose of 10 mg/day. After 2 weeks, the dose should be increased to 20 mg/day. Additional dose increases may be considered after several more weeks if insufficient clinical improvement is observed. A dose range of 20 to 60 mg/day is recommended.

In lower weight children, treatment should be initiated with dose of 10 mg/day. Additional dose increases may be considered after several more weeks if insufficient clinical improvement is observed. A dose range of 20 to 30 mg/day is recommended. Experience with daily doses greater than 20 mg is very minimal, and there is no experience with doses greater than 60 mg.

All patients—As with the use of Prozac in the treatment of major depressive disorder, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (*see* Liver disease *and* Renal disease *under* CLINICAL PHARMACOLOGY, *and* Use in patients with concomitant illness *under* PRECAUTIONS).

Maintenance/Continuation Treatment

While there are no systematic studies that answer the question of how long to continue Prozac, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Prozac after 13 weeks has not been documented in controlled trials, adult patients have been continued in therapy under double-blind conditions for up to an additional 6 months without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment.

Bulimia Nervosa

Initial Treatment

In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of bulimia nervosa, patients were administered fixed daily fluoxetine doses of 20 or 60 mg, or placebo (*see* CLINICAL TRIALS). Only the 60-mg dose was statistically significantly superior to placebo in reducing the frequency of binge-eating and vomiting. Consequently, the recommended dose is 60 mg/day, administered in the morning. For some patients it may be advisable to titrate up to this target dose over several days. Fluoxetine doses above 60 mg/day have not been systematically studied in patients with bulimia.

As with the use of Prozac in the treatment of major depressive disorder and OCD, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (*see* Liver disease *and* Renal disease *under* CLINICAL PHARMACOLOGY, *and* Use in patients

Maintenance/Continuation Treatment

Systematic evaluation of continuing Prozac 60 mg/day for periods of up to 52 weeks in patients with bulimia who have responded while taking Prozac 60 mg/day during an 8-week acute treatment phase has demonstrated a benefit of such maintenance treatment (*see* CLINICAL TRIALS). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

Panic Disorder

Initial Treatment

In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of panic disorder, patients were administered fluoxetine doses in the range of 10 to 60 mg/day (*see* CLINICAL TRIALS). Treatment should be initiated with a dose of 10 mg/day. After 1 week, the dose should be increased to 20 mg/day. The most frequently administered dose in the 2 flexible-dose clinical trials was 20 mg/day.

A dose increase may be considered after several weeks if no clinical improvement is observed. Fluoxetine doses above 60 mg/day have not been systematically evaluated in patients with panic disorder.

As with the use of Prozac in other indications, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (*see* Liver disease *and* Renal disease *under* CLINICAL PHARMACOLOGY, *and* Use in patients with concomitant illness *under* PRECAUTIONS).

Maintenance/Continuation Treatment

While there are no systematic studies that answer the question of how long to continue Prozac, panic disorder is a chronic condition and it is reasonable to consider continuation for a responding patient. Nevertheless, patients should be periodically reassessed to determine the need for continued treatment.

HOW SUPPLIED

The following products are manufactured by Eli Lilly and Company for Dista Products Company.

Prozac® Pulvules®, USP, are available in:

The 10-mg[1] Pulvule is opaque green and green, imprinted with DISTA 3104 on the cap and Prozac 10 mg on the body:

NDC 0777-3104-02 (PU3104[2]) – Bottles of 100
NDC 0777-3104-07 (PU3104[2]) – Bottles of 2000
NDC 0777-3104-82 (PU3104[2]) – 20 FlexPak™[3] blister cards of 31

The 20-mg[1] Pulvule is an opaque green cap and off-white body, imprinted with DISTA 3105 on the cap and Prozac 20 mg on the body:

NDC 0777-3105-30 (PU3105[2]) – Bottles of 30
NDC 0777-3105-02 (PU3105[2]) – Bottles of 100
NDC 0777-3105-07 (PU3105[2]) – Bottles of 2000
NDC 0777-3105-33 (PU3105[2]) – (ID[4]100) Blisters
NDC 0777-3105-82 (PU3105[2]) – 20 FlexPak™[3] blister cards of 31

The 40-mg[1] Pulvule is an opaque green cap and opaque orange body, imprinted with DISTA 3107 on the cap and Prozac 40 mg on the body:

NDC 0777-3107-30 (PU3107[2]) – Bottles of 30

Liquid, Oral Solution is available in:

20 mg[1] per 5 mL with mint flavor:

NDC 0777-5120-58 (MS-5120[5]) – Bottles of 120 mL

The following products are manufactured and distributed by Eli Lilly and Company.

Prozac® Tablets are available in:

The 10-mg[1] tablet is green, elliptical shaped, and scored, with PROZAC 10 debossed on opposite side of score.

NDC 0002-4006-30 (TA4006) – Bottles of 30
NDC 0002-4006-02 (TA4006) – Bottles of 100

Prozac® Weekly™ Capsules are available in:

The 90-mg[1] capsule is an opaque green cap and clear body containing discretely visible white pellets through the clear body of the capsule, imprinted with Lilly on the cap and 3004 and 90 mg on the body.

NDC 0002-3004-75 (PU3004) – Blister package of 4

[1]Fluoxetine base equivalent.
[2]Protect from light.
[3]FlexPak™ (flexible blister card, Lilly).
[4]Identi-Dose® (unit dose medication, Lilly).
[5]Dispense in a tight, light resistant container.

Store at Controlled Room Temperature, 15° to 30°C (59° to 86°F).

ANIMAL TOXICOLOGY

Phospholipids are increased in some tissues of mice, rats, and dogs given fluoxetine chronically. This effect is reversible after cessation of fluoxetine treatment. Phospholipid accumulation in animals has been observed with many cationic amphiphilic drugs, including fenfluramine, imipramine, and ranitidine. The significance of this effect in humans is unknown.

Literature revised January 3, 2003

PV 3453 DPP

REOPRO® ℞

[rē-ō-prō]
(abciximab)
For intravenous administration

DESCRIPTION

Abciximab, ReoPro®, is the Fab fragment of the chimeric human-murine monoclonal antibody 7E3. Abciximab binds to the glycoprotein (GP) IIb/IIIa receptor of human platelets and inhibits platelet aggregation. Abciximab also binds to the vitronectin ($\alpha_v\beta_3$) receptor found on platelets and vessel wall endothelial and smooth muscle cells.

The chimeric 7E3 antibody is produced by continuous perfusion in mammalian cell culture. The 47,615 dalton Fab fragment is purified from cell culture supernatant by a series of steps involving specific viral inactivation and removal procedures, digestion with papain and column chromatography.

ReoPro® is a clear, colorless, sterile, non-pyrogenic solution for intravenous (IV) use. Each single use vial contains 2 mg/mL of Abciximab in a buffered solution (pH 7.2) of 0.01 M sodium phosphate, 0.15 M sodium chloride and 0.001% polysorbate 80 in Water for Injection. No preservatives are added.

CLINICAL PHARMACOLOGY

General- Abciximab binds to the intact platelet GPIIb/IIIa receptor, which is a member of the integrin family of adhesion receptors and the major platelet surface receptor involved in platelet aggregation. Abciximab inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor, and other adhesive molecules to GPIIb/IIIa receptor sites on activated platelets. The mechanism of action is thought to involve steric hindrance and/or conformational effects to block access of large molecules to the receptor rather than direct interaction with the RGD (arginine-glycine-aspartic acid) binding site of GPIIb/IIIa.

Abciximab binds with similar affinity to the vitronectin receptor, also known as the $\alpha_v\beta_3$ integrin. The vitronectin receptor mediates the procoagulant properties of platelets and the proliferative properties of vascular endothelial and smooth muscle cells. In *in vitro* studies using a model cell line derived from melanoma cells, Abciximab blocked $\alpha_v\beta_3$-mediated effects including cell adhesion (IC_{50} = 0.34 µg/mL). At concentrations which, *in vitro*, provide > 80% GPIIb/IIIa receptor blockade, but above the *in vivo* therapeutic range, Abciximab more effectively blocked the burst of thrombin generation that followed platelet activation than select comparator antibodies which inhibit GPIIb/IIIa alone (1). The relationship of these *in vitro* data to clinical efficacy is unknown.

Abciximab also binds to the activated Mac-1 receptor on monocytes and neutrophils (2). In *in vitro* studies, Abciximab and 7E3 IgG blocked Mac-1 receptor function as evidenced by inhibition of monocyte adhesion (3). In addition, the degree of activated Mac-1 expression on circulating leukocytes and the numbers of circulating leukocyte-platelet complexes has been shown to be reduced in patients treated with Abciximab compared to control patients (4). The relationship of these *in vitro* data to clinical efficacy is uncertain.

Pre-clinical experience- Maximal inhibition of platelet aggregation was observed when ≥ 80% of GPIIb/IIIa receptors were blocked by Abciximab. In non-human primates, Abciximab bolus doses of 0.25 mg/kg generally achieved a blockade of at least 80% of platelet receptors and fully inhibited platelet aggregation. Inhibition of platelet function was temporary following a bolus dose, but receptor blockade could be sustained at ≥ 80% by continuous intravenous infusion. The inhibitory effects of Abciximab were substantially reversed by the transfusion of platelets in monkeys. The antithrombotic efficacy of prototype antibodies [murine 7E3 Fab and $F(ab')_2$] and Abciximab was evaluated in dog, monkey and baboon models of coronary, carotid, and femoral artery thrombosis. Doses of the murine version of 7E3 or Abciximab sufficient to produce high-grade (≥ 80%) GPIIb/IIIa receptor blockade prevented acute thrombosis and yielded lower rates of thrombosis compared with aspirin and/or heparin.

Pharmacokinetics- Following intravenous bolus administration, free plasma concentrations of Abciximab decrease rapidly with an initial half-life of less than 10 minutes and a second phase half-life of about 30 minutes, probably related to rapid binding to the platelet GPIIb/IIIa receptors. Platelet function generally recovers over the course of 48 hours (5,6), although Abciximab remains in the circulation for 15 days or more in a platelet-bound state. Intravenous administration of a 0.25 mg/kg bolus dose of Abciximab followed by continuous infusion of 10 µg/min (or a weight-adjusted infusion of 0.125 µg/kg/min to a maximum of 10 µg/min) produces approximately constant free plasma concentrations throughout the infusion. At the termination of the infusion period, free plasma concentrations fall rapidly for approximately six hours then decline at a slower rate.

Pharmacodynamics- Intravenous administration in humans of single bolus doses of Abciximab from 0.15 mg/kg to 0.30 mg/kg produced rapid dose-dependent inhibition of platelet function as measured by *ex vivo* platelet aggregation in response to adenosine diphosphate (ADP) or by prolongation of bleeding time. At the two highest doses (0.25 and 0.30 mg/kg) at two hours post injection (the first time point evaluated), over 80% of the GPIIb/IIIa receptors were blocked and platelet aggregation in response to 20 µM ADP

to over 30 minutes at both doses compared with a baseline value of approximately five minutes.

Intravenous administration in humans of a single bolus dose of 0.25 mg/kg followed by a continuous infusion of 10 µg/min for periods of 12 to 96 hours produced sustained high-grade GPIIb/IIIa receptor blockade (≥ 80%) and inhibition of platelet function (*ex vivo* platelet aggregation in response to 5 µM or 20 µM ADP less than 20% of baseline and bleeding time greater than 30 minutes) for the duration of the infusion in most patients. Similar results were obtained when a weight-adjusted infusion dose (0.125 µg/kg/min to a maximum of 10 µg/min) was used in patients weighing up to 80 kg. Results in patients who received the 0.25 mg/kg bolus followed by a 5 µg/min infusion for 24 hours showed a similar initial receptor blockade and inhibition of platelet aggregation, but the response was not maintained throughout the infusion period. The onset of Abciximab-mediated platelet inhibition following a 0.25 mg/kg bolus and 0.125 µg/kg/min infusion was rapid and platelet aggregation was reduced to less than 20% of baseline in 8 of 10 patients at 10 minutes after treatment initiation.

Low levels of GPIIb/IIIa receptor blockade are present for more than 10 days following cessation of the infusion. After discontinuation of Abciximab infusion, platelet function returns gradually to normal. Bleeding time returned to ≤ 12 minutes within 12 hours following the end of infusion in 15 of 20 patients (75%), and within 24 hours in 18 of 20 patients (90%). *Ex vivo* platelet aggregation in response to 5 µM ADP returned to ≥ 50% of baseline within 24 hours following the end of infusion in 11 of 32 patients (34%) and within 48 hours in 23 of 32 patients (72%). In response to 20 µM ADP, *ex vivo* platelet aggregation returned to ≥ 50% of baseline within 24 hours in 20 of 32 patients (62%) and within 48 hours in 28 of 32 patients (88%).

CLINICAL STUDIES

Abciximab has been studied in four Phase 3 clinical trials, all of which evaluated the effect of Abciximab in patients undergoing percutaneous coronary intervention (PCI): in patients at high risk for abrupt closure of the treated coronary vessel (EPIC), in a broader group of patients (EPILOG), in unstable angina patients not responding to conventional medical therapy (CAPTURE), and in patients suitable for either conventional angioplasty/atherectomy or primary stent implantation (EPILOG Stent; EPISTENT). Percutaneous intervention included balloon angioplasty, atherectomy, or stent placement. All trials involved the use of various, concomitant heparin dose regimens and, unless contraindicated, aspirin (325 mg) was administered orally two hours prior to the planned procedure and then once daily.

EPIC was a multicenter, double-blind, placebo-controlled trial of Abciximab in patients undergoing percutaneous transluminal coronary angioplasty or atherectomy (PTCA) who were at high risk for abrupt closure of the treated coronary vessel (7). Patients were allocated to treatment with: 1) Abciximab bolus plus infusion for 12 hours; 2) Abciximab bolus plus placebo infusion, or; 3) placebo bolus plus infusion. All patients received concomitant heparin (10,000 to 12,000 U bolus followed by an infusion for 12 hours).

The primary endpoint was the composite of death, myocardial infarction (MI), or urgent intervention for recurrent ischemia within 30 days of randomization. The primary endpoint event rates in the Abciximab bolus plus infusion group were reduced mostly in the first 48 hours and this benefit was sustained through 30 days (7), 6 months (8), and three years (9).

EPILOG was a randomized, double-blind, multicenter, placebo-controlled trial which evaluated Abciximab in a broad population of patients undergoing PCI (excluding patients with myocardial infarction and unstable angina meeting the EPIC high risk criteria) (10). Study procedures emphasized discontinuation of heparin after the procedure with early femoral arterial sheath removal and careful access site management (see PRECAUTIONS). EPILOG was a three-arm trial comparing Abciximab plus standard-dose heparin, Abciximab plus low-dose heparin, and placebo plus standard-dose heparin. Abciximab and heparin infusions were weight-adjusted in all arms. The Abciximab bolus plus infusion regimen was: 0.25 mg/kg bolus followed by a 0.125 µg/kg/min infusion (to a maximum of 10 µg/min) for 12 hours. The heparin regimen was either a standard-dose regimen (initial 100 U/kg bolus, target ACT ≥ 300 seconds) or a low-dose regimen (initial 70 U/kg bolus, target ACT ≥ 200 seconds).

The primary endpoint of the EPILOG trial was the composite of death or MI occurring within 30 days of PCI. The composite of death, MI, or urgent intervention was an important secondary endpoint. The endpoint events in the Abciximab treatment group were reduced mostly in the first 48 hours and this benefit was sustained through 30 days and six months (10) and one year (11). The (Kaplan-Meier) endpoint event rates at 30 days are shown in Table 1.

[See table 1 above]

At the six-month follow up visit, the event rate for death, MI, or repeat (urgent or non-urgent) intervention remained lower in the Abciximab treatment arms (22.3% and 22.8%, respectively, for the standard- and low-dose heparin arms) than in the placebo arm (25.8%) and the event rate for death, MI, or urgent intervention was substantially lower in the Abciximab treatment arms (8.3% and 8.4%, respectively, for the standard- and low-dose heparin arms) than in the placebo arm (14.7%). The treatment associated effects consistent reductions in endpoint event rates were similar irrespective of the type of coronary intervention used (balloon angioplasty, atherectomy, or stent placement). Risk assessment using the American College of Cardiology/American Heart Association clinical /morphological criteria had large inter-observer variability. Consequently, a low risk subgroup could not be reproducibly identified in which to evaluate efficacy.

Table 1
ENDPOINT EVENT RATES AT 30 DAYS - EPILOG TRIAL

	Placebo + Standard Dose Heparin (n=939)	Abciximab + Standard Dose Heparin (n=918)	Abciximab + Low Dose Heparin (n=935)
		Number of Patients (%)	
Death or MI[a]	85 (9.1)	38 (4.2)	35 (3.8)
p-value vs. placebo		<0.001	<0.001
Death, MI, or urgent intervention[a]	109 (11.7)	49 (5.4)	48 (5.2)
p-value vs. placebo		<0.001	<0.001
Components of Composite Endpoints[b]			
Death	7 (0.8)	4 (0.4)	3 (0.3)
Acute myocardial infarctions in surviving patients	78 (8.4)	34 (3.7)	32 (3.4)
Urgent interventions in surviving patients without an acute myocardial infarction	24 (2.6)	11 (1.2)	13 (1.4)

[a]Patients who experienced more than one event in the first 30 days are counted only once.
[b]Patients are counted only once under the most serious component (death > acute MI > urgent intervention).

Table 2
PRIMARY ENDPOINT EVENT RATE AT 30 DAYS - EPISTENT TRIAL

	Placebo + Stent (n=809)	Abciximab + Stent (n=794)	Abciximab + PTCA (n=796)
		Number of Patients (%)	
Death, MI, or urgent intervention[a]	87 (10.8%)	42 (5.3%)	55 (6.9%)
p-value vs. placebo		<0.001	0.007
Components of Composite Endpoint[b]			
Death	5 (0.6%)	2 (0.3%)	6 (0.8%)
Acute myocardial infarctions in surviving patients	77 (9.6%)	35 (4.4%)	40 (5.0%)
Urgent interventions in surviving patients without an acute myocardial infarction	5 (0.6%)	5 (0.6%)	9 (1.1%)

[a]Patients who experienced more than one event in the first 30 days are counted only once.
[b]Patients are counted only once under the most serious component (death > acute MI > urgent intervention).

The EPISTENT trial was a randomized, multicenter trial evaluating three different treatment strategies in patients undergoing PCI: conventional PTCA with Abciximab plus low-dose heparin, primary intracoronary stent implantation with Abciximab plus low-dose heparin, and primary intracoronary stent implantation with placebo plus standard-dose heparin (12). The heparin dose was weight-adjusted in all arms. The JJIS Palmaz-Schatz stent was used in over 90% of the patients receiving stents. The two stent arms were blinded with respect to study agent (Abciximab or placebo) and heparin dose; the PCI arm with Abciximab was open-label. The Abciximab bolus plus infusion regimen was the same as that used in the EPILOG trial. The standard-dose and low-dose heparin regimens were the same as those used in the EPILOG trial. All patients were to receive aspirin; ticlopidine, if given, was to be started prior to study agent. Patient and access site management guidelines were the same as those for EPILOG, including a strong recommendation for early sheath removal.

The results demonstrated benefit in both Abciximab arms (i.e., with and without stents) compared with stenting alone on the composite of death, MI, or urgent intervention (repeat PCI or CABG) within 30 days of PCI (12). The (Kaplan-Meier) endpoint event rates at 30 days are shown in Table 2.

[See table 2 above]

This benefit was maintained at 6 months: 12.1% of patients in the placebo/stent group experienced death, MI, or urgent revascularization compared with 6.4% of patients in the Abciximab/stent group (p<0.001 vs placebo/stent) and 9.2% in the Abciximab/PTCA group (p=0.051 vs placebo/stent). At 6 months, a reduction in the composite of death, MI, or all repeat (urgent or non-urgent) intervention was observed in the Abciximab/stent group compared with the placebo/stent group (15.4% vs 20.4%, p=0.006); the rate of this composite endpoint was similar in the Abciximab/PTCA and placebo/stent groups (22.4% vs 20.4%, p=0.467). (13)

CAPTURE was a randomized, double-blind, multicenter, placebo-controlled trial of the use of Abciximab in unstable angina patients not responding to conventional medical therapy for whom PCI was planned, but not immediately performed (14). The CAPTURE trial involved the administration of placebo or Abciximab starting 18 to 24 hours prior to PCI and continuing until one hour after completion of the intervention.

Patients were assessed as having unstable angina not responding to conventional medical therapy if they had at least one episode of myocardial ischemia despite bed rest and at least two hours of therapy with intravenous heparin and oral or intravenous nitrates. These patients were enrolled into the CAPTURE trial, if during a screening angiogram, they were determined to have a coronary lesion amenable to PCI. Patients received a bolus dose and intravenous infusion of placebo or Abciximab for 18 to 24 hours. At the end of the infusion period, the intervention was performed. The Abciximab or placebo infusion was discontinued with intravenous heparin and oral or intravenous nitrates throughout the 18- to 24-hour Abciximab infusion period prior to the PCI.

The Abciximab dose was a 0.25 mg/kg bolus followed by a continuous infusion at a rate of 10 µg/min. The CAPTURE trial incorporated weight adjustment of the standard heparin dose only during the performance of the intervention, but did not investigate the effect of a lower heparin dose, and arterial sheaths were left in place for approximately 40 hours. The primary endpoint of the CAPTURE trial was the occurrence of any of the following events within 30 days of PCI: death, MI, or urgent intervention. The 30-day (Kaplan-Meier) primary endpoint event rates are shown in Table 3.

[See table 3 at top of next page]

The 30-day results are consistent with the results of the other three trials, with the greatest effects on the myocardial infarction and urgent intervention components of the composite endpoint. As secondary endpoints, the components of the composite endpoint were analyzed separately for the period prior to the PCI and the period from the beginning of the intervention through Day 30. The greatest difference in MI occurred in the post-intervention period: the rates of MI were lower in the Abciximab group compared with placebo (Abciximab 3.6%, placebo 6.1%). There was also a reduction in MI occurring prior to the PCI (Abciximab 0.6%, placebo 2.0%). An Abciximab-associated reduction in the incidence of urgent intervention occurred in the post-intervention period. No effect on mortality was observed in either period. At six months of follow up, the composite endpoint of death, MI, or all repeat intervention (urgent or non-urgent) was not different between the Abciximab and placebo groups (Abciximab 31.0%, placebo 30.8%, p=0.77).

Mortality was uncommon in all four trials. Similar mortality rates were observed in all arms within each trial. Patient follow-up through one year of the EPISTENT trial suggested decreased mortality among patients treated with Abciximab and stent placement compared to patients treated with stent alone (8/794 vs. 19/809, p=0.037). Data from earlier studies with balloon angioplasty were not suggestive of the same benefit. In all four trials, the rates of acute MI were significantly lower in the groups treated with Abciximab. Most of the Abciximab treatment effect was seen in reduction in the rate of acute non-Q-wave MI. Urgent intervention rates were also lower in Abciximab-treated groups in these trials.

Anticoagulation:

EPILOG and EPISTENT: Weight-adjusted low dose heparin, weight-adjusted Abciximab, careful vascular access site management and discontinuation of heparin after the procedure with early femoral arterial sheath removal were used.

The initial heparin bolus was based upon the results of the baseline ACT, according to the following regimen:

Continued on next page

* Identi-Code® symbol. This product information was prepared in June 2002. Current information on these and other products of Eli Lilly and Company may be obtained by direct inquiry to Lilly Research Laboratories, Lilly Corporate Center,

ReoPro—Cont.

ACT < 150 seconds: administer 70 U/kg heparin
ACT 150-199 seconds: administer 50 U/kg heparin
ACT ≥ 200 seconds: administer no heparin

Additional 20 U/kg heparin boluses were given to achieve and maintain an ACT of ≥ 200 seconds during the procedure.

Discontinuation of heparin immediately after the procedure and removal of the arterial sheath within six hours were strongly recommended in the trials. If prolonged heparin therapy or delayed sheath removal was clinically indicated, heparin was adjusted to keep the APTT at a target of 60 to 85 seconds (EPILOG) or 55 to 75 seconds (EPISTENT).

CAPTURE trial: Anticoagulation was initiated prior to the administration of Abciximab. Anticoagulation was initiated with an intravenous heparin infusion to achieve a target APTT of 60 to 85 seconds. The heparin infusion was not uniformly weight adjusted in this trial. The heparin infusion was maintained during the Abciximab infusion and was adjusted to achieve an ACT of 300 seconds or an APTT of 70 seconds during the PCI. Following the intervention, heparin management was as outlined above for the EPILOG trial.

Table 3
PRIMARY ENDPOINT EVENT RATE AT 30 DAYS - CAPTURE TRIAL

	Placebo (n=635)	Abciximab (n=630)
	Number of Patients (%)	
Death, MI, or urgent intervention[a]	101 (15.9)	71 (11.3)
p-value vs. placebo		0.012
Components of Primary Endpoint[b]		
Death	8 (1.3)	6 (1.0)
MI in surviving patients	49 (7.7)	24 (3.8)
Urgent intervention in surviving patients without an acute MI	44 (6.9)	41 (6.6)

[a] Patients who experienced more than one event in the first 30 days are counted only once. Urgent interventions included any unplanned PCI after the planned intervention, as well as any stent placement for immediate patency and any unplanned CABG or use of an intra-aortic balloon pump.
[b] Patients are counted only once under the most serious component (death > acute MI > urgent intervention).

INDICATIONS AND USAGE

Abciximab is indicated as an adjunct to percutaneous coronary intervention for the prevention of cardiac ischemic complications.

- in patients undergoing percutaneous coronary intervention
- in patients with unstable angina not responding to conventional medical therapy when percutaneous coronary intervention is planned within 24 hours

Abciximab use in patients not undergoing percutaneous coronary intervention has not been studied.

Abciximab is intended for use with aspirin and heparin and has been studied only in that setting, as described in CLINICAL STUDIES.

CONTRAINDICATIONS

Because Abciximab may increase the risk of bleeding, Abciximab is contraindicated in the following clinical situations:

- Active internal bleeding
- Recent (within six weeks) gastrointestinal (GI) or genitourinary (GU) bleeding of clinical significance.
- History of cerebrovascular accident (CVA) within two years, or CVA with a significant residual neurological deficit
- Bleeding diathesis
- Administration of oral anticoagulants within seven days unless prothrombin time is ≤ 1.2 times control
- Thrombocytopenia (< 100,000 cells/µL)
- Recent (within six weeks) major surgery or trauma
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Severe uncontrolled hypertension
- Presumed or documented history of vasculitis
- Use of intravenous dextran before PCI, or intent to use it during an intervention

Abciximab is also contraindicated in patients with known hypersensitivity to any component of this product or to murine proteins.

WARNINGS

Abciximab has the potential to increase the risk of bleeding, particularly in the presence of anticoagulation, e.g., from heparin, other anticoagulants, or thrombolytics (see ADVERSE REACTIONS: Bleeding).

The risk of major bleeds due to Abciximab therapy may be increased in patients receiving thrombolytics and should be weighed against the anticipated benefits.

Should serious bleeding occur that is not controllable with pressure, the infusion of Abciximab and any concomitant heparin should be stopped.

PRECAUTIONS

Bleeding Precautions- To minimize the risk of bleeding with Abciximab, it is important to use a low-dose, weight-adjusted heparin regimen, a weight-adjusted Abciximab bolus and infusion, strict anticoagulation guidelines, careful vascular access site management, discontinuation of heparin after the procedure and early femoral arterial sheath removal.

Therapy with Abciximab requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites, needle puncture sites, and gastrointestinal, genitourinary, and retroperitoneal sites).

Arterial and venous punctures, intramuscular injections, and use of urinary catheters, nasotracheal intubation, nasogastric tubes and automatic blood pressure cuffs should be minimized. When obtaining intravenous access, noncompressible sites (e.g., subclavian or jugular veins) should be avoided. Saline or heparin locks should be considered for blood drawing. Vascular puncture sites should be documented and monitored. Gentle care should be provided when removing dressings.

Femoral artery access site: Arterial access site care is important to prevent bleeding. Care should be taken when attempting vascular access that only the anterior wall of the femoral artery is punctured, avoiding a Seldinger (through and through) technique for obtaining sheath access. Femo-

maintained on complete bed rest with the head of the bed ≤ 30° and the affected limb restrained in a straight position. Patients may be medicated for back/groin pain as necessary.

Discontinuation of heparin immediately upon completion of the procedure and removal of the arterial sheath within six hours is strongly recommended if APTT ≤ 50 sec or ACT ≤ 175 sec (See PRECAUTIONS: Laboratory Tests). In all circumstances, heparin should be discontinued at least two hours prior to arterial sheath removal.

Following sheath removal, pressure should be applied to the femoral artery for at least 30 minutes using either manual compression or a mechanical device for hemostasis. A pressure dressing should be applied following hemostasis. The patient should be maintained on bed rest for six to eight hours following sheath removal or discontinuation of Abciximab, or four hours following discontinuation of heparin, whichever is later. The pressure dressing should be removed prior to ambulation. The sheath insertion site and distal pulses of affected leg(s) should be frequently checked while the femoral artery sheath is in place and for six hours after femoral artery sheath removal. Any hematoma should be measured and monitored for enlargement.

The following conditions have been associated with an increased risk of bleeding and may be additive with the effect of Abciximab in the angioplasty setting: PCI within 12 hours of the onset of symptoms for acute myocardial infarction, prolonged PCI (lasting more than 70 minutes) and failed PCI.

Use of Thrombolytics, Anticoagulants and Other Antiplatelet Agents- In the EPIC, EPILOG, CAPTURE, and EPISTENT trials, Abciximab was used concomitantly with heparin and aspirin. For details of the anticoagulation algorithms used in these clinical trials, see CLINICAL STUDIES: Anticoagulation. Because Abciximab inhibits platelet aggregation, caution should be employed when it is used with other drugs that affect hemostasis, including thrombolytics, oral anticoagulants, non-steroidal anti-inflammatory drugs, dipyridamole, and ticlopidine.

In the EPIC trial, there was limited experience with the administration of Abciximab with low molecular weight dextran. Low molecular weight dextran was usually given for the deployment of a coronary stent, for which oral anticoagulants were also given. In the 11 patients who received low molecular weight dextran with Abciximab, five had major bleeding events and four had minor bleeding events. None of the five placebo patients treated with low molecular weight dextran had a major or minor bleeding event (see CONTRAINDICATIONS).

There are limited data on the use of Abciximab in patients receiving thrombolytic agents. Because of concern about synergistic effects on bleeding, systemic thrombolytic therapy should be used judiciously.

Thrombocytopenia- Platelet counts should be monitored prior to treatment, two to four hours following the bolus dose of Abciximab and at 24 hours or prior to discharge, whichever is first. If a patient experiences an acute platelet decrease (e.g., a platelet decrease to less than 100,000 cells/µL and a decrease of at least 25% from pre-treatment value), additional platelet counts should be determined. These platelet counts should be drawn in three separate tubes containing ethylenediaminetetraacetic acid (EDTA), citrate and heparin, respectively, to exclude pseudothrombocytopenia due to *in vitro* anticoagulant interaction. If true thrombocytopenia is verified, Abciximab should be immediately discontinued and the condition appropriately monitored and treated. For patients with thrombocytopenia in the clinical trials, a daily platelet count was obtained until it returned to normal. If a patient's platelet count dropped to 60,000 cells/µL, heparin and aspirin were discontinued. If a patient's platelet count dropped below 50,000 cells/µL, platelets were transfused. Most cases of severe thrombocytopenia (< 50,000 cells/µL) occurred within the first 24 hours of Abciximab administration.

Restoration of Platelet Function- In the event of serious uncontrolled bleeding or the need for emergency surgery, Abciximab should be discontinued. If platelet function does not return to normal, it may be restored, at least in part, with platelet transfusions.

Laboratory Tests- Before infusion of Abciximab, platelet count, prothrombin time, ACT and APTT should be measured to identify pre-existing hemostatic abnormalities.

Based on an integrated analysis of data from all studies, the

When Abciximab is initiated 18 to 24 hours before PCI, the APTT should be maintained between 60 and 85 seconds during the Abciximab and heparin infusion period.

During PCI the ACT should be maintained between 200 and 300 seconds.

If anticoagulation is continued in these patients following PCI, the APTT should be maintained between 55 and 75 seconds.

The APTT or ACT should be checked prior to arterial sheath removal. The sheath should not be removed unless APTT ≤ 50 seconds or ACT ≤ 175 seconds.

Readministration- Administration of Abciximab may result in human anti-chimeric antibody (HACA) formation that could potentially cause allergic or hypersensitivity reactions (including anaphylaxis), thrombocytopenia or diminished benefit upon readministration of Abciximab. In the EPIC, EPILOG, and CAPTURE trials, positive HACA responses occurred in approximately 5.8% of the Abciximab-treated patients. There was no excess of hypersensitivity or allergic reactions related to Abciximab treatment.

Readministration of Abciximab to 29 healthy volunteers who had not developed a HACA response after first administration has not led to any change in Abciximab pharmacokinetics or to any reduction in antiplatelet potency. However, results in this small group of patients suggest that the incidence of HACA response may be increased after readministration. Readministration to patients who have developed a positive HACA response after initial administration has not been evaluated in clinical trials.

Allergic Reactions- Anaphylaxis has not been reported for Abciximab-treated patients in any of the Phase 3 clinical trials. However, anaphylaxis may occur. If it does, administration of Abciximab should be immediately stopped and standard appropriate resuscitative measures should be initiated.

Drug Interactions- Although drug interactions with Abciximab have not been studied systematically, Abciximab has been administered to patients with ischemic heart disease treated concomitantly with a broad range of medications used in the treatment of angina, myocardial infarction and hypertension. These medications have included heparin, warfarin, beta-adrenergic receptor blockers, calcium channel antagonists, angiotensin converting enzyme inhibitors, intravenous and oral nitrates, ticlopidine, and aspirin. Heparin, other anticoagulants, thrombolytics, and antiplatelet agents may be associated with an increase in bleeding. Patients with HACA titers may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

Carcinogenesis, Mutagenesis and Impairment of Fertility- *In vitro* and *in vivo* mutagenicity studies have not demonstrated any mutagenic effect. Long-term studies in animals have not been performed to evaluate the carcinogenic potential or effects on fertility in male or female animals.

Pregnancy Category C- Animal reproduction studies have not been conducted with Abciximab. It is also not known whether Abciximab can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Abciximab should be given to a pregnant woman only if clearly needed.

Nursing Mothers- It is not known whether this drug is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, caution should be exercised when Abciximab is administered to a nursing woman.

Pediatric Use- Safety and effectiveness in pediatric patients have not been studied.

Geriatric Use- Of the total number of 7860 patients in the four Phase 3 trials, 2933 (37%) were 65 and over, while 653 (8%) were 75 and over. No overall differences in safety or efficacy were observed between patients of age 65 to less than 75 as compared to younger patients. The clinical experience is not adequate to determine whether patients of age 75 or greater respond differently than younger patients.

ADVERSE REACTIONS

Bleeding- Abciximab has the potential to increase the risk of bleeding, particularly in the presence of anticoagulation, e.g., from heparin, other anticoagulants or thrombolytics. Bleeding in the Phase 3 trials was classified as major, minor or insignificant by the criteria of the Thrombolysis in Myocardial Infarction study group (15). Major bleeding events were defined as either an intracranial hemorrhage or a de-

hematemesis, observed blood loss with a hemoglobin decrease of more than 3 g/dL, or a decrease in hemoglobin of at least 4 g/dL without an identified bleeding site. Insignificant bleeding events were defined as a decrease in hemoglobin of less than 3 g/dL or a decrease in hemoglobin between 3-4 g/dL without observed bleeding. In patients who received transfusions, the number of units of blood lost was estimated through an adaptation of the method of Landefeld, et al. (16).

In the EPIC trial, in which a non-weight-adjusted, longer-duration heparin dose regimen was used, the most common complication during Abciximab therapy was bleeding during the first 36 hours. The incidences of major bleeding, minor bleeding and transfusion of blood products were significantly increased. Major bleeding occurred in 10.6% of patients in the Abciximab bolus plus infusion arm compared with 3.3% of patients in the placebo arm. Minor bleeding was seen in 16.8% of Abciximab bolus plus infusion patients and 9.2% of placebo patients (7). Approximately 70% of Abciximab-treated patients with major bleeding had bleeding at the arterial access site in the groin. Abciximab-treated patients also had a higher incidence of major bleeding events from gastrointestinal, genitourinary, retroperitoneal, and other sites.

Bleeding rates were reduced in the CAPTURE trial, and further reduced in the EPILOG and EPISTENT trials by use of modified dosing regimens and specific patient management techniques. In EPILOG and EPISTENT, using the heparin and Abciximab dosing, sheath removal and arterial access site guidelines described under PRECAUTIONS, the incidence of major bleeding in patients treated with Abciximab and low-dose, weight-adjusted heparin was not significantly different from that in patients receiving placebo.

Subgroup analyses in the EPIC and CAPTURE trials showed that non-CABG major bleeding was more common in Abciximab patients weighing ≤ 75 kg. In the EPILOG and EPISTENT trials, which used weight-adjusted heparin dosing, the non-CABG major bleeding rates for Abciximab-treated patients did not differ substantially by weight subgroup.

Although data are limited, Abciximab treatment was not associated with excess major bleeding in patients who underwent CABG surgery. (The range among all treatment arms was 3-5% in EPIC, and 1-2% in the CAPTURE, EPILOG, and EPISTENT trials.) Some patients with prolonged bleeding times received platelet transfusions to correct the bleeding time prior to surgery. (See PRECAUTIONS: Restoration of Platelet Function.)

The rates of major bleeding, minor bleeding and bleeding events requiring transfusions in the CAPTURE, EPILOG, and EPISTENT trials are shown in Table 4. The rates of insignificant bleeding events are not included in Table 4. [See table 4 at right]

Intracranial Hemorrhage and Stroke- The total incidence of intracranial hemorrhage and non-hemorrhagic stroke across all four trials was not significantly different, 9/3023 for placebo patients and 15/4680 for Abciximab-treated patients. The incidence of intracranial hemorrhage was 3/3023 for placebo patients and 7/4680 for Abciximab patients.

Thrombocytopenia- In the clinical trials, patients treated with Abciximab were more likely than patients treated with placebo to experience decreases in platelet counts.

Among patients in the EPILOG and EPISTENT trials who were treated with Abciximab plus low-dose heparin, the proportion of patients with any thrombocytopenia (platelets less than 100,000 cells/μL) ranged from 2.5 to 3.0%. The incidence of severe thrombocytopenia (platelets less than 50,000 cells/μL) ranged from 0.4 to 1.0% and platelet transfusions were required in 0.9 to 1.1%, respectively. Modestly lower rates were observed among patients treated with placebo plus standard-dose heparin. Overall higher rates were observed among patients in the EPIC and CAPTURE trials treated with Abciximab plus longer duration heparin: 2.6 to 5.2% were found to have any thrombocytopenia, 0.9 to 1.7% had severe thrombocytopenia, and 2.1 to 5.5% required platelet transfusion, respectively.

Other Adverse Reactions- Table 5 shows adverse events other than bleeding and thrombocytopenia from the combined EPIC, EPILOG and CAPTURE trials which occurred in patients in the bolus plus infusion arm at an incidence of more than 0.5% higher than in those treated with placebo. [See table 5 at right]

The following additional adverse events from the EPIC, EPILOG and CAPTURE trials were reported by investigators for patients treated with a bolus plus infusion of Abciximab at incidences which were less than 0.5% higher than for patients in the placebo arm.

Cardiovascular System: ventricular tachycardia (1.4%), pseudoaneurysm (0.8%), palpitation (0.5%), arteriovenous fistula (0.4%), incomplete AV block (0.3%), nodal arrhythmia (0.2%), complete AV block (0.1%), embolism (limb)(0.1%); thrombophlebitis (0.1%);

Gastrointestinal System: dyspepsia (2.1%), diarrhea (1.1%), ileus (0.1%), gastroesophogeal reflux (0.1%);

Hemic and Lymphatic System: anemia (1.3%), leukocytosis (0.5%), petechiae (0.2%);

Nervous System: dizziness (2.9%), anxiety (1.7%), abnormal thinking (1.3%), agitation (0.7%), hypesthesia (0.6%), confusion (0.5%) muscle contractions (0.4%), coma (0.2%), hypertonia (0.2%), diplopia (0.1%);

Respiratory System: pneumonia (0.4%), rales (0.4%), pleural effusion (0.3%), bronchitis (0.3%) bronchospasm (0.3%), pleurisy (0.2%), pulmonary embolism (0.2%), rhonchi (0.1%);

Musculoskeletal System: myalgia (0.2%);

Urogenital System: urinary retention (0.7%), dysuria (0.4%), abnormal renal function (0.4%), frequent micturition (0.1%), cystalgia (0.1%), urinary incontinence (0.1%), prostatitis (0.1%);

Miscellaneous: pain (5.4%), sweating increased (1.0%), asthenia (0.7%), incisional pain (0.6%), pruritus (0.5%), abnormal vision (0.3%), edema (0.3%), wound (0.2%), abscess (0.2%), cellulitis (0.2%), peripheral coldness (0.2%), injection site pain (0.1%), dry mouth (0.1%), pallor (0.1%), diabetes mellitus (0.1%), hyperkalemia (0.1%), enlarged abdomen (0.1%), bullous eruption (0.1%), inflammation (0.1%), drug toxicity (0.1%).

Table 4
NON-CABG BLEEDING IN TRIALS OF PERCUTANEOUS CORONARY INTERVENTION (EPILOG, EPISTENT and CAPTURE)
Number of Patients with Bleeds (%)

EPILOG and EPISTENT:

	Placebo[c] (n = 1748)	Abciximab + Low-dose Heparin[d] (n=2525)	Abciximab + Standard-dose Heparin[e] (n=918)
Major[a]	18 (1.0)	21 (0.8)	17 (1.9)
Minor	46 (2.6)	82 (3.2)	70 (7.6)
Requiring transfusion[b]	15 (0.9)	13 (0.5)	7 (0.8)

CAPTURE:

	Placebo[f] (n=635)	Abciximab[f] (n=630)
Major[a]	12 (1.9)	24 (3.8)
Minor	13 (2.0)	30 (4.8)
Requiring transfusion[b]	9 (1.4)	15 (2.4)

[a] Patients who had bleeding in more than one classification are counted only once according to the most severe classification. Patients with multiple bleeding events of the same classification are also counted once within that classification.
[b] Patients with major non-CABG bleeding who received packed red blood cells or whole blood transfusion.
[c] Standard-dose heparin with or without stent (EPILOG and EPISTENT)
[d] Low-dose heparin with or without stent (EPILOG and EPISTENT)
[e] Standard-dose heparin (EPILOG)
[f] Standard-dose heparin (CAPTURE)

Table 5
ADVERSE EVENTS AMONG TREATED PATIENTS IN THE EPIC, EPILOG, AND CAPTURE TRIALS

Event	Placebo (n=2226)	Bolus + Infusion (n=3111)
	Number of Patients (%)	
Cardiovascular system		
Hypotension	230 (10.3)	447 (14.4)
Bradycardia	79 (3.5)	140 (4.5)
Gastrointestinal system		
Nausea	255 (11.5)	423 (13.6)
Vomiting	152 (6.8)	226 (7.3)
Abdominal pain	49 (2.2)	97 (3.1)
Miscellaneous		
Back pain	304 (13.7)	546 (17.6)
Chest pain	208 (9.3)	356 (11.4)
Headache	122 (5.5)	200 (6.4)
Puncture site pain	58 (2.6)	113 (3.6)
Peripheral edema	25 (1.1)	49 (1.6)

OVERDOSAGE

There has been no experience of overdosage in human clinical trials.

DOSAGE AND ADMINISTRATION

The safety and efficacy of Abciximab have only been investigated with concomitant administration of heparin and aspirin as described in CLINICAL STUDIES.

In patients with failed PCIs, the continuous infusion of Abciximab should be stopped because there is no evidence for Abciximab efficacy in that setting.

In the event of serious bleeding that cannot be controlled by compression, Abciximab and heparin should be discontinued immediately.

The recommended dosage of Abciximab in adults is a 0.25 mg/kg intravenous bolus administered 10-60 minutes before the start of PCI, followed by a continuous intravenous infusion of 0.125 μg/kg/min (to a maximum of 10 μg/min) for 12 hours.

Patients with unstable angina not responding to conventional medical therapy and who are planned to undergo PCI within 24 hours may be treated with an Abciximab 0.25 mg/kg intravenous bolus followed by an 18- to 24-hour intravenous infusion of 10 μg/min, concluding one hour after the PCI.

Instructions for Administration

1. Parenteral drug products should be inspected visually for particulate matter prior to administration. Preparations of Abciximab containing visibly opaque particles should NOT be used.
2. Hypersensitivity reactions should be anticipated whenever protein solutions such as Abciximab are administered. Epinephrine, dopamine, theophylline, antihistamines and corticosteroids should be available for immediate use. If symptoms of an allergic reaction or anaphylaxis appear, the infusion should be stopped and appropriate treatment given.
3. As with all parenteral drug products, aseptic procedures should be used during the administration of Abciximab.
4. Withdraw the necessary amount of Abciximab for bolus injection into a syringe. Filter the bolus injection using a sterile, non-pyrogenic, low protein-binding 0.2 or 0.22 μm syringe filter (Millipore SLGV025LS or equivalent) or upon administration using an in-line, sterile, non-pyrogenic, low protein-binding 0.2 or 0.22 μm filter (Abbott #4524 or equivalent). Discard the unused portion at the end of the bolus injection.
5. Withdraw the necessary amount of Abciximab for the continuous infusion into a syringe. Inject into an appropriate container of sterile 0.9% saline or 5% dextrose and infuse at the calculated rate via a continuous infusion pump. The continuous infusion should be filtered either upon admixture using a sterile, non-pyrogenic, low protein-binding 0.2 or 0.22 μm syringe filter (Millipore SLGV025LS or equivalent) or upon administration using an in-line, sterile, non-pyrogenic, low protein-binding 0.2 or 0.22 μm filter (Abbott #4524 or equivalent). Discard the unused portion at the end of the infusion.
6. No incompatibilities have been shown with intravenous infusion fluids or commonly used cardiovascular drugs. Nevertheless, Abciximab should be administered in a separate intravenous line whenever possible and not mixed with other medications.
7. No incompatibilities have been observed with glass bottles or polyvinyl chloride bags and administration sets.

HOW SUPPLIED

Abciximab (ReoPro®) 2 mg/mL is supplied in 5 mL vials containing 10 mg (NDC 0002-7140-01).

Vials should be stored at 2 to 8°C (36 to 46°F). Do not freeze. Do not shake. Do not use beyond the expiration date. Discard any unused portion left in the vial.

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Continued on next page

* Identi-Code® symbol. This product information was prepared in June 2002. Current information on these and other products of Eli Lilly and Company may be obtained by direct inquiry to Lilly Research Laboratories, Lilly Corporate Center,

ReoPro—Cont.

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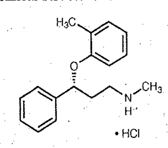
Manufactured by:
Centocor B.V.
Leiden, The Netherlands
U.S. License Number: 1178
Distributed by:
Eli Lilly and Company
Indianapolis, IN 46285
Revision Date: May 14, 2001
Shown in Product Identification Guide, page 322

STRATTERA™ ℞
[*stră-tĕr-ă*]
(atomoxetine HCl)

DESCRIPTION

STRATTERA™ (atomoxetine HCl) is a selective norepinephrine reuptake inhibitor. Atomoxetine HCl is the *R*(-) isomer as determined by x-ray diffraction. The chemical designation is (-)-*N*-methyl-3-phenyl-3-(*o*-tolyloxy)-propylamine hydrochloride. The molecular formula is $C_{17}H_{21}NO{\bullet}HCl$, which corresponds to a molecular weight of 291.82. The chemical structure is:



Atomoxetine HCl is a white to practically white solid, which has a solubility of 27.8 mg/mL in water.
STRATTERA capsules are intended for oral administration only.
Each capsule contains atomoxetine HCl equivalent to 10, 18, 25, 40, or 60 mg of atomoxetine. The capsules also contain pregelatinized starch and dimethicone. The capsule shells contain gelatin, sodium lauryl sulfate, and other inactive ingredients. The capsule shells also contain one or more of the following: FD&C Blue No. 2, synthetic yellow iron oxide, titanium dioxide. The capsules are imprinted with edible black ink.

CLINICAL PHARMACOLOGY

Pharmacodynamics and Mechanism of Action

The precise mechanism by which atomoxetine produces its therapeutic effects in Attention-Deficit/Hyperactivity Disorder (ADHD) is unknown, but is thought to be related to selective inhibition of the pre-synaptic norepinephrine transporter, as determined in ex vivo uptake and neurotransmitter depletion studies.

Human Pharmacokinetics

Atomoxetine is well-absorbed after oral administration and is minimally affected by food. It is eliminated primarily by oxidative metabolism through the cytochrome P450 2D6 (CYP2D6) enzymatic pathway and subsequent glucuronidation. Atomoxetine has a half-life of about 5 hours. A fraction of the population (about 7% of Caucasians and 2% of African Americans) are poor metabolizers (PMs) of CYP2D6 metabolized drugs. These individuals have reduced activity in this pathway resulting in 10-fold higher AUCs, 5-fold higher peak plasma concentrations, and slower elimination (plasma half-life of about 24 hours) of atomoxetine compared with people with normal activity [extensive metabolizers (EMs)]. Drugs that inhibit CYP2D6, such as fluoxetine, paroxetine, and quinidine, cause similar increases in exposure.
The pharmacokinetics of atomoxetine have been evaluated in more than 400 children and adolescents in selected clinical trials, primarily using population pharmacokinetic studies. Single-dose and steady-state individual pharmacokinetic data were also obtained in children, adolescents, and adults. When doses were normalized to a mg/kg basis, similar half-life, C_{max}, and AUC values were observed in children, adolescents, and adults. Clearance and volume of distribution after adjustment for body weight were also similar.
Absorption and Distribution—Atomoxetine is rapidly absorbed after oral administration, with absolute bioavailability of about 63% in EMs and 94% in PMs. Maximal plasma concentrations (C_{max}) are reached approximately 1 to 2 hours after dosing.
STRATTERA can be administered with or without food. Administration of STRATTERA with a standard high-fat meal in adults did not affect the extent of oral absorption of atomoxetine (AUC), but did decrease the rate of absorption, resulting in a 37% lower C_{max}, and delayed T_{max} by 3 hours. In clinical trials with children and adolescents, administration of STRATTERA with food resulted in a 9% lower C_{max}.
The steady-state volume of distribution after intravenous administration is 0.85 L/kg indicating that atomoxetine distributes primarily into total body water. Volume of distribution is similar across the patient weight range after normalizing for body weight.
At therapeutic concentrations, 98% of atomoxetine in plasma is bound to protein, primarily albumin.
Metabolism and Elimination—Atomoxetine is metabolized primarily through the CYP2D6 enzymatic pathway. People with reduced activity in this pathway (PMs) have higher plasma concentrations of atomoxetine compared with people with normal activity (EMs). For PMs, AUC of atomoxetine is approximately 10-fold and $C_{ss,max}$ is about 5-fold greater than EMs. Laboratory tests are available to identify CYP2D6 PMs. Coadministration of STRATTERA with potent inhibitors of CYP2D6, such as fluoxetine, paroxetine, or quinidine, results in a substantial increase in atomoxetine plasma exposure, and dosing adjustment may be necessary (*see* Drug-Drug Interactions). Atomoxetine did not inhibit or induce the CYP2D6 pathway.
The major oxidative metabolite formed, regardless of CYP2D6 status, is 4-hydroxyatomoxetine, which is glucuronidated. 4-Hydroxyatomoxetine is equipotent to atomoxetine as an inhibitor of the norepinephrine transporter but circulates in plasma at much lower concentrations (1% of atomoxetine concentration in EMs and 0.1% of atomoxetine concentration in PMs). 4-Hydroxyatomoxetine is primarily formed by CYP2D6, but in PMs, 4-hydroxyatomoxetine is formed at a slower rate by several other cytochrome P450 enzymes. N-Desmethylatomoxetine is formed by CYP2C19 and other cytochrome P450 enzymes, but has substantially less pharmacological activity compared with atomoxetine and circulates in plasma at lower concentrations (5% of atomoxetine concentration in EMs and 45% of atomoxetine concentration in PMs).
Mean apparent plasma clearance of atomoxetine after oral administration in adult EMs is 0.35 L/hr/kg and the mean half-life is 5.2 hours. Following oral administration of atomoxetine to PMs, mean apparent plasma clearance is 0.03 L/hr/kg and mean half-life is 21.6 hours. For PMs, AUC of atomoxetine is approximately 10-fold and $C_{ss,max}$ is about 5-fold greater than EMs. The elimination half-life of 4-hydroxyatomoxetine is similar to that of N-desmethylatomoxetine (6 to 8 hours) in EM subjects, while the half-life of N-desmethylatomoxetine is much longer in PM subjects (34 to 40 hours).
Atomoxetine is excreted primarily as 4-hydroxyatomoxetine-O-glucuronide, mainly in the urine (greater than 80% of the dose) and to a lesser extent in the feces (less than 17% of the dose). Only a small fraction of the STRATTERA dose is excreted as unchanged atomoxetine (less than 3% of the dose), indicating extensive biotransformation.

Special Populations

Hepatic insufficiency—Atomoxetine exposure (AUC) is increased, compared with normal subjects, in EM subjects with moderate (Child-Pugh Class B) (2-fold increase) and severe (Child-Pugh Class C) (4-fold increase) hepatic insufficiency. Dosage adjustment is recommended for patients with moderate or severe hepatic insufficiency (*see* DOSAGE AND ADMINISTRATION).
Renal insufficiency—EM subjects with end stage renal disease had higher systemic exposure to atomoxetine than healthy subjects (about a 65% increase), but there was no difference when exposure was corrected for mg/kg dose. STRATTERA can therefore be administered to ADHD patients with end stage renal disease or lesser degrees of renal insufficiency using the normal dosing regimen.
Geriatric—The pharmacokinetics of atomoxetine have not been evaluated in the geriatric population.
Pediatric—The pharmacokinetics of atomoxetine in children and adolescents are similar to those in adults. The pharmacokinetics of atomoxetine have not been evaluated in children under 6 years of age.
Gender—Gender did not influence atomoxetine disposition.
Ethnic origin—Ethnic origin did not influence atomoxetine disposition (except that PMs are more common in Caucasians).

Drug-Drug Interactions

CYP2D6 activity and atomoxetine plasma concentration—Atomoxetine is primarily metabolized by the CYP2D6 pathway to 4-hydroxyatomoxetine. In EMs, inhibitors of CYP2D6 increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in PMs. Dosage adjustment of STRATTERA in EMs may be necessary when coadministered with CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine (*see* Drug Interactions *under* PRECAUTIONS). In vitro studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine.
Effect of atomoxetine on P450 enzymes—Atomoxetine did not cause clinically important inhibition or induction of cytochrome P450 enzymes, including CYP1A2, CYP3A, CYP2D6, and CYP2C9.
Albuterol—Albuterol (600 mcg iv over 2 hours) induced increases in heart rate and blood pressure. These effects were potentiated by atomoxetine (60 mg BID for 5 days) and were most marked after the initial coadministration of albuterol and atomoxetine (*see* Drug-Drug Interactions *under* PRECAUTIONS).
Alcohol—Consumption of ethanol with STRATTERA did not change the intoxicating effects of ethanol.
Desipramine—Coadministration of STRATTERA (40 or 60 mg BID for 13 days) with desipramine, a model compound for CYP2D6 metabolized drugs (single dose of 50 mg), did not alter the pharmacokinetics of desipramine. No dose adjustment is recommended for drugs metabolized by CYP2D6.
Methylphenidate—Coadministration of methylphenidate with STRATTERA did not increase cardiovascular effects beyond those seen with methylphenidate alone.
Midazolam—Coadministration of STRATTERA (60 mg BID for 12 days) with midazolam, a model compound for CYP3A4 metabolized drugs, (single dose of 5 mg), resulted in 15% increase in AUC of midazolam. No dose adjustment is recommended for drugs metabolized by CYP3A.
Drugs highly bound to plasma protein—In vitro drug-displacement studies were conducted with atomoxetine and other highly-bound drugs at therapeutic concentrations. Atomoxetine did not affect the binding of warfarin, acetylsalicylic acid, phenytoin, or diazepam to human albumin. Similarly, these compounds did not affect the binding of atomoxetine to human albumin.
Drugs that affect gastric pH—Drugs that elevate gastric pH (magnesium hydroxide/aluminum hydroxide, omeprazole) had no effect on STRATTERA bioavailability.

CLINICAL STUDIES

The effectiveness of STRATTERA in the treatment of ADHD was established in 6 randomized, double-blind, placebo-controlled studies in children, adolescents, and adults who met Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for ADHD (*see* INDICATIONS AND USAGE).

Children and Adolescents

The effectiveness of STRATTERA in the treatment of ADHD was established in 4 randomized, double-blind, placebo-controlled studies of pediatric patients (ages 6 to 18). Approximately one-third of the patients met DSM-IV criteria for inattentive subtype and two-thirds met criteria for both inattentive and hyperactive/impulsive subtypes (*see* INDICATIONS AND USAGE).
Signs and symptoms of ADHD were evaluated by a comparison of mean change from baseline to endpoint for STRATTERA- and placebo-treated patients using an intent-to-treat analysis of the primary outcome measure, the investigator administered and scored ADHD Rating Scale-IV-Parent Version (ADHDRS) total score including hyperactive/impulsive and inattentive subscales. Each item on the ADHDRS maps directly to one symptom criterion for ADHD in the DSM-IV.
In Study 1, an 8-week randomized, double-blind, placebo-controlled, dose-response, acute treatment study of children and adolescents aged 8 to 18 (N=297), patients received either a fixed dose of STRATTERA (0.5, 1.2, or 1.8 mg/kg/day) or placebo. STRATTERA was administered as a divided dose in the early morning and late afternoon/early evening. At the 2 higher doses, improvements in ADHD symptoms were statistically significantly superior in STRATTERA-treated patients compared with placebo-treated patients as measured on the ADHDRS scale. The 1.8-mg/kg/day STRATTERA dose did not provide any additional benefit over that observed with the 1.2-mg/kg/day dose. The 0.5-mg/kg/day STRATTERA dose was not superior to placebo.
In Study 2, a 6-week randomized, double-blind, placebo-controlled, acute treatment study of children and adolescents aged 6 to 16 (N=171), patients received either

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Biochemie GmbH, Schaftenau, Austria
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East Hanover, New Jersey 07936

Shown in Product Identification Guide, page 327

SIMULECT® ℞
[sĭm ew lĕkt]
(basiliximab)
For Injection
Rx only

The following prescribing information is based on official labeling in effect July 2003.
Prescribing Information

WARNING
Only physicians experienced in immunosuppression therapy and management of organ transplantation patients should prescribe Simulect® (basiliximab). The physician responsible for Simulect® administration should have complete information requisite for the follow-up of the patient. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources.

DESCRIPTION

Simulect® (basiliximab) is a chimeric (murine/human) monoclonal antibody ($IgG_{1\kappa}$), produced by recombinant DNA technology, that functions as an immunosuppressive agent, specifically binding to and blocking the interleukin-2 receptor α-chain (IL-2Rα, also known as CD25 antigen) on the surface of activated T-lymphocytes. Based on the amino acid sequence, the calculated molecular weight of the protein is 144 kilodaltons. It is a glycoprotein obtained from fermentation of an established mouse myeloma cell line genetically engineered to express plasmids containing the human heavy and light chain constant region genes and mouse heavy and light chain variable region genes encoding the RFT5 antibody that binds selectively to the IL-2Rα.

The active ingredient, basiliximab, is water soluble. The drug product, Simulect®, is a sterile lyophilisate which is available in 6 mL colorless glass vials and is available in 10 mg and 20 mg strengths.

Each 10 mg vial contains 10 mg basiliximab, 3.61 mg monobasic potassium phosphate, 0.50 mg disodium hydrogen phosphate (anhydrous), 0.80 sodium chloride, 10 mg sucrose, 40 mg mannitol and 20 mg glycine, to be reconstituted in 2.5 mL of Sterile Water for Injection, USP. No preservatives are added.

Each 20 mg vial contains 20 mg basiliximab, 7.21 mg monobasic potassium phosphate, 0.99 mg disodium hydrogen phosphate (anhydrous), 1.61 mg sodium chloride, 20 mg sucrose, 80 mg mannitol and 40 mg glycine, to be reconstituted in 5 mL of Sterile Water for Injection, USP. No preservatives are added.

CLINICAL PHARMACOLOGY

General

Mechanism of action: Basiliximab functions as an IL-2 receptor antagonist by binding with high affinity ($K_a = 1 \times 10^{10} M^{-1}$) to the alpha chain of the high affinity IL-2 receptor complex and inhibiting IL-2 binding. Basiliximab is specifically targeted against IL-2Rα, which is selectively expressed on the surface of activated T-lymphocytes. This specific high affinity binding of Simulect® to IL-2Rα competitively inhibits IL-2-mediated activation of lymphocytes, a critical pathway in the cellular immune response involved in allograft rejection.

While in the circulation, Simulect® impairs the response of the immune system to antigenic challenges. Whether the ability to respond to repeated or ongoing challenges with those antigens returns to normal after Simulect® is cleared is unknown *(See PRECAUTIONS).*

Pharmacokinetics

Adults: Single-dose and multiple-dose pharmacokinetic studies have been conducted in patients undergoing first kidney transplantation. Cumulative doses ranged from 15 mg up to 150 mg. Peak mean ± SD serum concentration following intravenous infusion of 20 mg over 30 minutes is 7.1 ± 5.1 mg/L. There is a dose-proportional increase in C_{max} and AUC up to the highest tested single dose of 60 mg. The volume of distribution at steady state is 8.6 ± 4.1 L. The extent and degree of distribution to various body compartments have not been fully studied. The terminal half-life is 7.2 ± 3.2 days. Total body clearance is 41 ± 19 mL/h. No clinically relevant influence of body weight or gender on distribution volume or clearance has been observed in adult patients. Elimination half-life was not influenced by age (20-69 years), gender or race *(See DOSAGE AND ADMINISTRATION).*

Pediatric: The pharmacokinetics of Simulect® have been assessed in 39 pediatric patients undergoing renal transplantation. In infants and children (1-11 years of age, n=25), the distribution volume and clearance were reduced by 2.1 L, half-life was 9.5 ± 4.5 days and clearance was 17 ± 6 mL/h. Disposition parameters were not influenced to a clinically relevant extent by age (1-11 years of age), body weight (9-37 kg) or body surface area (0.44-1.20 m^2) in this age group. In adolescents (12-16 years of age, n=14), disposition was similar to that in adult renal transplantation patients. The volume of distribution at steady state was 7.8 ± 5.1 L, half-life was 9.1 ± 3.9 days and clearance was 31 ± 19 mL/h *(See DOSAGE AND ADMINISTRATION).*

Pharmacodynamics

Complete and consistent binding to IL-2Rα in adults is maintained as long as serum Simulect® levels exceed 0.2 μg/mL. As concentrations fall below this threshold, the IL-2Rα sites are no longer fully bound and the number of T-cells expressing unbound IL-2Rα returns to pretherapy values within 1-2 weeks. The relationship between serum concentration and receptor saturation was assessed in 13 pediatric patients and was similar to that characterized in adult renal transplantation patients. *In vitro* studies using human tissues indicate that Simulect® binds only to lymphocytes. The duration of clinically relevant IL-2 receptor blockade after the recommended course of Simulect® is not known. When basiliximab was added to a regimen of cyclosporine, USP (MODIFIED) and corticosteroids in adult patients, the duration of IL-2Rα saturation was 36 ± 14 days (mean ± SD), similar to that observed in pediatric patients (36 ± 14 days) *(See DOSAGE AND ADMINISTRATION).* When basiliximab was added to a triple therapy regimen consisting of cyclosporine, USP (MODIFIED), corticosteroids, and azathioprine in adults, the duration was 50 ± 20 days and when added to cyclosporine, USP (MODIFIED), corticosteroids, and mycophenolate mofetil in adults, the duration was 59 ± 17 days *(See PRECAUTIONS-DRUG INTERACTIONS).* No significant changes to circulating lymphocyte numbers or cell phenotypes were observed by flow cytometry.

CLINICAL STUDIES

The safety and efficacy of Simulect® for the prophylaxis of acute organ rejection in adults following cadaveric- or living-donor renal transplantation were assessed in four randomized, double-blind, placebo-controlled clinical studies (1184 patients). Of these four, two studies [Study 1 (EU/CAN) and Study 2 (US study)] compared two 20 mg doses of Simulect® with placebo, each administered intravenously as an infusion, as part of a standard immunosuppressive regimen comprised of cyclosporine, USP (MODIFIED) and corticosteroids. The other two controlled studies compared two 20 mg doses of Simulect® with placebo, each administered intravenously as a bolus injection, as part of a standard triple immunosuppressive regimen comprised of cyclosporine, USP (MODIFIED), corticosteroids and either azathioprine or mycophenolate mofetil (Study 3 and Study 4, respectively). The first dose of Simulect® or placebo was administered within 2 hours prior to transplantation surgery (Day 0) and the second dose administered on Day 4 post-transplantation. The regimen of Simulect® was chosen to provide 30-45 days of IL-2Rα saturation.

729 patients were enrolled in the two studies using a dual maintenance immunosuppressive regimen comprised of cyclosporine, USP (MODIFIED) and corticosteroids, of which 363 patients were treated with Simulect® and 358 patients were placebo-treated. Study 1 was conducted at 21 sites in Europe and Canada (EU/CAN Study); Study 2 was conducted at 21 sites in the USA (US Study). Patients 18-75 years of age undergoing first cadaveric (Study 1 and Study 2) or living-donor (Study 2 only) renal transplantation, with ≥1 HLA mismatch, were enrolled.[1,2]

The primary efficacy endpoint in both studies was the incidence of death, graft loss or an episode of acute rejection during the first 6 months post-transplantation. Secondary efficacy endpoints included the primary efficacy variable measured during the first 12 months post-transplantation, the incidence of biopsy-confirmed acute rejection during the first 6 and 12 months post-transplantation, and patient survival and graft survival, each measured at 12 months post-transplantation. Table 1 summarizes the results of these studies. Figure 1 displays the Kaplan-Meier estimates of post-transplantation for Study 2. Patients in both studies receiving Simulect® experienced a significantly lower incidence of biopsy-confirmed rejection episodes at both 6 and 12 months post-transplantation. There was no difference in the rate of delayed graft function, patient survival, or graft survival between Simulect®-treated patients and placebo-treated patients in either study.

There was no evidence that the clinical benefit of Simulect® was limited to specific subpopulations based on age, gender, race, donor type (cadaveric or living-donor allograft) or history of diabetes mellitus.

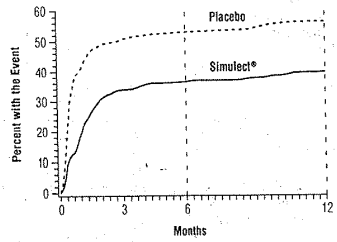
[See table 1 above]

Table 1 Efficacy Parameters (Percentage of Patients)

	Dual-therapy Regimen (cyclosporine* and corticosteroids)					
	Study 1			Study 2		
	Placebo (N=185)	Simulect® (N=190)	p-value	Placebo (N=173)	Simulect® (N=173)	p-value
Primary endpoint						
Death, graft loss or acute rejection episode (0-6 months)	57%	42%	0.003	55%	38%	0.002
Secondary endpoints						
Death, graft loss or acute rejection episode (0-12 months)	60%	46%	0.007	58%	41%	0.001
Biopsy-confirmed rejection episode (0-6 months)	44%	30%	0.007	46%	33%	0.015
Biopsy-confirmed rejection episode (0-12 months)	46%	32%	0.005	49%	35%	0.009
Patient survival (12 months)	97%	95%	0.29	96%	97%	0.56
Patients with functioning graft (12 months)	87%	88%	0.70	93%	95%	0.50

* USP (MODIFIED)

Figure 1
Kaplan-Meier Estimate of the Percentage of Subjects with Death, Graft Loss or First Rejection Episode (Dual Therapy)
Month: 0 –12



Two double-blind, randomized, placebo-controlled studies (Study 3 and Study 4) assessed the safety and efficacy of Simulect® for the prophylaxis of acute renal transplant rejection in adults when used in combination with a triple immunosuppressive regimen. In Study 3, 340 patients were concomitantly treated with cyclosporine, USP (MODIFIED), corticosteroids and azathioprine (AZA), of which 168 patients were treated with Simulect® and 172 patients were treated with placebo. In Study 4, 123 patients were concomitantly treated with cyclosporine, USP (MODIFIED), corticosteroids and mycophenolate mofetil (MMF), of which 59 patients were treated with Simulect® and 64 patients were treated with placebo. Patients 18-70 years of age undergoing first or second cadaveric or living-donor (related or unrelated) renal transplantation were enrolled in both studies. The results of Study 3 are shown in Table 2. These results are consistent with the findings from Study 1 and Study 2.

[See table 2 at top of next page]

In Study 4, the percentage of patients experiencing biopsy-proven acute rejection by 6 months was 15% (9 of 59 patients) in the Simulect® group and 27% (17 of 64 patients) in the placebo group. Although numerically lower, the difference in acute rejection was not significant.

In a multicenter, randomized, double-blind, placebo-controlled trial of Simulect® for the prevention of allograft rejection in liver transplant recipients (n=381) receiving concomitant cyclosporine, USP (MODIFIED) and steroids, the incidence of the combined endpoint of death, graft loss, or first biopsy-confirmed rejection episode at either 6 or 12 months was similar between patients randomized to receive Simulect® and those randomized to receive placebo.

The efficacy of Simulect® for the prophylaxis of acute rejection in recipients of a second renal allograft has not been demonstrated.

INDICATIONS AND USAGE

Simulect® is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplantation when used as part of an immunosuppressive regimen that includes cyclosporine, USP (MODIFIED) and corticosteroids. The efficacy of Simulect® for the prophylaxis of acute rejection in recipients of other solid organ allografts has not been demonstrated.

Simulect—Cont.

CONTRAINDICATIONS

Simulect® is contraindicated in patients with known hypersensitivity to basiliximab or any other component of the formulation. *See composition of Simulect® under DESCRIPTION.*

WARNINGS. *See Boxed WARNING.*

General

Simulect® should be administered under qualified medical supervision. Patients should be informed of the potential benefits of therapy and the risks associated with administration of immunosuppressive therapy.

While neither the incidence of lymphoproliferative disorders nor opportunistic infections was higher in Simulect®-treated patients than in placebo-treated patients, patients on immunosuppressive therapy are at increased risk for developing these complications and should be monitored accordingly.

Hypersensitivity

Severe acute (onset within 24 hours) hypersensitivity reactions including anaphylaxis have been observed both on initial exposure to Simulect® and/or following re-exposure after several months. These reactions may include hypotension, tachycardia, cardiac failure, dyspnea, wheezing, bronchospasm, pulmonary edema, respiratory failure, urticaria, rash, pruritus, and/or sneezing. If a severe hypersensitivity reaction occurs, therapy with Simulect® should be permanently discontinued. Medications for the treatment of severe hypersensitivity reactions including anaphylaxis should be available for immediate use. Patients previously administered Simulect® should only be re-exposed to a subsequent course of therapy with extreme caution. The potential risks of such re-administration, specifically those associated with immunosuppression, are not known.

PRECAUTIONS

General

It is not known whether Simulect® use will have a long-term effect on the ability of the immune system to respond to antigens first encountered during Simulect®-induced immunosuppression.

Immunogenicity

Of renal transplantation patients treated with Simulect® and tested for anti-idiotype antibodies, 4/339 developed an anti-idiotype antibody response, with no deleterious clinical effect upon the patient. In none of these cases was there evidence that the presence of anti-idiotype antibody accelerated Simulect® clearance or decreased the period of receptor saturation. In Study 2, the incidence of human anti-murine antibody (HAMA) in renal transplantation patients treated with Simulect® was 2/138 in patients not exposed to muromonab-CD3 and 4/34 in patients who subsequently received muromonab-CD3. The available clinical data on the use of muromonab-CD3 in patients previously treated with Simulect® suggest that subsequent use of muromonab-CD3 or other murine anti-lymphocytic antibody preparations is not precluded.

These data reflect the percentage of patients whose test results were considered positive for antibodies to Simulect® in an 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, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Simulect® with the incidence of antibodies to other products may be misleading.

Drug Interactions

No dose adjustment is necessary when Simulect® is added to triple immunosuppression regimens including cyclosporine, corticosteroids, and either azathioprine or mycophenolate mofetil. Three clinical trials have investigated Simulect® use in combination with triple therapy regimens. Pharmacokinetics were assessed in two of these trials. Total body clearance of Simulect® was reduced by an average 22% and 51% when azathioprine and mycophenolate mofetil, respectively, were added to a regimen consisting of cyclosporine, USP (MODIFIED) and corticosteroids. Nonetheless, the range of individual Simulect® clearance values in the presence of azathioprine (12-57 ml/h) or mycophenolate mofetil (7-54 ml/h) did not extend outside the range observed with dual therapy (10-78 ml/h). The following medications have been administered in clinical trials with Simulect® with no increase in adverse reactions: ATG/ALG, azathioprine, corticosteroids, cyclosporine, mycophenolate mofetil, and muromonab-CD3.

Carcinogenesis/Mutagenesis/Impairment of Fertility

No mutagenic potential of Simulect® was observed in the *in vitro* assays with Salmonella (Ames) and V79 Chinese hamster cells. No long-term or fertility studies in laboratory animals have been performed to evaluate the potential of Simulect® to produce carcinogenicity or fertility impairment, respectively.

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. No maternal toxicity, embryotoxicity, or teratogenicity was observed in cynomolgus monkeys 100 days post coitum following dosing with basiliximab during the organogenesis period; blood levels in pregnant monkeys were 13-fold higher than those seen in human patients. Immunotoxicity studies have not been performed in the offspring barrier, because the IL-2 receptor may play an important role in development of the immune system, and because animal reproduction studies are not always predictive of human response, Simulect® should only be used in pregnant women when the potential benefit justifies the potential risk to the fetus. Women of childbearing potential should use effective contraception before beginning Simulect® therapy, during therapy, and for 4 months after completion of Simulect® therapy.

Nursing Mothers

It is not known whether Simulect® is excreted in human milk. Because many drugs including human antibodies are excreted in human milk, and because of the potential for adverse reactions, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

No randomized, placebo-controlled studies have been completed in pediatric patients. In a safety and pharmacokinetic study, 41 pediatric patients [1-11 years of age (n=27), 12-16 years of age (n=14), median age 8.1 years] were treated with Simulect® via intravenous bolus injection in addition to standard immunosuppressive agents including cyclosporine, USP (MODIFIED), corticosteroids, azathioprine, and mycophenolate mofetil. The acute rejection rate at six months was comparable to that in adults in the triple therapy trials. The most frequently reported adverse events were hypertension, hypertrichosis, and rhinitis (49% each), urinary tract infections (46%), and fever (39%). Overall, the adverse event profile was consistent with general clinical experience in the pediatric renal transplantation population and with the profile in the controlled adult renal transplantation studies. The available pharmacokinetic data in children and adolescents are described in *CLINICAL PHARMACOLOGY* and *DOSAGE AND ADMINISTRATION*.

It is not known whether the immune response to vaccines, infection, and other antigenic stimuli administered or encountered during Simulect® therapy is impaired or whether such response will remain impaired after Simulect® therapy.

Geriatric Use

Controlled clinical studies of Simulect® have included a small number of patients 65 years and older (Simulect® 28; placebo 32). From the available data comparing Simulect® and placebo-treated patients, the adverse event profile in patients ≥65 years of age is not different from patients <65 years of age and no age-related dosing adjustment is required. Caution must be used in giving immunosuppressive drugs to elderly patients.

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 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.

The incidence of adverse events for Simulect® was determined in four randomized, double-blind, placebo-controlled clinical trials for the prevention of renal allograft rejection. Two of the studies (Study 1 and Study 2), used a dual maintenance immunosuppressive regimen comprised of cyclosporine, USP (MODIFIED) and corticosteroids, whereas the other two studies (Study 3 and Study 4) used a triple immunosuppressive regimen comprised of cyclosporine, USP (MODIFIED), corticosteroids, and either azathioprine or mycophenolate mofetil.

Simulect® did not appear to add to the background of adverse events seen in organ transplantation patients as a consequence of their underlying disease and the concurrent administration of immunosuppressants and other medications. Adverse events were reported by 96% of the patients in the placebo-treated group and 96% of the patients in the Simulect®-treated group. In the four placebo-controlled studies, the pattern of adverse events in 590 patients treated with the recommended dose of Simulect® was similar to that in 594 patients treated with placebo. Simulect® did not increase the incidence of serious adverse events

Table 2 Efficacy Parameters (Percentage of Patients)

Study 3: Triple-therapy Regimen (cyclosporine*, corticosteroids, and azathioprine)

	Placebo (N=172)	Simulect® (N=168)	p-value
Primary endpoint			
Acute rejection episode (0-6 months)	35%	21%	0.005
Secondary endpoints			
Death, graft loss or acute rejection episode (0-6 months)	40%	26%	0.008
Biopsy-confirmed rejection episode (0-6 months)	29%	18%	0.023
Patient survival (12 months)	97%	98%	1.000
Patients with functioning graft (12 months)	88%	90%	0.599

*USP (MODIFIED)

The most frequently reported adverse events were gastrointestinal disorders, reported in 69% of Simulect®-treated patients and 67% of placebo-treated patients.

The incidence and types of adverse events were similar in Simulect®-treated and placebo-treated patients. The following adverse events occurred in ≥10% of Simulect®-treated patients: ***Gastrointestinal System:*** constipation, nausea, abdominal pain, vomiting, diarrhea, dyspepsia; ***Body as a Whole-General:*** pain, peripheral edema, fever, viral infection; ***Metabolic and Nutritional:*** hyperkalemia, hypokalemia, hyperglycemia, hypercholesterolemia, hypophosphatemia, hyperuricemia; ***Urinary System:*** urinary tract infection; ***Respiratory System:*** dyspnea, upper respiratory tract infection; ***Skin and Appendages:*** surgical wound complications, acne; ***Cardiovascular Disorders-General:*** hypertension; ***Central and Peripheral Nervous System:*** headache, tremor; ***Psychiatric:*** insomnia; ***Red Blood Cell:*** anemia.

The following adverse events, not mentioned above, were reported with an incidence of ≥3% and <10% in pooled analysis of patients treated with Simulect® in the four controlled clinical trials, or in an analysis of the two dual therapy trials: ***Body as a Whole-General:*** accidental trauma, asthenia, chest pain, increased drug level, infection, face edema, fatigue, dependent edema, generalized edema, leg edema, malaise, rigors, sepsis; ***Cardiovascular:*** abnormal heart sounds, aggravated hypertension, angina pectoris, cardiac failure, chest pain, hypotension; ***Endocrine:*** increased glucocorticoids; ***Gastrointestinal:*** enlarged abdomen, esophagitis, flatulence, gastrointestinal disorder, gastroenteritis, GI hemorrhage, gum hyperplasia, melena, moniliasis, ulcerative stomatitis; ***Heart Rate and Rhythm:*** arrhythmia, atrial fibrillation, tachycardia; ***Metabolic and Nutritional:*** acidosis, dehydration, diabetes mellitus, fluid overload, hypercalcemia, hyperlipemia, hypertriglyceridemia, hypocalcemia, hypoglycemia, hypomagnesemia, hypoproteinemia, weight increase; ***Musculo-Skeletal:*** arthralgia, arthropathy, back pain, bone fracture, cramps, hernia, myalgia, leg pain; ***Nervous System:*** dizziness, neuropathy, paraesthesia, hypoesthesia; ***Platelet and Bleeding:*** hematoma, hemorrhage, purpura, thrombocytopenia, thrombosis; ***Psychiatric:*** agitation, anxiety, depression; ***Red Blood Cell:*** polycythemia; ***Reproductive Disorders, Male:*** genital edema, impotence; ***Respiratory:*** bronchitis, bronchospasm, abnormal chest sounds, coughing, pharyngitis, pneumonia, pulmonary disorder, pulmonary edema, rhinitis, sinusitis; ***Skin and Appendages:*** cyst, herpes simplex, herpes zoster, hypertrichosis, pruritus, rash, skin disorder, skin ulceration; ***Urinary:*** albuminuria, bladder disorder, dysuria, frequent micturition, hematuria, increased non-protein nitrogen, oliguria, abnormal renal function, renal tubular necrosis, surgery, ureteral disorder, urinary retention; ***Vascular Disorders:*** vascular disorder; ***Vision Disorders:*** cataract, conjunctivitis, abnormal vision; ***White Blood Cell:*** leucopenia. Among these events, leucopenia and hypertriglyceridemia occurred more frequently in the two triple-therapy studies using azathioprine and mycophenolate mofetil than in the dual-therapy studies.

Malignancies

The overall incidence of malignancies among all patients in the controlled studies was not significantly different between the Simulect®- and placebo-treatment groups. Overall, lymphoma/lymphoproliferative disease occurred in 1/590 patients in the Simulect® group compared with 3/594 patients in the placebo group. Other malignancies were reported among 8/590 patients in the Simulect® group compared with 9/594 patients in the placebo group.

Infections

The overall incidence of cytomegalovirus infection was similar in Simulect®- and placebo-treated patients (15% vs. 17%) receiving a dual or triple immunosuppression regimen. However, in patients receiving a triple immunosuppression regimen, the incidence of serious cytomegalovirus infection was higher in Simulect®-treated patients compared to placebo-treated patients (11% vs. 5%). The rates of infections, serious infections, and infectious organisms were similar in the Simulect® and placebo treatment groups among dual- and triple therapy-treated patients.

Post-Marketing Experience

Severe acute hypersensitivity reactions including anaphylaxis characterized by hypotension, tachycardia, cardiac

edema, respiratory failure, urticaria, rash, pruritus, and/or sneezing, as well as capillary leak syndrome and cytokine release syndrome, have been reported during post-marketing experience with Simulect®.

OVERDOSAGE

A maximum tolerated dose of Simulect® has not been determined in patients. During the course of clinical studies, Simulect® has been administered to adult renal transplantation patients in single doses of up to 60 mg, or in divided doses over 3-5 days of up to 120 mg, without any associated serious adverse events. There has been one spontaneous report of a pediatric renal transplantation patient who received a single 20 mg dose (2.3 mg/kg) without adverse events.

DOSAGE AND ADMINISTRATION

Simulect® is used as part of an immunosuppressive regimen that includes cyclosporine, USP (MODIFIED) and corticosteroids. Simulect® is for central or peripheral intravenous administration only. Reconstituted Simulect® should be given either as a bolus injection or diluted to a volume of 25 mL (10 mg vial) or 50 mL (20 mg vial) with normal saline or dextrose 5% and administered as an intravenous infusion over 20 to 30 minutes. Bolus administration may be associated with nausea, vomiting and local reactions, including pain.

Simulect® should only be administered once it has been determined that the patient will receive the graft and concomitant immunosuppression. Patients previously administered Simulect® should only be re-exposed to a subsequent course of therapy with extreme caution.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration. After reconstitution, Simulect® should be a clear to opalescent, colorless solution. If particulate matter is present or the solution is colored, do not use.

Care must be taken to assure sterility of the prepared solution because the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

It is recommended that after reconstitution, the solution should be used immediately. If not used immediately, it can be stored at 2°C to 8°C for 24 hours or at room temperature for 4 hours. Discard the reconstituted solution if not used within 24 hours.

No incompatibility between Simulect® and polyvinyl chloride bags or infusion sets has been observed. No data are available on the compatibility of Simulect® with other intravenous substances. Other drug substances should not be added or infused simultaneously through the same intravenous line.

Adults

In adult patients, the recommended regimen is two doses of 20 mg each. The first 20 mg dose should be given within 2 hours prior to transplantation surgery. The recommended second 20 mg dose should be given 4 days after transplantation. The second dose should be withheld if complications such as severe hypersensitivity reactions to Simulect® or graft loss occur.

Pediatric

In pediatric patients weighing less than 35 kg, the recommended regimen is two doses of 10 mg each. In pediatric patients weighing 35 kg or more, the recommended regimen is two doses of 20 mg each. The first dose should be given within 2 hours prior to transplantation surgery. The recommended second dose should be given 4 days after transplantation. The second dose should be withheld if complications such as severe hypersensitivity reactions to Simulect® or graft loss occur.

Reconstitution of 10 mg Simulect Vial

To prepare the reconstituted solution, add 2.5 mL of Sterile Water for Injection, USP, using aseptic technique, to the vial containing the Simulect® powder. Shake the vial gently to dissolve the powder.

The reconstituted solution is isotonic and may be given either as a bolus injection or diluted to a volume of 25 mL with normal saline or dextrose 5% for infusion. When mixing the solution, gently invert the bag in order to avoid foaming; DO NOT SHAKE.

Reconstitution of 20 mg Simulect Vial

To prepare the reconstituted solution, add 5 mL of Sterile Water for Injection, USP, using aseptic technique, to the vial containing the Simulect® powder. Shake the vial gently to dissolve the powder.

The reconstituted solution is isotonic and may be given either as a bolus injection or diluted to a volume of 50 mL with normal saline or dextrose 5% for infusion. When mixing the solution, gently invert the bag in order to avoid foaming; DO NOT SHAKE.

HOW SUPPLIED

Simulect® (basiliximab) is supplied in a single use glass vial.

Each carton contains one of the following:

1 Simulect® **10 mg** vial ..... NDC 0078-0393-61
1 Simulect® **20 mg** vial ..... NDC 0078-0331-84

Store lyophilized Simulect® under refrigerated conditions (2°C to 8°C; 36°F to 46°F).

Do not use beyond the expiration date stamped on the vial.

REFERENCES

1. Kahan, B.D., Rajagopalan P.R. and Hall M., Transplantation, 67, 276-284 (1999).
2. Nashan, B., Moore R., Amlot P., Schmidt A.-G., Abeywick-

T2002-91
REV: January 2003 89007805
US License No. 1244
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

Shown in Product Identification Guide, page 327

STALEVO™ 50
STALEVO™ 100
STALEVO™ 150

℞

[stă-lē-vō]

(carbidopa, levodopa and entacapone)
Tablets
Rx only

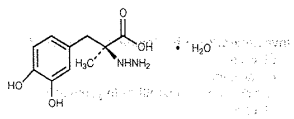
Prescribing Information

The follow prescribing information is base on official labeling in effect July 2003.

DESCRIPTION

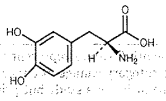
Stalevo™ (carbidopa, levodopa and entacapone) is a combination of carbidopa, levodopa and entacapone for the treatment of Parkinson's disease.

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designated chemically as (-)-L-(α-hydrazino-(α-methyl-β-(3,4-dihydroxybenzene) propanoic acid monohydrate. Its empirical formula is $C_{10}H_{14}N_2O_4 \cdot H_2O$, and its structural formula is

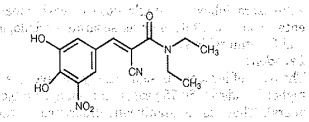


Tablet content is expressed in terms of anhydrous carbidopa, which has a molecular weight of 226.3.

Levodopa, an aromatic amino acid, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 197.2. It is designated chemically as (-)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid. Its empirical formula is $C_9H_{11}NO_4$, and its structural formula is



Entacapone, an inhibitor of catechol-O-methyltransferase (COMT), is a nitro-catechol-structured compound with a molecular weight of 305.3. The chemical name of entacapone is (E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-2-propenamide. Its empirical formula is $C_{14}H_{15}N_3O_5$ and its structural formula is



Stalevo™ (carbidopa, levodopa and entacapone) is supplied as tablets in three strengths:

Stalevo 50, containing 12.5 mg of carbidopa, 50 mg of levodopa and 200 mg of entacapone;
Stalevo 100, containing 25 mg of carbidopa, 100 mg of levodopa and 200 mg of entacapone;
Stalevo 150, containing 37.5 mg of carbidopa, 150 mg of levodopa and 200 mg of entacapone.

The inactive ingredients of the Stalevo tablet are corn starch, croscarmellose sodium, glycerol 85%, hypromellose, magnesium stearate, mannitol, polysorbate 80, povidone, sucrose, red iron oxide, titanium dioxide, and yellow iron oxide.

CLINICAL PHARMACOLOGY

Parkinson's disease is a progressive, neurodegenerative disorder of the extrapyramidal nervous system affecting the mobility and control of the skeletal muscular system. Its characteristic features include resting tremor, rigidity, and bradykinetic movements.

Mechanism of Action

Levodopa

Current evidence indicates that symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. Administration of dopamine is ineffective in the treatment of Parkinson's disease apparently because it does not cross the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa relieves symptoms of Parkinson's disease.

Carbidopa

When levodopa is administered orally it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. Carbidopa inhibits the decarboxylation of peripheral levodopa, making more levodopa available for transport to the brain. When coadministered with levodopa, carbidopa increases plasma levels of levodopa and reduces the amount of levodopa required to produce a given response by about 75%. Carbidopa prolongs the plasma half-life of levodopa from 50 minutes to 1.5 hours and decreases plasma and urinary dopamine and its major metabolite, homovanillic acid. The T_{max} of levodopa, however, was unaffected by the coadministration.

Entacapone

Entacapone is a selective and reversible inhibitor of catechol-O-methyltransferase (COMT).

In mammals, COMT is distributed throughout various organs with the highest activities in the liver and kidney. COMT also occurs in neuronal tissues, especially in glial cells. COMT catalyzes the transfer of the methyl group of S-adenosyl-L-methionine to the phenolic group of substrates that contain a catechol structure. Physiological substrates of COMT include DOPA, catecholamines (dopamine, norepinephrine, and epinephrine) and their hydroxylated metabolites. The function of COMT is the elimination of biologically active catechols and some other hydroxylated metabolites. When decarboxylation of levodopa is prevented by carbidopa, COMT becomes the major metabolizing enzyme for levodopa, catalyzing its metabolism to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD).

When entacapone is given in conjunction with levodopa and carbidopa, plasma levels of levodopa are greater and more sustained than after administration of levodopa and carbidopa alone. It is believed that at a given frequency of levodopa administration, these more sustained plasma levels of levodopa result in more constant dopaminergic stimulation in the brain, leading to greater effects on the signs and symptoms of Parkinson's disease. The higher levodopa levels may also lead to increased levodopa adverse effects, sometimes requiring a decrease in the dose of levodopa.

When 200 mg entacapone is coadministered with levodopa/carbidopa, it increases levodopa plasma exposure (AUC) by 35%-40% and prolongs its elimination half-life in Parkinson's disease patients from 1.3 to 2.4 hours. Plasma levels of the major COMT-mediated dopamine metabolite, 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD), are also markedly decreased proportionally with increasing dose of entacapone. In animals, while entacapone enters the CNS to a minimal extent, it has been shown to inhibit central COMT activity. In humans, entacapone inhibits the COMT enzyme in peripheral tissues. The effects of entacapone on central COMT activity in humans have not been studied.

Pharmacokinetics

The pharmacokinetics of Stalevo™ (carbidopa, levodopa and entacapone) tablets have been studied in healthy subjects (age 45-75 years old). Overall, following administration of corresponding doses of levodopa, carbidopa and entacapone as Stalevo or as carbidopa/levodopa product plus Comtan® (entacapone) tablets, the mean plasma concentrations of levodopa, carbidopa, and entacapone are comparable.

Absorption/Distribution: Both levodopa and entacapone are rapidly absorbed and eliminated, and their distribution volume is moderately small. Carbidopa is absorbed and eliminated slightly more slowly compared with levodopa and entacapone. There are substantial inter- and intra-individual variations in the absorption of levodopa, carbidopa and entacapone, particularly concerning its C_{max}.

The food-effect on the Stalevo tablet has not been evaluated.

Levodopa

The pharmacokinetic properties of levodopa following the administration of single dose Stalevo™ (carbidopa, levodopa and entacapone) tablets are summarized in Table 1.

[See table 1 below]

Since levodopa competes with certain amino acids for transport across the gut wall, the absorption of levodopa may be impaired in some patients on a high protein diet. Meals rich in large neutral amino acids may delay and reduce the absorption of levodopa *(see PRECAUTIONS)*.

Levodopa is bound to plasma protein only to a minor extent (about 10%–30%).

Carbidopa

Following administration of Stalevo as a single dose to healthy male and female subjects, the peak concentration of carbidopa was reached within 2.5 to 3.4 hours on average.

Continued on next page

Table 1
Pharmacokinetic Characteristics of Levodopa
With Different Tablet Strengths of Stalevo (mean ± SD)

Tablet Strength	$AUC_{0-\infty}$ (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)
12.5 - 50 - 200 mg	1040 ± 314	470 ± 154	1.1 ± 0.5
25 - 100 - 200 mg	2010 ± 715	975 ± 247	1.4 ± 0.6

Leustatin—Cont.

	Dose of LEUSTATIN Injection	Recommended Diluent	Quantity of Diluent
7-day infusion method (use sterile 0.22μ filter when preparing infusion solution)	7 (days) × 0.09 mg/kg	Bacteriostatic 0.9% Sodium Chloride Injection, USP (0.9% benzyl alcohol)	q.s. to 100 mL

Since limited compatibility data are available, adherence to the recommended diluents and infusion systems is advised. Solutions containing LEUSTATIN Injection should not be mixed with other intravenous drugs or additives or infused simultaneously via a common intravenous line, since compatibility testing has not been performed. Preparations containing benzyl alcohol should not be used in neonates (see WARNINGS).

Care must be taken to assure the sterility of prepared solutions. Once diluted, solutions of LEUSTATIN Injection should be administered promptly or stored in the refrigerator (2° to 8°C) for no more than 8 hours prior to start of administration. Vials of LEUSTATIN Injection are for single-use only. Any unused portion should be discarded in an appropriate manner (see Handling and Disposal).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. A precipitate may occur during the exposure of LEUSTATIN Injection to low temperatures; it may be resolubilized by allowing the solution to warm naturally to room temperature and by shaking vigorously. **DO NOT HEAT OR MICROWAVE.**

Chemical Stability of Vials:

When stored in refrigerated conditions between 2° to 8°C (36° to 46°F) protected from light, unopened vials of LEUSTATIN Injection are stable until the expiration date indicated on the package. Freezing does not adversely affect the solution. If freezing occurs, thaw naturally to room temperature. DO NOT heat or microwave. Once thawed, the vial of LEUSTATIN Injection is stable until expiry if refrigerated. DO NOT refreeze. Once diluted, solutions containing LEUSTATIN Injection should be administered promptly or stored in the refrigerator (2° to 8°C) for no more than 8 hours prior to administration.

Handling and Disposal:

The potential hazards associated with cytotoxic agents are well established and proper precautions should be taken when handling, preparing, and administering LEUSTATIN Injection. The use of disposable gloves and protective garments is recommended. If LEUSTATIN Injection contacts the skin or mucous membranes, wash the involved surface immediately with copious amounts of water. Several guidelines on this subject have been published.[2–8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate. Refer to your Institution's guidelines and all applicable state/local regulations for disposal of cytotoxic waste.

HOW SUPPLIED

LEUSTATIN Injection is supplied as a sterile, preservative-free, isotonic solution containing 10mg (1mg/mL) of cladribine as 10 mL filled into a single-use clear flint glass 20 mL vial. LEUSTATIN® Injection is supplied in 10 mL (1 mg/mL) single-use vials (NDC 59676-201-01) available in a treatment set (case) of seven vials.

Store refrigerated 2° to 8°C (36° to 46°F). Protect from light during storage.

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Rx ONLY

† Viaflex® containers, manufactured by Baxter Healthcare Corporation - Code No. 2B8013 (tested in 1991)
‡ MEDICATION CASSETTE™ Reservoir, manufactured by SIMS Deltec, Inc. - Reorder No. 602100A (tested in 1991)

ORTHO BIOTECH PRODUCTS, L.P.
Raritan, New Jersey 08869

ORTHO BIOTECH

 638-10-940-8
Revised October 2002

ORTHOCLONE OKT®3 STERILE SOLUTION ℞
(muromonab-CD3)
For Intravenous Use Only

> **WARNING:**
> Only physicians experienced in immunosuppressive therapy and management of solid organ transplant patients should use ORTHOCLONE OKT3 (muromonab-CD3). Patients treated with ORTHOCLONE OKT3 must be managed in a facility equipped and staffed for cardiopulmonary resuscitation and where the patient can be closely monitored for an appropriate period based on his or her health status.
> Anaphylactic and anaphylactoid reactions may occur following administration of any dose or course of ORTHOCLONE OKT3. In addition, serious, occasionally life-threatening or lethal, systemic, cardiovascular, and central nervous system reactions have been reported following administration of ORTHOCLONE OKT3. These have included: pulmonary edema, especially in patients with volume overload; shock, cardiovascular collapse, cardiac or respiratory arrest, seizures, coma, cerebral edema, cerebral herniation, blindness, and paralysis. Fluid status should be carefully monitored prior to and during ORTHOCLONE OKT3 administration. Pretreatment with methylprednisolone is recommended to minimize symptoms of Cytokine Release Syndrome. (See: WARNINGS: Cytokine Release Syndrome, Central Nervous System Events, Anaphylactic Reactions; DOSAGE AND ADMINISTRATION.)

DESCRIPTION

ORTHOCLONE OKT3 (muromonab-CD3) Sterile Solution is a murine monoclonal antibody to the CD3 antigen of human T cells which functions as an immunosuppressant. It is for intravenous use only. The antibody is a biochemically purified IgG_{2a} immunoglobulin with a heavy chain of approximately 50,000 daltons and a light chain of approximately 25,000 daltons. It is directed to a glycoprotein with a molecular weight of 20,000 in the human T cell surface which is essential for T cell functions. Because it is a monoclonal antibody preparation, ORTHOCLONE OKT3 Sterile Solution is a homogeneous, reproducible antibody product with consistent, measurable reactivity to human T cells.

Each 5 mL ampule of ORTHOCLONE OKT3 Sterile Solution contains 5 mg (1 mg/mL) of muromonab-CD3 in a clear colorless solution which may contain a few fine translucent protein particles. Each ampule contains a buffered solution (pH 7.0 ± 0.5) of monobasic sodium phosphate (2.25 mg), dibasic sodium phosphate (9.0 mg), sodium chloride (43 mg), and polysorbate 80 (1.0 mg) in water for injection.

The proper name, muromonab-CD3, is derived from the descriptive term murine monoclonal antibody. The CD3 designation identifies the specificity of the antibody as the Cell Differentiation (CD) cluster 3 defined by the First International Workshop on Human Leukocyte Differentiation Antigens.

CLINICAL PHARMACOLOGY

ORTHOCLONE OKT3 reverses graft rejection, probably by blocking the function of T cells which play a major role in acute allograft rejection. ORTHOCLONE OKT3 reacts with and blocks the function of a 20,000 dalton molecule (CD3) in the membrane of human T cells that has been associated *in vitro* with the antigen recognition structure of T cells and is essential for signal transduction. In *in vitro* cytolytic assays, ORTHOCLONE OKT3 blocks both the generation and function of effector cells. Binding of ORTHOCLONE OKT3 to T lymphocytes results in early activation of T cells, which leads to cytokine release, followed by blocking T cell functions. After termination of ORTHOCLONE OKT3 therapy, T cell function usually returns to normal within one week. *In vivo*, ORTHOCLONE OKT3 reacts with most peripheral blood T cells and T cells in body tissues, but has not been found to react with other hematopoietic elements or other tissues of the body.

A rapid and concomitant decrease in the number of circulating CD3 positive cells, including those that are CD2, CD4, or CD8 positive has been observed in patients studied within minutes after the administration of ORTHOCLONE OKT3. This decrease in the number of CD3 positive T cells results from the specific interaction between ORTHOCLONE OKT3 and the CD3 antigen on the surface of all T lymphocytes. T cell activation results in the release of numerous cytokines/lymphokines, which are felt to be re-

following ORTHOCLONE OKT3 administration. (See: WARNINGS: Cytokine Release Syndrome, Central Nervous System Events.)

While CD3 positive cells are not detectable between days two and seven, increasing numbers of circulating CD2, CD4, and CD8 positive cells have been observed. The presence of these CD2, CD4, and CD8 positive cells has not been shown to affect reversal of rejection. After termination of ORTHOCLONE OKT3 therapy, CD3 positive cells reappear rapidly and reach pre-treatment levels within a week. In some patients however, increasing numbers of CD3 positive cells have been observed prior to termination of ORTHOCLONE OKT3 therapy. This reappearance of CD3 positive cells has been attributed to the development of neutralizing antibodies to ORTHOCLONE OKT3, which in turn block its ability to bind to the CD3 antigen on T lymphocytes. (See: PRECAUTIONS: Sensitization.)

Pediatric patients are known to have higher CD3 lymphocyte counts than adults. Pediatric patients receiving ORTHOCLONE OKT®3 therapy often require progressively higher doses of ORTHOCLONE OKT3 to achieve depletion of CD3 positive cells (<25 cells/mm^3) and ensure therapeutic ORTHOCLONE OKT3 serum concentrations (>800 ng/mL). (See: DOSAGE AND ADMINISTRATION; PRECAUTIONS: Laboratory Tests.)

Serum levels of ORTHOCLONE OKT3 are measurable using an enzyme-linked immunosorbent assay (ELISA). During the initial clinical trials in renal allograft rejection, in patients treated with 5 mg per day for 14 days, mean serum trough levels of the drug rose over the first three days and then averaged 900 ng/mL on days 3 to 14. Serum concentrations measured daily during treatment with ORTHOCLONE OKT3 in renal, hepatic, and cardiac allograft recipients revealed that pediatric patients less than 10 years of age have higher levels than patients 10-50 years of age. Subsequent clinical experience has demonstrated that serum levels greater than or equal to 800 ng/mL of ORTHOCLONE OKT3 blocks the function of cytotoxic T cells *in vitro* and *in vivo*. Reduced T cell clearance or low plasma ORTHOCLONE OKT3 levels provide a basis for adjusting ORTHOCLONE OKT3 dosage or for discontinuing therapy. (See: WARNINGS: Anaphylactic Reactions; PRECAUTIONS: Laboratory Tests; ADVERSE EVENTS: Hypersensitivity Reactions; DOSAGE AND ADMINISTRATION.)

Following administration of ORTHOCLONE OKT3 *in vivo*, leukocytes have been observed in cerebrospinal and peritoneal fluids. The mechanism for this effect is not completely understood, but probably is related to cytokines altering membrane permeability, rather than an active inflammatory process. (See: WARNINGS: Cytokine Release Syndrome, Central Nervous System Events.)

CLINICAL STUDIES

Acute Renal Rejection:

In a controlled randomized clinical trial, ORTHOCLONE OKT3 was compared with conventional high-dose steroid therapy in reversing acute renal allograft rejection. In this trial, 122 evaluable patients undergoing acute rejection of cadaveric renal transplants were treated either with ORTHOCLONE OKT3 daily for a mean of 14 days, with concomitant lowering of the dosage of azathioprine and maintenance steroids (62 patients), or with conventional high-dose steroids (60 patients). ORTHOCLONE OKT3 reversed 94% of the rejections compared to a 75% reversal rate obtained with conventional high-dose steroid treatment (p=0.006). The one year Kaplan-Meier (actuarial) estimates of graft survival rates for these patients who had acute rejection were 62% and 45% for ORTHOCLONE OKT3 and steroid-treated patients, respectively (p=0.04). At two years the rates were 56% and 42%, respectively (p=0.06).

One- and two-year patient survivals were not significantly different between the two groups, being 85% and 75% for ORTHOCLONE OKT3 treated patients and 90% and 85% for steroid-treated patients.

In additional open clinical trials, the observed rate of reversal of acute renal allograft rejection was 92% (n=126) for ORTHOCLONE OKT3 therapy. ORTHOCLONE OKT3 was also effective in reversing acute renal allograft rejections in 65% (n=225) of cases where steroids and lymphocyte immune globulin preparations were contraindicated or were not successful.

The effectiveness of ORTHOCLONE OKT3 for prophylaxis of renal allograft rejection has not been established.

Acute Cardiac or Hepatic Allograft Rejection:

ORTHOCLONE OKT3 was studied for use in reversing acute cardiac and hepatic allograft rejection in patients who are unresponsive to high-doses of steroids. The rate of reversal in acute cardiac allograft rejection was 90% (n=61) and was 83% for hepatic allograft rejection (n=124) in patients unresponsive to treatment with steroids.

Controlled randomized trials have not been conducted to evaluate the effectiveness of ORTHOCLONE OKT3 compared to conventional therapy as first line treatment for acute cardiac and hepatic allograft rejection.

INDICATIONS AND USAGE

ORTHOCLONE OKT3 is indicated for the treatment of acute allograft rejection in renal transplant patients.

ORTHOCLONE OKT3 is indicated for the treatment of steroid-resistant acute allograft rejection in cardiac and hepatic transplant patients.

the lowest level compatible with an effective therapeutic response. (See: WARNINGS and ADVERSE EVENTS: Infections, Neoplasia; DOSAGE AND ADMINISTRATION.)

CONTRAINDICATIONS

ORTHOCLONE OKT3 should not be given to patients who:

- are hypersensitive to this or any other product of murine origin;
- have anti-mouse antibody titers ≥1:1000;
- are in (uncompensated) heart failure or in fluid overload, as evidenced by chest X-ray or a greater than 3 percent weight gain within the week prior to planned ORTHOCLONE OKT3 administration;
- have uncontrolled hypertension;
- have a history of seizures, or are predisposed to seizures;
- are determined or suspected to be pregnant, or who are breast-feeding. (See: PRECAUTIONS: Pregnancy, Nursing Mothers.)

WARNINGS

SEE BOXED WARNING

Cytokine Release Syndrome

Most patients develop an acute clinical syndrome [i.e., Cytokine Release Syndrome (CRS)] that has been attributed to the release of cytokines by activated lymphocytes or monocytes and is temporally associated with the administration of the first few doses of ORTHOCLONE OKT®3 (particularly, the first two to three doses). This clinical syndrome has ranged from a more frequently reported mild, self-limited, "flu-like" illness to a less frequently reported severe, life-threatening shock-like reaction, which may include serious cardiovascular and central nervous system manifestations. The syndrome typically begins approximately 30 to 60 minutes after administration of a dose of ORTHOCLONE OKT3 (but may occur later) and may persist for several hours. The frequency and severity of this symptom complex is usually greatest with the first dose. With each successive dose of ORTHOCLONE OKT3, both the frequency and severity of the Cytokine Release Syndrome tends to diminish. Increasing the amount of ORTHOCLONE OKT3 or resuming treatment after a hiatus may result in a reappearance of the CRS.

Common clinical manifestations of CRS may include: high fever (often spiking, up to 107°F), chills/rigors, headache, tremor, nausea/vomiting, diarrhea, abdominal pain, malaise, muscle/joint aches and pains, and generalized weakness. Less frequently reported adverse experiences include: minor dermatologic reactions (e.g., rash, pruritus, etc.) and a spectrum of often serious, occasionally fatal, cardiorespiratory and central nervous system adverse experiences.

Cardiorespiratory findings may include: dyspnea, shortness of breath, bronchospasm/wheezing, tachypnea, respiratory arrest/failure/distress, cardiovascular collapse, cardiac arrest, angina/myocardial infarction, chest pain/tightness, tachycardia (including ventricular), hypertension, hemodynamic instability, hypotension including profound shock, heart failure, pulmonary edema (cardiogenic and non-cardiogenic), adult respiratory distress syndrome, hypoxemia, apnea, and arrhythmias. (See: BOXED WARNING; PRECAUTIONS; ADVERSE EVENTS.)

In the initial studies of renal allograft rejection, potentially fatal, severe pulmonary edema occurred in 5% of the initial 107 patients. Fluid overload was present before treatment in all of these cases. It occurred in none of the subsequent 311 patients treated with first-dose volume/weight restrictions. In subsequent trials and in post-marketing experience, severe pulmonary edema has occurred in patients who appeared to be euvolemic. The pathogenesis of pulmonary edema may involve all or some of the following: volume overload; increased pulmonary vascular permeability; and/or reduced left ventricular compliance/contractility.

During the first 1 to 3 days of ORTHOCLONE OKT3 therapy, some patients have experienced an acute and transient decline in the glomerular filtration rate (GFR) and diminished urine output with a resulting increase in the level of serum creatinine. Massive release of cytokines appears to lead to reversible renal functional impairment and/or delayed renal allograft function. Similarly, transient elevations in hepatic transaminases have been reported following administration of the first few doses of ORTHOCLONE OKT3.

Patients at risk for more serious complications of CRS may include those with the following conditions: unstable angina; recent myocardial infarction or symptomatic ischemic heart disease; heart failure of any etiology; pulmonary edema of any etiology; any form of chronic obstructive pulmonary disease; intravascular volume overload or depletion of any etiology (e.g., excessive dialysis, recent intensive diuresis, blood loss, etc.); cerebrovascular disease; patients with advanced symptomatic vascular disease or neuropathy; a history of seizures; and septic shock. Efforts should be made to correct or stabilize background conditions prior to the initiation of therapy. (See: PRECAUTIONS.)

Prior to administration of ORTHOCLONE OKT3, the patient's volume (fluid) status and a chest X-ray should be assessed to rule out volume overload, uncontrolled hypertension, or uncompensated heart failure. Patients should not weigh >3% above their minimum weight during the week prior to injection.

The Cytokine Release Syndrome is associated with increased serum levels of cytokines (e.g., TNF-α, IL-2, IL-6, IFN-γ) that peak between 1 and 4 hours following administration of ORTHOCLONE OKT3. The ... treatment with 8 mg/kg of methylprednisolone (i.e., high-dose steroids), given 1 to 4 hours prior to administration of the first dose of ORTHOCLONE OKT3, and by closely following recommendations for dosage and treatment duration. (See: DOSAGE AND ADMINISTRATION.) It is not known if corticosteroid pretreatment decreases organ damage and sequelae associated with CRS. For example, increased intracranial pressure and cerebral herniation have occurred despite pretreatment with currently recommended doses and schedules of methylprednisolone.

If any of the more serious presentations of the Cytokine Release Syndrome occur, intensive treatment including oxygen, intravenous fluids, corticosteroids, pressor amines, antihistamines, intubation, etc., may be required.

Central Nervous System Events

Seizures, encephalopathy, cerebral edema, aseptic meningitis, and headache have been reported, even following the first dose, during therapy with ORTHOCLONE OKT®3. Seizures, some accompanied by loss of consciousness or cardiorespiratory arrest, or death, have occurred independently or in conjunction with any of the neurologic syndromes described below.

A few cases of fatal cerebral herniations subsequent to cerebral edema have been reported. All patients, particularly pediatric patients, must be carefully evaluated for fluid retention and hypertension before the initiation of ORTHOCLONE OKT3 therapy. Close monitoring for neurologic symptoms must be performed during the first twenty-four (24) hours following each of the first few doses of ORTHOCLONE OKT3 injection.

Patients should be closely monitored for convulsions and manifestations of encephalopathy, including: impaired cognition, confusion, obtundation, altered mental status, disorientation, auditory/visual hallucinations, psychosis (delirium, paranoia), mood changes (e.g., mania, agitation, combativeness, etc.), diffuse hypotonus, hyperreflexia, myoclonus, tremor, asterixis, involuntary movements, major motor seizures, lethargy/stupor/coma, and diffuse weakness. Approximately one-third of patients with a diagnosis of encephalopathy may have had coexisting aseptic meningitis syndrome.

Signs and symptoms of the aseptic meningitis syndrome described in association with the use of ORTHOCLONE OKT3 have included: fever, headache, meningismus (stiff neck), and photophobia. Diagnosis is confirmed by cerebrospinal fluid (CSF) analysis demonstrating leukocytosis with pleocytosis, elevated protein and normal or decreased glucose, with negative viral, bacterial, and fungal cultures. The possibility of infection should be evaluated in any immunosuppressed transplant patient with clinical findings suggesting meningitis. Approximately one-third of the patients with a diagnosis of aseptic meningitis had coexisting signs and symptoms of encephalopathy. Most patients with the aseptic meningitis syndrome had a benign course and recovered without any permanent sequelae during therapy or subsequent to its completion or discontinuation. However, because meningitis is a frequent infection encountered in pediatric allograft recipients, and the immunosuppression associated with transplantation increases the risk of opportunistic infection, pediatric patients with signs or symptoms suggestive of meningeal irritation while receiving ORTHOCLONE OKT3 should have lumbar punctures performed to rule out an infectious etiology. (See: PRECAUTIONS: Pediatric Use.)

Signs or symptoms of encephalopathy, meningitis, seizures, and cerebral edema, with or without headache, typically have been reversible. Headache, aseptic meningitis, seizures, and less severe forms of encephalopathy resolved in most patients despite continued treatment with ORTHOCLONE OKT3. However, some events resulted in permanent neurologic impairment.

The following additional central nervous system events have each been reported: irreversible blindness, impaired vision, quadri- or paraparesis/plegia, cerebrovascular accident (hemiparesis/plegia), aphasia, transient ischemic attack, subarachnoid hemorrhage, palsy of the VI cranial nerve, hearing decrease, and deafness.

Patients who may be at greater risk for CNS adverse experiences include those: with known or suspected CNS disorders (e.g., history of seizure disorder, etc.); with cerebrovascular disease (small or large vessel); with conditions having associated neurologic problems (e.g., head trauma, uremia, infection, fluid and electrolyte disturbance, etc.); with underlying vascular diseases; or who are receiving a medication concomitantly that may, by itself, affect the central nervous system. (See: WARNINGS, PRECAUTIONS and ADVERSE EVENTS: Cytokine Release Syndrome.)

Anaphylactic Reactions

Serious and occasionally fatal, immediate (usually within 10 minutes) hypersensitivity (anaphylactic) reactions have been reported in patients treated with ORTHOCLONE OKT3. **Manifestations of anaphylaxis may appear similar to manifestations of the Cytokine Release Syndrome (described above). It may be impossible to determine the mechanism responsible for any systemic reaction(s).** Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release. Acute hypersensitivity reactions may be characterized by: cardiovascular collapse, cardiorespiratory arrest, loss of consciousness, hypotension/shock, tachycardia, tingling, angioedema (including laryngeal, pharyngeal, or fa...

Serious allergic events, including anaphylactic or anaphylactoid reactions, have been reported in patients re-exposed to ORTHOCLONE OKT3 subsequent to their initial course of therapy. Pretreatment with antihistamines and/or steroids may not reliably prevent anaphylaxis in this setting. Possible allergic hazards of retreatment should be weighed against expected therapeutic benefits and alternatives. If a patient is retreated with ORTHOCLONE OKT3, it is particularly important that epinephrine and other emergency life-support equipment should be immediately available.

If hypersensitivity is suspected, discontinue the drug immediately; do not resume therapy or re-expose the patient to ORTHOCLONE OKT3. Serious acute hypersensitivity reactions may require emergency treatment with 0.3 mL to 0.5 mL aqueous epinephrine (1:1000 dilution) subcutaneously and other resuscitative measures including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated. (See: PRECAUTIONS: Cytokine Release Syndrome vs. Anaphylactic Reactions; ADVERSE EVENTS: Hypersensitivity Reactions.)

Consequences of Immunosuppression

Serious and sometimes fatal infections and neoplasias have been reported in association with all immunosuppressive therapies, including those regimens containing ORTHOCLONE OKT®3.

Infections: ORTHOCLONE OKT3 is usually added to immunosuppressive therapeutic regimens, thereby augmenting the degree of immunosuppression. This increase in the total amount of immunosuppression may alter the spectrum of infections observed and increase the risk, the severity, and the morbidity of infectious complications. During the first month post-transplant, patients are at greatest risk for the following infections: (1) those present prior to transplant, perhaps exacerbated by post-transplant immunosuppression; (2) infection conveyed by the donor organ; and (3) the usual post-operative urinary tract, intravenous line related, wound, or pulmonary infections due to bacterial pathogens. (See: ADVERSE EVENTS: Infections.)

Approximately one to six months post-transplant, patients are at risk for viral infections [e.g., cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV), etc.] which produce serious systemic disease and which also increase the overall state of immunosuppression.

Reactivation (1 to 4 months post-transplant) of EBV and CMV has been reported. When administration of an anti-lymphocyte antibody, including ORTHOCLONE OKT3, is followed by an immunosuppressive regimen including cyclosporine, there is an increased risk of reactivating CMV and impaired ability to limit its proliferation, resulting in symptomatic and disseminated disease. EBV infection, either primary or reactivated, may play an important role in the development of post-transplant lymphoproliferative disorders. (See: WARNINGS and ADVERSE EVENTS: Neoplasia.)

In the pediatric transplant population, viral infections often include pathogens uncommon in adults, such as varicella zoster virus (VZV), adenovirus, and respiratory syncytial virus (RSV). A large proportion of pediatric patients have not been infected with the herpes viruses prior to transplantation and, therefore, are susceptible to developing primary infections from the grafted organ and/or blood products.

Anti-infective prophylaxis may reduce the morbidity associated with certain potential pathogens and should be considered for pediatric and other high-risk patients. Judicious use of immunosuppressive drugs, including type, dosage, and duration, may limit the risk and seriousness of some opportunistic infections. It is also possible to reduce the risk of serious CMV or EBV infection by avoiding transplantation of a CMV-seropositive (donor) and/or EBV-seropositive (donor) organ into a seronegative patient.

Neoplasia: As a result of depressed cell-mediated immunity from immunosuppressive agents, organ transplant patients have an increased risk of developing malignancies. This risk is evidenced almost exclusively by the occurrence of lymphoproliferative disorders, squamous cell carcinomas of the skin and lip, and sarcomas. In immunosuppressed patients, T cell cytotoxicity is impaired allowing for transformation and proliferation of EBV-infected B lymphocytes. Transformed B lymphocytes are thought to initiate oncogenesis, which ultimately culminates in the development of most post-transplant lymphoproliferative disorders. Patients, especially pediatric patients, with primary EBV infection may be at a higher risk for the development of EBV-associated lymphoproliferative disorders. Data support an association between the development of lymphoproliferative disorders at the time of active EBV infection and ORTHOCLONE OKT3 administration in pediatric liver allograft recipients. (See: ADVERSE EVENTS Infections, Neoplasia.)

Following the initiation of ORTHOCLONE OKT3 therapy, patients should be continuously monitored for evidence of lymphoproliferative disorders through physical examination and histological evaluation of any suspect lymphoid tissue. Close surveillance is advised, since early detection with subsequent reduction of total immunosuppression may result in regression of some of these lymphoproliferative disorders. Since the potential for the development of lymphoproliferative disorders is related to the duration and extent (intensity) of total immunosuppression, physicians are ad-

Orthoclone OKT 3—Cont.

vised: to adhere to the recommended dosage and duration of ORTHOCLONE OKT3 therapy; to limit the number of courses of ORTHOCLONE OKT3 and other anti- T lymphocyte antibody preparations administered within a short period of time; and, if appropriate, to reduce the dosage(s) of immunosuppressive drugs used concomitantly to the lowest level compatible with an effective therapeutic response. (See: DOSAGE AND ADMINISTRATION.)

A recent study examined the incidence of non-Hodgkin's lymphoma (NHL) among 45,000 kidney transplant recipients and over 7,500 heart transplant recipients. This study suggested that all transplant patients, regardless of the immunosuppressive regimen employed, are at increased risk of NHL over the general population. The relative risk was highest among those receiving the most aggressive regimens.

The long-term risk of neoplastic events in patients being treated with ORTHOCLONE OKT3 has not been determined.

PRECAUTIONS

General

When using combinations of immunosuppressive agents, the dose of each agent, including ORTHOCLONE OKT®3, should be reduced to the lowest level compatible with an effective therapeutic response so as to reduce the potential for and severity of infections and malignant transformations.

Fever: If the temperature of the patient exceeds 37.8°C (100°F), it should be lowered by antipyretics before administration of each dose of ORTHOCLONE OKT3. The possibility of infection should be evaluated.

Severe Cytokine Release Syndrome Versus Anaphylactic Reactions: **It may not be possible to distinguish between an acute hypersensitivity reaction (e.g., anaphylaxis, angioedema, etc.) and the Cytokine Release Syndrome. Potentially serious signs and symptoms having an immediate onset (usually within 10 minutes) following administration of ORTHOCLONE OKT3 are probably due to acute hypersensitivity. If hypersensitivity is suspected, discontinue the drug immediately; do not resume therapy or re-expose the patient to ORTHOCLONE OKT3.** Clinical manifestations beginning approximately 30 to 60 minutes (or later) following administration of ORTHOCLONE OKT3 are more likely cytokine-mediated. (See: WARNINGS: Cytokine Release Syndrome Anaphylactic Reactions.)

Central Nervous System Events: Since some seizures (and other serious central nervous system events) following ORTHOCLONE OKT3 administration have been life-threatening, anti-seizure precautions (e.g., an airway ready for use, if needed) should be taken. (See: WARNINGS and ADVERSE EVENTS: Central Nervous System Events.)

Infection / Viral-Induced Lymphoproliferative Disorders: If infection or a viral induced lymphoproliferative disorder occurs, culture or biopsy as soon as possible, promptly institute appropriate anti-infective therapy, and (if possible) reduce/discontinue immunosuppressive therapy. (See: WARNINGS, ADVERSE EVENTS.)

Low Protein-Binding Filter: Use a low protein-binding 0.2 or 0.22 micrometer (μm) filter to prepare the injections. (See: ADMINISTRATION INSTRUCTIONS.)

Sensitization: ORTHOCLONE OKT3 is a mouse (immunoglobulin) protein that can induce human anti-mouse antibody production (i.e., sensitization) in some patients following exposure; a titer ≥1:1000 is a contraindication for use. (See: WARNINGS, ADVERSE EVENTS.)

In the initial clinical trials using low doses of prednisone and azathioprine during ORTHOCLONE OKT3 therapy for renal allograft rejection, antibodies to ORTHOCLONE OKT3 were observed with an incidence of 21% (n=43) for IgM, 86% (n=43) for IgG and 29% (n=35) for IgE. The mean time of appearance of IgG antibodies was 20 ± 2 days (mean ± SD). Early IgG antibodies appeared towards the end of the second week of treatment in 3% (n=86) of the patients.

Subsequent clinical experience has shown that the dose, duration, and type of immunosuppressive medications used in combination with ORTHOCLONE OKT3 may affect both the incidence and magnitude of the host antibody response. Furthermore, immunosuppressive agents used concomitantly with ORTHOCLONE OKT3 (i.e., steroids, azathioprine, prednisone, or cyclosporine) have altered the time course of anti-mouse antibody development and the specificity of the antibodies formed (i.e., idiotypic, isotypic, allotypic).

Thrombosis: As with other immunosuppressive therapies, arterial, venous, and capillary thromboses of allografts and other vascular beds (e.g., heart, lungs, brain, bowel, etc.) have been reported in patients treated with ORTHOCLONE OKT3. In addition, microangiopathic changes (e.g., platelet microthrombi) in the renal allograft associated in some patients with microangiopathic hemolytic anemia have been reported. This was observed in 5 of 93 (5%) patients receiving doses above the recommended dose. The relationship to dose remains uncertain; however, the relative risk appears to be greater with doses above the recommended dose. Patients with a history of thrombosis or underlying vascular disease should be given

Information for Patients:

Patients should be advised:

- of the signs and symptoms associated with the Cytokine Release Syndrome and the potentially serious nature of this syndrome (e.g., systemic, cardiovascular, central nervous system events).
- to seek medical attention for skin rash, urticaria, rapid heart beat, respiratory distress, dysphagia, or any swelling suggesting an allergic reaction or angioedema.
- that ORTHOCLONE OKT3 may impair mental alertness and coordination and may effect the ability to operate an automobile or machinery.
- of other risks associated with the use of ORTHOCLONE OKT3. (See: BOXED WARNING; WARNINGS; PRECAUTIONS; ADVERSE EVENTS.)

Laboratory Tests: The following tests should be monitored prior to and during ORTHOCLONE OKT®3 therapy:

- Renal: BUN, serum creatinine, etc.;
- Hepatic: transaminases, alkaline phosphatase, bilirubin;
- Hematopoietic: WBCs and differential, platelet count, etc.;
- Chest X-ray within 24 hours before initiating ORTHOCLONE OKT3 treatment to rule out heart failure or fluid overload.
- Blood Tests: Periodic assessment of organ system functions (renal, hepatic, and hematopoietic) should be performed.

During therapy with ORTHOCLONE OKT3: In adults, periodic monitoring to ensure plasma ORTHOCLONE OKT3 levels (≥800 ng/mL) or T cell clearance (CD3 positive T cells <25 cells/mm^3) is recommended. In pediatric patients, both plasma ORTHOCLONE OKT3 levels (≥800 ng/mL) and T cell clearance (CD3 positive T cells <25 cells/mm^3) should be monitored daily. (See: CLINICAL PHARMACOLOGY.)

Carcinogenesis: Long-term studies have not been performed in laboratory animals to evaluate the carcinogenic potential of ORTHOCLONE OKT3; however, neoplasia has been reported in patients receiving this product. (See: WARNINGS and ADVERSE EVENTS: Neoplasia.)

Pregnancy Category C: Animal reproductive studies have not been conducted with ORTHOCLONE OKT3. It is also not known whether ORTHOCLONE OKT3 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, ORTHOCLONE OKT3 is an IgG antibody and may cross the human placenta. The effect on the fetus of the release of cytokines and/or immunosuppression after treatment with ORTHOCLONE OKT3 is not known. ORTHOCLONE OKT3 should be given to a pregnant woman only if clearly needed. If this drug is used during pregnancy, or the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. (See: CONTRAINDICATIONS, WARNINGS, and ADVERSE EVENTS.)

Nursing Mothers: It is not known whether ORTHOCLONE OKT3 is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse events/oncogenesis shown for ORTHOCLONE OKT3 in human studies, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (See: CONTRAINDICATIONS.)

Pediatric Use: Safety and effectiveness have been established in infants (1 mo. up to 2 yr.); children (2 yr. up to 12 yr.); and adolescents (12 yr. up to 16 yr.). Use of ORTHOCLONE OKT3 in these age groups is supported by clinical studies that included adults and pediatric patients. In those studies, the safety and efficacy of ORTHOCLONE OKT3 in pediatric patients receiving renal or hepatic transplants was similar to that in the overall cohort. There were insufficient data to compare the safety and efficacy of ORTHOCLONE OKT3 in pediatric patients in a study of patients receiving cardiac transplants. Additional pharmacokinetic, pharmacodynamic, and clinical studies in infants, children, and adolescents have been reported in published literature.

Pediatric patients are known to have higher CD3 lymphocyte counts than adults; therefore, progressively higher doses of ORTHOCLONE OKT3 are often required to achieve therapeutic levels of lymphocyte clearance. (See: DOSAGE AND ADMINISTRATION.)

Specific Safety Concerns in Pediatric Patients

Deaths Due to Cerebral Herniation:

The postmarketing data base indicates that pediatric patients may be at increased risk of developing cerebral edema with or without herniation compared to adults. In the period between 1986 and 1996, twenty-five cases (6 in pediatric patients) of cerebral edema were identified with subsequent cerebral herniation and death in five cases (4 in pediatric patients). Herniation in the pediatric patients and one 19 year old subject occurred within a few hours to one day after the first dose (2.5 or 5 mg) of ORTHOCLONE OKT3 administered in the investigational setting for prophylaxis of renal allograft rejection. All pediatric patients and especially those receiving a renal allograft must be carefully evaluated for fluid retention and hypertension before the initiation of ORTHOCLONE OKT3 therapy. (See: WARNINGS: Cytokine Release Syndrome; DOSAGE AND ADMINISTRATION: General.) Patients should be closely monitored for neurologic symptoms during the first twenty four (24) hours following each of the first few doses of ORTHOCLONE OKT3 injection.

Other Serious Central Nervous System Adverse Events:

include status epilepticus, cerebral edema, diffuse encephalopathy, cerebritis, seizures, cortical dysfunction, and intracranial hemorrhage. Permanent neurologic impairments (e.g., blindness, deafness, paralysis) have been reported rarely. Because meningitis is a frequent infection encountered in pediatric allograft recipients, and the immunosuppression associated with transplantation increases the risk of opportunistic infection, patients with meningeal irritation following treatment with ORTHOCLONE OKT3 therapy should be evaluated with lumbar puncture as early as possible to rule out an infectious etiology.

Viral Infection:

The overall incidence of infections appeared to be similar in pediatric patients compared to the overall population studied. In the pediatric population, viral infections often include pathogens uncommon in adults, such as varicella zoster virus (VZV), adenovirus, enterovirus, parainfluenza virus, and respiratory syncytial virus (RSV). In addition, many viral diseases often manifest differently in pediatric patients than they do in adults. Because a large proportion of pediatric patients have not been infected by herpes viruses (e.g., EBV, HSV, CMV) prior to transplantation they may be more susceptible to acquiring primary infections from the grafted organ and/or blood products when immunosuppressed. Antiviral prophylactic therapy may be particularly useful in these high risk pediatric patients. (See: ADVERSE EVENTS: Infections.)

Neoplasia:

Patients with primary EBV infection may be at higher risk for the development of EBV-associated lymphoproliferative disorders. There are data to support an association between the development of lymphoproliferative disorders at the time of active EBV infection and ORTHOCLONE OKT®3 administration in pediatric liver allograft recipients. Antiviral prophylactic therapy may be particularly useful in these high risk pediatric patients.

Gastrointestinal Fluid Losses:

Parenteral hydration may be required for gastrointestinal fluid loss secondary to diarrhea and/or vomiting resulting from the "Cytokine Release Syndrome".

Thrombosis:

Pediatric patients may be at an increased risk of thrombosis. Pediatric patients weighing less than 15 kg are at high-risk for hepatic artery thrombosis. Thrombosis has been reported in pediatric transplant recipients treated with ORTHOCLONE OKT3. A number of factors, including surgical technique, the presence of a hypercoaguable state, and the absence of prior dialysis experience may be relevant to the pathophysiology of the increased risk of thrombosis. (See: BOXED WARNING; WARNINGS; PRECAUTIONS; ADVERSE EVENTS; DOSAGE AND ADMINISTRATION.)

ADVERSE EVENTS

Cytokine Release Syndrome

In controlled clinical trials for treatment of acute renal allograft rejection, patients treated with ORTHOCLONE OKT3 plus concomitant low-dose immunosuppressive therapy (primarily azathioprine and corticosteroids) were observed to have an increased incidence of adverse experiences during the first two days of treatment, as compared with the group of patients receiving azathioprine and high-dose steroid therapy. During this period the majority of patients experienced pyrexia (90%), of which 19% were 40.0°C (104°F) or above, and chills (59%). In addition, other adverse experiences occurring in 8% or more of the patients during the first two days of ORTHOCLONE OKT3 therapy included: dyspnea (21%), nausea (19%), vomiting (19%), chest pain (14%), diarrhea (14%), tremor (13%), wheezing (13%), headache (11%), tachycardia (10%), rigor (8%), and hypertension (8%). A similar spectrum of clinical manifestations has been observed in open clinical studies and in post-marketing experience involving patients treated with ORTHOCLONE OKT3 for rejection following renal, cardiac, and hepatic transplantation.

Additional serious and occasionally fatal cardiorespiratory manifestations have been reported following any of the first few doses. (See: WARNINGS: Cytokine Release Syndrome ADVERSE EVENTS: Cardiovascular, Respiratory.)

In the acute renal allograft rejection trials, potentially fatal pulmonary edema had been reported following the first two doses in less than 2% of the patients treated with ORTHOCLONE OKT3. Pulmonary edema was usually associated with fluid overload. However, post-marketing experience revealed that pulmonary edema has occurred in patients who appeared to be euvolemic, presumably as a consequence of cytokine-mediated increased vascular permeability ("leaky capillaries") and/or reduced myocardial contractility/compliance (i.e., left ventricular dysfunction). (See: WARNINGS: Cytokine Release Syndrome DOSAGE AND ADMINISTRATION.)

Infections

In the controlled randomized renal allograft rejection trial conducted before cyclosporine was marketed, the most common infections during the first 45 days of ORTHOCLONE OKT3 therapy were due to herpes simplex virus (27%) and cytomegalovirus (19%). Other severe and life-threatening infections were *Staphylococcus epidermidis* (5%), *Pneumocystis carinii* (3%), *Legionella* (2%), *Cryptococcus* (2%), *Serratia* (2%) and gram-negative bacteria (2%). The incidence of infections was similar in patients treated with ORTHOCLONE OKT3 and in patients treated with high-dose steroids.

In a clinical trial of acute hepatic allograft rejection, refrac-

during the first 45 days of the study were cytomegalovirus (16% of patients, of which 43% of infections were severe), fungal infections (15% of patients, of which 30% were severe), and herpes simplex virus (8% of patients, of which 10% were severe). Other severe and life-threatening infections were gram-positive infections (9% of patients), gram-negative infections (8% of patients), viral infections (2% of patients), and *Legionella* (1% of patients). In another trial studying the use of ORTHOCLONE OKT®3 in patients with hepatic allografts, the incidence of fungal infections was 34% and infections with the herpes simplex virus was 31%.

In a clinical trial studying the use of ORTHOCLONE OKT3 in patients with acute cardiac rejection refractory to conventional treatment, the most common infections in the ORTHOCLONE OKT3 group reported during the first 45 days of the study were herpes simplex virus (5% of patients, of which 20% were severe), fungal infections (4% of patients, of which 75% were severe), and cytomegalovirus (3% of patients, of which 33% were severe). No other severe or life-threatening infections were reported during this period.

In a retrospective analysis of pediatric patients treated for acute hepatic rejection, the most common infections reported in patients treated with ORTHOCLONE OKT3 therapy were due to bacterial infections (47%), fungal infections (21%), cytomegalovirus (19%), herpes simplex virus (15%), adenovirus (8%), and Epstein-Barr virus (8%). The overall rates of viral, fungal, and bacterial infections were similar in patients treated with ORTHOCLONE OKT3 (n=53) and in patients whose rejection was treated with steroids alone (n=27). In another study of 149 pediatric liver allograft patients where 59 episodes of steroid-resistant rejection were treated with ORTHOCLONE OKT3, the incidence of invasive cytomegalovirus infection was higher in patients receiving ORTHOCLONE OKT3 than in those receiving steroids alone.

Clinically significant infections (e.g., pneumonia, sepsis, etc.) due to the following pathogens have been reported:

Bacterial: *Clostridium* species (including *perfringens*), *Corynebacterium*, Enterococcus, *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiella* species, *Lactobacillus*, *Legionella*, *Listeria monocytogenes*, *Mycobacteria* species, *Nocardia asteroides*, *Proteus* species, *Providencia* species, *Pseudomonas aeruginosa*, *Serratia* species, *Staphylococcus* species, *Streptococcus* species, *Yersinia enterocolitica*, and other gram-negative bacteria.

*Fungal:** *Aspergillus*, *Candida*, *Cryptococcus*, *Dermatophytes*.

Protozoa: *Pneumocystis carinii*, *Toxoplasma gondii*.

Viral: cytomegalovirus* (CMV), Epstein-Barr virus* (EBV), herpes simplex virus* (HSV), hepatitis viruses, varicella zoster virus (VZV), adenovirus, enterovirus, respiratory syncytial virus (RSV), parainfluenza virus.

As a consequence of being a potent immunosuppressive, the incidence and severity of infections with designated(*) pathogens, especially the herpes family of viruses, may be increased. (See: WARNINGS: Infections.)

Neoplasia

In patients treated with ORTHOCLONE OKT3, post-transplant lymphoproliferative disorders have ranged from lymphadenopathy or benign polyclonal B cell hyperplasias to malignant and often fatal monoclonal B cell lymphomas. In post-marketing experience, approximately one-third of the lymphoproliferations reported were benign and two-thirds were malignant. Lymphoma types included: B cell, large cell, polyclonal, non-Hodgkin's, lymphocytic, T cell, Burkitt's. The majority were not histologically classified. Malignant lymphomas appear to develop early after transplantation, the majority within the first four months post-treatment. Many of these have been rapidly progressive. Some were fulminant, involving the allografted organ and were widely disseminated at the time of diagnosis. Carcinomas of the skin included: basal cell, squamous cell, sarcoma, melanoma, and keratoacanthoma. Other neoplasms infrequently reported include: multiple myeloma, leukemia, carcinoma of the breast, adenocarcinoma, cholangiocarcinoma, and recurrences of pre-existing hepatoma and renal cell carcinoma. (See: WARNINGS: Neoplasia.)

Hypersensitivity Reactions

Reported adverse reactions resulting from the formation of antibodies to ORTHOCLONE OKT3 have included antigen-antibody (immune complex) mediated syndromes and IgE-mediated reactions. Hypersensitivity reactions have ranged from a mild, self-limited rash or pruritus to severe, life-threatening anaphylactic reactions/shock or angioedema (including: swelling of lips, eyelids, laryngeal spasm and airway obstruction with hypoxia). (See: WARNINGS: Anaphylactic Reactions.)

Other hypersensitivity reactions have included: ineffectiveness of treatment, serum sickness, arthritis, allergic interstitial nephritis, immune complex deposition resulting in glomerulonephritis, vasculitis (including temporal and retinal), and eosinophilia.

Adverse Reactions by Body System

Adverse events reported in greater than or equal to 1% of

Table 1: Adverse Events Reported in Clinical Trials (≥1% incidence, n=393)

Body System	Incidence (%)
Autonomic Nervous System Disorders	
Diaphoresis	7
Vasodilation	7
Body as a Whole, General Disorders	
Anorexia	4
Asthenia	10
Chills	43
Fatigue	9
Lethargy	6
Malaise	5
Pain, trunk	6
Pyrexia	77
Cardiovascular Disorders, General	
Arrhythmia	4
Bradycardia	4
Hypertension	19
Hypotension	25
Pain, chest	9
Tachycardia	26
Vascular Occlusion	2
Central & Peripheral Nervous System Disorders	
Convulsions	1
Dizziness	6
Headache	28
Meningitis	1
Tremor	14
Gastrointestinal System Disorders	
Diarrhea	37
Nausea	32
Pain, abdominal	6
Pain, GI	7
Vomiting	25
Hematopoietic Disorders	
Anemia	2
Leukocytosis	1
Thrombocytopenia	2
Metabolic and Nutritional Disorders	
Edema	12
Musculoskeletal System Disorders	
Arthralgia	7
Myalgia	1
Psychiatric Disorders	
Confusion	6
Depression	3
Nervousness	5
Somnolence	2
Renal Disorders	
Renal Dysfunction	3
Respiratory System Disorders	
Abnormal Chest Sound	10
Dyspnea	16
Hyperventilation	7
Hypoxia	1
Pneumonia	1
Pulmonary Edema	2
Respiratory Congestion	4
Wheezing	6
Skin and Appendages Disorders	
Pruritus	7
Rash	14
Rash Erythematous	2
Special Senses	
Photophobia	1
Tinnitus	1
White Cell and Reticuloendothelial System Disorders	
Leukopenia	7

Selected Adverse Events Reported In Clinical Trials (< 1% incidence, n=393):

Cardiovascular Disorders, General: Angina, Cardiac Arrest, Fluctuation in Blood Pressure, Heart Failure, Myocardial Infarction, Shock, Thrombosis.

Central and Peripheral Nervous System Disorders: Coma, Encephalopathy, Epilepsy, Hypotonia.

Gastrointestinal Disorders: Gastrointestinal Hemorrhage.

Hemapoietic Disorders: Coagulation Disorder, Lymphadenopathy, Lymphopenia.

Hepatobiliary: Hepatitis, SGOT Increased, SGPT Increased.

Psychiatric Disorders: Hallucinations, Mood Changes, Paranoia, Psychosis.

Renal Disorders: Anuria, Oliguria.

Respiratory System Disorders: Apnea, Pneumonitis.

Special Senses: Conjunctivitis, Hearing Decrease.

Worldwide Postmarketing Experience - Body Systems/Events Listed Alphabetically:

Body as a Whole, General Disorders: Fever (including spiking temperatures as high as 107°F), Flu-like Syndrome.

Cardiovascular Disorders: Cardiovascular Collapse, Hemodynamic Instability, Left Ventricular Dysfunction.

Central and Peripheral Nervous System Disorders: Agitation, Aphasia, Asterixis, Cerebritis, Cerebral Edema, Cerebral Herniation, Cerebrovascular Accident, CNS Infection, CNS Malignancy, Cranial Nerve VI Palsy, Encephalitis, Hyperreflexia, Involuntary Movements, Intracranial Hemorrhage, Impaired Cognition, Myoclonus, Obnubilation, Pare-

In a post-marketing survey involving 214 renal transplant patients, the incidence of aseptic meningitis syndrome was 6%. Fever (89%), headache (44%), neck stiffness (14%), and photophobia (10%) were the most commonly reported symptoms; a combination of these four symptoms occurred in 5% of patients.

Between 1987 and 1992, 75 post-marketing reports have described seizures, averaging about 12 per year, and including 23 fatalities. More than two-thirds of these reports (53) were of domestic spontaneous origin, and their age and sex distributions were broad. Post-licensure reports generally provide insufficient data to allow accurate estimation of risk or of incidence.

Gastrointestinal Disorders: Bowel Infarction.

Hematopoietic Disorders: Aplastic anemia, Arterial, Venous and Capillary Thrombosis of allografts and other vascular beds e.g., heart, lung, brain and bowel etc., Disseminated Intravascular Coagulation, Microangiopathic Changes (e.g., platelet microthrombi), Microangiopathic Hemolytic Anemia, Neutropenia, Pancytopenia.

Hepatobiliary: Hepatitis or Hepato/splenomegaly, usually secondary to viral infection or lymphoma.

Musculoskeletal Disorders: Arthritis, Stiffness/Aches/Pains.

Renal Disorders: Azotemia, Abnormal Urinary Cytology including exfoliation of damaged lymphocytes, collecting duct cells and cellular casts, Delayed Graft Function, Renal Insufficiency/Renal Failure, usually transient and reversible and occasionally in association with Cytokine Release Syndrome.

Respiratory System Disorders: Adult Respiratory Distress Syndrome, Respiratory Arrest, Respiratory Failure.

Skin and Appendages: Erythema, Flushing, Stevens-Johnson Syndrome, Urticaria.

Special Senses: Blindness, Blurred Vision, Deafness, Diplopia, Otitis Media, Nasal and Ear Stuffiness, Papilledema.

OVERDOSAGE

Symptoms of overdosage with ORTHOCLONE OKT®3 may include hyperthermia, severe chills, myalgia, vomiting, diarrhea, edema, oliguria, pulmonary edema, and acute renal failure. A high incidence (5%) of microangiopathic hemolytic anemia/HUS syndrome in patients receiving 10 mg per day of ORTHOCLONE OKT3 was also reported. In the event of acute overdosage with ORTHOCLONE OKT3, the patient should be carefully observed and given symptomatic and supportive treatment.

DOSAGE AND ADMINISTRATION

Adults

The recommended dose of ORTHOCLONE OKT3 for the treatment of acute renal, steroid-resistant cardiac, or steroid-resistant hepatic allograft rejection is 5 mg per day in a single (bolus) intravenous injection in less than one minute for 10 to 14 days. For acute renal rejection, treatment should begin upon diagnosis. For steroid-resistant cardiac or hepatic allograft rejection, treatment should begin when the treating physician deems a rejection has not been reversed by an adequate course of corticosteroid therapy. (See: CLINICAL PHARMACOLOGY; PRECAUTIONS: Sensitization, Laboratory Tests.)

Pediatric Patients

The initial recommended dose is 2.5 mg per day in pediatric patients weighing less than or equal to 30 kg and 5 mg per day in pediatric patients weighing greater than 30 kg in a single (bolus) intravenous injection in less than one minute for 10 to 14 days. Daily increases in ORTHOCLONE OKT3 doses (i.e., 2.5 mg increments) may be required to achieve depletion of CD3 positive cells (<25 cells/mm^3) and ensure therapeutic ORTHOCLONE OKT3 serum concentrations (> 800 ng/mL). Pediatric patients may require augmentation of the ORTHOCLONE OKT3 dose. For acute renal rejection, treatment should begin upon diagnosis. For steroid-resistant cardiac or hepatic allograft rejection, treatment should begin when the treating physician deems a rejection has not been reversed by an adequate course of corticosteroid therapy. (See: CLINICAL PHARMACOLOGY; PRECAUTIONS; Laboratory Tests; Pediatric Use.)

General

For the first few doses, patients should be monitored in a facility equipped and staffed for cardiopulmonary resuscitation (CPR). Patients receiving subsequent doses of ORTHOCLONE OKT3, should also be monitored in a facility equipped and staffed for CPR. Vital signs should be monitored frequently. Patients receiving ORTHOCLONE OKT3 should also be carefully monitored for signs and symptoms of Cytokine Release Syndrome, particularly after the first few doses but also after a treatment hiatus with resumption of therapy. The patient's temperature should be lowered to <37.8°C (100°F) before the administration of any dose of ORTHOCLONE OKT3.

Prior to administration of ORTHOCLONE OKT3, the patient's volume status should be assessed carefully. It is imperative, especially prior to the first few doses, that there be no clinical evidence of volume overload, uncontrolled hypertension, or uncompensated heart failure. Patients should have a clear chest X-ray and should not weigh more than 3% above their minimum weight during the week prior to injection.

To decrease the incidence and severity of Cytokine Release Syndrome, associated with the first dose of ORTHOCLONE OKT3, it is strongly recommended that methylprednisolone sodium succinate 8.0 mg/kg be admin-

Orthoclone OKT 3—Cont.

istered intravenously 1 to 4 hours prior to the initial dose of ORTHOCLONE OKT3. Acetaminophen and antihistamines given concomitantly with ORTHOCLONE OKT3 may also help to reduce some early reactions. (See: WARNINGS and ADVERSE EVENTS: Cytokine Release Syndrome.)

When using concomitant immunosuppressive drugs, the dose of each should be reduced to the lowest level compatible with an effective therapeutic response in order to reduce the potential for malignancy and infections. Maintenance immunosuppression should be resumed approximately three days prior to the cessation of ORTHOCLONE OKT®3 therapy. (See: WARNINGS and ADVERSE EVENTS: Infection, Neoplasia.)

Reduced T cell clearance or low plasma ORTHOCLONE OKT3 levels provide a basis for adjusting ORTHOCLONE OKT3 dosage or for discontinuing therapy. (See: WARNINGS: Anaphylactic Reactions; PRECAUTIONS: Laboratory Tests; ADVERSE EVENTS: Hypersensitivity Reactions.)

ADMINISTRATION INSTRUCTIONS

1. Before administration, ORTHOCLONE OKT3 should be inspected for particulate matter and discoloration. Because ORTHOCLONE OKT3 is a protein solution, it may develop fine translucent particles (shown not to affect potency).
2. No bacteriostatic agent is present in this product. Adherence to aseptic technique is advised. Once the ampule is opened, use immediately and discard the unused portion.
3. Prepare ORTHOCLONE OKT3 for injection by drawing solution into a syringe through a low protein-binding 0.2 or 0.22 micrometer (μm) filter. Detach filter and attach a new needle for a single intravenous (bolus) injection.
4. Because no data is available on compatibility of ORTHOCLONE OKT3 with other intravenous substances or additives, other medications/substances should not be added or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed with saline before and after injection of ORTHOCLONE OKT3.
5. Administer ORTHOCLONE OKT3 as a single intravenous (bolus) injection in less than one minute. Do **not** administer by intravenous infusion or in conjunction with other drug solutions.

HOW SUPPLIED

ORTHOCLONE OKT3 is supplied as a sterile solution in packages of 5 ampules (NDC 59676-101-01). Each 5 mL ampule contains 5 mg of muromonab-CD3.

Storage: Store in a refrigerator at 2° to 8°C (36° to 46°F). DO NOT FREEZE OR SHAKE.

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U.S.A. ORTHO BIOTECH

631-10-191-4
Revised January 2003

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(epoetin alfa)
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FOR INJECTION

DESCRIPTION

Erythropoietin is a glycoprotein which stimulates red blood cell production. It is produced in the kidney and stimulates the division and differentiation of committed erythroid progenitors in the bone marrow. PROCRIT (Epoetin alfa), a 165 amino acid glycoprotein manufactured by recombinant DNA technology, has the same biological effects as endogenous erythropoietin.[1] It has a molecular weight of 30,400 daltons and is produced by mammalian cells into which the human erythropoietin gene has been introduced. The product contains the identical amino acid sequence of isolated natural erythropoietin.

PROCRIT is formulated as a sterile, colorless, liquid in an isotonic sodium chloride/sodium citrate or a sodium chloride/sodium phosphate buffered solution for intravenous (IV) or subcutaneous (SC) administration.

Single-Dose, Preservative-Free Vial: 1 mL (2,000, 3,000, 4,000 or 10,000 Units/mL). Each 1 mL of solution contains 2,000, 3,000, 4,000 or 10,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 5.8 mg sodium citrate, 5.8 mg sodium chloride, and 0.06 mg citric acid in Water for Injection, USP (pH 6.9±0.3). This formulation contains no preservative.

Single-Dose, Preservative-Free Vial: 1 mL (40,000 Units/mL). Each 1 mL of solution contains 40,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 1.164 mg sodium phosphate monobasic monohydrate, 1.766 mg sodium phosphate dibasic anhydrate, 0.696 mg sodium citrate, 5.78 mg sodium chloride, and 6.8 mcg citric acid in Water for Injection, USP (pH 6.9±0.3). This formulation contains no preservative.

Multidose, Preserved Vial: 2 mL (20,000 Units, 10,000 Units/mL). Each 1 mL of solution contains 10,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 1.3 mg sodium citrate, 8.2 mg sodium chloride, 0.11 mg citric acid, and 1% benzyl alcohol as preservative in Water for Injection, USP (pH 6.1±0.3).

Multidose, Preserved Vial: 1 mL (20,000 Units/mL). Each 1 mL of solution contains 20,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 1.3 mg sodium citrate, 8.2 mg sodium chloride, 0.11 mg citric acid, and 1% benzyl alcohol as preservative in Water for Injection, USP (pH 6.1±0.3).

CLINICAL PHARMACOLOGY

Chronic Renal Failure Patients

Endogenous production of erythropoietin is normally regulated by the level of tissue oxygenation. Hypoxia and anemia generally increase the production of erythropoietin, which in turn stimulates erythropoiesis.[2] In normal subjects, plasma erythropoietin levels range from 0.01 to 0.03 Units/mL, and increase up to 100- to 1000-fold during hypoxia or anemia.[2] In contrast, in patients with chronic renal failure (CRF), production of erythropoietin is impaired, and this erythropoietin deficiency is the primary cause of their anemia.[3,4]

Chronic renal failure is the clinical situation in which there is a progressive and usually irreversible decline in kidney function. Such patients may manifest the sequelae of renal dysfunction, including anemia, but do not necessarily require regular dialysis. Patients with end-stage renal disease (ESRD) are those patients with CRF who require regular dialysis or kidney transplantation for survival.

PROCRIT has been shown to stimulate erythropoiesis in anemic patients with CRF, including both patients on dialysis and those who do not require regular dialysis.[4–13] The first evidence of a response to the three times weekly (T.I.W.) administration of PROCRIT is an increase in the reticulocyte count within 10 days, followed by increases in the red cell count, hemoglobin, and hematocrit, usually within 2-6 weeks.[4,5] Because of the length of time required for erythropoiesis – several days for erythroid progenitors to mature and be released into the circulation – a clinically significant increase in hematocrit is usually not observed in less than 2 weeks and may require up to 6 weeks in some patients. Once the hematocrit reaches the suggested target range (30-36%), that level can be sustained by PROCRIT therapy in the absence of iron deficiency and concurrent illnesses.

The rate of hematocrit increase varies between patients and is dependent upon the dose of PROCRIT, within a therapeutic range of approximately 50-300 Units/kg (T.I.W.).[4] A greater biologic response if not observed at doses exceeding 300 Units/kg (T.I.W.).[8] Other factors affecting the rate and extent of response include availability of iron stores, the baseline hematocrit, and the presence of concurrent medical problems.

Zidovudine-Treated HIV-Infected Patients

Responsiveness to PROCRIT in HIV-infected patients is dependent upon the endogenous serum erythropoietin level prior to treatment. Patients with endogenous serum erythropoietin levels ≤ 500 mUnits/mL, and who are receiving a dose of zidovudine ≤ 4,200 mg/week, may respond to PROCRIT therapy. Patients with endogenous serum erythropoietin levels > 500 mUnits/mL, and who are receiving a dose of zidovudine ≤ 4,200 mg/week, may respond to PROCRIT therapy. In a series of four clinical trials involving 255 patients, 60% to 80% of HIV-infected patients treated with zidovudine had endogenous serum erythropoietin levels ≤ 500 mUnits/mL.

Response to PROCRIT in zidovudine-treated, HIV-infected patients is manifested by reduced transfusion requirements and increased hematocrit.

Cancer Patients on Chemotherapy

Anemia in cancer patients may be related to the disease itself or the effect of concomitantly administered chemotherapeutic agents. PROCRIT has been shown to increase hematocrit and decrease transfusion requirements after the first month of therapy (months 2 and 3), in anemic cancer patients undergoing chemotherapy.

A series of clinical trials enrolled 131 anemic cancer patients who were receiving cyclic cisplatin- or non-cisplatin-containing chemotherapy. Endogenous baseline serum erythropoietin levels varied among patients in these trials with approximately 75% (N=83/110) having endogenous serum erythropoietin levels ≤ 132 mUnits/mL, and approximately 4% (N=4/110) of patients having endogenous serum erythropoietin levels > 500 mUnits/mL. In general, patients with lower baseline serum erythropoietin levels responded more vigorously to PROCRIT than patients with higher baseline erythropoietin levels. Although no specific serum erythropoietin level can be stipulated above which patients would be unlikely to respond to PROCRIT therapy, treatment of patients with grossly elevated serum erythropoietin levels (e.g., > 200 mUnits/mL) is not recommended.

Pharmacokinetics

Intravenously administered PROCRIT is eliminated at a rate consistent with first order kinetics with a circulating half-life ranging from approximately 4 to 13 hours in adult and pediatric patients with CRF.[14–18] Within the therapeutic dose range, detectable levels of plasma erythropoietin are maintained for at least 24 hours. After subcutaneous administration of PROCRIT to patients with CRF, peak serum levels are achieved within 5-24 hours after administration and decline slowly thereafter. There is no apparent difference in half-life between adult patients not on dialysis whose serum creatinine levels were greater than 3, and adult patients maintained on dialysis.

In normal volunteers, the half-life of intravenously administered PROCRIT is approximately 20% shorter than the half-life in CRF patients. The pharmacokinetics of PROCRIT have not been studied in HIV-infected patients. The pharmacokinetic profile of Epoetin alfa in children and adolescents appears to be similar to that of adults. Limited data are available in neonates.[17]

It has been demonstrated in normal volunteers that the 10,000 U/mL citrate-buffered Epoetin alfa formulation and the 40,000 U/mL phosphate-buffered Epoetin alfa formulation are bioequivalent after subcutaneous administration of single 750 Units/kg doses. The C_{max} and $t_{1/2}$ after administration of the phosphate buffered Epoetin alfa formulation were 1.80 ± 0.7 U/mL and 19.0 ± 5.9 hours (mean ± SD), respectively. The corresponding mean ± SD values for the citrate-buffered Epoetin alfa formulation were 2 ± 0.9 U/mL and 16.3 ± 3.0 hours. There was minimal accumulation in serum after two weekly 750 Units/kg subcutaneous doses of Epoetin alfa.

INDICATIONS AND USAGE

Treatment of Anemia of Chronic Renal Failure Patients

PROCRIT is indicated in the treatment of anemia associated with chronic renal failure, including patients on dialysis (end-stage renal disease) and patients not on dialysis. PROCRIT is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need to transfusions in these patients.

Non-dialysis patients with symptomatic anemia considered for therapy should have a hematocrit less than 30%.

PROCRIT is not intended for patients who require immediate correction of severe anemia. PROCRIT may obviate the need for maintenance transfusions but is not a substitute for emergency transfusion.

Prior to initiation of therapy, the patient's iron stores should be evaluated. Transferrin saturation should be at least 20% and ferritin at least 100 ng/mL. Blood pressure should be adequately controlled prior to initiation of PROCRIT therapy, and must be closely monitored and controlled during therapy.

PROCRIT should be administered under the guidance of a qualified physician (see "DOSAGE AND ADMINISTRATION").

Treatment of Anemia in Zidovudine-Treated HIV-Infected Patients

PROCRIT is indicated for the treatment of anemia related to therapy with zidovudine in HIV-infected patients. PROCRIT is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients. PROCRIT is not indicated for the treatment of anemia in HIV-infected patients due to other factors such as iron or folate deficiencies, hemolysis or gastrointestinal bleeding, which should be managed appropriately.

PROCRIT, at a dose of 100 Units/kg three times per week, is effective in decreasing the transfusion requirement and increasing the red blood cell level of anemic, HIV-infected patients treated with zidovudine, when the endogenous serum erythropoietin level is ≤ 500 mUnits/mL and when patients

WHAT TO DO DURING THE MONTH

1. **TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.**
Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
Do not skip pills even if you do not have sex very often.
2. **WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:**
21 pills: Wait 7 days to start the next pack. You will probably have your period during that week. Be sure that no more than 7 days pass between 21-day packs.
28 pills: Start the next pack on the day after your last "reminder" pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

The pill may not be as effective if you miss white "active" pills, and particularly if you miss the first few or the last few white "active" pills in a pack.
If you **MISS 1** white "active" pill:
1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.
If you **MISS 2** white "active" pills in a row in **WEEK 1 OR WEEK 2** of your pack:
1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, spermicide, or sponge) as a back-up for those 7 days.
If you **MISS 2** white "active" pills in a row in **THE 3rd WEEK**:
The ***Day 1 Starter*** instructions are for the 21-day pill pack only. The 28-day pill pack does not accommodate a **DAY 1 START** dosage regimen. The ***Sunday Starter*** instructions are for either the 21-day or 28-day pill pack.
1. ***If you are a Day 1 Starter:***
THROW OUT the rest of the pill pack and start a new pack that same day.
If you are a Sunday Starter:
Keep taking 1 pill every day until Sunday.
On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, spermicide, or sponge) as a back-up for those 7 days.
If you **MISS 3 OR MORE** white "active" pills in a row (during the first 3 weeks):
The ***Day 1 Starter*** instructions are for the 21-day pill pack only. The 28-day pill pack does not accommodate a **DAY 1 START** dosage regimen. The ***Sunday Starter*** instructions are for either the 21-day or 28-day pill pack.
1. ***If you are a Day 1 Starter:***
THROW OUT the rest of the pill pack and start a new pack that same day.
If you are a Sunday Starter:
Keep taking 1 pill every day until Sunday.
On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, spermicide, or sponge) as a back-up for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS

If you forget any of the 7 pink "reminder" pills in Week 4:
THROW AWAY the pills you missed.
Keep taking 1 pill each day until the pack is empty.
You do not need a back-up method if you start your next pack on time.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED

Use a BACK-UP METHOD anytime you have sex.
KEEP TAKING ONE PILL EACH DAY until you can reach your doctor or clinic.
Pregnancy due to pill failure
The incidence of pill failure resulting in pregnancy is approximately less than 1.0% if taken every day as directed, but average failure rates are 5%. If you do become pregnant, the risk to the fetus is minimal, but you should stop taking your pills and discuss the pregnancy with your doctor.
Pregnancy after stopping the pill
There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.
There does not appear to be any increase in birth defects in

Overdosage
Serious ill effects have not been reported following ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding in females. In case of overdosage, contact your health-care provider or pharmacist.
Other information
Your health-care provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the health-care provider believes that it is appropriate to postpone it. You should be reexamined at least once a year. Be sure to inform your health-care provider if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your health-care provider, because this is a time to determine if there are early signs of side effects of oral-contraceptive use.
Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth-control pills.
HEALTH BENEFITS FROM ORAL CONTRACEPTIVES
In addition to preventing pregnancy, use of oral contraceptives may provide certain benefits. They are:
- Menstrual cycles may become more regular.
- Blood flow during menstruation may be lighter, and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.
- Pain or other symptoms during menstruation may be encountered less frequently.
- Ovarian cysts may occur less frequently.
- Ectopic (tubal) pregnancy may occur less frequently.
- Noncancerous cysts or lumps in the breast may occur less frequently.
- Acute pelvic inflammatory disease may occur less frequently.
- Oral-contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus.

If you want more information about birth-control pills, ask your doctor or pharmacist. They have a more technical leaflet called the Professional Labeling which you may wish to read.
Wyeth Laboratories
A Wyeth-Ayerst Company
Philadelphia, PA 19101
CI 4259-7 Revised November 30, 2001
Shown in Product Identification Guide, page 339

MYLOTARG®

℞

[mī 'lō-tärg]
(gemtuzumab ozogamicin for Injection)
FOR INTRAVENOUS USE ONLY

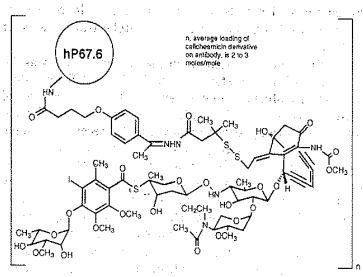
WARNINGS
Mylotarg should be administered under the supervision of physicians experienced in the treatment of acute leukemia and in facilities equipped to monitor and treat leukemia patients.
There are no controlled trials demonstrating efficacy and safety using Mylotarg in combination with other chemotherapeutic agents. Therefore, Mylotarg should only be used as single agent chemotherapy and not in combination chemotherapy regimens outside clinical trials.
Severe myelosuppression occurs when Mylotarg is used at recommended doses.

HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS, INFUSION REACTIONS, PULMONARY EVENTS
Mylotarg administration can result in severe hypersensitivity reactions (including anaphylaxis), and other infusion-related reactions which may include severe pulmonary events. Infrequently, hypersensitivity reactions and pulmonary events have been fatal. In most cases, infusion-related symptoms occurred during the infusion or within 24 hours of administration of Mylotarg and resolved. Mylotarg infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of Mylotarg treatment should be strongly considered for patients who develop anaphylaxis, pulmonary edema, or acute respiratory distress syndrome. Since patients with high peripheral blast counts may be at greater risk for pulmonary events and tumor lysis syndrome, physicians should consider leukoreduction with hydroxyurea or leukapheresis to reduce the peripheral white count to below 30,000/μL prior to administration of Mylotarg. (See **WARNINGS**.)

HEPATOTOXICITY:
Hepatotoxicity, including severe hepatic veno-occlusive disease (VOD), has been reported in association with the use of Mylotarg as a single agent, as part of a combination chemotherapy regimen, and in patients without a history of liver disease or hematopoietic stem-cell transplant (HSCT). (See **WARNINGS** and **ADVERSE REACTIONS** sections.) Patients who receive Mylotarg either before or after HSCT, patients with underlying therapy may be at increased risk for developing severe VOD. Death from liver failure and from VOD has been reported in patients who received Mylotarg. Physicians should monitor their patients carefully for symptoms of hepatotoxicity, particularly VOD. These symptoms can include rapid weight gain, right upper quadrant pain, hepatomegaly, ascites, elevations in bilirubin and/or liver enzymes. However, careful monitoring may not identify all patients at risk or prevent the complications of hepatotoxicity.

DESCRIPTION

Mylotarg® (gemtuzumab ozogamicin for Injection) is a chemotherapy agent composed of a recombinant humanized IgG4, kappa antibody conjugated with a cytotoxic antitumor antibiotic, calicheamicin, isolated from fermentation of a bacterium, *Micromonospora echinospora* ssp. *calichensis*. The antibody portion of Mylotarg binds specifically to the CD33 antigen, a sialic acid-dependent adhesion protein found on the surface of leukemic blasts and immature normal cells of myelomonocytic lineage, but not on normal hematopoietic stem cells. The anti-CD33 hP67.6 antibody is produced by mammalian cell suspension culture using a myeloma NS0 cell line and is purified under conditions which remove or inactivate viruses. Three separate and independent steps in the hP67.6 antibody purification process achieves retrovirus inactivation and removal. These include low pH treatment, DEAE-Sepharose chromatography, and viral filtration. Mylotarg contains amino acid sequences of which approximately 98.3% are of human origin. The constant region and framework regions contain human sequences while the complementarity-determining regions are derived from a murine antibody (p67.6) that binds CD33. This antibody is linked to N-acetyl-gamma calicheamicin via a bifunctional linker. Gemtuzumab ozogamicin has approximately 50% of the antibody loaded with 4-6 moles calicheamicin per mole of antibody. The remaining 50% of the antibody is not linked to the calicheamicin derivative. Gemtuzumab ozogamicin has a molecular weight of 151 to 153 kDa.



Mylotarg (gemtuzumab ozogamicin for Injection) is a sterile, white, preservative-free lyophilized powder containing 5 mg of drug conjugate (protein equivalent) in a 20-mL amber vial. The drug product is light sensitive and must be protected from direct and indirect sunlight and unshielded fluorescent light during the preparation and administration of the infusion. The inactive ingredients are: dextran 40; sucrose; sodium chloride; monobasic and dibasic sodium phosphate.

CLINICAL PHARMACOLOGY

General
Gemtuzumab ozogamicin binds to the CD33 antigen. This antigen is expressed on the surface of leukemic blasts in more than 80% of patients with acute myeloid leukemia (AML). CD33 is also expressed on normal and leukemic myeloid colony-forming cells, including leukemic clonogenic precursors, but it is not expressed on pluripotent hematopoietic stem cells or on nonhematopoietic cells.
Mechanism of Action: Mylotarg is directed against the CD33 antigen expressed by hematopoietic cells. Binding of the anti-CD33 antibody portion of Mylotarg with the CD33 antigen results in the formation of a complex that is internalized. Upon internalization, the calicheamicin derivative is released inside the lysosomes of the myeloid cell. The released calicheamicin derivative binds to DNA in the minor groove resulting in DNA double strand breaks and cell death.
Gemtuzumab ozogamicin is cytotoxic to the CD33 positive HL-60 human leukemia cell line. Gemtuzumab ozogamicin produces significant inhibition of colony formation in cultures of adult leukemic bone marrow cells. The cytotoxic effect on normal myeloid precursors leads to substantial myelosuppression, but this is reversible because pluripotent hematopoietic stem cells are spared. In preclinical animal studies, gemtuzumab ozogamicin demonstrates antitumor effects in the HL-60 human promyelocytic leukemia xenograft tumor in athymic mice.
Human Pharmacokinetics
After administration of the first recommended 9 mg/m^2 dose of gemtuzumab ozogamicin, given as a 2 hour infusion, the elimination half lives of total and unconjugated calicheamicin were about 45 and 100 hours, respectively. After the second 9 mg/m^2 dose, the half life of total calicheamicin was

Mylotarg—Cont.

tration-time curve (AUC) was about twice that in the first dose period. The pharmacokinetics of unconjugated calicheamicin did not appear to change from period one to two. Metabolic studies indicate hydrolytic release of the calicheamicin derivative from gemtuzumab ozogamicin. Many metabolites of this derivative were found after *in vitro* incubation of gemtuzumab ozogamicin in human liver microsomes and cytosol, and in HL-60 promyelocytic leukemia cells. Metabolic studies characterizing the possible isozymes involved in the metabolic pathway of Mylotarg have not been performed.

CLINICAL STUDIES

The efficacy and safety of Mylotarg as a single agent have been evaluated in 142 patients in three single arm open-label studies in patients with CD33 positive AML in first relapse. The studies included 65, 40, and 37 patients. In studies 1 and 2 patients were ≥ 18 years of age with a first remission duration of at least 6 months. In study 3, only patients ≥ 60 were enrolled and their first remission had to have lasted for at least 3 months. Patients with secondary leukemia or white blood cell (WBC) counts ≥ 30,000/µL were excluded. Some patients were leukoreduced with hydroxyurea or leukapheresis to lower WBC counts below 30,000/µL in order to minimize the risk of tumor lysis syndrome. The treatment course included two 9 mg/m^2 doses separated by 14 days and a 28-day follow-up after the last dose. Although smaller doses had elicited responses in earlier studies, the 9 mg/m^2 was chosen because it would be expected to saturate all CD33 sites regardless of leukemic burden. A total of 80 patients were 60 years of age and older. The primary endpoint of the three clinical studies was the rate of complete remission (CR), which was defined as

a) leukemic blasts absent from the peripheral blood;
b) ≤ 5% blasts in the bone marrow, as measured by morphology studies;
c) hemoglobin (Hgb) ≥ 9 g/dL, platelets ≥ 100,000/µL, absolute neutrophil count (ANC) ≥ 1500/µL; and
d) red cell and platelet-transfusion independence (no red cell transfusions for 2 weeks; no platelet transfusions for 1 week).

In addition to CR, a second response category, CRp, was defined as patients satisfying the definition of CR, including platelet transfusion independence, with the exception of platelet recovery ≥100,000/µL. This category was added because Mylotarg appears to delay platelet recovery in some patients. Most of these patients (18/19) achieved platelet counts of at least 25,000/µL and about two-thirds (13/19) achieved platelet counts of at least 50,000/µL, before any additional therapy was administered. It is not yet clear whether CR and CRp responses are clinically equivalent; but survival in the two groups appeared similar.

All patients were pre-medicated with acetaminophen 650–1000 mg and diphenhydramine 50 mg to decrease acute infusion-related symptoms. Growth factors and cytokines were not permitted. Use of prophylactic antibiotics was not specified.

Response Rate

The overall response (OR) rate for the three pooled monotherapy studies was 30% (42/142) consisting of 16% (23/142) of patients with CR and 13% (19/142) of patients with CRp. The median time to remission was 60 days for both CR and CRp. Remission rates in the individual studies are shown in Table 1.

[See table 1 above]

Two of the most important determinants of response following relapse are age and duration of first remission. Remission rates by prognostic category are outlined in Table 2; the impact of age and duration of first remission in these patients was minimal:

[See table 2 above]

Among patients < 60 years of age the overall response rate was 34%; among patients ≥ 60 years of age the overall response rate was 26%. The overall response rates were similar for females and males: 31% of females and 29% of males achieved remission.

The majority of patients (94%) in the Phase 2 clinical trials were white, only 6% were non-white. All 42 of the responding patients were white.

Relapse-Free Survival

Relapse-free survival was calculated from the date of initial therapy (Table 3).

[See table 3 above]

Overall Survival

Median duration of overall survival for the 142 patients was 5.9 months and 55/142 patients were alive as of the data cutoff date.

Post-Remission Therapy

Fifteen (15/42, 36%) OR patients (8 CRs and 7 CRps) received hematopoietic stem cell transplantation. The survival of these 15 patients ranged from 3.5 to 26.9 months as of the data cut-off date. Nine OR patients (4 CR and 5 CRp) had an overall survival of >12 months as of the data cut-off date.

Repeat Courses

Five patients have received a second treatment course of Mylotarg (gemtuzumab ozogamicin for Injection) in clinical trials. These patients were initially treated with Mylotarg after receiving the second course of Mylotarg. Prolonged severe myelosuppression was observed in four patients receiving a third dose.

TABLE 1: PERCENTAGE OF PATIENTS BY REMISSION CATEGORY

	Study 1	Study 2	Study 3[a]	All Studies
Type of Remission	n = 65	n = 40	n = 37	n = 142
CR (95% CI)	17 (9, 28)	20 (9, 36)	11 (3, 25)	16 (11, 23)
CRp (95% CI)	15 (8, 26)	13 (4, 27)	11 (3, 25)	13 (8, 20)
OR (CR + CRp) (95% CI)	32 (21, 45)	33 (19, 49)	22 (10, 38)	30 (22, 38)

a: Patients 60 years of age or greater

TABLE 2: PERCENTAGE OF PATIENTS BY REMISSION CATEGORY AND PROGNOSTIC GROUP

	Age < 60 years	Age ≥ 60 years	First Remission ≥ 1 yr	First Remission < 1 yr
Type of Remission	n = 62	n = 80	n = 62	n = 80
CR (95% CI)	18 (9, 30)	15 (8, 25)	21 (12, 33)	13 (6, 22)
CRp (95% CI)	16 (8, 28)	11 (5, 20)	11 (5, 22)	15 (8, 25)
OR (CR + CRp) (95% CI)	34 (22, 47)	26 (17, 37)	32 (21, 45)	28 (18, 39)

TABLE 3: SUMMARY OF RELAPSE-FREE SURVIVAL[a] FOR PATIENTS WITH CR AND CRp

Remission Group	n	No. Relapsed	Median months	Min-Max months[b]
CR	23	14	7.2	0.5–24.8
CRp	19	9	4.4	0.33[b]–21.5
OR[c]	42	23	6.8	0.33[b]–24.8

a: Number of months after achieving CR or CRp.
b: Data are limited by data cut-off date; first event occurred in 0.83 months for CRp and in 0.5 months for OR.
c: Six OR patients (1 CR and 5 CRp) had a relapse-free survival of > 12 months.

Overview of Clinical Data

Available single arm trial data do not provide valid comparisons with various cytotoxic regimens that have been used in relapsed acute myeloid leukemia. Response rates are in the range of rates reported with such regimens only if the CRp responses are included. Nevertheless, treatment with Mylotarg can provide responses, including some of reasonable duration. The data support its use in patients for whom aggressive cytotoxic regimens would be considered unsuitable, such as many patients 60 years of age or older.

INDICATIONS AND USAGE

Mylotarg is indicated for the treatment of patients with CD33 positive acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy. The safety and efficacy of Mylotarg in patients with poor performance status and organ dysfunction has not been established.

The effectiveness of Mylotarg is based on OR rates (see **CLINICAL STUDIES** section). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival, compared to any other treatment.

CONTRAINDICATIONS

Mylotarg is contraindicated in patients with a known hypersensitivity to gemtuzumab ozogamicin or any of its components: anti-CD33 antibody (hP67.6), calicheamicin derivitives, or inactive ingredients.

WARNINGS

Mylotarg should be administered under the supervision of physicians experienced in the treatment of acute leukemia and in facilities equipped to monitor and treat leukemia patients.

There are no controlled trials demonstrating efficacy and safety using Mylotarg in combination with other chemotherapeutic agents. Therefore, Mylotarg should only be used as single agent chemotherapy and not in combination chemotherapy regimens outside clinical trials.

Myelosuppression: Severe myelosuppression will occur in all patients given the recommended dose of this agent. Careful hematologic monitoring is required. Systemic infections should be treated.

Hypersensitivity Reactions Including Anaphylaxis, Infusion Reactions, Pulmonary Events: Mylotarg administration can result in severe hypersensitivity reactions (including anaphylaxis), and other infusion-related reactions which may include severe pulmonary events. Infrequently, hypersensitivity reactions and pulmonary events have been fatal. In most cases, infusion-related symptoms occurred during Mylotarg (gemtuzumab ozogamicin for Injection) infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of further Mylotarg treatment should be strongly considered for patients who develop anaphylaxis, pulmonary edema, or acute respiratory distress syndrome. Since patients with high peripheral blast counts may be at greater risk for such reactions, physicians should consider leukoreduction with hydroxyurea or leukapheresis to reduce the peripheral white count to below 30,000/µL prior to administration of Mylotarg.

Infusion Reactions: Mylotarg can produce a post-infusion symptom complex of fever and chills, and less commonly hypotension and dyspnea that may occur during the first 24 hours after administration. Grade 3 or 4 non-hematologic infusion-related adverse events included chills, fever, hypotension, hypertension, hyperglycemia, hypoxia, and dyspnea. Most patients received the following prophylactic medications before administration: diphenhydramine 50 mg po and acetaminophen 650–1000 mg po; thereafter, two additional doses of acetaminophen 650–1000 mg po, one every 4 hours as needed. Vital signs should be monitored during infusion and for the four hours following infusion.

In clinical studies, these symptoms generally occurred after the end of the 2-hour intravenous infusion and resolved after 2 to 4 hours with a supportive therapy of acetaminophen, diphenhydramine, and IV fluids. Fewer infusion-related events were observed after the second dose.

Pulmonary Events: Severe pulmonary events leading to death have been reported infrequently with the use of Mylotarg in the postmarketing 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 occur as sequelae of infusion reactions; patients with WBC counts > 30,000/µL may be at increased risk. (See Infusion Reactions section of **WARNINGS**.) Physicians should consider leukoreduction with hydroxyurea or leukapheresis to reduce the peripheral white count to below 30,000 µL prior to administration of Mylotarg. Patients with symptomatic intrinsic lung disease may also be at greater risk of severe pulmonary reactions.

Hepatotoxicity: Hepatotoxicity, including severe VOD, has been reported in association with the use of Mylotarg as a single agent, as part of a combination chemotherapy regimen, and in patients without a history of liver disease or HSCT. (See **ADVERSE REACTIONS** section.) Patients who receive Mylotarg either before or after HSCT, patients with underlying hepatic disease or abnormal liver function, and patients receiving Mylotarg in combinations with other chemotherapy may be at increased risk for developing severe VOD. Death from liver failure and from VOD has been

atotoxicity, particularly VOD. These symptoms can include: rapid weight gain, right upper quadrant pain, hepatomegaly, ascites, elevations in bilirubin and/or liver enzymes. However, careful monitoring may not identify all patients at risk or prevent the complications of hepatotoxicity.

Use in Patients with Hepatic Impairment: Mylotarg has not been studied in patients with bilirubin > 2 mg/dL. Extra caution should be exercised when administering Mylotarg in patients with hepatic impairment (see **ADVERSE REACTIONS** section).

Tumor Lysis Syndrome (TLS): TLS may be a consequence of leukemia treatment with any chemotherapeutic agent including Mylotarg. Renal failure secondary to TLS has been reported in association with the use of Mylotarg. Appropriate measures, (e.g. hydration and allopurinol), must be taken to prevent hyperuricemia. Physicians should consider leukoreduction with hydroxyurea or leukapheresis to reduce the peripheral white blood count to < 30,000/μL prior to administration of Mylotarg (see **CLINICAL STUDIES** section).

Pregnancy: Mylotarg may cause fetal harm when administered to a pregnant woman. Daily treatment of pregnant rats with gemtuzumab ozogamicin during organogenesis caused dose-related decreases in fetal weight in association with dose-related decreases in fetal skeletal ossification beginning at 0.025 mg/kg/day. Doses of 0.060 mg/kg/day (approximately 0.04 times the recommended human single dose on a mg/m^2 basis) produced increased embryo-fetal mortality (increased numbers of resorptions and decreased numbers of live fetuses per litter). Gross external, visceral, and skeletal alterations at the 0.060 mg/kg/day dose level included digital malformations (ectrodactyly, brachydactyly) in one or both hind feet, absence of the aortic arch, wavy ribs, anomalies of the long bones in the forelimb(s) (short/thick humerus, misshapen radius and ulna, and short/thick ulna), misshapen scapula, absence of vertebral centrum, and fused sternebrae. This dose was also associated with maternal toxicity (decreased weight gain, decreased food consumption). There are no adequate and well-controlled studies in pregnant women. If Mylotarg is used in pregnancy, or if the patient becomes pregnant while taking it, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Mylotarg.

PRECAUTIONS

DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS

General

Treatment by Experienced Physicians: Mylotarg should be administered under the supervision of physicians experienced in the treatment of acute leukemia and in facilities equipped to monitor and treat leukemia patients.

Laboratory Monitoring: Electrolytes, tests of hepatic function, complete blood counts (CBCs) and platelet counts should be monitored during Mylotarg therapy.

Drug Interactions: There have been no formal drug-interaction studies performed with Mylotarg.

Laboratory Test Interactions: Mylotarg is not known to interfere with any routine diagnostic tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of Mylotarg. Gemtuzumab ozogamicin was clastogenic in the mouse *in vivo* micronucleus test. This positive result is consistent with the known ability of calicheamicin to cause double-stranded breaks in DNA. Gemtuzumab ozogamicin adversely affected male, but not female, fertility in rats. Following daily administration of gemtuzumab ozogamicin to male rats for 28 days at doses of 0.02 to 0.16 mg/kg/day (approximately 0.01 to 0.11 times the human dose on a mg/m^2 basis) gemtuzumab ozogamicin caused: decreased fertility rates, epididymal sperm counts, and sperm motility; increased incidence of sperm abnormalities; and microscopic evidence of decreased spermatogonia and spermatocyte count. These findings did not resolve following a 9-week recovery period.

Pregnancy Category D: See **WARNINGS** section.

Nursing Mothers: It is not known if Mylotarg is excreted in human milk. Because many drugs, including immunoglobulins, are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Mylotarg, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of Mylotarg (gemtuzumab ozogamicin for Injection) in pediatric patients have not been studied.

Use in Patients with Renal Impairment: Patients with renal impairment were not studied.

ADVERSE REACTIONS

Mylotarg has been administered to 142 patients with relapsed AML at 9 mg/m^2. Mylotarg was generally given as two intravenous infusions separated by 14 days.

Acute Infusion-Related Events (Table 4)

TABLE 4: PERCENTAGE OF PATIENTS REPORTED TO HAVE ACUTE INFUSION-RELATED ADVERSE EVENTS

Adverse Event	(%) Any Severity	(%) Grade 3 or 4
Chills	62	11
Fever	61	7
Nausea	38	<1
Vomiting	32	<1
Headache	12	<1
Hypotension	11	4
Hypertension	6	3
Hypoxia	6	2
Dyspnea	4	1
Hyperglycemia	2	2

These symptoms generally occurred after the end of the 2-hour intravenous infusion and resolved after 2 to 4 hours with a supportive therapy of acetaminophen, diphenhydramine, and IV fluids (see **WARNINGS** section). Fewer infusion-related events were observed after the second dose.

Antibody Formation: Antibodies to gemtuzumab ozogamicin were not detected in a total of 142 patients in the Phase 2 clinical studies. Two patients in a Phase 1 study developed antibody titers against the calicheamicin/calicheamicin-linker portion of gemtuzumab ozogamicin after three doses. One patient experienced transient fever, hypotension and dyspnea; the other patient had no clinical symptoms. No patient developed antibody responses to the hP67.6 antibody portion of Mylotarg.

Myelosuppression: Severe myelosuppression is the major toxicity associated with Mylotarg. During the treatment phase, 137/140 (98%) patients experienced Grade 3 or Grade 4 neutropenia. Responding patients recovered ANCs to 500/μL by a median of 40.5 days after the first dose of Mylotarg.

Anemia, Thrombocytopenia: During the treatment phase, 139/141 (99%) patients experienced Grade 3 or Grade 4 thrombocytopenia. Responding patients recovered platelet counts to 25,000/μL by a median of 39 days after the first dose of Mylotarg. 66/141 (47%) patients experienced Grade 3 or Grade 4 anemia.

Infection: During the treatment phase, 40/142 (28%) patients experienced Grade 3 or Grade 4 infections, including opportunistic infections. The most frequent Grade 3 or Grade 4 infection-related treatment-emergent adverse events (TEAEs) were sepsis (16%) and pneumonia (7%). Herpes simplex infection was reported in 22% of the patients.

Bleeding: During the treatment phase, 21/142 (15%) patients experienced Grade 3 or Grade 4 bleeding. The most frequent severe TEAE was epistaxis (3%). There were also reports of cerebral hemorrhage (2%), disseminated intravascular coagulation (2%), intracranial hemorrhage (2%), and hematuria (1%).

Transfusions: During the treatment phase, more transfusions were required in the NR and CRp patients compared with the CRs (Table 5):

[See table 5 below]

Mucositis: A total of 50/142 (35%) patients were reported to have a TEAE consistent with oral mucositis or stomatitis. During the treatment phase, 5/142 (4%) patients experienced Grade 3 or 4 stomatitis/ mucositis after the first dose. The mucositis events for the remaining 45/142 (32%) patients were categorized as Grade 1 or 2.

Hepatotoxicity: Abnormalities of liver function were transient and generally reversible. In clinical studies, 33/141 (23%) patients experienced Grade 3 or Grade 4 hyperbilirubinemia. Nine percent (12/141) of patients experienced Grade 3 or Grade 4 abnormalities in levels of ALT, and 24/141 (17%) patients experienced Grade 3 or Grade 4 abnormalities in levels of AST. Thirteen patients had concurrent elevations of transaminases (grade 3 to 4) and bilirubin. One patient died with liver failure in the setting of tumor lysis syndrome and multisystem organ failure 22 days after treatment. Another patient died after an episode of persistent jaundice and hepatosplenomegaly 156 days after treatment. Among 27 patients who received hematopoietic stem cell transplantation following Mylotarg (gemtuzumab ozogamicin for Injection), three (2 NRs and 1 CR) died of hepatic veno-occlusive disease (VOD) 22 to 35 days following transplantation.

Skin: No patients experienced alopecia. A nonspecific rash was reported in 22%.

Retreatment Events: Five (5) patients have received more than one course of Mylotarg, 4 of these patients at 9 mg/m^2. The adverse event profile for retreated patients was similar to that following their initial treatment. One of the repeat dose patients was in a Phase I study and received a first course of 3 doses at 1 mg/m^2 and 2 doses of a second course at 6 mg/m^2. This patient was discontinued from further dose administration as a result of an immune response to the calicheamicin/calicheamicin-linker portion of gemtuzumab ozogamicin. The 4 other retreated patients did not experience an immune response.

Dose Relationship for Adverse Events: Dose-relationship data were generated from a small dose-escalation study. The most common clinical adverse event observed in this study was an infusion-related symptom complex of fever and chills. In general, the severity of fever, but not chills, increased as the dose level increased. Only one dose level of Mylotarg was studied in the Phase 2 clinical trials in relapsed AML.

Treatment-Emergent Adverse Events (TEAE): TEAEs (Grades 1–4) that occurred in ≥ 10% of the patients regardless of causality are listed in Table 6.

TABLE 6: NUMBER (%) OF PATIENTS REPORTING TREATMENT-EMERGENT ADVERSE EVENTS[a]-ALL GRADES (INCIDENCE ≥ 10%[b])

Adverse Event	Efficacy and Safety Studies All Patients (n = 142)	Efficacy and Safety Studies Age ≥ 60 (n = 80)
Body as a whole		
Abdomen enlarged	13 (9)	9 (11)
Abdominal pain	52 (37)	23 (29)
Asthenia	63 (44)	36 (45)
Back pain	22 (15)	14 (18)
Chills	104 (73)	53 (66)
Fever	121 (85)	64 (80)
Headache	50 (35)	21 (26)
Neutropenic fever	30 (21)	16 (20)
Pain	30 (21)	20 (25)
Sepsis	36 (25)	19 (24)
Cardiovascular system		
Hemorrhage	14 (10)	6 (8)
Hypertension	29 (20)	16 (20)
Hypotension	28 (20)	13 (16)
Tachycardia	15 (11)	8 (10)
Digestive system		
Anorexia	41 (29)	25 (31)
Constipation	36 (25)	22 (28)
Diarrhea	54 (38)	30 (38)
Dyspepsia	16 (11)	9 (11)
Nausea	100 (70)	51 (64)
Stomatitis	45 (32)	20 (25)
Vomiting	89 (63)	44 (55)
Hemic and lymphatic system		
Ecchymosis	18 (13)	12 (15)
Metabolic		
Hypokalemia	44 (31)	24 (30)
Hypomagnesemia	14 (10)	3 (4)
Lactic dehydrogenase increased	19 (13)	14 (18)
Musculoskeletal system		
Arthralgia	12 (8)	8 (10)
Nervous system		
Depression	13 (9)	8 (10)
Dizziness	22 (15)	9 (11)
Insomnia	22 (15)	14 (18)
Respiratory system		
Cough increased	28 (20)	15 (19)
Dyspnea	46 (32)	29 (36)
Epistaxis	44 (31)	23 (29)
Pharyngitis	20 (14)	11 (14)
Pneumonia	14 (10)	8 (10)
Pulmonary physical finding[c]	16 (11)	10 (13)
Rhinitis	14 (10)	8 (10)
Skin and appendages		
Herpes simplex	31 (22)	12 (15)
Rash	31 (22)	18 (23)
Local reaction	35 (25)	20 (25)
Peripheral edema	23 (16)	17 (21)
Petechiae	28 (20)	17 (21)

TABLE 5: NUMBER OF TRANSFUSIONS BY RESPONSE GROUP

Transfusions	All Patients	CR	CRp	NR
	n = 142	n = 23	n = 19	n = 100
Platelet transfusions				
Mean (SD)	14 (23)	5.4 (6)	14.8 (12)	15.8 (27)
(95% CI)	(10.2, 17.8)	(3, 7.8)	(9.3, 20.4)	(10.6, 21.1)
RBC transfusions				
Mean	8.2 (26)	2.6 (2)	6.2 (5)	9.9 (31)

Mylotarg—Cont.

Urogenital system[d]		
Hematuria	14 (10)	8 (10)
Vaginal hemorrhage	7 (12)	2 (7)

a: Does not include changes in laboratory values reported as adverse events for events included in the NCI common toxicity scale.
b: ≥ 10% limit specifies the minimum percentage threshold from at least 1 column for an event to be displayed in the table.
c: Includes rales, rhonchi, and changes in breath sounds.
d: Percentages for sex-specific adverse events are based on the number of patients of the relevant sex.

TEAE with a Grade 3 or 4 severity are listed in Table 7.

TABLE 7: PERCENT (%) OF PATIENTS REPORTED TO HAVE SEVERE OR NCI GRADE 3 OR 4 TREATMENT-EMERGENT ADVERSE EVENTS[a] (INCIDENCE ≥ 5%[b])

Body System / Adverse Event	Efficacy and Safety Studies Grades 3–4 All Patients (n = 142)	Age ≥ 60 (n = 80)
Any adverse event	129 (91)	70 (88)
Body as a whole		
Asthenia	10 (7)	8 (10)
Chills	18 (13)	12 (15)
Fever	21 (15)	11 (14)
Neutropenic fever	10 (7)	4 (5)
Sepsis	23 (16)	12 (16)
Cardiovascular system		
Hypertension	13 (9)	9 (11)
Hypotension	11 (8)	6 (8)
Digestive system		
Nausea	13 (9)	6 (8)
Metabolic		
Hypokalemia	4 (3)	4 (5)
Lactic dehydrogenase increased	6 (4)	6 (8)
Respiratory system		
Dyspnea	13 (9)	10 (13)
Pneumonia	10 (7)	5 (6)

a: Does not include changes in laboratory values reported as adverse events for events included in the NCI common toxicity scale.
b: ≥ 5% limit specifies the minimum percentage threshold from at least 1 column for an event to be displayed in the table.

Clinically important laboratory abnormalities with a Grade 3 or 4 severity are listed in Table 8.

TABLE 8: NUMBER (%[a]) OF PATIENTS WITH LABORATORY TEST RESULTS OF GRADE 3 OR 4 SEVERITY[b]

Test	Efficacy and Safety Studies Grades 3–4 All Patients (n = 142)	Age ≥ 60 (n = 80)
Hematologic		
Hemoglobin	66/141 (47)	36/80 (45)
WBC	136/141 (96)	75/80 (94)
Total neutrophils, absolute	137/140 (98)	78/79 (99)
Lymphocytes	130/140 (93)	70/79 (89)
Platelet count	139/141 (99)	79/80 (99)
Prothrombin time	2/47 (4)	1/23 (4)
Partial thromboplastin time	1/79 (1)	1/42 (2)
Non-hematologic		
Glucose	17/140 (12)	9/79 (11)
Creatinine	2/141 (1)	0/80
Total bilirubin	33/141 (23)	18/80 (23)
AST	24/141 (17)	12/80 (15)
ALT	12/141 (9)	7/80 (9)
Alkaline phosphatase	5/141 (4)	1/80 (1)
Calcium	17/141 (12)	5/80 (6)

a: Percentage is based on the number of patients receiving a particular laboratory test during the study as is indicated for each test.
b: Severity as defined by NCI common toxicity scale version 1.

There were considered to be no clinically important differences in TEAEs between patients < 60 years of age and those patients ≥ 60. Laboratory parameters associated with hepatic dysfunction (e.g., elevated levels of bilirubin, AST, and ALT) were more consistently observed in patients ≥ 60 years old than in those < 60 years old.

There were considered to be no clinically important differences in TEAEs between female and male patients.

Other Clinical Experience:

In postmarketing experience and other clinical trials, additional cases of VOD have been reported, some in association or subsequent HSCT. Renal failure secondary to TLS, hypersensitivity reactions, anaphylaxis, and pulmonary events, have also been reported in association with the use of Mylotarg (gemtuzumab ozogamicin for Injection). (See **WARNINGS** section).

OVERDOSAGE

No cases of overdose with Mylotarg were reported in clinical experience. Single doses higher than 9 mg/m^2 in adults were not tested. When a single dose of Mylotarg was administered to animals, mortality was observed in rats at the dose of 2 mg/kg (approximately 1.3-times the recommended human dose on a mg/m^2 basis), and in male monkeys at the dose of 4.5 mg/kg (approximately 6-times the recommended human dose on a mg/m^2 basis).

Signs and Symptoms: Signs of overdose with Mylotarg are unknown.

Recommended Treatment: General supportive measures should be followed in case of overdose. Blood pressure and blood counts should be carefully monitored. Gemtuzumab ozogamicin is not dialyzable.

DOSAGE AND ADMINISTRATION

The recommended dose of Mylotarg is 9 mg/m^2, administered as a 2-hour intravenous infusion. Physicians should consider leukoreduction with hydroxyurea or leukapheresis to reduce the peripheral white blood count to below 30,000/μL prior to administration of Mylotarg. Appropriate measures (e.g. hydration and allopurinol) must be taken to prevent hyperuricemia. Patients should receive the following prophylactic medications one hour before Mylotarg administration: diphenhydramine 50 mg po and acetaminophen 650–1000 mg po; thereafter, two additional doses of acetaminophen 650–1000 mg po, one every 4 hours as needed. Vital signs should be monitored during infusion and for four hours following infusion. The recommended treatment course with Mylotarg is a total of 2 doses with 14 days between the doses. Full recovery from hematologic toxicities is not a requirement for administration of the second dose.

Hepatic Insufficiency: Patients with hepatic impairment were not included in the clinical studies. See **WARNINGS** section.

Renal Insufficiency: Patients with renal impairment were not included in the clinical studies.

Instructions for Reconstitution

The drug product is light sensitive and must be protected from direct and indirect sunlight and unshielded fluorescent light during the preparation and administration of the infusion. **All preparation should take place in a biologic safety hood with the fluorescent light off.** Prior to reconstitution, allow drug vials to come to room temperature. Reconstitute the contents of each vial with 5 mL Sterile Water for Injection, USP, using sterile syringes. Gently swirl each vial. Each vial should be inspected for complete solution and for particulate. The final concentration of drug in the vial is 1 mg/mL. While in the vial, the reconstituted drug may be stored refrigerated (2–8° C) and protected from light for up to 8 hours.

Instructions for Dilution

Withdraw the desired volume from each vial and inject into a 100 mL IV bag of 0.9% Sodium Chloride Injection. Place the 100-mL IV bag into an UV protectant bag. The resulting drug solution in the IV bag should be used immediately.

Administration

DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS

Once the reconstituted Mylotarg is diluted into the IV bag containing normal saline, the resulting solution should be infused over a 2-hour period. A separate IV line equipped with a low protein-binding 1.2-micron terminal filter must be used for administration of the drug. Mylotarg may be given peripherally or through a central line. Premedication, consisting of acetaminophen and diphenhydramine, should be given before each infusion to reduce the incidence of a post-infusion symptom complex (see **ADVERSE REACTIONS, Acute Infusion-Related Events**).

Stability and Storage: Mylotarg should be stored refrigerated 2° to 8° C (36° to 46° F) and protected from light.

Instructions for Use, Handling and for Disposal: Mylotarg should be inspected visually for particulate matter and discoloration, following reconstitution and prior to administration. Protect from light and use an UV protective bag over the IV bag during infusion. Procedures for handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1,2,3]

HOW SUPPLIED

Mylotarg® (gemtuzumab ozogamicin for Injection) is supplied as a single-vial package with an amber glass vial containing 5 mg of Mylotarg lyophilized powder. Single-unit 5 mg package: each 20 mL vial contains 5 mg of Mylotarg. NDC 0008-4510-01.

REFERENCES

[1] Recommendation for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For Sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
[2] AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA* 1985; 253 (11): 1590–1592.
[3] National Study Commission on Cytotoxic Exposure—Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts Col-

Manufactured by:
Wyeth Laboratories
Division of Wyeth-Ayerst Pharmaceuticals Inc.
Philadelphia, PA 19101
CI 7407-4
Revised May 28, 2002

Shown in Product Identification Guide, page 339

NEUMEGA®

℞

[*nu-meg<a*]
(oprelvekin)
℞ **ONLY**

BOXED WARNING

Allergic Reactions Including Anaphylaxis

Neumega has caused allergic or hypersensitivity reactions, including anaphylaxis. Administration of Neumega should be permanently discontinued in any patient who develops an allergic or hypersensitivity reaction (see **WARNINGS, CONTRAINDICATIONS, ADVERSE REACTIONS** and **ADVERSE REACTIONS, Immunogenicity**).

DESCRIPTION

Interleukin eleven (IL-11) is a thrombopoietic growth factor that directly stimulates the proliferation of hematopoietic stem cells and megakaryocyte progenitor cells and induces megakaryocyte maturation resulting in increased platelet production. IL-11 is a member of a family of human growth factors which includes human growth hormone, granulocyte colony-stimulating factor (G-CSF), and other growth factors.

Oprelvekin, the active ingredient in Neumega, is produced in *Escherichia coli (E. coli)* by recombinant DNA technology. The protein has a molecular mass of approximately 19,000 daltons, and is non-glycosylated. The polypeptide is 177 amino acids in length and differs from the 178 amino acid length of native IL-11 only in lacking the amino-terminal proline residue. This alteration has not resulted in measurable differences in bioactivity either *in vitro* or *in vivo*.

Neumega is formulated in single-use vials containing 5 mg of oprelvekin (specific activity approximately 8 x 10^6 Units/mg) as a sterile, lyophilized powder with 23 mg Glycine, USP, 1.6 mg Dibasic Sodium Phosphate Heptahydrate, USP, and 0.55 mg Monobasic Sodium Phosphate Monohydrate, USP. When reconstituted with 1 mL of Sterile Water for Injection, USP, the resulting solution has a pH of 7.0 and a concentration of 5 mg/mL.

CLINICAL PHARMACOLOGY

The primary hematopoietic activity of Neumega is stimulation of megakaryocytopoiesis and thrombopoiesis. Neumega has shown potent thrombopoietic activity in animal models of compromised hematopoiesis, including moderately to severely myelosuppressed mice and nonhuman primates. In these models, Neumega improved platelet nadirs and accelerated platelet recoveries compared to controls.

Preclinical trials have shown that mature megakaryocytes which develop during *in vivo* treatment with Neumega are ultrastructurally normal. Platelets produced in response to Neumega were morphologically and functionally normal and possessed a normal life span.

IL-11 has also been shown to have non-hematopoietic activities in animals including the regulation of intestinal epithelium growth (enhanced healing of gastrointestinal lesions), the inhibition of adipogenesis, the induction of acute-phase protein synthesis, inhibition of pro-inflammatory cytokine production by macrophages, and the stimulation of osteoclastogenesis and neurogenesis. Non-hematopoietic pathologic changes observed in animals include fibrosis of tendons and joint capsules, periosteal thickening, papilledema, and embryotoxicity (see **PRECAUTIONS, Pediatric Use** and **PRECAUTIONS, Pregnancy Category C**).

IL-11 is produced by bone marrow stromal cells and is part of the cytokine family that shares the gp130 signal transducer. Primary osteoblasts and mature osteoclasts express mRNAs for both IL-11 receptor (IL-11R alpha) and gp130. Both bone-forming and bone-resorbing cells are potential targets of IL-11.[1]

Pharmacokinetics

The pharmacokinetics of Neumega have been evaluated in studies of healthy, adult subjects and cancer patients receiving chemotherapy. In a study in which a single 50 μg/kg subcutaneous dose was administered to eighteen healthy men, the peak serum concentration (C_{max}) of 17.4 ± 5.4 ng/mL (mean ± S.D.) was reached at 3.2 ± 2.4 hrs (T_{max}) following dosing. The terminal half-life was 6.9 ± 1.7 hrs. In a second study, in which single 75 μg/kg subcutaneous and intravenous doses were administered to twenty-four healthy subjects, the pharmacokinetic profiles were similar between men and women. The absolute bioavailability of Neumega was >80%. In a study in which multiple subcutaneous doses of both 25 and 50 μg/kg were administered to cancer patients receiving chemotherapy, Neumega did not accumulate and clearance of Neumega was not impaired following multiple doses.

In a dose escalation Phase 1 study, Neumega was also administered to 43 pediatric (ages 8 months to 18 years) and 1 adult patient receiving ICE (ifosfamide, carboplatin, etoposide) chemotherapy. Administered doses ranged from 25 to