PDR®
58
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PHYSICIANS' DESK REFERENCE®

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Faslodex—Cont.

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Becton Dickinson guarantees the contents of their unopened or undamaged packages to be sterile, nontoxic and nonpyrogenic.

Figure 1

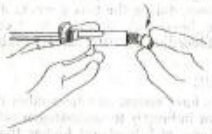
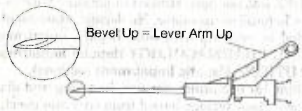


Figure 2

Figure 3



HOW SUPPLIED

One 5 mL clear neutral glass (Type 1) barrel containing 250 mg/5 mL (50 mg/mL) FASLODEX Injection for intramuscular injection and fitted with a tamper evident closure. The syringe is presented in a tray with polystyrene plunger rod and a safety needle (SafetyGlide™) for connection to the barrel.
NDC 0310-0720-50 One 5 mL Prefilled Syringe
Two 5 mL clear neutral glass (Type 1) barrels, each containing 125 mg/2.5 mL (50 mg/mL) of FASLODEX Injection for intramuscular injection and fitted with a tamper-evident closure. The syringes are presented in a tray with polystyrene plunger rod and safety needles (SafetyGlide™) for connection to the barrels.
NDC 0310-0720-25 Two 5 mL Prefilled Syringes each containing 125 mg/2.5 mL

Storage

REFRIGERATE, 2°–8°C (36°–46°F). TO PROTECT FROM LIGHT, STORE IN THE ORIGINAL CARTON UNTIL TIME OF USE.
SafetyGlide™ is a trademark of Becton Dickinson and Company

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Shown in Product Identification Guide, page 306

IRESSA®

[ĕr' ə́s-sə]
(gefitinib tablets)
250 mg
FOR ONCOLOGY USE ONLY

DESCRIPTION

IRESSA® (gefitinib tablets) contain 250 mg of gefitinib and are available as brown film-coated tablets for daily oral administration.
Gefitinib is an anilinoquinazoline with the chemical name 4-Quinazolinamine, *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-4-morpholin) propoxy] and the following structural formula:

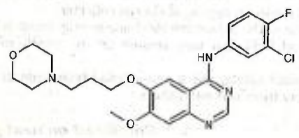


Table 1: Demographic and Disease Characteristics

Characteristic	IRESSA Dose 250 mg/day N = 66 (%)	IRESSA Dose 500 mg/day N = (76%)
Age Group		
18–64 years	43 (65)	43 (57)
64–74 years	19 (29)	30 (39)
75 years and above	4 (6)	3 (4)
Sex		
Male	38 (58)	41 (54)
Female	28 (42)	35 (46)
Race		
White	61 (92)	68 (89)
Black	1 (2)	2 (3)
Asian/Oriental	1 (2)	2 (3)
Hispanic	0 (0)	3 (4)
Other	3 (5)	1 (1)
Smoking History		
Yes (Previous or current smoker)	45 (68)	62 (82)
No (Never smoked)	21 (32)	14 (18)
Baseline WHO Performance Status		
0	14 (21)	9 (12)
1	36 (55)	53 (70)
2	15 (23)	14 (18)
Not recorded	1 (2)	0 (0)
Tumor Histology		
Squamous	9 (14)	11 (14)
Adenocarcinoma	47 (71)	50 (66)
Undifferentiated	6 (9)	4 (5)
Large Cell	1 (2)	2 (3)
Squamous & Adenocarcinoma	3 (5)	7 (9)
Not Recorded	0 (0)	2 (3)
Current Disease Status		
Locally advanced	11 (17)	5 (7)
Metastatic	55 (83)	71 (93)

It has the molecular formula $C_{22}H_{24}ClFN_4O_3$, a relative molecular mass of 446.9 and is a white-colored powder. Gefitinib is a free base. The molecule has pK_as of 5.4 and 7.2 and therefore ionizes progressively in solution as the pH falls. Gefitinib can be defined as sparingly soluble at pH 1, but is practically insoluble above pH 7, with the solubility dropping sharply between pH 4 and pH 6. In non-aqueous solvents, gefitinib is freely soluble in glacial acetic acid and dimethylsulphoxide, soluble in pyridine, sparingly soluble in tetrahydrofuran, and slightly soluble in methanol, ethanol (99.5%), ethyl acetate, propan-2-ol and acetonitrile.
The inactive ingredients of IRESSA tablets are: **Tablet core:** Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate and magnesium stearate. **Coating:** Hydroxypropyl methylcellulose, polyethylene glycol 300, titanium dioxide, red ferric oxide and yellow ferric oxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of the clinical antitumor action of gefitinib is not fully characterized. Gefitinib inhibits the intracellular phosphorylation of numerous tyrosine kinases associated with transmembrane cell surface receptors, including the tyrosine kinases associated with the epidermal growth factor receptor (EGFR-TK). EGFR is expressed on the cell surface of many normal cells and cancer cells. No clinical studies have been performed that demonstrate a correlation between EGFR receptor expression and response to gefitinib.

Pharmacokinetics

Gefitinib is absorbed slowly after oral administration with mean bioavailability of 60%. Elimination is by metabolism (primarily CYP3A4) and excretion in feces. The elimination half-life is about 48 hours. Daily oral administration of gefitinib to cancer patients resulted in a 2-fold accumulation compared to single dose administration. Steady state plasma concentrations are achieved within 10 days.

Absorption and Distribution:

Gefitinib is slowly absorbed, with peak plasma levels occurring 3-7 hours after dosing and mean oral bioavailability of 60%. Bioavailability is not significantly altered by food. Gefitinib is extensively distributed throughout the body with a mean steady state volume of distribution of 1400 L following intravenous administration. *In vitro* binding of gefitinib to human plasma proteins (serum albumin and α1-acid glycoprotein) is 90% and is independent of drug concentrations.

Metabolism and Elimination:

Gefitinib undergoes extensive hepatic metabolism in humans, predominantly by CYP3A4. Three sites of biotransformation have been identified: metabolism of the N-propoxymorpholino-group, demethylation of the methoxy-substituent on the quinazoline, and oxidative defluorination of the halogenated phenyl group.
Five metabolites were identified in human plasma. Only O-desmethyl gefitinib has exposure comparable to gefitinib. Although this metabolite has similar EGFR-TK activity to gefitinib in the isolated enzyme assay, it had only 1/14 of the potency of gefitinib in one of the cell-based assays.
Gefitinib is cleared primarily by the liver, with total plasma clearance and elimination half-life values of 595 mL/min and 48 hours, respectively, after intravenous administration. Excretion is predominantly via the feces (86%), with renal elimination of drug and metabolites accounting for less than 4% of the administered dose.

Special Populations:

In population based data analyses, no relationships were identified between predicted steady state trough concentration and patient age, body weight, gender, ethnicity or creatinine clearance.

Pediatric:

There are no pharmacokinetic data in pediatric patients.

Hepatic Impairment:

The influence of hepatic metastases with elevation of serum aspartate aminotransferase (AST/SGOT), alkaline phosphatase, and bilirubin has been evaluated in patients with normal (14 patients), moderately elevated (13 patients) and severely elevated (4 patients) levels of one or more of these biochemical parameters. Patients with moderately and severely elevated biochemical liver abnormalities had gefitinib pharmacokinetics similar to individuals without liver abnormalities (see **PRECAUTIONS** section).

Renal Impairment:

No clinical studies were conducted with IRESSA in patients with severely compromised renal function (see **PRECAUTIONS** section). Gefitinib and its metabolites are not significantly excreted via the kidney (<4%).

Drug-Drug Interactions:

In human liver microsome studies, gefitinib had no inhibitory effect on CYP1A2, CYP2C9, and CYP3A4 activities at concentrations ranging from 2–5000 ng/mL. At the highest concentration studied (5000 ng/mL), gefitinib inhibited CYP2C19 by 24% and CYP2D6 by 43%. Exposure to metoprolol, a substrate of CYP2D6, was increased by 30% when it was given in combination with gefitinib (500 mg daily for 28 days) in patients with solid tumors.
Rifampicin, an inducer of CYP3A4, reduced mean AUC of gefitinib by 85% in healthy male volunteers (see **PRECAUTIONS—Drug Interactions** and **DOSAGE AND ADMINISTRATION—Dosage Adjustment** sections).
Concomitant administration of itraconazole (200 mg QD for 12 days), an inhibitor of CYP3A4, with gefitinib (250 mg single dose) to healthy male volunteers, increased mean gefitinib AUC by 88% (see **PRECAUTIONS—Drug Interactions** section).
Co-administration of high doses of ranitidine with sodium bicarbonate (to maintain the gastric pH above pH 5.0) reduced mean gefitinib AUC by 44% (See **PRECAUTIONS—Drug Interactions** section).
International Normalized Ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin while on IRESSA therapy. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR (see **PRECAUTIONS—Drug Interactions** and **ADVERSE REACTIONS** sections).

Clinical Studies

Non-Small Cell Lung Cancer (NSCLC)—A multicenter clinical trial in the United States evaluated the tumor response rate of IRESSA 250 and 500 mg/day in patients with advanced non-small cell lung cancer whose disease had progressed after at least two prior chemotherapy regimens including a platinum drug and docetaxel. IRESSA was taken once daily at approximately the same time each day.
Two hundred and sixteen patients received IRESSA, 102 (47%) and 114 (53%) receiving 250 mg and 500 mg daily doses, respectively. Study patient demographics and disease characteristics are summarized in Table 1. Forty-one percent of the patients had received two prior treatment regimens, 33% three prior treatment regimens, and 25% four or more prior treatment regimens. Effectiveness of IRESSA as

third line therapy was determined in the 142 evaluable patients with documented disease progression on platinum and docetaxel therapies or who had had unacceptable toxicity on these agents.

[See table 1 at top of previous page]

Table 2 shows tumor response rates and response duration. The overall response rate for the 250 and 500 mg doses combined was 10.6% (95% CI: 6%, 16.8%). Response rates appeared to be highly variable in subgroups of the treated population: 5.1% (4/79) in males, 17.5% (11/63) in females, 4.6% (5/108) in previous or current smokers, 29.4% (10/34) in nonsmokers, 12.4% (12/97) with adenocarcinoma histology, and 6.7% (3/45) with other NSCLC histologies. Similar differences were seen in a multinational study in patients who had received 1 or 2 prior chemotherapy regimens, at least 1 of which was platinum-based. In responders, the median time from diagnosis to study randomization was 16.7 months (range 8 to 34 months).

[See table 2 above]

Non-Small Cell Lung Cancer (NSCLC); Studies of First-line Treatment in Combination with Chemotherapy—Two large trials were conducted in chemotherapy-naïve patients with stage III and IV non-small cell lung cancer. Two thousand one hundred thirty patients were randomized to receive IRESSA 250 mg daily, IRESSA 500 mg daily, or placebo in combination with platinum-based chemotherapy regimens. The chemotherapies given in these first-line trials were gemcitabine and cis-platinum (N=1093) or carboplatin and paclitaxel (N=1037). The addition of IRESSA did not demonstrate any increase, or trend toward such an increase, in tumor response rates, time to progression, or overall survival.

INDICATIONS AND USAGE

IRESSA is indicated as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies.

The effectiveness of IRESSA is based on objective response rates (see **CLINICAL PHARMACOLOGY—Clinical Studies** section). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Results from two large, controlled, randomized trials in first-line treatment of non-small cell lung cancer showed no benefit from adding IRESSA to doublet, platinum-based chemotherapy. Therefore, IRESSA is not indicated for use in this setting.

CONTRAINDICATIONS

IRESSA is contraindicated in patients with severe hypersensitivity to gefitinib or to any other component of IRESSA.

WARNINGS

Pulmonary Toxicity

Cases of interstitial lung disease (ILD) have been observed in patients receiving IRESSA at an overall incidence of about 1%. Approximately 1/3 of the cases have been fatal. The reported incidence of ILD was about 2% in the Japanese post-marketing experience, about 0.3% in approximately 23,000 patients treated with IRESSA in a US expanded access program and about 1% in the studies of first-line use in NSCLC (but with similar rates in both treatment and placebo groups). Reports have described the adverse event as interstitial pneumonia, pneumonitis and alveolitis. Patients often present with the acute onset of dyspnea, sometimes associated with cough or low-grade fever, often becoming severe within a short time and requiring hospitalization. ILD has occurred in patients who have received prior radiation therapy (31% of reported cases), prior chemotherapy (57% of reported patients), and no previous therapy (12% of reported cases). Patients with concurrent idiopathic pulmonary fibrosis whose condition worsens while receiving IRESSA have been observed to have an increased mortality compared to those without concurrent idiopathic pulmonary fibrosis.

In the event of acute onset or worsening of pulmonary symptoms (dyspnea, cough, fever), IRESSA therapy should be interrupted and a prompt investigation of these symptoms should occur. If interstitial lung disease is confirmed, IRESSA should be discontinued and the patient treated appropriately (see **PRECAUTIONS—Information for Patients**, **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION—Dosage Adjustment** sections).

Pregnancy Category D

IRESSA may cause fetal harm when administered to a pregnant woman. A single dose study in rats showed that gefitinib crosses the placenta after an oral dose of 5 mg/kg (30 mg/m^2, about 1/5 the recommended human dose on a mg/m^2 basis). When pregnant rats were treated with 5 mg/kg from the beginning of organogenesis to the end of weaning gave birth, there was a reduction in the number of offspring born alive. This effect was more severe at 20 mg/kg and was accompanied by high neonatal mortality soon after parturition. In this study a dose of 1 mg/kg caused no adverse effects.

In rabbits, a dose of 20 mg/kg/day (240 mg/m^2, about twice the recommended dose in humans on a mg/m^2 basis) caused reduced fetal weight.

There are no adequate and well-controlled studies in pregnant women using IRESSA. If IRESSA is used during pregnancy or if the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

Table 2: Efficacy Results

	Evaluable Patients		
	250 mg (N=66)	500 mg (N=76)	Combined (N=142)
Objective Tumor Response Rate (%)	13.6	7.9	10.6
95% CI (%)	6.4-24.3	3.0-16.4	6.0-16.8
Median Duration of Objective Response (months)	8.9	4.5	7.0
Range (months)	4.6-18.6+	4.4-7.6	4.4-18.6+

+=data are ongoing

PRECAUTIONS

Hepatotoxicity

Asymptomatic increases in liver transaminases have been observed in IRESSA treated patients; therefore, periodic liver function (transaminases, bilirubin, and alkaline phosphatase) testing should be considered. Discontinuation of IRESSA should be considered if changes are severe.

Patients with Hepatic Impairment

In vitro and *in vivo* evidence suggest that gefitinib is cleared primarily by the liver. Therefore, gefitinib exposure may be increased in patients with hepatic dysfunction. In patients with liver metastases and moderately to severely elevated biochemical liver abnormalities, however, gefitinib pharmacokinetics were similar to the pharmacokinetics of individuals without liver abnormalities (see **CLINICAL PHARMACOLOGY—Pharmacokinetics—Special Populations** section). The influence of non-cancer related hepatic impairment on the pharmacokinetics of gefitinib has not been evaluated.

Information for Patients

Patients should be advised to seek medical advice promptly if they develop 1) severe or persistent diarrhea, nausea, anorexia, or vomiting, as these have sometimes been associated with dehydration; 2) an onset or worsening of pulmonary symptoms, ie, shortness of breath or cough; 3) an eye irritation; or, 4) any other new symptom (see **WARNINGS—Pulmonary Toxicity**, **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION—Dosage Adjustment** sections).

Women of childbearing potential must be advised to avoid becoming pregnant (see **WARNINGS—Pregnancy Category D**).

Drug Interactions

Substances that are inducers of CYP3A4 activity increase the metabolism of gefitinib and decrease its plasma concentrations. In patients receiving a potent CYP3A4 inducer such as rifampicin or phenytoin, a dose increase to 500 mg daily should be considered in the absence of severe adverse drug reaction, and clinical response and adverse events should be carefully monitored (see **CLINICAL PHARMACOLOGY—Pharmacokinetics—Drug-Drug Interactions** and **DOSAGE AND ADMINISTRATION—Dosage Adjustment** sections).

International Normalized Ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin while on IRESSA therapy. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR (see **CLINICAL PHARMACOLOGY—Pharmacokinetics—Drug-Drug Interactions** and **ADVERSE REACTIONS** sections).

Substances that are potent inhibitors of CYP3A4 activity (eg, ketoconazole and itraconazole) decrease gefitinib metabolism and increase gefitinib plasma concentrations. This increase may be clinically relevant as adverse experiences are related to dose and exposure; therefore, caution should be used when administering CYP3A4 inhibitors with IRESSA (see **CLINICAL PHARMACOLOGY—Pharmacokinetics—Drug-Drug Interactions** and **ADVERSE REACTIONS** sections).

Drugs that cause significant sustained elevation in gastric pH (histamine H_2-receptor antagonists such as ranitidine or cimetidine) may reduce plasma concentrations of IRESSA and therefore potentially may reduce efficacy (see **CLINICAL PHARMACOLOGY—Drug-Drug Interactions** section).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Gefitinib has been tested for genotoxicity in a series of *in vitro* (bacterial mutation, mouse lymphoma, and human lymphocyte) assays and an *in vivo* rat micronucleus test. Under the conditions of these assays, gefitinib did not cause genetic damage.

Carcinogenicity studies have not been conducted with gefitinib.

Pregnancy

Pregnancy Category D (see **WARNINGS** and **PRECAUTIONS—Information for Patients** sections).

Nursing Mothers

It is not known whether IRESSA is excreted in human milk. Following oral administration of carbon-14 labeled gefitinib to rats 14 days postpartum, concentrations of radioactivity in milk were higher than in blood. Levels of gefitinib and its metabolites were 11-to-19-fold higher in milk than in blood, after oral exposure of lactating rats to a dose of 5 mg/kg. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should be advised against breastfeeding while receiving IRESSA therapy.

Pediatric Use

Safety and effectiveness of IRESSA in pediatric patients have not been studied.

Geriatric Use

Of the total number of patients participating in trials of second- and third-line IRESSA treatment of NSCLC, 65% were aged 64 years or less, 30.5 % were aged 65 to 74 years, and 5% of patients were aged 75 years or older. No differences in safety or efficacy were observed between younger and older patients.

Patients with Severe Renal Impairment

The effect of severe renal impairment on the pharmacokinetics of gefitinib is not known. Patients with severe renal impairment should be treated with caution when given IRESSA.

ADVERSE REACTIONS

The safety database includes 941 patients from clinical trials and approximately 23,000 patients in the Expanded Access Program.

Table 3 includes drug-related adverse events with an incidence of ≥5% for the 216 patients who received either 250 mg or 500 mg of IRESSA monotherapy for treatment of NSCLC. The most common adverse events reported at the recommended 250 mg daily dose were diarrhea, rash, acne, dry skin, nausea, and vomiting (see **PRECAUTIONS—Information for Patients** and **DOSAGE AND ADMINISTRATION—Dosage Adjustment** sections). The 500 mg dose showed a higher rate for most of these adverse events. Table 4 provides drug-related adverse events with an incidence of ≥5% by CTC grade for the patients who received the 250 mg/day dose of IRESSA monotherapy for treatment of NSCLC. Only 2% of patients stopped therapy due to an adverse drug reaction (ADR). The onset of these ADRs occurred within the first month of therapy.

Table 3: Drug-Related Adverse Events with an Incidence of ≥5% in either 250 mg or 500 mg Dose Group

	Number (%) of Patients	
Drug-related adverse event[a]	250 mg/day (N=102) %	500 mg/day (N=114) %
Diarrhea	49 (48)	76 (67)
Rash	44 (43)	61 (54)
Acne	25 (25)	37 (33)
Dry skin	13 (13)	30 (26)
Nausea	13 (13)	20 (18)
Vomiting	12 (12)	10 (9)
Pruritus	8 (8)	10 (9)
Anorexia	7 (7)	11 (10)
Asthenia	6 (6)	5 (4)
Weight loss	3 (3)	6 (5)

[a]A patient may have had more than 1 drug-related adverse event.

Table 4: Drug Related Adverse Events ≥5% at 250 mg dose by Worst CTC Grade (n=102)

	% of Patients				
Adverse event	All Grades	CTC Grade 1	CTC Grade 2	CTC Grade 3	CTC Grade 4
Diarrhea	48	41	6	1	0
Rash	43	39	4	0	0
Acne	25	19	6	0	0
Dry Skin	13	12	1	0	0
Nausea	13	7	5	1	0
Vomiting	12	9	2	1	0
Pruritus	8	7	1	0	0
Anorexia	7	3	4	0	0
Asthenia	6	2	2	1	1

Other adverse events reported at an incidence of <5% in patients who received either 250 mg or 500 mg as monotherapy for treatment of NSCLC (along with their frequency at the 250 mg recommended dose) include the following: peripheral edema (2%), amblyopia (2%), dyspnea (2%), conjunctivitis (1%), vesiculobullous rash (1%), and mouth ulceration (1%).

Interstitial Lung Disease

Cases of interstitial lung disease (ILD) have been observed in patients receiving IRESSA at an overall incidence of about 1%. Approximately 1/3 of the cases have been fatal. The reported incidence of ILD was about 2% in the Japanese post-marketing experience, about 0.3% in approximately 23,000 patients treated with IRESSA in a US expanded access program and about 1% in the studies of first-line use in NSCLC (but with similar rates in both

Continued on next page

Iressa—Cont.

treatment and placebo groups). Reports have described the adverse event as interstitial pneumonia, pneumonitis and alveolitis. Patients often present with the acute onset of dyspnea, sometimes associated with cough or low-grade fever, often becoming severe within a short time and requiring hospitalization. ILD has occurred in patients who have received prior radiation therapy (31% of reported cases), prior chemotherapy (57% of reported patients), and no previous therapy (12% of reported cases). Patients with concurrent idiopathic pulmonary fibrosis whose condition worsens while receiving IRESSA have been observed to have an increased mortality compared to those without concurrent idiopathic pulmonary fibrosis.

In the event of acute onset or worsening of pulmonary symptoms (dyspnea, cough, fever), IRESSA therapy should be interrupted and a prompt investigation of these symptoms should occur. If interstitial lung disease is confirmed, IRESSA should be discontinued and the patient treated appropriately (see **WARNINGS—Pulmonary Toxicity, PRECAUTIONS—Information for Patients** and **DOSAGE AND ADMINISTRATION—Dosage Adjustment** sections).

In patients receiving IRESSA therapy, there were reports of eye pain and corneal erosion/ulcer, sometimes in association with aberrant eyelash growth (see **PRECAUTIONS—Information for Patients** section). There were also rare reports of pancreatitis and very rare reports of corneal membrane sloughing, ocular ischemia/hemorrhage, toxic epidermal necrolysis, erythema multiforme, and allergic reactions, including angioedema and urticaria.

International Normalized Ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin while on IRESSA therapy. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR (see **CLINICAL PHARMACOLOGY—Drug-Drug Interactions** and **PRECAUTIONS—Drug Interactions** sections).

Data from non-clinical (*in vitro and in vivo*) studies indicate that gefitinib has the potential to inhibit the cardiac action potential repolarization process (eg, QT interval). The clinical relevance of these findings is unknown.

OVERDOSAGE

The acute toxicity of gefitinib up to 500 mg in clinical studies has been low. In non-clinical studies, a single dose of 12,000 mg/m^2 (about 80 times the recommended clinical dose on a mg/m^2 basis) was lethal to rats. Half this dose caused no mortality in mice.

There is no specific treatment for an IRESSA overdose and possible symptoms of overdose are not established. However, in Phase 1 clinical trials, a limited number of patients were treated with daily doses of up to 1000 mg. An increase in frequency and severity of some adverse reactions was observed, mainly diarrhea and skin rash. Adverse reactions associated with overdose should be treated symptomatically; in particular, severe diarrhea should be managed appropriately.

DOSAGE AND ADMINISTRATION

The recommended daily dose of IRESSA is one 250 mg tablet with or without food. Higher doses do not give a better response and cause increased toxicity.

Dosage Adjustment

Patients with poorly tolerated diarrhea (sometimes associated with dehydration) or skin adverse drug reactions may be successfully managed by providing a brief (up to 14 days) therapy interruption followed by reinstatement of the 250 mg daily dose.

In the event of acute onset or worsening of pulmonary symptoms (dyspnea, cough, fever), IRESSA therapy should be interrupted and a prompt investigation of these symptoms should occur and appropriate treatment initiated. If interstitial lung disease is confirmed, IRESSA should be discontinued and the patient treated appropriately (see **WARNINGS—Pulmonary Toxicity, PRECAUTIONS—Information for Patients** and **ADVERSE REACTIONS** sections).

Patients who develop onset of new eye symptoms such as pain should be medically evaluated and managed appropriately, including IRESSA therapy interruption and removal of an aberrant eyelash if present. After symptoms and eye changes have resolved, the decision should be made concerning reinstatement of the 250 mg daily dose (see **PRECAUTIONS—Information for Patients** and **ADVERSE REACTIONS** sections).

In patients receiving a potent CYP3A4 inducer such as rifampicin or phenytoin, a dose increase to 500 mg daily should be considered in the absence of severe adverse drug reaction, and clinical response and adverse events should be carefully monitored (see **CLINICAL PHARMACOLOGY—Pharmacokinetics—Drug-Drug Interactions** and **PRECAUTIONS—Drug Interactions** sections).

No dosage adjustment is required on the basis of patient age, body weight, gender, ethnicity, or renal function; or in patients with moderate to severe hepatic impairment due to liver metastases (see **CLINICAL PHARMACOLOGY—Pharmacokinetics—Special Populations** section).

HOW SUPPLIED

IRESSA tablets are supplied as round, biconvex, brown film-coated tablets intagliated with "IRESSA 250" on one side and plain on the other side, each containing 250 mg of gefitinib.

Bottles of 30 Tablets (NDC 0310-0482-30)

Storage

Store at controlled room temperature 20-25°C (68-77°F) [see USP].

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
By: AstraZeneca UK Limited
Macclesfield, Cheshire, England
Made in the United Kingdom
Rev 05-03

Shown in Product Identification Guide, page 306

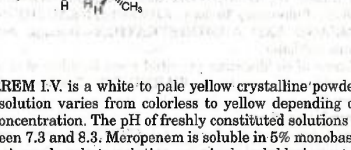
MERREM® I.V.

meropenem for injection

For Intravenous Use Only

DESCRIPTION

MERREM® I.V. (meropenem for injection) is a sterile, pyrogen-free, synthetic, broad-spectrum, carbapenem antibiotic for intravenous administration. It is (4R,5S,6S)-3-[[(3S,5S)-5-(Dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate. Its empirical formula is $C_{17}H_{25}N_3O_5S \cdot 3H_2O$ with a molecular weight of 437.52. Its structural formula is:



MERREM I.V. is a white to pale yellow crystalline powder. The solution varies from colorless to yellow depending on the concentration. The pH of freshly constituted solutions is between 7.3 and 8.3. Meropenem is soluble in 5% monobasic potassium phosphate solution, sparingly soluble in water, very slightly soluble in hydrated ethanol, and practically insoluble in acetone or ether.

When constituted as instructed (see **DOSAGE AND ADMINISTRATION; PREPARATION OF SOLUTION**), each 1 g MERREM I.V. vial will deliver 1 g of meropenem and 90.2 mg of sodium as sodium carbonate (3.92 mEq). Each 500 mg MERREM I.V. vial will deliver 500 mg meropenem and 45.1 mg of sodium as sodium carbonate (1.96 mEq).

MERREM I.V. in the ADD-Vantage† vial is intended for intravenous use only after dilution with the appropriate volume of diluent solution in the Abbott ADD-Vantage® diluent container. (See **DOSAGE AND ADMINISTRATION; PREPARATION OF SOLUTION.**) MERREM I.V. in the ADD-Vantage vial is available in two strengths. Each 1 g ADD-Vantage vial of MERREM I.V. will deliver 90.2 mg of sodium as sodium carbonate (3.92 mEq), and each 500 mg ADD-Vantage vial will deliver 45.1 mg of sodium as sodium carbonate (1.96 mEq).

CLINICAL PHARMACOLOGY

At the end of a 30-minute intravenous infusion of a single dose of MERREM I.V. in normal volunteers, mean peak plasma concentrations are approximately 23 µg/mL (range 14–26) for the 500 mg dose and 49 µg/mL (range 39–58) for the 1 g dose. A 5-minute intravenous bolus injection of MERREM I.V. in normal volunteers results in mean peak plasma concentrations of approximately 45 µg/mL (range 18–65) for the 500 mg dose and 112 µg/mL (range 83–140) for the 1 g dose.

Following intravenous doses of 500 mg, mean plasma concentrations of meropenem usually decline to approximately 1 µg/mL at 6 hours after administration.

In subjects with normal renal function, the elimination half-life of MERREM I.V. is approximately 1 hour. Approximately 70% of the intravenously administered dose is recovered as unchanged meropenem in the urine over 12 hours, after which little further urinary excretion is detectable. Urinary concentrations of meropenem in excess of 10 µg/mL are maintained for up to 5 hours after a 500 mg dose. No accumulation of meropenem in plasma or urine was observed with regimens using 500 mg administered every 8 hours or 1 g administered every 6 hours in volunteers with normal renal function.

Plasma protein binding of meropenem is approximately 2%. There is one metabolite which is microbiologically inactive. Meropenem penetrates well into most body fluids and tissues including cerebrospinal fluid, achieving concentrations matching or exceeding those required to inhibit most susceptible bacteria. After a single intravenous dose of MERREM I.V., the highest mean concentrations of meropenem were found in tissues and fluids at 1 hour (0.5 to 1.5 hours) after the start of infusion, except where indicated in the tissues and fluids listed in the table below.

[See table below]

The pharmacokinetics of MERREM I.V. in pediatric patients 2 years of age or older are essentially similar to those in adults. The elimination half-life for meropenem was approximately 1.5 hours in pediatric patients of age 3 months to 2 years. The pharmacokinetics are linear over the dose range from 10 to 40 mg/kg.

Pharmacokinetic studies with MERREM I.V. in patients with renal insufficiency have shown that the plasma clearance of meropenem correlates with creatinine clearance. Dosage adjustments are necessary in subjects with renal impairment. (See **DOSAGE AND ADMINISTRATION—Use in Adults with Renal Impairment.**) A pharmacokinetic study with MERREM I.V. in elderly patients with renal insufficiency has shown a reduction in plasma clearance of meropenem that correlates with age-associated reduction in creatinine clearance.

Meropenem I.V. is hemodialyzable. However, there is no information on the usefulness of hemodialysis to treat overdosage. (See **OVERDOSAGE.**)

A pharmacokinetic study with MERREM I.V. in patients with hepatic impairment has shown no effects of liver disease on the pharmacokinetics of meropenem.

Microbiology

The bactericidal activity of meropenem results from the inhibition of cell wall synthesis. Meropenem readily penetrates the cell wall of most gram-positive and gram-negative bacteria to reach penicillin-binding-protein (PBP) targets. Its strongest affinities are toward PBPs 2, 3 and 4 of *Escherichia coli* and *Pseudomonas aeruginosa;* and PBPs 1, 2 and 4 of *Staphylococcus aureus.* Bactericidal concentrations (defined as a 3 $\log_{10}$ reduction in cell counts within 12 to 24 hours) are typically 1–2 times the bacteriostatic concentrations of meropenem, with the exception of *Listeria monocytogenes,* against which lethal activity is not observed.

Meropenem has significant stability to hydrolysis by β-lactamases of most categories, both penicillinases and cephalosporinases produced by gram-positive and gram-negative

Meropenem Concentrations in Selected Tissues (Highest Concentrations Reported)

Tissue	I.V. Dose (g)	Number of Samples	Mean [µg/mL or µg/(g)]***	Range [µg/mL or µg/(g)]
Endometrium	0.5	7	4.2	1.7–10.2
Myometrium	0.5	15	3.8	0.4–8.1
Ovary	0.5	8	2.8	0.8–4.8
Cervix	0.5	2	7.0	5.4–8.5
Fallopian tube	0.5	9	1.7	0.3–3.4
Skin	0.5	22	3.3	0.5–12.6
Skin	1.0	10	5.3	1.3–16.7
Colon	1.0	2	2.6	2.5–2.7
Bile	1.0	7	14.6 (3 h)	4.0–25.7
Gall bladder	1.0	1	—	3.9
Interstitial fluid	1.0	5	26.3	20.9–37.4
Peritoneal fluid	1.0	9	30.2	7.4–54.6
Lung	1.0	2	4.8 (2 h)	1.4–8.2
Bronchial mucosa	1.0	7	4.5	1.3–11.1
Muscle	1.0	2	6.1 (2 h)	5.3–6.9
Fascia	1.0	9	8.8	1.5–20
Heart valves	1.0	7	9.7	6.4–12.1
Myocardium	1.0	10	15.5	5.2–25.5
CSF (inflamed)	20 mg/kg*	8	1.1 (2 h)	0.2–2.8
	40 mg/kg**	5	3.3 (3 h)	0.9–6.5
CSF (uninflamed)	1.0	4	0.2 (2 h)	0.1–0.3

* in pediatric patients of age 5 months to 8 years
** in pediatric patients of age 1 month to 15 years
***at 1 hour unless otherwise noted

Uroqid-Acid—Cont.

sidual urine accompanying neurogenic bladder. When used as recommended, **UROQID-Acid® No.2** is particularly suitable for long-term therapy because of its relative safety and because resistance to the nonspecific bactericidal action of formaldehyde does not develop. Pathogens resistant to other antibacterial agents may respond because of the nonspecific effect of formaldehyde formed in an acid urine.

Prophylactic Use Rationale: Urine is a good culture medium for many urinary pathogens. Inoculation by a few organisms (relapse or reinfection) may lead to bacteriuria in susceptible individuals. Thus, the rationale of management in recurring urinary tract infection (bacteriuria) is to change the urine from a growth-supporting to a growth-inhibiting medium. There is a growing body of evidence that long-term administration of methenamine can prevent recurrence of bacteriuria in patients with chronic pyelonephritis.

Therapeutic Use Rationale: Helps to sterilize the urine and, in some situations in which underlying pathologic conditions prevent sterilization by any means, can help to suppress bacteriuria. As part of the overall management of the urinary tract infection, a thorough diagnostic evaluation should accompany the use of this product.

CONTRAINDICATIONS

UROQID-Acid® No.2 is contraindicated in patients with renal insufficiency, severe hepatic disease, severe dehydration, hyperphosphatemia, and in patients who have exhibited hypersensitivity to any components of this product.

PRECAUTIONS

General

This product should not be used as the sole therapeutic agent in acute parenchymal infections causing systemic symptoms such as chills and fever.

UROQID-Acid® No.2 contains approximately 83 mg of sodium per tablet and should be used with caution in patients on a sodium-restricted diet.

Sodium phosphates should be used with caution in the following conditions: cardiac failure; peripheral or pulmonary edema; hypernatremia; hypertension; toxemia of pregnancy; hypoparathyroidism; and acute pancreatitis. High serum phosphate levels increase the incidence of extraskeletal calcification.

Large doses of methenamine (8 grams daily for 3 to 4 weeks) have caused bladder irritation, painful and frequent micturition, albuminuria and gross hematuria. Dysuria may occur, although usually at higher than recommended doses, and can be controlled by reducing the dosage. This product contains a urinary acidifier and can cause metabolic acidosis.

Care should be taken to maintain an acidic urinary pH (below 5.5), especially when treating infections due to urea-splitting organisms such as Proteus and strains of Pseudomonas.

Drugs and/or foods which produce an alkaline urine should be restricted. Frequent urine pH tests are essential. If acidification of the urine is contraindicated or unattainable, use of this product should be discontinued.

Information For Patients: To assure an acidic pH, patients should be instructed to restrict or avoid most fruits, milk and milk products, and antacids containing sodium carbonate or bicarbonate.

Laboratory Tests: As with all urinary tract infections, the efficacy of therapy should be monitored by repeated urine cultures. During long-term therapy, careful monitoring of renal function, serum phosphorus and sodium may be required at periodic intervals.

Drug Interactions: Formaldehyde and sulfamethizole form an insoluble precipitate in acid urine and increase the risk of crystalluria; therefore, these products should not be used concurrently. Thiazide diuretics, carbonic anhydrase inhibitors, antacids, or urinary alkalinizing agents should not be used concurrently since they may cause the urine to become alkaline and reduce the effectiveness of methenamine by inhibiting its conversion to formaldehyde. Concurrent use of antihypertensives, especially diazoxide, guanethidine, hydralazine, methyldopa, or rauwolfia alkaloids; or corticosteroids, especially mineralocorticoids or corticotropin, with sodium phosphates may result in hypernatremia. Concurrent use of salicylates may lead to increased serum salicylate levels since excretion of salicylates is reduced in acidified urine. Serum salicylate levels should be closely monitored to avoid toxicity.

Laboratory Test Interactions: Formaldehyde interferes with fluorometric procedures for determination of urinary catecholamines and vanilmandelic acid (VMA) causing erroneously high results. Formaldehyde also causes falsely decreased urine estriol levels by reacting with estriol when acid hydrolysis techniques are used; estriol determinations which use enzymatic hydrolysis are unaffected by formaldehyde. Formaldehyde causes falsely elevated 17-hydroxycorticosteroid levels when the Porter-Silber method is used and falsely decreased 5-hydroxyindoleacetic acid (5HIAA) levels by inhibiting color development when nitrosonaphthol methods are used.

Carcinogenesis, Mutagenesis, Impairment Of Fertility: Long-term animal studies to evaluate the carcinogenic, mutagenic, or impairment of fertility potential of this product have not been performed.

Pregnancy: Teratogenic Effects. Pregnancy Category C. Animal reproduction studies have not been conducted with **UROQID-Acid® No.2.** It is also not known whether this product can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Since methenamine is known to cross the placental barrier, this product should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Methenamine is excreted in breast milk. Caution should be exercised when this product is administered to a nursing woman.

ADVERSE REACTIONS

Gastrointestinal disturbances (nausea, stomach upset), generalized skin rash, dysuria, painful or difficult urination may occur occasionally with the use of methenamine preparations. Microscopic and rarely, gross hematuria have also been reported.

Gastrointestinal upset (diarrhea, nausea, stomach pain, and vomiting) may occur with the use of sodium phosphates. Also, bone or joint pain (possible phosphate induced osteomalacia) could occur. The following adverse effects may be observed (primarily from sodium): headaches; dizziness; mental confusion; seizures; weakness or heaviness of legs; unusual tiredness or weakness; muscle cramps; numbness, tingling, pain, or weakness of hands or feet; numbness or tingling around lips; fast or irregular heartbeat; shortness of breath or troubled breathing; swelling of feet or lower legs; unusual weight gain; low urine output, unusual thirst.

DOSAGE AND ADMINISTRATION

UROQID-Acid® No.2: *Adults:* Initially, 2 tablets 4 times daily with a full glass of water. For maintenance, 2 to 4 tablets daily, in divided doses with a full glass of water.

HOW SUPPLIED

UROQID-Acid® No.2 is a yellow, film-coated, capsule-shaped tablet with the name **BEACH** and the number **1114** imprinted on each tablet. Packaged in bottles of 100 tablets (NDC 0486-1114-01).

Shown in Product Identification Guide, page 309

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ADRIAMYCIN ℞

[a'dree-a-my-sin]
(DOXOrubicin HCl)
for Injection, USP

ADRIAMYCIN

(DOXOrubicin HCl)
Injection, USP
For Intravenous Use Only
℞ ONLY

WARNINGS

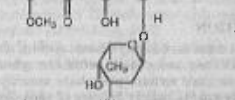
1. Severe local tissue necrosis will occur if there is extravasation during administration (see **DOSAGE AND ADMINISTRATION**). Doxorubicin must not be given by the intramuscular or subcutaneous route.
2. Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure may occur either during therapy or months to years after termination of therapy. The probability of developing impaired myocardial function based on a combined index of signs, symptoms and decline in left ventricular ejection fraction (LVEF) is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m^2 of doxorubicin, 3 to 5% at a dose of 400 mg/m^2, 5 to 8% at 450 mg/m^2 and 6 to 20% at 500 mg/m^2.* The risk of developing CHF increases rapidly with increasing total cumulative doses of doxorubicin in excess of 450 mg/m^2. *Risk factors (active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, concomitant use of other cardiotoxic drugs) may increase the risk of cardiac toxicity. Cardiac toxicity with doxorubicin may occur at lower cumulative doses whether or not cardiac risk factors are present.* Pediatric patients are at increased risk for developing delayed cardiotoxicity.
3. Secondary acute myelogenous leukemia (AML) has been reported in patients treated with anthracyclines, including doxorubicin (see **ADVERSE REACTIONS**). The occurrence of refractory secondary leukemia is more common when such drugs are given in combination with DNA-damaging anti-neoplastic agents, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated. The rate of developing treatment-related leukemia was estimated in an analysis of 1474 breast cancer patients who received adjuvant treatment with doxorubicin-containing regimens (i.e., FAC) in clinical trials. The estimated risk of developing treatment-related leukemia at 10 years was 2.1% for the 810 patients receiving radiotherapy plus chemotherapy and 0.5% for the 664 patients receiving chemotherapy alone. The overall risk was estimated at 1.5% at 10 years for the entire patient population. Pediatric patients are also at risk of developing secondary AML.
4. Dosage should be reduced in patients with impaired hepatic function.
5. Severe myelosuppression may occur.
6. Doxorubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

*Data on file at Pharmacia & Upjohn

DESCRIPTION

Doxorubicin is a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius* var. *caesius*. Doxorubicin consists of a naphthacenequinone nucleus linked through a glycosidic bond at ring atom 7 to an amino sugar, daunosamine.

Chemically, doxorubicin hydrochloride is (8*S*,10*S*)-10-[(3-Amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)-oxy]-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride. The structural formula is as follows:



$C_{27}H_{29}NO_{11} \cdot HCl$ M.W.=579.99

Doxorubicin binds to nucleic acids, presumably by specific intercalation of the planar anthracycline nucleus with the DNA double helix. The anthracycline ring is lipophilic, but the saturated end of the ring system contains abundant hydroxyl groups adjacent to the amino sugar, producing a hydrophilic center. The molecule is amphoteric, containing acidic functions in the ring phenolic groups and a basic function in the sugar amino group. It binds to cell membranes, as well as plasma proteins.

It is supplied in the hydrochloride form as a sterile red-orange lyophilized powder containing lactose and as a sterile parenteral, isotonic solution with sodium chloride for intravenous use only.

Adriamycin (DOXOrubicin HCl) for Injection, USP:
Each 10 mg lyophilized vial contains 10 mg of Doxorubicin Hydrochloride, USP and 50 mg of Lactose Monohydrate, NF.
Each 20 mg lyophilized vial contains 20 mg of Doxorubicin Hydrochloride, USP and 100 mg of Lactose Monohydrate, NF.
Each 50 mg lyophilized vial contains 50 mg of Doxorubicin Hydrochloride, USP and 250 mg of Lactose Monohydrate, NF.

Adriamycin (DOXOrubicin HCl) Injection, USP:
Each 2 mg/mL, 5 mL (10 mg) vial contains 10 mg Doxorubicin Hydrochloride, USP; Sodium Chloride 0.9% (to adjust tonicity) and Water for Injection q.s.; pH adjusted to 3 using Hydrochloric Acid.
Each 2 mg/mL, 10 mL (20 mg) vial contains 20 mg Doxorubicin Hydrochloride, USP; Sodium Chloride 0.9% (to adjust tonicity) and Water for Injection q.s.; pH adjusted to 3 using Hydrochloric Acid.
Each 2 mg/mL, 25 mL (50 mg) vial contains 50 mg Doxorubicin Hydrochloride, USP; Sodium Chloride 0.9% (to adjust tonicity) and Water for Injection q.s.; pH adjusted to 3 using Hydrochloric Acid.
Each 2 mg/mL, 100 mL (200 mg) multiple dose vial contains 200 mg Doxorubicin Hydrochloride, USP; Sodium Chloride 0.9% (to adjust tonicity) and Water for Injection q.s.; pH adjusted to 3 using Hydrochloric Acid.

CLINICAL PHARMACOLOGY

The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin cytocidal activity. Doxorubicin cellular membrane binding may effect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases and dehydrogenases generate highly reactive species including the hydroxyl free radical OH*. Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level. Cells treated with doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death.

Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both.

Animal studies have shown activity in a spectrum of experimental tumors, immunosuppression, carcinogenic properties in rodents, induction of a variety of toxic effects, including delayed and progressive cardiac toxicity, myelosuppression in all species and atrophy to testes in rats and dogs.

Pharmacokinetic studies, determined in patients with various types of tumors undergoing either single or multi-agent therapy have shown that doxorubicin follows a multiphasic disposition after intravenous injection. The initial distributive half-life of approximately 5 minutes suggests rapid tissue uptake of doxorubicin, while its slow elimination from tissues is reflected by a terminal half-life of 20 to 48 hours. Steady-state distribution volumes exceed 20 to 30 L/kg and are indicative of extensive drug uptake into tissues. Plasma clearance is in the range of 8 to 20 mL/min/kg and is predominately by metabolism and biliary excretion. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. Binding of doxorubicin and its major metabolite, doxorubicinol to plasma proteins is about 74 to 76% and is independent of plasma concentration of doxorubicin up to 2 µM. Enzymatic reduction at the 7 position and cleavage of the daunosamine sugar yields aglycones which are accompanied by free radical formation, the local production of which may contribute to the cardiotoxic activity of doxorubicin. Disposition of doxorubicinol (DOX-OL) in patients is formation rate limited. The terminal half-life of DOX-OL is similar to doxorubicin. The relative exposure of DOX-OL, compared to doxorubicin ranges between 0.4 to 0.6. In urine, <3% of the dose was recovered as DOX-OL over 7 days.

A published clinical study involving 6 men and 21 women with no prior anthracycline therapy reported a significantly higher median doxorubicin clearance in the men compared to the women (113 versus 45 L/hr). However, the terminal half-life of doxorubicin was longer in men compared to the women (54 versus 35 hrs).

In four patients, dose-independent pharmacokinetics have been shown for doxorubicin in the dose range of 30 to 70 mg/m^2. Systemic clearance of doxorubicin is significantly reduced in obese women with ideal body weight greater than 130%. There was a significant reduction in clearance without any change in volume of distribution in obese patients when compared with normal patients with less than 115% ideal body weight. The clearance of doxorubicin and doxorubicinol was also reduced in patients with impaired hepatic function. Doxorubicin was excreted in the milk of one lactating patient, with peak milk concentration at 24 hours after treatment being approximately 4.4 -fold greater than the corresponding plasma concentration. Doxorubicin was detectable in the milk up to 72 hours after therapy with 70 mg/m^2 of doxorubicin given as a 15 minute intravenous infusion and 100 mg/m^2 of cisplatin as a 26 hour intravenous infusion. The peak concentration of doxorubicinol in milk at 24 hours was 0.2 µM and AUC up to 24 hours was 16.5 µM.hr while the AUC for doxorubicin was 9.9 µM.hr.

Following administration of 10 to 75-mg/m^2 doses of doxorubicin to 60 children and adolescents ranging from 2 months to 20 years of age, doxorubicin clearance averaged 1443 +/- 114 mL/min/m^2. Further analysis demonstrated that clearance in 52 children greater than 2 years of age (1640 mL/min/m^2) was increased compared with adults. However, clearance in infants younger than 2 years of age (813 mL/min/m^2) was decreased compared with older children and approached the range of clearance values determined in adults.

Doxorubicin does not cross the blood brain barrier.

INDICATIONS AND USAGE

Adriamycin (DOXOrubicin HCl) Injection, USP and Adriamycin (DOXOrubicin HCl) for Injection, USP have been used successfully to produce regression in disseminated neoplastic conditions such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms' tumor, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, ovarian carcinoma, transitional cell bladder carcinoma, thyroid carcinoma, gastric carcinoma, Hodgkin's disease, malignant lymphoma and bronchogenic carcinoma in which the small cell histologic type is the most responsive compared to other cell types.

CONTRAINDICATIONS

Doxorubicin therapy should not be started in patients who have marked myelosuppression induced by previous treatment with other antitumor agents or by radiotherapy.

Doxorubicin treatment is contraindicated in patients who received previous treatment with complete cumulative doses of doxorubicin, daunorubicin, idarubicin, and/or other anthracyclines and anthracenes.

WARNINGS

Special attention must be given to the cardiotoxicity induced by doxorubicin. Irreversible myocardial toxicity, manifested in its most severe form by life-threatening or fatal congestive heart failure, may occur either during therapy or months to years after termination of therapy. The probability of developing impaired myocardial function, based on a combined index of signs, symptoms and decline in left ventricular ejection fraction (LVEF) is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m^2 of doxorubicin, 3 to 5% at a dose of 400 mg/m^2, 5 to 8% at a dose of 450 mg/m^2 and 6 to 20% at a dose of 500 mg/m^2 given in a schedule of a bolus injection once every 3 weeks (data on file at Pharmacia & Upjohn). In a retrospective review by Von Hoff et al, the probability of developing congestive heart failure was reported to be 5/168 (3%) at a cumulative dose of 430 mg/m^2 of doxorubicin, 8/110 (7%) at 575 mg/m^2 and 3/14 (21%) at 728 mg/m^2. The cumulative incidence of CHF was 2.2%. In a prospective study of doxorubicin in combination with cyclophosphamide, fluorouracil and/or vincristine in patients with breast cancer or small cell lung cancer, the cumulative incidence of congestive heart failure was 5 to 6%. The probability of CHF at various cumulative doses of doxorubicin was 1.5% at 300 mg/m^2, 4.9% at 400 mg/m^2, 7.7% at 450 mg/m^2 and 20.5% at 500 mg/m^2.

Cardiotoxicity may occur at lower doses in patients with prior mediastinal irradiation, concurrent cyclophosphamide therapy, exposure at an early age and advanced age. Data also suggest that pre-existing heart disease is a co-factor for increased risk of doxorubicin cardiotoxicity. In such cases, cardiac toxicity may occur at doses lower than the respective recommended cumulative dose of doxorubicin. Studies have suggested that concomitant administration of doxorubicin and calcium channel entry blockers may increase the risk of doxorubicin cardiotoxicity. The total dose of doxorubicin administered to the individual patient should also take into account previous or concomitant therapy with related compounds such as daunorubicin, idarubicin and mitoxantrone. Cardiomyopathy and/or congestive heart failure may be encountered several months or years after discontinuation of doxorubicin therapy.

The risk of congestive heart failure and other acute manifestations of doxorubicin cardiotoxicity in pediatric patients may be as much or lower than in adults. Pediatric patients appear to be at particular risk for developing delayed cardiac toxicity in that doxorubicin induced cardiomyopathy impairs myocardial growth as pediatric patients mature, subsequently leading to possible development of congestive heart failure during early adulthood. As many as 40% of pediatric patients may have subclinical cardiac dysfunction and 5 to 10% of pediatric patients may develop congestive heart failure on long term follow up. This late cardiac toxicity may be related to the dose of doxorubicin. The longer the length of follow-up the greater the increase in the detection rate.

Treatment of doxorubicin induced congestive heart failure includes the use of digitalis, diuretics, after load reducers such as angiotensin I converting enzyme (ACE) inhibitors, low salt diet, and bed rest. Such intervention may relieve symptoms and improve the functional status of the patient.

Monitoring Cardiac Function: In adult patients severe cardiac toxicity may occur precipitously without antecedent ECG changes. Cardiomyopathy induced by anthracyclines is usually associated with very characteristic histopathologic changes on an endomyocardial biopsy (EM biopsy), and a decrease of left ventricular ejection fraction (LVEF), as measured by multi-gated radionuclide angiography (MUGA scans) and/or echocardiogram (ECHO), from pretreatment baseline values. However, it has not been demonstrated that monitoring of the ejection fraction will predict when individual patients are approaching their maximally tolerated cumulative dose of doxorubicin. Cardiac function should be carefully monitored during treatment to minimize the risk of cardiac toxicity. A baseline cardiac evaluation with an ECG, LVEF, and/or an echocardiogram (ECHO) is recommended especially in patients with risk factors for increased cardiac toxicity (pre-existing heart disease, mediastinal irradiation, or concurrent cyclophosphamide therapy). Subsequent evaluations should be obtained at a cumulative dose of doxorubicin of at least 400 mg/m^2 and periodically thereafter during the course of therapy. Pediatric patients are at increased risk for developing delayed cardiotoxicity following doxorubicin administration and therefore a follow-up cardiac evaluation is recommended periodically to monitor for this delayed cardiotoxicity.

In adults, a 10% decline in LVEF to below the lower limit of normal or an absolute LVEF of 45%, or a 20% decline in LVEF at any level is indicative of deterioration in cardiac function. In pediatric patients, deterioration in cardiac function during or after the completion of therapy with doxorubicin is indicated by a drop in fractional shortening (FS) by an absolute value of ≥10 percentile units or below 29%, and a decline in LVEF of 10 percentile units or an LVEF below 55%. In general, if test results indicate deterioration in cardiac function associated with doxorubicin, the benefit of continued therapy should be carefully evaluated against the risk of producing irreversible cardiac damage.

Acute life-threatening arrhythmias have been reported to occur during or within a few hours after doxorubicin administration.

There is a high incidence of bone marrow depression, primarily of leukocytes, requiring careful hematologic monitoring. With the recommended dosage schedule, leukopenia is usually transient, reaching its nadir at 10 to 14 days after treatment with recovery usually occurring by the 21st day. White blood counts as low as 1000/mm^3 are to be expected during treatment with appropriate doses of doxorubicin. Red blood and platelet levels should also be monitored since they may also be depressed. Hematologic toxicity may require dose reduction or suspension or delay of doxorubicin therapy. Persistent severe myelosuppression may result in superinfection or hemorrhage.

Doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide-induced hemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported. Radiation-induced toxicity to the myocardium, mucosae, skin, and liver have been reported to be increased by the administration of doxorubicin. Pediatric patients receiving concomitant doxorubicin and actinomycin-D have manifested acute 'recall' pneumonitis at variable times after local radiation therapy.

Since metabolism and excretion of doxorubicin occurs predominantly by the hepatobiliary route, toxicity to recommended doses of doxorubicin can be enhanced by hepatic impairment; therefore, prior to the individual dosing, evaluation of hepatic function is recommended using conventional laboratory tests such as SGOT, SGPT, alkaline phosphatase, and bilirubin (see **DOSAGE AND ADMINISTRATION**).

Necrotizing colitis manifested by typhlitis (cecal inflammation), bloody stools and severe and sometimes fatal infections, have been associated with a combination of doxorubicin given by IV push daily for 3 days and cytarabine given by continuous infusion daily for 7 or more days.

On intravenous administration of doxorubicin, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle (see **DOSAGE AND ADMINISTRATION**). If any signs or symptoms of extravasation have occurred the injection or infusion should be immediately terminated and restarted in another vein.

Pregnancy Category D: Safe use of doxorubicin in pregnancy has not been established. Doxorubicin is embryotoxic and teratogenic in rats and embryotoxic and abortifacient in rabbits. There are no adequate and well-controlled studies in pregnant women. If doxorubicin is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be apprised of the potential hazard to the fetus. Women of childbearing age should be advised to avoid becoming pregnant.

PRECAUTIONS

General: Doxorubicin is not an anti-microbial agent.

Information for Patients: Adriamycin (DOXOrubicin HCl) Injection, USP and Adriamycin (DOXOrubicin HCl) for Injection, USP impart a red coloration to the urine for 1 to 2 days after administration, and patients should be advised to expect this during active therapy.

Drug Interactions: Literature contains the following drug interactions with doxorubicin in humans: cyclosporine (Sandimmune) may induce coma and/or seizures, phenobarbital increases the elimination of doxorubicin, phenytoin levels may be decreased by doxorubicin, streptozocin (Zanosar) may inhibit the hepatic metabolism, and administration of live vaccines to immunosuppressed patients, including those undergoing cytotoxic chemotherapy, may be hazardous.

Paclitaxel: Two published studies report that initial administration of paclitaxel infused over 24 hours followed by doxorubicin administered over 48 hours resulted in a significant decrease in doxorubicin clearance with more profound neutropenic and stomatitis episodes than the reverse sequence of administration.

Progesterone: In a published study, progesterone was given intravenously to patients with advanced malignancies (ECOG PS < 2) at high doses (up to 10 g over 24 hours) concomitantly with a fixed doxorubicin dose (60 mg/m^2) via bolus. Enhanced doxorubicin-induced neutropenia and thrombocytopenia were observed.

Verapamil: A study of the effects of verapamil on the acute toxicity of doxorubicin in mice revealed higher intial peak concentrations of doxorubicin in the heart with a higher incidence and severity of degenerative changes in cardiac tissue resulting in a shorter survival.

Cyclosporine: The addition of cyclosporine to doxorubicin may result in increases in AUC for both doxorubicin and doxorubicinol possibly due to a decrease in clearance of parent drug and a decrease in metabolism of doxorubicinol. Literature reports suggest that adding cyclosporine to doxorubicin results in more profound and prolonged hematologic toxicity than doxorubicin alone. Coma and/or seizures have also been described.

Literature reports have also described the following drug interactions: phenobarbital increases the elimination of doxorubicin, phenytoin levels may be decreased by doxorubicin, streptozocin (Zanosar) may inhibit hepatic metabolism of doxorubicin, and administration of live vaccines to immunosuppressed patients including those undergoing cytotoxic chemotherapy may be hazardous.

Laboratory Tests: Initial treatment with doxorubicin requires observation of the patient and periodic monitoring of complete blood counts, hepatic function tests, and radionuclide left ventricular ejection fraction (see **WARNINGS**).

Like other cytotoxic drugs, doxorubicin may induce "tumor lysis syndrome" and hyperuricemia in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Formal long-term carcinogenicity studies have not been conducted with doxorubicin. Doxorubicin and related compounds have been shown to have mutagenic and carcinogenic properties when tested in experimental models (including bacterial systems, mammalian cells in culture, and female Sprague-Dawley rats).

The possible adverse effect on fertility in males and females in humans or experimental animals have not been adequately evaluated. Testicular atrophy was observed in rats and dogs.

Continued on next page

Adriamycin—Cont.

Treatment-related acute myelogenous leukemia has been reported in patients treated with doxorubicin-containing adjuvant chemotherapy regimens (see **ADVERSE REACTIONS, Hematologic**). The exact role of doxorubicin has not been elucidated. Pediatric patients treated with doxorubicin or other topoisomerase II inhibitors are at risk for developing acute myelogenous leukemia and other neoplasms. The extent of increased risk associated with doxorubicin has not been precisely quantified.

Pregnancy Category D: (See **WARNINGS.**)

Nursing Mothers: Because of the potential for serious adverse reactions in nursing infants from doxorubicin, mothers should be advised to discontinue nursing during doxorubicin therapy.

Pediatric Use: Pediatric patients are at increased risk for developing delayed cardiotoxicity. Follow-up cardiac evaluations are recommended periodically to monitor for this delayed cardiotoxicity (see **WARNINGS**).

Doxorubicin, as a component of intensive chemotherapy regimens administered to pediatric patients, may contribute to prepubertal growth failure. It may also contribute to gonadal impairment, which is usually temporary.

ADVERSE REACTIONS

Dose-limiting toxicities of therapy are myelosuppression and cardiotoxicity (see **WARNINGS**). Other reactions reported are:

Cardiotoxicity: (See **WARNINGS.**)

Cutaneous: Reversible complete alopecia occurs in most cases. Hyperpigmentation of nailbeds and dermal creases, primarily in children, and onycholysis have been reported in a few cases. Recall of skin reaction due to prior radiotherapy has occurred with doxorubicin administration.

Gastrointestinal: Acute nausea and vomiting occurs frequently and may be severe. This may be alleviated by antiemetic therapy. Mucositis (stomatitis and esophagitis) may occur 5 to 10 days after administration. The effect may be severe leading to ulceration and represents a site of origin for severe infections. The dosage regimen consisting of administration of doxorubicin on 3 successive days results in the greater incidence and severity of mucositis. Ulceration and necrosis of the colon, especially the cecum, may occur leading to bleeding or severe infections which can be fatal. This reaction has been reported in patients with acute nonlymphocytic leukemia treated with a 3-day course of doxorubicin combined with cytarabine. Anorexia and diarrhea have been occasionally reported.

Vascular: Phlebosclerosis has been reported especially when small veins are used or a single vein is used for repeated administration. Facial flushing may occur if the injection is given too rapidly.

Local: Severe cellulitis, vesication and tissue necrosis will occur if extravasation of doxorubicin occurs during administration. Erythematous streaking along the vein proximal to the site of the injection has been reported (see **DOSAGE AND ADMINISTRATION**).

Hematologic: The occurrence of secondary acute myeloid leukemia with or without a preleukemic phase has been reported in patients concurrently treated with doxorubicin in association with DNA-damaging antineoplastic agents. Such cases could have a short (1-3 years) latency period. An analysis of 1474 breast cancer patients who received adjuvant doxorubicin treatment in clinical trials, showed a 10-year estimated risk of developing treatment-related leukemia at 2.5% (95% confidence interval [CI], 1.0% to 5.1%) for the 810 patients receiving radiotherapy plus chemotherapy and 0.5% (95% CI, 0.1% to 2.4%) for the 664 patients receiving chemotherapy alone. The overall risk was 1.5% (95% CI, 0.7%-2.9%) at 10 years for the entire patient population. Pediatric patients are also at risk of developing secondary acute myeloid leukemia.

Hypersensitivity: Fever, chills, and urticaria have been reported occasionally. Anaphylaxis may occur. A case of apparent cross-sensitivity to lincomycin has been reported.

Other: Conjunctivitis and lacrimation occur rarely.

OVERDOSAGE

Acute overdosage with doxorubicin enhances the toxic effects of mucositis, leukopenia, and thrombocytopenia. Treatment of acute overdosage consists of treatment of the severely myelosuppressed patient with hospitalization, antimicrobials, platelet transfusion and symptomatic treatment of mucositis. Use of hemopoietic growth factor (G-CSF, GM-CSF) may be considered.

The 200 mg Adriamycin (DOXOrubicin HCl) Injection, USP is packaged as a multiple dose vial, and caution should be exercised to prevent inadvertent overdosage.

Cumulative dosage with doxorubicin increases the risk of cardiomyopathy and resultant congestive heart failure (see **WARNINGS**). Treatment consists of vigorous management of congestive heart failure with digitalis preparations, diuretics, and afterload reducers such as ACE inhibitors.

DOSAGE AND ADMINISTRATION

Care in the administration of Adriamycin (DOXOrubicin HCl) Injection, USP and Adriamycin (DOXOrubicin HCl) for Injection, USP will reduce the chance of perivenous infiltration (see **WARNINGS**). It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On intravenous administration of doxorubicin, extravasation may occur with or without an accompanying burning or stinging sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein. If extravasation is suspected, intermittent application of ice to the site for 15 min. q.i.d. × 3 days may be useful. The benefit of local administration of drugs has not been clearly established. Because of the progressive nature of extravasation reactions, close observation and plastic surgery consultation is recommended. Blistering, ulceration and/or persistent pain are indications for wide excision surgery, followed by split-thickness skin grafting.[1]

The most commonly used dose schedule when used as a single agent is 60 to 75 mg/m^2 as a single intravenous injection administered at 21-day intervals. The lower dosage should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration. Adriamycin (DOXOrubicin HCl) Injection, USP and Adriamycin (DOXOrubicin HCl) for Injection, USP have been used concurrently with other approved chemotherapeutic agents. Evidence is available that in some types of neoplastic disease, combination chemotherapy is superior to single agents. The benefits and risks of such therapy continue to be elucidated. When used in combination with other chemotherapy drugs, the most commonly used dosage of doxorubicin is 40 to 60 mg/m^2 given as a single intravenous injection every 21 to 28 days. Doxorubicin dosage must be reduced in case of hyperbilirubinemia as follows:

Plasma bilirubin concentration (mg/dL)	Dosage reduction (%)
1.2–3.0	50
3.1–5.0	75

Reconstitution Directions: Adriamycin (DOXOrubicin HCl) for Injection, USP 10 mg, 20 mg, and 50 mg vials should be reconstituted with 5 mL, 10 mL, and 25 mL respectively of 0.9% Sodium Chloride Injection to give a final concentration of 2 mg/mL of doxorubicin hydrochloride. An appropriate volume of air should be withdrawn from the vial during reconstitution to avoid excessive pressure build up. Bacteriostatic diluents are not recommended.

After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature and under normal room light (100 foot-candles) and 15 days under refrigeration, 2° to 8°C (36° to 46°F). It should be protected from exposure to sunlight. Discard any unused solution from the 10 mg, 20 mg, and 50 mg single dose vials. Unused solutions of the multiple dose vial remaining beyond the recommended storage times should be discarded.

It is recommended that Adriamycin (DOXOrubicin HCl) Injection, USP and Adriamycin (DOXOrubicin HCl) for Injection, USP be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection or 5% Dextrose Injection. The tubing should be attached to a Butterfly® needle inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. The rate of administration is dependent on the size of the vein and the dosage. However, the dose should be administered in not less than 3 to 5 minutes. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid an administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Perivenous infiltration may occur painlessly.

Doxorubicin should not be mixed with heparin or fluorouracil since it has been reported that these drugs are incompatible to the extent that a precipitate may form. Until specific compatibility data are available, it is not recommended that doxorubicin be mixed with other drugs.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Handling and Disposal: Skin reactions associated with doxorubicin have been reported. Skin accidently exposed to doxorubicin should be rinsed copiously with soap and warm water, and if the eyes are involved, standard irrigation techniques should be used immediately. The use of goggles, gloves, and protective gowns is recommended during preparation and administration of the drug.

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Caregivers of pediatric patients receiving doxorubicin should be counseled to take precautions (such as wearing latex gloves) to prevent contact with the patient's urine and other body fluids for at least 5 days after each treatment.

HOW SUPPLIED

Adriamycin (DOXOrubicin HCl) for Injection, USP is supplied as a sterile red-orange lyophilized powder in single dose flip-top vials in the following package strengths:

NDC 55390-231-10: 10 mg vial; carton of 10.
NDC 55390-232-10: 20 mg vial; carton of 10.
NDC 55390-233-01: 50 mg vial; individually boxed.

Store unreconstituted vial at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP]. **Protect from light.** Retain in carton until time of use. Discard unused portion.

Reconstituted Solution Stability: After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature and under normal room light (100 foot-candles) and 15 days under refrigeration (2° to 8°C). It should be protected from exposure to sunlight. Discard any unused solution from the 10 mg, 20 mg and 50 mg single dose vials. Unused solutions of the multiple dose vial remaining beyond the recommended storage times should be discarded.

Adriamycin (DOXOrubicin HCl) Injection, USP is supplied in single-dose, flip-top vials, as a red-orange solution containing Doxorubicin Hydrochloride, USP 2 mg/mL in the following package strengths:

NDC 55390-235-10: 510 mg in 5 mL; carton of 10.
NDC 55390-236-10: 20 mg in 10 mL; carton of 10.
NDC 55390-237-01: 50 mg in 25 mL; individually boxed.

Store refrigerated, 2° to 8°C (36° to 46°F).

Protect from light. Retain in carton until time of use. Discard unused portion.

Adriamycin (DOXOrubicin HCl) Injection, USP is supplied in a sterile, multiple dose, flip-top vial, as a red-orange solution containing Doxorubicin Hydrochloride, USP 2 mg/mL in the following package strength:

NDC 55390-238-01: 200 mg in 100 mL; individually boxed.

Store refrigerated, 2° to 8°C (36° to 46°F).

Protect from light. Retain in carton until contents are used.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.
2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA*, 1985; 253 (11): 1590-1592.
3. National Study Commission on Cytotoxic Exposure – Recommendation for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Ave., Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia* 1983; *1*:426-428.
5. Jones RB, *et al.* Safe Handling of Chemotherapeutic Agents: A Report From the Mount Sinai Medical Center. *CA-A Cancer Journal for Clinicians* 1983; Sept/Oct, 258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm* 1990; *47*:1033-1049.
7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines), *Am J Healthsyst Pharm*, 1996; *53*: 1669-1685.
8. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice Pittsburgh, Pa: Oncology Nursing Society; 1999:32-41.

Manufactured by: Ben Venue Laboratories, Inc. Bedford, OH 44146
Manufactured for: Bedford Laboratories™ Bedford, OH 44146
December 2002 ADR-P00

CERUBIDINE®

[*sy-rew"bĭ'dēan*]
(Daunorubicin HCl)
FOR INJECTION
Rx ONLY.

WARNING

1. Cerubidine must be given into a rapidly flowing intravenous infusion. It must *never* be given by the intramuscular or subcutaneous route. Severe local tissue necrosis will occur if there is extravasation during administration.
2. Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure may occur either during therapy or months to years after termination of therapy. The incidence of myocardial toxicity increases after a total cumulative dose exceeding 400 to 550 mg/m^2 in adults, 300 mg/m^2 in children more than 2 years of age, or 10 mg/kg in children less than 2 years of age.
3. Severe myelosuppression occurs when used in therapeutic doses; this may lead to infection or hemorrhage.
4. It is recommended that Cerubidine be administered only by physicians who are experienced in leukemia chemotherapy and in facilities with laboratory and supportive resources adequate to monitor drug tolerance and protect and maintain a patient compromised by drug toxicity. The physician and institution must be capable of responding rapidly and completely to severe hemorrhagic conditions and/or overwhelming infection.
5. Dosage should be reduced in patients with impaired hepatic or renal function.

DESCRIPTION

Cerubidine (daunorubicin hydrochloride) is the hydrochloride salt of an anthracycline cytotoxic antibiotic produced by a strain of *Streptomyces coeruleorubidus*. It is

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

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

Instructions for Administration

Preparation of Solution

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

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

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

Instillation of Solution into the Catheter

1. Inspect the product prior to administration for foreign matter and discoloration.
2. Withdraw 2.0 mL (2.0 mg) of solution from the reconstituted vial.
3. Instill the appropriate dose of Cathflo Activase (see DOSAGE AND ADMINISTRATION) into the occluded catheter.
4. After 30 minutes of dwell time, assess catheter function by attempting to aspirate blood. If the catheter is functional, go to Step 7. If the catheter is not functional, go to Step 5.
5. After 120 minutes of dwell time, assess catheter function by attempting to aspirate blood and catheter contents. If the catheter is functional, go to Step 7. If the catheter is not functional, go to Step 6.
6. If catheter function is not restored after one dose of Cathflo Activase, a second dose may be instilled. Repeat the procedure beginning with Step 1 under Preparation of Solution.
7. If catheter function has been restored, aspirate 4–5 mL of blood to remove Cathflo Activase and residual clot, and gently irrigate the catheter with 0.9% Sodium Chloride, USP.

Any unused solution should be discarded.

Stability and Storage

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

HOW SUPPLIED

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

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

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

REFERENCES

1. Collen D, Lijnen HR. Fibrinolysis and the control of hemostasis. In: Stamatoyannopoulos G, Nienhui AW, Majerus PW, Varmus H, editors. The molecular basis of blood diseases, 2nd edition. Philadelphia: Saunders, 1994:662–88.
2. Tanswell P, Tebbe U, Neuhaus K-L, Glasle-Schwarz L, Wojick J, Seifried E. Pharmacokinetics and fibrin specificity of alteplase during accelerated infusions in acute myocardial infarction. *J Am Coll Cardiol* 1992;19:1071–5.
3. Califf RM, Topol EJ, George BS, Boswick JM, Abbottsmith C, Sigmon KN, et al., and the Thrombolysis and Angioplasty in Myocardial Infarction Study Group. Hemorrhagic complications associated with the use of intravenous tissue plasminogen activator in treatment of acute myocardial infarction. *Am J Med* 1988;85:353–9.
4. Bovill EG, Terrin ML, Stump DC, Berke AD, Frederick M, Collen D, et al. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction: results of the thrombolysis in myocardial infarction (TIMI), phase II trial. *Ann Int Med* 1991;115:256–65.

Cathflo® Activase® (Alteplase) 7289101
Manufactured by: LB0551
Genentech, Inc. (4821101)
1 DNA Way Revision Date October 2002

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

Shown in Product Identification Guide, page 315

HERCEPTIN®

℞

[hər'sĕp-tĭn]

(trastuzumab)

anti-HER2 monoclonal antibody

WARNINGS:

CARDIOMYOPATHY

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

HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS

INFUSION REACTIONS

PULMONARY EVENTS

HERCEPTIN administration can result in severe hypersensitivity reactions (including anaphylaxis), infusion reactions, and pulmonary events. Rarely, these have been fatal. In most cases, symptoms occurred during or within 24 hours of administration of HERCEPTIN. HERCEPTIN infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of HERCEPTIN treatment should be strongly considered for patients who develop anaphylaxis, angioedema, or acute respiratory distress syndrome. (See WARNINGS.)

DESCRIPTION

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

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

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

CLINICAL PHARMACOLOGY

General

The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the epidermal growth factor receptor.[1] HER2 protein overexpression is observed in 24%–30% of primary breast cancers. HER2 protein overexpression can be determined using immunohistochemistry (IHC) and gene amplification can be determined using fluorescence in situ hybridization (FISH) of fixed tumor blocks.[2] In referenced studies where HERCEPTIN use was not studied,[3–5] approximately 96–98% of biopsy specimens that were found to have protein overexpression also had gene amplification and 100% of those with gene amplification also had protein overexpression.[3–5] The precision of the determination of protein overexpression or gene amplification, however, may vary depending on the sensitivity and specificity of the particular assay and assay procedures used (see PRECAUTIONS). When compared to the referenced studies noted above, the correlation between detectable protein overexpression using immunohistochemistry (IHC) and detectable gene amplification using fluorescence in situ hybridization (FISH) was not as high in the studies of HERCEPTIN clinical trial specimens (see CLINICAL STUDIES: HER2 Detection and HER2 Assay Concordance Studies and PRECAUTIONS: HER2 Testing).

Trastuzumab has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2.[6–8]

Trastuzumab is a mediator of antibody-dependent cellular cytotoxicity (ADCC).[9,10] *In vitro*, HERCEPTIN-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Pharmacokinetics

The pharmacokinetics of Trastuzumab were studied in breast cancer patients with metastatic disease. Short duration intravenous infusions of 10 to 500 mg once weekly demonstrated dose-dependent pharmacokinetics. Mean half-life increased and clearance decreased with increasing dose level. The half-life averaged 1.7 and 12 days at the 10 and 500 mg dose levels, respectively. Trastuzumab's volume of distribution was approximately that of serum volume (44 mL/kg). At the highest weekly dose studied (500 mg), mean peak serum concentrations were 377 microgram/mL. In studies using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg, a mean half-life of 5.8 days (range=1 to 32 days) was observed. Between Weeks 16 and 32, Trastuzumab serum concentrations reached a steady state with mean trough and peak concentrations of approximately 79 microgram/mL and 123 microgram/mL, respectively.

Detectable concentrations of the circulating extracellular domain of the HER2 receptor (shed antigen) are found in the sera of some patients with HER2 overexpressing tumors. Determination of shed antigen in baseline serum samples revealed that 64% (286/447) of patients had detectable shed antigen, which ranged as high as 1880 ng/mL (median=11 ng/mL) Patients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations. However, with weekly dosing, most patients with elevated shed antigen levels achieved target serum concentrations of Trastuzumab by Week 6.

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

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

CLINICAL STUDIES

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

A multicenter, randomized, controlled clinical trial was conducted in 469 patients with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease.[11] Patients were randomized to receive chemotherapy alone or in combination with HERCEPTIN given intravenously as a 4 mg/kg loading dose followed by weekly doses of HERCEPTIN at 2 mg/kg. For those who had received prior anthracycline therapy in the adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m^2 over 3 hours every 21 days for at least six cycles); for all other patients, chemotherapy consisted of anthracycline plus cyclophosphamide (AC: doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2 plus 600 mg/m^2 cyclophosphamide every 21 days for six cycles). Compared with patients in the AC subgroups (n=281), patients in the paclitaxel subgroup (n=188) were more likely to have had the following: poor prognostic factors (premenopausal status, estrogen or progesterone receptor negative tumors, positive lymph nodes), prior therapy (adjuvant chemotherapy, myeloblative chemotherapy, radiotherapy), and a shorter disease-free interval. Sixty-five percent of patients randomized to receive chemotherapy alone in this study received HERCEPTIN at the time of disease progression as part of a separate extension study.

Compared with patients randomized to chemotherapy alone, the patients randomized to HERCEPTIN and chemotherapy experienced a significantly longer median time to disease progression, a higher overall response rate (ORR), a longer median duration of response, and a longer median survival (see Table 1). These treatment effects were observed both in patients who received HERCEPTIN plus paclitaxel and in those who received HERCEPTIN plus AC, however the magnitude of the effects was greater in the paclitaxel subgroup (see CLINICAL STUDIES: HER2 Detection).

[See table 1 at top of next page]

HERCEPTIN was studied as a single agent in a multicenter, open-label, single-arm clinical trial in patients with HER2 overexpressing metastatic breast cancer who had relapsed following one or two prior chemotherapy regimens for metastatic disease. Of 222 patients enrolled, 66% had received prior adjuvant chemotherapy, 68% had received two prior chemotherapy regimens for metastatic disease, and 25% had received prior myeloablative treatment with hematopoietic rescue. Patients were treated with a loading dose of 4 mg/kg IV followed by weekly doses of HERCEPTIN at 2 mg/kg IV. The ORR (complete response + partial response), as determined by an independent Response Evaluation Committee, was 14%, with a 2% complete response rate and a 12% partial response rate. Complete responses

Continued on next page

Herceptin—Cont.

were observed only in patients with disease limited to skin and lymph nodes (see CLINICAL STUDIES: HER2 Detection).

HER2 Detection

(See PRECAUTIONS: HER2 Testing)

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

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

HER2 Protein Overexpression Detection Methods

HER2 protein overexpression can be established by measuring expressed HER2 protein using IHC methodology. In the clinical trial studies described above, specimens were tested with the CTA and scored as 0, 1+, 2+, or 3+ with 3+ indicating the strongest positivity. Only patients with 2+ or 3+ positive tumors were eligible (about 33% of those screened). Data from the randomized trial suggest that the beneficial treatment effects were largely limited to patients with the highest level of HER2 protein overexpression (3+) (see Table 2). In an exploratory analysis, the relative risk (rr) for time to progression was lower in the patients whose tumors tested as CTA 3+ (rr = 0.42 with 95% CI: 0.33, 0.54) than in those tested as CTA 2+ (rr = 0.76 with 95% CI: 0.50, 1.15). The relative risk represents the risk of progression in the HERCEPTIN plus chemotherapy arm versus the chemotherapy arm. Therefore, a lower ratio represents longer time to progression in the HERCEPTIN arm. In the single-arm study of HERCEPTIN as a single agent, the overall response rate in patients whose tumors tested as CTA 3+ was 18% while in those that tested as CTA 2+, it was 6%.

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

HER2 Gene Amplification Detection Methods

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

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

[See table 2 above]

HER2 Assay Concordance Studies

(See PRECAUTIONS: HER2 Testing)

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

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

Table 1
Phase III Clinical Efficacy in First-Line Treatment

	Combined Results		Paclitaxel subgroup		AC subgroup	
	HERCEPTIN + All Chemotherapy (n = 235)	All Chemotherapy (n = 234)	HERCEPTIN + Paclitaxel (n = 92)	Paclitaxel (n = 96)	HERCEPTIN + AC[a] (n = 143)	AC (n = 138)
Primary Endpoint						
Time to Progression[b,c]						
Median (months)	7.2	4.5	6.7	2.5	7.6	5.7
95% confidence interval	6.9, 8.2	4.3, 4.9	5.2, 9.9	2.0, 4.3	7.2, 9.1	4.6, 7.1
p-value (log rank)	< 0.0001		< 0.0001		0.002	
Secondary Endpoints						
Overall Response Rate[b]						
Rate (percent)	45	29	38	15	50	38
95% confidence interval	39, 51	23, 35	28, 48	8, 22	42, 58	30, 46
p-value (χ^2-test)	< 0.001		< 0.001		0.10	
Duration of Response[b,c]						
Median (months)	8.3	5.8	8.3	4.3	8.4	6.4
25%, 75% quantile	5.5, 14.8	3.9, 8.5	5.1, 11.0	3.7, 7.4	5.8, 14.8	4.5, 8.5
Survival Time[c]						
Median Survival (months)	25.1	20.3	22.1	18.4	26.8	21.4
95% confidence interval	22.2, 29.5	16.8, 24.2	16.9, 28.6	12.7, 24.4	23.3, 32.9	18.3, 26.6
p-value (log rank)	0.05		0.17		0.16	

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

Table 2
Treatment Effect versus Level of HER2 Expression
Phase III Randomized Trial (N = 469):
HERCEPTIN Plus Chemotherapy versus Chemotherapy

HER2 Assay Result	Number of Patients (N)	Relative Risk** for Time to Disease Progression (95% CI)	Relative Risk** for Mortality (95% CI)
CTA 2+ or 3+	469	0.49 (0.40, 0.61)	0.80 (0.64, 1.00)
FISH (+)*	325	0.44 (0.34, 0.57)	0.70 (0.53, 0.91)
FISH (−)*	126	0.62 (0.42, 0.94)	1.06 (0.70, 1.63)
CTA 2+	120	0.76 (0.50, 1.15)	1.26 (0.82, 1.94)
FISH (+)	32	0.54 (0.21, 1.35)	1.31 (0.53, 3.27)
FISH (−)	83	0.77 (0.48, 1.25)	1.11 (0.68, 1.82)
CTA 3+	349	0.42 (0.33, 0.54)	0.70 (0.51, 0.90)
FISH (+)	293	0.42 (0.32, 0.55)	0.67 (0.51, 0.89)
FISH (−)	43	0.43 (0.20, 0.94)	0.88 (0.39, 1.98)

* FISH testing results were available for 451 of the 469 patients enrolled on study.
** The relative risk represents the risk of progression or death in the HERCEPTIN plus chemotherapy arm versus the chemotherapy arm.

Table 3
Incidence and Severity of Cardiac Dysfunction

	HERCEPTIN[a] alone n=213	HERCEPTIN + Paclitaxel[b] n=91	Paclitaxel[b] n=95	HERCEPTIN + Anthracycline+ cyclophosphamide[b] n=143	Anthracycline + cyclophosphamide[b] n=135
Any Cardiac Dysfunction	7%	11%	1%	28%	7%
Class III-IV	5%	4%	1%	19%	3%

[a] Open-label, single-agent Phase II study (94% received prior anthracyclines).
[b] Randomized Phase III study comparing chemotherapy plus HERCEPTIN to chemotherapy alone, where chemotherapy is either anthracycline/cyclophosphamide or paclitaxel.

INDICATIONS AND USAGE

HERCEPTIN as a single agent is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. HERCEPTIN in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have not received chemotherapy for their metastatic disease. HERCEPTIN should be used in patients whose tumors have been evaluated with an assay validated to predict HER2 protein overexpression (see PRECAUTIONS: HER2 Testing and CLINICAL STUDIES: HER2 Detection).

CONTRAINDICATIONS

None known.

WARNINGS

Cardiotoxicity:

Signs and symptoms of cardiac dysfunction, such as dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, S_3 gallop, or reduced ejection fraction, have been observed in patients treated with HERCEPTIN. Congested heart failure associated with HERCEPTIN therapy may be severe and has been associated with disabling cardiac failure, death, and mural thrombosis leading to stroke (see BOXED WARNINGS: CARDIOMYOPATHY). The clinical status of patients in the trials who developed congestive heart failure was classified for severity using the New York Heart Association classification system (I-IV, where IV is the most severe level of cardiac failure). (See Table 3.)

[See table 3 above]

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

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

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

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

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

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

Hypersensitivity Reactions Including Anaphylaxis:

Severe hypersensitivity reactions have been infrequently reported in patients treated with HERCEPTIN (see BOXED WARNINGS: HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS). Signs and symptoms include anaphylaxis, urticaria, bronchospasm, angioedema, and/or hypotension. In some cases, the reactions have been fatal. The onset of symptoms generally occurred during an infusion, but there have also been reports of symptom onset after the completion of an infusion. Reactions were most commonly reported in association with the initial infusion.

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

There are no data regarding the most appropriate method of identification of patients who may safely be retreated with HERCEPTIN after experiencing a severe hypersensitivity reaction. HERCEPTIN has been readministered to some patients who fully recovered from a previous severe reaction. Prior to readministration of HERCEPTIN, the majority of these patients were prophylactically treated with pre-medications including antihistamines and/or corticosteroids. While some of these patients tolerated retreatment, others had severe reactions again despite the use of prophylactic pre-medications.

Infusion Reactions:

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

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

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

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

There are no data regarding the most appropriate method of identification of patients who may safely be retreated with HERCEPTIN after experiencing a severe infusion reaction. HERCEPTIN has been readministered to some patients who fully recovered from the previous severe reaction. Prior to readministration of HERCEPTIN, the majority of these patients were prophylactically treated with pre-medications including antihistamines and/or corticosteroids. While some of these patients tolerated retreatment, others had severe reactions again despite the use of prophylactic pre-medications.

Pulmonary Events:

Severe pulmonary events leading to death have been reported rarely with the use of HERCEPTIN 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 may or may not occur as sequelae of infusion reactions. (See WARNINGS: Infusion Reactions.) Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, may be at greater risk of severe reactions.

Other severe events reported rarely in the postmarketing setting include pneumonitis and pulmonary fibrosis.

PRECAUTIONS

General:

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

HER2 Testing:

Assessment for HER2 overexpression should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. Refer to the HercepTest™ and PathVysion™ package inserts for full instructions on assay performance (see CLINICAL STUDIES: HER2 Detection).

Drug Interactions:

There have been no formal drug interaction studies performed with HERCEPTIN in humans. Administration of paclitaxel in combination with HERCEPTIN resulted in a two-fold decrease in HERCEPTIN clearance in a non-human primate study and in a 1.5-fold increase in HERCEPTIN serum levels in clinical studies. (See PHARMACOKINETICS.)

Benzyl Alcohol:

For patients with a known hypersensitivity to benzyl alcohol (the preservative in Bacteriostatic Water for Injection) reconstitute HERCEPTIN with Sterile Water for Injection (SWFI), USP. DISCARD THE SWFI-RECONSTITUTED HERCEPTIN VIAL FOLLOWING A SINGLE USE.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis:

HERCEPTIN has not been tested for its carcinogenic potential.

Mutagenesis:

No evidence of mutagenic activity was observed in Ames tests using six different test strains of bacteria, with and without metabolic activation, at concentrations of up to 5000 µg/mL Trastuzumab. Human peripheral blood lymphocytes treated *in vitro* at concentrations of up to 5000 µg/plate Trastuzumab, with and without metabolic activation, revealed no evidence of mutagenic potential. In an *in vivo* mutagenic assay (the micronucleus assay), no evidence of chromosomal damage to mouse bone marrow cells was observed following bolus intravenous doses of up to 118 mg/kg Trastuzumab.

Impairment of Fertility:

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

Pregnancy Category B:

Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 times the weekly human maintenance dose of 2 mg/kg HERCEPTIN and have revealed no evidence of impaired fertility or harm to the fetus. However, HER2 protein expression is high in many embryonic tissues including cardiac and neural tissues; in mutant mice lacking HER2, embryos died in early gestation.[12] Placental transfer of HERCEPTIN during the early (Days 20–50 of gestation) and late (Days 120–150 of gestation) fetal development period was observed in monkeys. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers:

A study conducted in lactating cynomolgus monkeys at doses 25 times the weekly human maintenance dose of 2 mg/kg HERCEPTIN demonstrated that Trastuzumab is secreted in the milk. The presence of Trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 3 months of age. It is not known whether HERCEPTIN is excreted in human milk. Because human IgG is excreted in human milk, and the potential for absorption and harm to the infant is unknown, women should be advised to discontinue nursing during HERCEPTIN therapy and for 6 months after the last dose of HERCEPTIN.

Pediatric Use:

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

Geriatric Use:

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

ADVERSE REACTIONS

In clinical studies, a total of 958 patients have received HERCEPTIN alone or in combination with chemotherapy. Data in Table 4 are based on the experience with the recommended dosing regimen for HERCEPTIN in the randomized clinical trial in 234 patients who received HERCEPTIN in combination with chemotherapy and four open-label studies of HERCEPTIN as a single agent in 352 patients at doses of 10–500 mg administered weekly.

Cardiac Failure/Dysfunction:

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

Anemia and Leukopenia:

An increased incidence of anemia and leukopenia was observed in the treatment group receiving HERCEPTIN and chemotherapy, especially in the HERCEPTIN and AC subgroup, compared with the treatment group receiving chemotherapy alone. The majority of these cytopenic events were mild or moderate in intensity, reversible, and none resulted in discontinuation of therapy with HERCEPTIN.

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

Diarrhea:

Of patients treated with HERCEPTIN as a single agent, 25% experienced diarrhea. An increased incidence of diarrhea, primarily mild to moderate in severity, was observed in patients receiving HERCEPTIN in combination with chemotherapy.

Infection:

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

Infusion Reactions:

During the first infusion with HERCEPTIN, a symptom complex most commonly consisting of chills and/or fever was observed in about 40% of patients in clinical trials. The symptoms were usually mild to moderate in severity and were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of HERCEPTIN infusion). HERCEPTIN discontinuation was infrequent. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotention, rash and asthenia. The symptoms occurred infrequently with subsequent HERCEPTIN infusions. (See BOXED WARNINGS: and WARNINGS: Infusion Reactions.)

Additional adverse reactions have been identified during postmarketing use of HERCEPTIN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HERCEPTIN exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to HERCEPTIN.

Hypersensitivity Reactions Including Anaphylaxis

Pulmonary Events:

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

Glomerulopathy:

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

[See table 4 at top of next page]

Other Serious Adverse Events

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

Body as a Whole: cellulitis, anaphylactoid reaction, ascites, hydrocephalus, radiation injury, deafness, amblyopia

Cardiovascular: vascular thrombosis, pericardial effusion, heart arrest, hypotension, syncope, hemorrhage, shock, arrhythmia

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

Endocrine: hypothyroidism

Hematological: pancytopenia, acute leukemia, coagulation disorder, lymphangitis

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

Musculoskeletal: pathological fractures, bone necrosis, myopathy

Nervous: convulsion, ataxia, confusion, manic reaction

Respiratory: apnea, pneumothorax, asthma, hypoxia, laryngitis

Skin: herpes zoster, skin ulceration

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

Immunogenicity:

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

The data reflect the percentage of patients whose test results were considered positive for antibodies to HERCEPTIN in the HAHA assay for Trastuzumab, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these

Continued on next page

Herceptin—Cont.

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Usual Dose

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

Preparation for Administration

The diluent provided has been formulated to maintain the stability and sterility of HERCEPTIN for up to 28 days. Other diluents have not been shown to contain effective preservatives for HERCEPTIN. Each vial of HERCEPTIN should be reconstituted with 20 mL of BWFI, USP, 1.1% benzyl alcohol preserved, as supplied, to yield a multi-dose solution containing 21 mg/mL Trastuzumab. Immediately upon reconstitution with BWFI, the vial of HERCEPTIN must be labeled in the area marked "Do not use after:" with the future date that is 28 days from the date of reconstitution.

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

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

Use appropriate aseptic technique when performing the following reconstitution steps:

a. Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the lyophilized cake of Trastuzumab. The stream of diluent should be directed into the lyophilized cake.
b. Swirl the vial gently to aid reconstitution. Trastuzumab may be sensitive to shear-induced stress, e.g., agitation or rapid expulsion from a syringe. **DO NOT SHAKE.**
c. Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The solution should be essentially free of visible particulates, clear to slightly opalescent and colorless to pale yellow.

Determine the number of mg of Trastuzumab needed, based on a loading dose of 4 mg Trastuzumab/kg body weight or a maintenance dose of 2 mg Trastuzumab/kg body weight. Calculate the volume of 21 mg/mL Trastuzumab solution and withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP. **DEXTROSE (5%) SOLUTION SHOULD NOT BE USED.** Gently invert the bag to mix the solution. The reconstituted preparation results in a colorless to pale yellow transparent solution. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.

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

Administration

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

HERCEPTIN should not be mixed or diluted with other drugs. HERCEPTIN infusions should not be administered or mixed with Dextrose solutions.

Stability and Storage

Vials of HERCEPTIN are stable at 2–8°C (36–46°F) prior to reconstitution. Do not use beyond the expiration date stamped on the vial. A vial of HERCEPTIN reconstituted with BWFI, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2–8°C (36–46°F), and the solution is preserved for multiple use. Discard any remaining multi-dose reconstituted solution after 28 days. If unpreserved SWFI (not supplied) is used, the reconstituted HERCEPTIN solution should be used immediately and any unused portion must be discarded. DO NOT FREEZE HERCEPTIN THAT HAS BEEN RECONSTITUTED.

The solution of HERCEPTIN for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP, may be stored at 2–8°C (36–46°F) for up to 24 hours prior to use. Diluted HERCEPTIN has been shown to be stable for up to 24 hours at room temperature (2–25°C). However, since diluted HERCEPTIN contains no effective preservative, the reconstituted and diluted solution should be stored refrigerated (2–8°C).

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

	Single Agent n=352	HERCEPTIN + Paclitaxel n=91	Paclitaxel Alone n=95	HERCEPTIN + AC n=143	AC Alone n=135
Body as a Whole					
Pain	47	61	62	57	42
Asthenia	42	62	57	54	55
Fever	36	49	23	56	34
Chills	32	41	4	35	11
Headache	26	36	28	44	31
Abdominal pain	22	34	22	23	18
Back pain	22	34	30	27	15
Infection	20	47	27	47	31
Flu syndrome	10	12	5	12	6
Accidental injury	6	13	3	9	4
Allergic reaction	3	8	2	4	2
Cardiovascular					
Tachycardia	5	12	4	10	5
Congestive heart failure	7	11	1	28	7
Digestive					
Nausea	33	51	9	76	77
Diarrhea	25	45	29	45	26
Vomiting	23	37	28	53	49
Nausea and vomiting	8	14	11	18	9
Anorexia	14	24	16	31	26
Heme & Lymphatic					
Anemia	4	14	9	36	26
Leukopenia	3	24	17	52	34
Metabolic					
Peripheral edema	10	22	20	20	17
Edema	8	10	8	11	5
Musculoskeletal					
Bone pain	7	24	18	7	7
Arthralgia	6	37	21	8	9
Nervous					
Insomnia	14	25	13	29	15
Dizziness	13	22	24	24	18
Paresthesia	9	48	39	17	11
Depression	6	12	13	20	12
Peripheral neuritis	2	23	16	2	2
Neuropathy	1	13	5	4	4
Respiratory					
Cough increased	26	41	22	43	29
Dyspnea	22	27	26	42	25
Rhinitis	14	22	5	22	16
Pharyngitis	12	22	14	30	18
Sinusitis	9	21	7	13	6
Skin					
Rash	18	38	18	27	17
Herpes simplex	2	12	3	7	9
Acne	2	11	3	3	<1
Urogenital					
Urinary tract infection	5	18	14	13	7

HOW SUPPLIED

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

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

REFERENCES

1. Coussens L, Yang-Feng TL, Liao Y-C, Chen E, Gray A, McGrath J, et al. Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene. Science 1985;230:1132–9.
2. Press MF, Pike MC, Chazin VR, Hung G, Udove JA, Markowicz M, et al. Her-2/*neu* expression in node-negative breast cancer: direct tissue quantitation by computerized image analysis and association of overexpression with increased risk of recurrent disease. Cancer Res 1993;53:4960–70.
3. Slamon DJ, Godolphin W, Jones LA, Holt JA, Wong SG, Keith DE, et al. Studies of the HER2/*neu* proto-oncogene in human breast and ovarian cancer. Science 1989;244:707–12.
4. Killionieme OP, Kallionieme A, Kurisu W, Thor A, Chen L-C, Smith HS, et al. *ERBB2* amplification in breast cancer analyzed by fluorescence in situ hybridization. Proc Natl Acad Sci USA 1992:89:5321–5.
5. Pauletti G, Godolphin W, Press MF, Slamon DJ. Detection and quantitation of HER2/*neu* gene amplification in human breast cancer archival material using fluorescence in situ hybridization. Oncogene 1996;13:63–72.
6. Hudziak RM, Lewis GD, Winget M, Fendly BM, Shepard HM, Ullrich A. $p185^{HER2}$ monoclonal antibody has antiproliferative effects *in vitro* and sensitizes human breast tumor cells to tumor necrosis factor. Mol Cell Biol 1989;9:1165–72.
7. Lewis GD, Figari I, Fendly B, Wong WL, Carter P, Gorman C, et al. Differential responses of human tumor cell lines to anti-p185HER2 monoclonal antibodies. Cancer Immunol Immunother 1993;37:255–63.
8. Baselga J, Norton L, Albanell J, Kim Y-M, Mendelsohn J. Recombinant humanized anti-HER2 antibody (Herceptin™) enhances the antitumor activity of paclitaxel and doxorubicin against HER2/*neu* overexpressing human breast cancer xenografts. Cancer Res 1998;58:2825–31.
9. Hotaling TE, Reitz B, Wolfgang-Kimball D, Bauer K. Fox JA. The humanized anti-HER2 antibody rhuMAb HER2 mediates antibody dependent cell-mediated cytotoxicity via $Fc\gamma R$ III [abstract]. Proc Annu Meet Am Assoc Cancer Res 1996;37:471.
10. Pegram MD, Baly D, Wirth C, Gilkerson E, Slamon DJ, Sliwkowski MX, et al. Antibody dependent cell-mediated cytotoxicity in breast cancer patients in Phase III clinical trials of a humanized anti-HER2 antibody [abstract]. Proc Am Assoc Cancer Res 1997;38:602.
11. Slamon D J., Leyland-Jones B, Shak S., Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344:783–92.
12. Lee, KS. Requirement for neuroregulin receptor, erbB2, in neural and cardiac development. Nature 1995;379:394–6.

HERCEPTIN®
(Trastuzumab) 481740
Manufactured by:
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990
FDA revision August 2002
Code revision August 2002

Shown in Product Identification Guide, page 315

NUTROPIN®

[somatropin (rDNA origin) for injection]

DESCRIPTION

Nutropin® [somatropin (rDNA origin) for injection] is a human growth hormone (hGH) produced by recombinant DNA technology. Nutropin has 191 amino acid residues and a molecular weight of 22,125 daltons. The amino acid sequence of the product is identical to that of pituitary-derived human growth hormone. The protein is synthesized by a specific laboratory strain of *E. coli* as a precursor consisting of

Focalin—Cont.

- Are being treated for depression or have symptoms of depression such as feelings of sadness, worthlessness, and hopelessness.
- Have motion tics (hard-to-control, repeated twitching of any parts of your body) or verbal tics (hard-to-control repeating of sounds or words).
- Have someone in your family with motion tics, verbal tics, or Tourette's syndrome.
- Have abnormal thoughts or visions, hear abnormal sounds, or have been diagnosed with psychosis.
- Have had seizures (convulsions, epilepsy) or abnormal EEGs (electroencephalograms).
- Have high blood pressure.
- Have an abnormal heart rate or rhythm.

Tell your doctor ***immediately*** if you develop any of the above conditions or symptoms while taking Focalin.

Can I Take Focalin with Other Medicines?

Tell your doctor about ***all*** medicines that you are taking. Your doctor should decide whether you can take Focalin with other medicines. These include:

- Other medicines that a doctor has prescribed.
- Medicines that you buy yourself without a prescription.
- Any herbal remedies that you may be taking.

You should not take Focalin with monoamine oxidase (MAO) inhibitors.

While on Focalin, do not start taking a new medicine or herbal remedy before checking with your doctor.

Focalin may change the way your body reacts to certain medicines. These include medicines used to treat depression, prevent seizures, or prevent blood clots (commonly called "blood thinners"). Your doctor may need to change your dose of these medicines if you are taking them with Focalin.

Other Important Safety Information

Abuse of Focalin can lead to dependence.

Tell your doctor if you have ever abused or been dependent on alcohol or drugs, or if you are now abusing or dependent on alcohol or drugs.

Before taking Focalin, tell your doctor if you are pregnant or plan on becoming pregnant. If you take Focalin, it may be in your breast milk. Tell your doctor if you are nursing a baby. Tell your doctor if you have blurred vision when taking Focalin.

Slower growth (weight gain and/or height) has been reported with long-term use of methylphenidate in children. Your doctor will be carefully watching your height and weight. If you are not growing or gaining weight as your doctor expects, your doctor may stop your Focalin treatment.

Call your doctor ***immediately*** if you take more than the amount of Focalin prescribed by your doctor.

What Else Should I Know about Focalin?

Focalin has not been studied in children under 6 years of age.

Focalin may be a part of your overall treatment for ADHD. Your doctor may also recommend that you have counseling or other therapy.

As with all medicines, never share Focalin with anyone else and take only the number of Focalin tablets prescribed by your doctor.

Focalin may be taken at the same time as food or with no food. Focalin should be stored in a safe place at room temperature (between 59°F - 86°F). Do not store this medicine in hot, damp, or humid places.

Keep the container of Focalin in a safe place, away from high-traffic areas where other people could have accidental or unauthorized access to the medication. Keep track of the number of tablets so that you will know if any are missing. Sadly, someone who has easy access to Focalin may be able to give the tablets to others or misuse the medication.

Keep Out of the Reach of Children

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Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936
By:
Mikart, Inc.
Atlanta, GA 30318

Shown in Product Identification Guide, page 326

GLEEVEC®

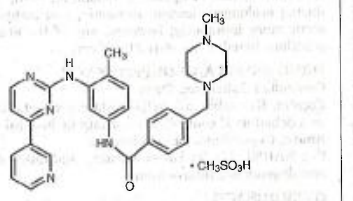
[glē-vĕk]
(imatinib mesylate)
Tablets
Rx only

Prescribing Information

The following prescribing information is base on official labeling in effect July 2003.

DESCRIPTION

Gleevec® (imatinib mesylate) film-coated tablets contain imatinib mesylate equivalent to 100 mg or 400 mg of imatinib free base. Imatinib mesylate is designated chemically as 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methanesulfonate and its structural formula is



Imatinib mesylate is a white to off-white to brownish or yellowish tinged crystalline powder. Its molecular formula is $C_{29}H_{31}N_7O \cdot CH_4SO_3$ and its molecular weight is 589.7. Imatinib mesylate is soluble in aqueous buffers ≤ pH 5.5 but is very slightly soluble to insoluble in neutral/alkaline aqueous buffers. In non-aqueous solvents, the drug substance is freely soluble to very slightly soluble in dimethyl sulfoxide, methanol and ethanol, but is insoluble in n-octanol, acetone and acetonitrile.

Inactive Ingredients: colloidal silicon dioxide (NF); crospovidone (NF); hydroxypropyl methylcellulose (USP); magnesium stearate (NF); and microcrystalline cellulose (NF). *Tablet coating:* ferric oxide, red (NF); ferric oxide, yellow (NF); hydroxypropyl methylcellulose (USP); polyethylene glycol (NF) and talc (USP).

CLINICAL PHARMACOLOGY

Mechanism of Action

Imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits the Bcr-Abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia (CML). It inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia. In colony formation assays using *ex vivo* peripheral blood and bone marrow samples, imatinib shows inhibition of Bcr-Abl positive colonies from CML patients.

In vivo, it inhibits tumor growth of Bcr-Abl transfected murine myeloid cells as well as Bcr-Abl positive leukemia lines derived from CML patients in blast crisis.

Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-kit, and inhibits PDGF- and SCF-mediated cellular events. *In vitro*, imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumor (GIST) cells, which express an activating c-kit mutation.

Pharmacokinetics

The pharmacokinetics of Gleevec® (imatinib mesylate) have been evaluated in studies in healthy subjects and in population pharmacokinetic studies in over 900 patients. Imatinib is well absorbed after oral administration with C_{max} achieved within 2-4 hours post-dose. Mean absolute bioavailability is 98%. Following oral administration in healthy volunteers, the elimination half-lives of imatinib and its major active metabolite, the N-desmethyl derivative, are approximately 18 and 40 hours, respectively. Mean imatinib AUC increases proportionally with increasing doses ranging from 25 mg-1000 mg. There is no significant change in the pharmacokinetics of imatinib on repeated dosing, and accumulation is 1.5-2.5 fold at steady state when Gleevec is dosed once daily. At clinically relevant concentrations of imatinib, binding to plasma proteins in *in vitro* experiments is approximately 95%, mostly to albumin and α_1-acid glycoprotein.

The pharmacokinetics of Gleevec are similar in CML and GIST patients.

Metabolism and Elimination

CYP3A4 is the major enzyme responsible for metabolism of imatinib. Other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19, play a minor role in its metabolism. The main circulating active metabolite in humans is the N-demethylated piperazine derivative, formed predominantly by CYP3A4. It shows *in vitro* potency similar to the parent imatinib. The plasma AUC for this metabolite is about 15% of the AUC for imatinib.

Elimination is predominately in the feces, mostly as metabolites. Based on the recovery of compound(s) after an oral ^{14}C-labeled dose of imatinib, approximately 81% of the dose was eliminated within 7 days, in feces (68% of dose) and urine (13% of dose). Unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces), the remainder being metabolites.

Typically, clearance of imatinib in a 50-year-old patient weighing 50 kg is expected to be 8 L/h, while for a 50-year-old patient weighing 100 kg the clearance will increase to 14 L/h. However, the inter-patient variability of 40% in clearance does not warrant initial dose adjustment based on body weight and/or age but indicates the need for close monitoring for treatment related toxicity.

Special Populations

Pediatric: As in adult patients, imatinib was rapidly absorbed after oral administration in pediatric patients, with a C_{max} of 2-4 hours. Apparent oral clearance was similar to adult values (11.0 L/hr/m^2 in children vs. 10.0 L/hr/m^2 in adults), as was the half-life (14.8 hours in children vs. 17.1 hr in adults). Dosing in children at both 260 mg/m^2 and 340 mg/m^2 achieved an AUC similar to the 400-mg dose in adults. The comparison of $AUC_{(0-24)}$ on Day 8 vs. Day 1 at 260 mg/m^2 and 340 mg/m^2 dose levels revealed a 1.5 and 2.2-fold drug accumulation, respectively, after repeated once-daily dosing. Mean imatinib AUC did not increase proportionally with increasing dose.

Hepatic Insufficiency: No clinical studies were conducted with Gleevec in patients with impaired hepatic function.

Renal Insufficiency: No clinical studies were conducted with Gleevec in patients with decreased renal function (studies excluded patients with serum creatinine concentration more than 2 times the upper limit of the normal range). Imatinib and its metabolites are not significantly excreted via the kidney.

Drug-Drug Interactions

CYP3A4 Inhibitors: There was a significant increase in exposure to imatinib (mean C_{max} and AUC increased by 26% and 40%, respectively) in healthy subjects when Gleevec was co-administered with a single dose of ketoconazole (a CYP3A4 inhibitor). *(See PRECAUTIONS.)*

CYP3A4 Substrates: Gleevec increased the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) by 2- and 3.5-fold, respectively, indicating an inhibition of CYP3A4 by Gleevec. *(See PRECAUTIONS.)*

CYP3A4 Inducers: Pretreatment of 14 healthy volunteers with multiple doses of rifampin, 600 mg daily for 8 days, followed by a single 400 mg dose of Gleevec, increased Gleevec oral-dose clearance by 3.8-fold (90% confidence interval = 3.5- to 4.3-fold), which represents mean decreases in C_{max}, $AUC_{(0-24)}$ and $AUC_{(0-\infty)}$ by 54%, 68% and 74%, of the respective values without rifampin treatment. *(See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)*

In Vitro Studies of CYP Enzyme Inhibition: Human liver microsome studies demonstrated that Gleevec is a potent competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4/5 with K_i values of 27, 7.5 and 8 μM, respectively. Gleevec is likely to increase the blood level of drugs that are substrates of CYP2C9, CYP2D6 and CYP3A4/5. *(See PRECAUTIONS.)*

CLINICAL STUDIES

Chronic Myeloid Leukemia

Chronic Phase, Newly Diagnosed

An open-label, multicenter, international randomized Phase 3 study has been conducted in patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. This study compared treatment with either single-agent Gleevec® (imatinib mesylate) or a combination of interferon-alfa (IFN) plus cytarabine (Ara-C). Patients were allowed to cross over to the alternative treatment arm if they failed to show a complete hematologic response (CHR) at 6 months, a major cytogenetic response (MCyR) at 12 months, or if they lost a CHR or MCyR. Patients with increasing WBC or severe intolerance to treatment were also allowed to cross over to the alternative treatment arm with the permission of the study monitoring committee (SMC). In the Gleevec arm, patients were treated initially with 400 mg daily. In the IFN arm, patients were treated with a target dose of IFN of 5 MIU/m^2/day subcutaneously in combination with subcutaneous Ara-C 20 mg/m^2/day for 10 days/month.

A total of 1106 patients were randomized from 177 centers in 16 countries, 553 to each arm. Baseline characteristics were well balanced between the two arms. Median age was 51 years (range 18-70 years), with 21.9% of patients ≥60 years of age. There were 59% males and 41% females; 89.9% Caucasian and 4.7% Black patients. With a median follow-up of 14 and 13 months for Gleevec and IFN, respectively, 90% of patients randomized to Gleevec were still receiving first-line treatment. Due to discontinuations and cross-overs, only 30% of patients randomized to IFN were still on first-line treatment. In the IFN arm, withdrawal of consent (13.4%) was the most frequent reason for discontinuation of first-line therapy, and the most frequent reason for cross over to the Gleevec arm was severe intolerance to treatment (22.7%).

The primary efficacy endpoint of the study was progression-free survival (PFS). The final analysis of progression-free survival was planned after 5 years, however, the reported analysis was conducted at one year after the last patient was randomized to the study. Progression was defined as any of the following events: progression to accelerated phase or blast crisis, death, loss of CHR or MCyR, or in patients not achieving a CHR an increasing WBC despite appropriate therapeutic management. The protocol specified that the progression analysis would compare the intent to treat (ITT) population: patients randomized to receive Gleevec were compared with patients randomized to receive interferon. Patients that crossed over prior to progression were not censored at the time of cross-over, and events that occurred in these patients following cross-over were attributed to the original randomized treatment. A total of 218 patients crossed over from the interferon arm to the Gleevec arm, and 7 patients crossed over from the Gleevec arm to the interferon arm. The estimated rate of progression-free survival at 12 months in the ITT population was 97.2% in the Gleevec arm and 80.3% in the control arm. (Figure 1.) The estimated rate of patients free of progression to accelerated phase (AP) or blast crisis (BC) at 12 months was 98.5% in the Gleevec arm compared to the 93.1% in the IFN

(Figure 2.) There were 11 and 20 deaths reported in the Gleevec and IFN arm, respectively.

Figure 1 Time to Progression (ITT Principle)

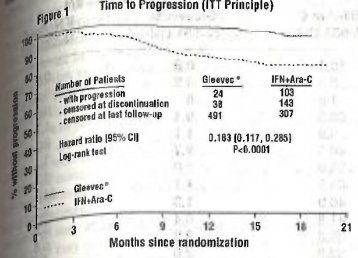
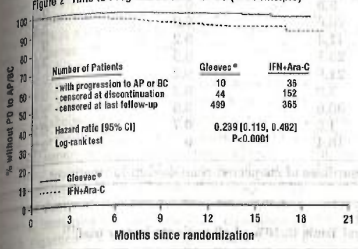


Figure 2 Time to Progression to AP or BC (ITT Principle)



Major cytogenetic response, hematologic response, time to accelerated phase or blast crisis and survival were main secondary endpoints. Response data are shown in Table 1. Complete hematologic response, major cytogenetic response and complete cytogenetic response were also statistically significantly higher in the Gleevec arm compared to the IFN + Ara-C arm.

[See table 1 at right]

Physical, functional, and treatment-specific biologic response modifier scales from the FACT-BRM (Functional Assessment of Cancer Therapy - Biologic Response Modifier) instrument were used to assess patient-reported general effects of interferon toxicity in 1067 patients with CML in chronic phase. After one month of therapy to six months of therapy, there was a 13%–21% decrease in median index from baseline in patients treated with interferon, consistent with increased symptoms of interferon toxicity. There was no apparent change from baseline in median index for patients treated with Gleevec.

Late Chronic Phase CML and Advanced Stage CML

Three international, open-label, single-arm Phase 2 studies were conducted to determine the safety and efficacy of Gleevec in patients with Ph+ CML: 1) in the chronic phase after failure of IFN therapy, 2) in accelerated phase disease, or 3) in myeloid blast crisis. About 45% of patients were women and 6% were Black. In clinical studies 38%-40% of patients were ≥60 years of age and 10%-12% of patients were ≥70 years of age.

Chronic Phase, Prior Interferon-Treatment

532 patients were treated at a starting dose of 400 mg; dose escalation to 600 mg was allowed. The patients were distributed in three main categories according to their response to prior interferon: failure to achieve (within 6 months), or loss of a complete hematologic response (29%), failure to achieve (within 1 year) or loss of a major cytogenetic response (35%), or intolerance to interferon (36%). Patients had received a median of 14 months of prior IFN therapy at doses ≥25 × 10^6 IU/week and were all in late chronic phase, with a median time from diagnosis of 32 months. Effectiveness was evaluated on the basis of the rate of hematologic response and by bone marrow exams to assess the rate of major cytogenetic response (up to 35% Ph+ metaphases) or complete cytogenetic response (0% Ph+ metaphases). Efficacy results are reported in Table 2. Results were similar in the three subgroups described above.

Accelerated Phase

235 patients with accelerated phase disease were enrolled. These patients met one or more of the following criteria: ≥15%-<30% blasts in PB or BM; ≥30% blasts + promyelocytes in PB or BM; ≥20% basophils in PB; and <100 × 10^9/L platelets. The first 77 patients were started at 400 mg, with the remaining 158 patients starting at 600 mg.

Effectiveness was evaluated primarily on the basis of the rate of hematologic response, reported as either complete hematologic response, no evidence of leukemia (i.e., clearance of blasts from the marrow and the blood, but without a full peripheral blood recovery as for complete responses), or return to chronic phase CML. Cytogenetic responses were also evaluated. Efficacy results are reported in Table 2. Response rates in accelerated phase CML were higher for the 600-mg dose group than for the 400 mg group: hematologic response (73% vs. 62%), confirmed and unconfirmed major cytogenetic response (28% vs. 18%).

Myeloid Blast Crisis

260 patients with myeloid blast crisis were enrolled. These patients had ≥30% blasts in PB or BM and/or extramedullary involvement other than spleen or liver; 95 (37%) had received prior chemotherapy for treatment of either accelerated phase or blast crisis ("pretreated patients") whereas 165 (63%) had not ("untreated patients"). The first 37 patients were started at 400 mg; the remaining 223 patients were started at 600 mg.

Effectiveness was evaluated primarily on the basis of rate of hematologic response, reported as either complete hematologic response, no evidence of leukemia, or return to chronic phase CML using the same criteria as for the study in accelerated phase. Cytogenetic responses were also assessed. Efficacy results are reported in Table 2. The hematologic response rate was higher in untreated patients than in treated patients (36% vs. 22%, respectively) and in the group receiving an initial dose of 600 mg rather than 400 mg (33% vs. 16%). The confirmed and unconfirmed major cytogenetic response rate was also higher for the 600-mg dose group than for the 400 mg group (17% vs. 8%).

[See table 2 above]

The median time to hematologic response was 1 month. Response duration cannot be precisely defined because follow-up on most patients is relatively short. In blast crisis, the estimated median duration of hematologic response is about 10 months. In accelerated phase, median duration of hematologic response is greater than 12 months but cannot yet be estimated. Follow-up is insufficient to estimate duration of cytogenetic response in all studies.

Efficacy results were similar in men and women and in patients younger and older than age 65. Responses were seen in Black patients, but there were too few Black patients to allow a quantitative comparison.

Pediatric CML

One open-label, single arm study enrolled 14 pediatric patients with Ph+ chronic phase CML recurrent after stem cell transplant or resistant to alpha interferon therapy. Patients ranged in age from 3 to 20 years old; 3 were 3-11 years old, 9 were 12-18 years old, and 2 were >18 years old. Patients were treated at doses of 260 mg/m^2/day (n=3), 340 mg/m^2/day (n=4), 440 mg/m^2/day (n=5) and 570 mg/m^2/day (n=2). In the 13 patients for whom cytogenetic data are available, 4 achieved a major cytogenetic response, 7 achieved a complete cytogenetic response, and 2 had minimal cytogenetic response. At the recommended dose of 260 mg/m^2/day, 2 of 3 patients achieved a complete cytogenetic response. Cytogenetic response rate was similar at all dose levels.

In a second study, 2 of 3 patients with Ph+ chronic phase CML resistant to alpha interferon achieved a complete cytogenetic response at doses of 242 and 257 mg/m^2/day.

Gastrointestinal Stromal Tumors

One open-label, multinational study was conducted in patients with unresectable or metastatic malignant gastrointestinal stromal tumors (GIST). In this study 147 patients were enrolled and randomized to receive either 400 mg or 600 mg orally q.d. for up to 24 months. The study was not powered to show a statistically significant difference in response rates between the two dose groups. Patients ranged in age from 18 to 83 years old and had a pathologic diagnosis of Kit-positive unresectable and/or metastatic malignant GIST. Immunohistochemistry was routinely performed with Kit antibody (A-4502, rabbit polyclonal antiserum, 1:100; DAKO Corporation, Carpinteria, CA) according to analysis by an avidin-biotin-peroxidase complex method after antigen retrieval.

The primary outcome of the study was objective response rate. Tumors were required to be measurable at entry in at least one site of disease, and response characterization was based on Southwestern Oncology Group (SWOG) criteria. Results are shown in Table 3.

Table 1
Response in Newly Diagnosed CML Study (First-Line)

(Best Response Rates)	Gleevec® n=553	IFN+Ara-C n=553
Hematologic Response[1]		
CHR Rate n (%)	522 (94.4%)*	302 (54.6%)*
[95% CI]	[92.1%, 96.2%]	[50.4%, 58.8%]
Cytogenetic Response[2]		
Major Cytogenetic Response n (%)	419 (75.8%)*	67 (12.1%)*
[95% CI]	[72.0%, 79.3%]	[9.5%, 15.1%]
Unconfirmed[3]	82.6%*	20.3%*
Complete Cytogenetic Response n (%)	297 (53.7%)*	15 (2.7%)*
Unconfirmed[3]	67.8%*	7.4%*

*p<0.001, Fischer's exact test

[1] **Hematologic response criteria (all responses to be confirmed after ≥4 weeks):** WBC<10 × 10^9/L, platelet <450 × 10^9/L, myelocyte + metamyelocyte <5% in blood, no blasts and promyelocytes in blood, basophils <20%, no extramedullary involvement.

[2] **Cytogenetic response criteria (confirmed after ≥4 weeks):** complete (0% Ph+ metaphases) or partial (1%-35%). A major response (0%–35%) combines both complete and partial responses.

[3] Unconfirmed cytogenetic response is based on a single bone marrow cytogenetic evaluation, therefore unconfirmed complete or partial cytogenetic responses might have had a lesser cytogenetic response on a subsequent bone marrow evaluation.

Table 2
Response in CML Studies

	Chronic Phase IFN Failure (n=532)	Accelerated Phase (n=235)	Myeloid Blast Crisis (n=260)
	400 mg	600 mg n=158 400 mg n=77	600 mg n=223 400 mg n=37
		% of patients [$CI_{95\%}$]	
Hematologic Response[1]	**93% [91.0-95.4]**	**69% [63.0-75.2]**	**31% [25.2-36.8]**
Complete Hematologic Response (CHR)	93%	37%	7%
No evidence of Leukemia (NEL)	Not applicable	12%	5%
Return to Chronic Phase (RTC)	Not applicable	20%	19%
Major Cytogenetic Response[2]	**53% [48.7-57.3]**	**19% [14.3-24.8]**	**7% [4.2-10.7]**
(Unconfirmed[3])	(61%)	(25%)	(15%)
Complete[4] (Unconfirmed[3])	32% (41%)	13% (17%)	1.5% (7%)

[1] **Hematologic response criteria (all responses to be confirmed after ≥4 weeks):**
CHR: Chronic phase study [WBC <10 ×10^9/L, platelet <450 ×10^9/L, myelocytes + metamyelocytes <5% in blood, no blasts and promyelocytes in blood, basophils <20%, no extramedullary involvement] and in the accelerated and blast crisis studies [ANC ≥1.5 ×10^9/L, platelets ≥100 ×10^9/L, no blood blasts, BM blasts <5% and no extramedullary disease]
NEL: same criteria as for CHR but ANC ≥1 ×10^9/L and platelets ≥20 ×10^9/L (accelerated and blast crisis studies)
RTC: <15% blasts BM and PB, <30% blasts + promyelocytes in BM and PB, <20% basophils in PB, no extramedullary disease other than spleen and liver (accelerated and blast crisis studies).
BM=bone marrow, PB=peripheral blood

[2] **Cytogenetic response criteria (confirmed after ≥4 weeks):** complete (0% Ph+ metaphases) or partial (1%-35%). A major response (0%-35%) combines both complete and partial responses.

[3] Unconfirmed cytogenetic response is based on a single bone marrow cytogenetic evaluation, therefore unconfirmed complete or partial cytogenetic responses might have had a lesser cytogenetic response on a subsequent bone marrow evaluation.

[4] Complete cytogenetic response confirmed by a second bone marrow cytogenetic evaluation performed at least one month after the initial bone marrow study.

Table 3
Tumor Response in GIST Study

Total Patients	N	Confirmed Partial Response N (%)	95% Confidence Interval
400 mg daily	73	24 (33%)	22%, 45%
600 mg daily	74	32 (43%)	32%, 55%
Total	147	56 (38%)	30%, 46%

A statistically significant difference in response rates between the two dose groups was not demonstrated. At the

Continued on next page

Gleevec—Cont.

time of interim analysis, when the median follow-up was less than 7 months, 55 of 56 patients with a confirmed partial response (PR) had a maintained PR. The data were too immature to determine a meaningful response duration. No responses were observed in 12 patients with progressive disease on 400 mg daily whose doses were increased to 600 mg daily.

INDICATIONS AND USAGE

Gleevec® (imatinib mesylate) is indicated for the treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in chronic phase. Follow-up is limited.

Gleevec is also indicated for the treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Gleevec is also indicated for the treatment of pediatric patients with Ph+ chronic phase CML whose disease has recurred after stem cell transplant or who are resistant to interferon alpha therapy. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Gleevec is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). *(See CLINICAL STUDIES: Gastrointestinal Stromal Tumors.)* The effectiveness of Gleevec in GIST is based on objective response rate *(see CLINICAL STUDIES)*. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

CONTRAINDICATIONS

Use of Gleevec® (imatinib mesylate) is contraindicated in patients with hypersensitivity to imatinib or to any other component of Gleevec.

WARNINGS

Pregnancy

Women of childbearing potential should be advised to avoid becoming pregnant.

Imatinib mesylate was teratogenic in rats when administered during organogenesis at doses ≥100 mg/kg, approximately equal to the maximum clinical dose of 800 mg/day (based on body surface area). Teratogenic effects included exencephaly or encephalocele, absent/reduced frontal and absent parietal bones. Female rats administered doses ≥45 mg/kg (approximately one-half the maximum human dose of 800 mg/day, based on body surface area) also experienced significant post-implantation loss as evidenced by either early fetal resorption or stillbirths, nonviable pups and early pup mortality between postpartum days 0 and 4. At doses higher than 100 mg/kg, total fetal loss was noted in all animals. Fetal loss was not seen at doses ≤30 mg/kg (one-third the maximum human dose of 800 mg).

Male and female rats were exposed *in utero* to a maternal imatinib mesylate dose of 45 mg/kg (approximately one-half the maximum human dose of 800 mg) from day 6 of gestation and through milk during the lactation period. These animals then received no imatinib exposure for nearly 2 months. Body weights were reduced from birth until terminal sacrifice in these rats. Although fertility was not affected, fetal loss was seen when these male and female animals were then mated.

There are no adequate and well-controlled studies in pregnant women. If Gleevec® (imatinib mesylate) is used during pregnancy, or if the patient becomes pregnant while taking (receiving) Gleevec, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

General

Fluid Retention and Edema: Gleevec® (imatinib mesylate) is often associated with edema and occasionally serious fluid retention *(see ADVERSE REACTIONS)*. Patients should be weighed and monitored regularly for signs and symptoms of fluid retention. An unexpected rapid weight gain should be carefully investigated and appropriate treatment provided. The probability of edema was increased with higher Gleevec dose and age >65 years in the CML studies. Severe superficial edema was reported in 0.9% of newly diagnosed CML patients taking Gleevec, and in 2%-5% of other adult CML patients taking Gleevec. In addition, severe fluid retention (e.g., pleural effusion, pericardial effusion, pulmonary edema, and ascites) was reported in 2%-8% of other adult CML patients taking Gleevec. There have been post-marketing reports, including fatalities, of cerebral edema, increased intracranial pressure, and papilledema in patients with CML treated with Gleevec.

Severe superficial edema and severe fluid retention (pleural effusion, pulmonary edema and ascites) were reported in 1%-6% of patients taking Gleevec for GIST.

GI Irritation: Gleevec is sometimes associated with GI irritation. Gleevec should be taken with food and a large glass of water to minimize this problem.

Hemorrhage: In the newly diagnosed CML trial, 0.7% of patients had grade 3/4 hemorrhage. In the GIST clinical trial seven patients (5%), four in the 600-mg dose group and three in the 400-mg dose group, had a total of eight events of CTC grade 3/4 - gastrointestinal (GI) bleeds (3 patients), intra-tumoral bleeds (3 patients) or both (1 patient). Gastrointestinal tumor sites may have been the source of GI bleeds.

Hematologic Toxicity: Treatment with Gleevec is associated with anemia, neutropenia, and thrombocytopenia. Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example every 2-3 months). In CML, the occurrence of these cytopenias is dependent on the stage of disease and is more frequent in patients with accelerated phase CML or blast crisis than in patients with chronic phase CML. *(See DOSAGE AND ADMINISTRATION.)*

Hepatotoxicity: Hepatotoxicity, occasionally severe, may occur with Gleevec *(see ADVERSE REACTIONS)*. Liver function (transaminases, bilirubin, and alkaline phosphatase) should be monitored before initiation of treatment and monthly or as clinically indicated. Laboratory abnormalities should be managed with interruption and/or dose reduction of the treatment with Gleevec. *(See DOSAGE AND ADMINISTRATION.)* Patients with hepatic impairment should be closely monitored because exposure to Gleevec may be increased. As there are no clinical studies of Gleevec in patients with impaired liver function, no specific advice concerning initial dosing adjustment can be given.

Table 4
Adverse Experiences Reported in Newly Diagnosed CML Clinical Trial (≥10% of all patients)[1]

Preferred Term	All Grades Gleevec® N=551 (%)	All Grades IFN+Ara-C N=533 (%)	CTC Grades 3/4 Gleevec® N=551 (%)	CTC Grades 3/4 IFN+Ara-C N=533 (%)
Fluid Retention	54.1	10.1	0.9	0.9
– Superficial Edema	53.2	8.8	0.9	0.4
– Other Fluid Retention Events	3.4	1.5	0	0.6
Nausea	42.5	60.8	0.4	5.1
Muscle Cramps	35.4	9.9	1.1	0.2
Musculoskeletal Pain	33.6	40.5	2.7	7.7
Rash	31.9	25.0	2.0	2.1
Fatigue	30.7	64.7	1.1	24.0
Diarrhea	30.3	40.9	1.3	3.2
Headache	28.5	41.8	0.4	3.2
Joint Pain	26.7	38.3	2.2	6.8
Abdominal Pain	23.4	22.9	2.0	3.6
Myalgia	20.9	38.6	1.5	8.1
Nasopharyngitis	19.2	7.7	0	0.2
Hemorrhage	18.9	19.9	0.7	1.3
Dyspepsia	15.1	9.0	0	0.8
Vomiting	14.7	26.6	0.9	3.4
Pharyngolaryngeal Pain	14.2	11.4	0.2	0
Dizziness	13.2	23.1	0.5	3.4
Cough	12.5	21.6	0.2	0.6
Upper Respiratory Tract Infection	12.5	7.9	0.2	0.4
Pyrexia	11.8	38.6	0.5	2.8
Weight Increased	11.6	1.5	0.7	0.2
Insomnia	11.4	18.4	0	2.3

[1] All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship to treatment.

Table 5
Adverse Experiences Reported in Other CML Clinical Trials (≥10% of all patients in any trial)[1]

Preferred Term	Myeloid Blast Crisis (n=260) % All Grades	Myeloid Blast Crisis (n=260) % Grade 3/4	Accelerated Phase (n=235) % All Grades	Accelerated Phase (n=235) % Grade 3/4	Chronic Phase, IFN Failure (n=532) % All Grades	Chronic Phase, IFN Failure (n=532) % Grade 3/4
Nausea	70	4	71	5	60	2
Fluid Retention	71	12	73	6	66	3
– Superficial Edema	67	5	71	4	64	2
– Other Fluid Retention Events[2]	22	8	10	3	7	2
Muscle Cramps	27	0.8	42	0.4	55	1
Diarrhea	42	4	55	4	43	2
Vomiting	54	4	56	3	32	1
Hemorrhage	52	19	44	9	22	2
– CNS Hemorrhage	7	5	2	0.9	1	1
– Gastrointestinal Hemorrhage	8	3	5	3	2	0.4
Musculoskeletal Pain	43	9	46	9	35	2
Skin Rash	35	5	44	4	42	3
Headache	27	5	30	2	34	0.2
Fatigue	29	3	41	4	40	1
Arthralgia	25	4	31	6	36	1
Dyspepsia	11	0	21	0	24	0
Myalgia	8	0	22	2	25	0.2
Weight Increase	5	0.8	14	3	30	5
Pyrexia	41	7	39	8	17	1
Abdominal Pain	31	6	33	3	29	0.6
Cough	14	0.8	26	0.9	17	0
Dyspnea	14	4	20	7	9	0.6
Anorexia	14	2	17	2	6	0
Constipation	15	2	15	0.9	6	0.2
Nasopharingitis	8	0	16	0	18	0.2
Night Sweats	12	0.8	14	1	10	0.2
Pruritus	8	1	13	0.9	12	0.8
Epistaxis	13	3	13	0	5	0.2
Hypokalemia	13	4	8	2	5	0.2
Petechiae	10	2	5	0.9	1	0
Pneumonia	12	6	8	6	3	0.8
Weakness	12	3	9	3	7	0.2
Upper Respiratory Tract Infection	3	0	9	0.4	15	0
Dizziness	11	0.4	12	0	13	0.2
Insomnia	10	0	13	0	13	0.2
Sore Throat	8	0	11	0	11	0
Ecchymosis	11	0.4	6	0.9	2	0
Rigors	10	0	11	0.4	8	0
Asthenia	5	2	11	2	6	0
Influenza	0.8	0.4	6	0	10	0.2

[1] All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship to treatment.
[2] Other fluid retention events include pleural effusion, ascites, pulmonary edema, pericardial effusion, anasarca, edema aggravated, and fluid retention not otherwise specified.

Toxicities From Long-Term Use: It is important to consider potential toxicities suggested by animal studies, specifically, *liver and kidney toxicity and immunosuppression.* Severe liver toxicity was observed in dogs treated for 2 weeks, with elevated liver enzymes, hepatocellular necrosis, bile duct necrosis, and bile duct hyperplasia. Renal toxicity was observed in monkeys treated for 2 weeks, with focal mineralization and dilation of the renal tubules and tubular nephrosis. Increased BUN and creatinine were observed in several of these animals. An increased rate of opportunistic infections was observed with chronic imatinib treatment in laboratory animal studies. In a 39-week monkey study, treatment with imatinib resulted in worsening of normally suppressed malarial infections in these animals. Lymphopenia was observed in animals (as in humans).

Drug Interactions

Drugs that may alter imatinib plasma concentrations

Drugs that may **increase** imatinib plasma concentrations: Caution is recommended when administering Gleevec with inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin). Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity may decrease metabolism and increase imatinib concentrations. There is a significant increase in exposure to imatinib when Gleevec is coadministered with ketoconazole (CYP3A4 inhibitor).

Drugs that may **decrease** imatinib plasma concentrations: Substances that are inducers of CYP3A4 activity may increase metabolism and decrease imatinib plasma concentrations. Co-medications that induce CYP3A4 (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital or St. John's Wort) may significantly reduce exposure to Gleevec. Pretreatment of healthy volunteers with multiple doses of rifampin followed by a single dose of Gleevec, increased Gleevec oral-dose clearance by 3.8-fold, which significantly ($p<0.05$) decreased mean C_{max} and $AUC_{(0-\infty)}$. In patients where rifampin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less enzyme induction potential should be considered. *(See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)*

Drugs that may have their plasma concentration altered by Gleevec

Gleevec increases the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5-fold, respectively, suggesting an inhibition of the CYP3A4 by Gleevec. Particular caution is recommended when administering Gleevec with CYP3A4 substrates that have a narrow therapeutic window (e.g., cyclosporine or pimozide). Gleevec will increase plasma concentration of other CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.).

Because *warfarin* is metabolized by CYP2C9 and CYP3A4, patients who require anticoagulation should receive low-molecular weight or standard heparin.

In vitro, Gleevec inhibits the cytochrome P450 isoenzyme CYP2D6 activity at similar concentrations that affect CYP3A4 activity. Systemic exposure to substrates of CYP2D6 is expected to be increased when coadministered with Gleevec. No specific studies have been performed and caution is recommended.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with imatinib mesylate.

Positive genotoxic effects were obtained for imatinib in an *in vitro* mammalian cell assay (Chinese hamster ovary) for clastogenicity (chromosome aberrations) in the presence of metabolic activation. Two intermediates of the manufacturing process, which are also present in the final product, are positive for mutagenesis in the Ames assay. One of these intermediates was also positive in the mouse lymphoma assay. Imatinib was not genotoxic when tested in an *in vitro* bacterial cell assay (Ames test), an *in vitro* mammalian cell assay (mouse lymphoma) and an *in vivo* rat micronucleus assay.

In a study of fertility, in male rats dosed for 70 days prior to mating, testicular and epididymal weights and percent motile sperm were decreased at 60 mg/kg, approximately three-fourths the maximum clinical dose of 800 mg/day, based on body surface area. This was not seen at doses ≤20 mg/kg (one-fourth the maximum human dose of 800 mg). When female rats were dosed 14 days prior to mating and through to gestational day 6, there was no effect on mating or on number of pregnant females.

In female rats dosed with imatinib mesylate at 45 mg/kg (approximately one-half the maximum human dose of 800 mg, based on body surface area) from gestational day 6 until the end of lactation, red vaginal discharge was noted on either gestational day 14 or 15.

Pregnancy

Pregnancy Category D. (See WARNINGS.)

Nursing Mothers

It is not known whether imatinib mesylate or its metabolites are excreted in human milk. However, in lactating female rats administered 100 mg/kg, a dose approximately equal to the maximum clinical dose of 800 mg/day based on body surface area, imatinib and its metabolites were extensively excreted in milk. Concentration in milk was approximately three-fold higher than in plasma. It is estimated that approximately 1.5% of a maternal dose is excreted into milk, which is equivalent to a dose to the infant of 30% the maternal dose per unit body weight. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should be advised against breastfeeding while taking Gleevec.

Pediatric Use

Gleevec safety and efficacy have been demonstrated only in children with Ph+ chronic phase CML with recurrence after stem cell transplantation or resistance to interferon alpha therapy. There are no data in children under 3 years of age.

Geriatric Use

In the CML clinical studies, approximately 40% of patients were older than 60 years and 10% were older than 70 years. In the study of patients with newly diagnosed CML, 22% of patients were 60 years of age or older. No difference was observed in the safety profile in patients older than 65 years as compared to younger patients, with the exception of a higher frequency of edema. *(See PRECAUTIONS.)* The efficacy of Gleevec was similar in older and younger patients. In the GIST study, 29% of patients were older than 60 years and 10% of patients were older than 70 years. No obvious differences in the safety or efficacy profile were noted in patients older than 65 years as compared to younger patients, but the small number of patients does not allow a formal analysis.

ADVERSE REACTIONS

Chronic Myeloid Leukemia

The majority of Gleevec-treated patients experienced adverse events at some time. Most events were of mild-to-moderate grade, but drug was discontinued for adverse events in 2% of patients in chronic phase, 3% in accelerated phase and 5% in blast crisis.

The most frequently reported drug-related adverse events were nausea, vomiting, diarrhea, edema, and muscle cramps (Table 4 for newly diagnosed CML, Table 5 for other CML patients). Edema was most frequently periorbital or in lower limbs and was managed with diuretics, other supportive measures, or by reducing the dose of Gleevec® (imatinib mesylate). *(See DOSAGE AND ADMINISTRATION.)* The frequency of severe superficial edema was 0.9%-5%.

A variety of adverse events represent local or general fluid retention including pleural effusion, ascites, pulmonary edema and rapid weight gain with or without superficial edema. These events appear to be dose related, were more common in the blast crisis and accelerated phase studies (where the dose was 600 mg/day), and are more common in the elderly. These events were usually managed by interrupting Gleevec treatment and with diuretics or other appropriate supportive care measures. However, a few of these events may be serious or life threatening, and one patient with blast crisis died with pleural effusion, congestive heart failure, and renal failure.

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of the patients treated in the Gleevec studies are shown in Tables 4 and 5.

[See table 4 at top of previous page]

Table 6
Lab Abnormalities in Newly Diagnosed CML Trial

	Gleevec® N=551 %		IFN+Ara-C N=533 %	
CTC Grades	Grade 3	Grade 4	Grade 3	Grade 4
Hematology Parameters				
- Neutropenia*	11.4	2.2	20.3	4.3
- Thrombocytopenia*	6.9	0.2	15.8	0.6
- Anemia	2.7	0.4	4.1	0.2
Biochemistry Parameters				
- Elevated Creatinine	0	0	0.4	0
- Elevated Bilirubin	0.2	0.5	0.2	0
- Elevated Alkaline Phosphatase	0.2	0	0.8	0
- Elevated SGOT (AST)	2.9	0.2	3.8	0.4
- Elevated SGPT (ALT)	3.1	0.4	5.6	0

*$p<0.001$ (difference in grade 3 plus 4 abnormalities between the two treatment groups)

Table 7
Lab Abnormalities in Other CML Clinical Trials

	Myeloid Blast Crisis (n=260) 600 mg n=223 400 mg n=37 %		Accelerated Phase (n=235) 600 mg n=158 400 mg n=77 %		Chronic Phase, IFN Failure (n=532) 400 mg %	
CTC Grades	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Hematology Parameters						
- Neutropenia	16	48	23	36	27	8
- Thrombocytopenia	29	33	31	13	19	<1
- Anemia	41	11	34	6	6	1
Biochemistry Parameters						
- Elevated Creatinine	1.5	0	1.3	0	0.2	0
- Elevated Bilirubin	3.8	0	2.1	0	0.8	0
- Elevated Alkaline Phosphatase	4.6	0	5.1	0.4	0.2	0
- Elevated SGOT (AST)	1.9	0	3.0	0	2.3	0
- Elevated SGPT (ALT)	2.3	0.4	3.8	0	1.9	0

CTC grades: neutropenia (grade 3 ≥0.5-1.0 × 10^9/L), grade 4 <0.5 × 10^9/L), thrombocytopenia (grade 3 ≥10-50 × 10^9/L, grade 4 <10 × 10^9/L), anemia (hemoglobin ≥65-80 g/L, grade 4 <65 g/L), elevated creatinine (grade 3 >3-6 × upper limit normal range [ULN], grade 4 >6 × ULN), elevated bilirubin (grade 3 >3-10 × ULN, grade 4 >10 × ULN), elevated alkaline phosphatase (grade 3 >5-20 × ULN, grade 4 >20 × ULN), elevated SGOT or SGPT (grade 3 >5-20 × ULN, grade 4 >20 × ULN)

[See table 5 on previous page]

Hematologic Toxicity

Cytopenias, and particularly neutropenia and thrombocytopenia, were a consistent finding in all studies, with a higher frequency at doses ≥750 mg (Phase 1 study). However, the occurrence of cytopenias in CML patients was also dependent on the stage of the disease.

In patients with newly diagnosed CML, cytopenias were less frequent than in the other CML patients *(see Tables 6 and 7).* The frequency of grade 3 or 4 neutropenia and thrombocytopenia was between 2- and 3-fold higher in blast crisis and accelerated phase compared to chronic phase *(see Tables 6 and 7).* The median duration of the neutropenic and thrombocytopenic episodes varied from 2 to 3 weeks, and from 2 to 4 weeks, respectively.

These events can usually be managed with either a reduction of the dose or an interruption of treatment with Gleevec, but in rare cases require permanent discontinuation of treatment.

Hepatotoxicity

Severe elevation of transaminases or bilirubin occurred in 1%-4% *(see Tables 6 and 7)* and were usually managed with dose reduction or interruption (the median duration of these episodes was approximately one week). Treatment was discontinued permanently because of liver laboratory abnormalities in less than 0.5% of patients. However, one patient, who was taking acetaminophen regularly for fever, died of acute liver failure.

Adverse Reactions in Pediatric Population

The overall safety profile of pediatric patients treated with Gleevec in 39 children studied was similar to that found in studies with adult patients, except that musculoskeletal pain was less frequent (20.5%) and peripheral edema was not reported.

Adverse Effects in Other Subpopulations

In older patients (≥65 years old), with the exception of edema, where it was more frequent, there was no evidence of an increase in the incidence or severity of adverse events. In women there was an increase in the frequency of neutropenia, as well as grade 1/2 superficial edema, headache, nausea, rigors, vomiting, rash, and fatigue. No differences were seen related to race but the subsets were too small for proper evaluation.

[See table 6 above]
[See table 7 above]

Gastrointestinal Stromal Tumors

The majority of Gleevec-treated patients experienced adverse events at some time. The most frequently reported adverse events were edema, nausea, diarrhea, abdominal pain, muscle cramps, fatigue, and rash. Most events were of mild-to-moderate severity. Drug was discontinued for adverse events in 6 patients (8%) in both dose levels studied.

Continued on next page

Gleevec—Cont.

Superficial edema, most frequently periorbital or lower extremity edema, was managed with diuretics, other supportive measures, or by reducing the dose of Gleevec® (imatinib mesylate). *(See DOSAGE AND ADMINISTRATION.)* Severe (CTC grade 3/4) superficial edema was observed in 3 patients (2%), including face edema in one patient. Grade 3/4 pleural effusion or ascites was observed in 3 patients (2%).

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of the patients treated with Gleevec are shown in Table 8. No major differences were seen in the severity of adverse events between the 400-mg or 600-mg treatment groups, although overall incidence of diarrhea, muscle cramps, headache, dermatitis, and edema was somewhat higher in the 600-mg treatment group.

[See table 8 at right]

Clinically relevant or severe abnormalities of routine hematologic or biochemistry laboratory values are presented in Table 9.

[See table 9 at right]

Post-Marketing Experiences

The following less common (estimated 1%-10%), infrequent (estimated 0.1%-1%), and rare (estimated less than 0.1%) adverse events have been reported in patients receiving Gleevec:

Cardiovascular: *Infrequent:* cardiac failure, tachycardia, hypertension, hypotension, flushing, peripheral coldness

Clinical Laboratory Tests: *Infrequent:* blood CPK increased, blood LDH increased

Dermatologic: *Less common:* dry skin, alopecia; *Infrequent:* exfoliative dermatitis, bullous eruption, nail disorder, skin pigmentation changes, photosensitivity reaction, purpura; *Rare:* vesicular rash, Stevens-Johnson syndrome

Digestive: *Less common:* abdominal distention, gastroesophageal reflux, mouth ulceration; *Infrequent:* gastric ulcer, gastroenteritis, gastritis; *Rare:* colitis

Hematologic: *Infrequent:* pancytopenia

Hypersensitivity: *Rare:* angioedema

Infections: *Infrequent:* sepsis, herpes simplex, herpes zoster

Metabolic and Nutritional: *Infrequent:* hypophosphatemia, dehydration, gout, appetite disturbances, weight decreased; *Rare:* hyperkalemia, hyponatremia

Musculoskeletal: *Less common:* joint swelling; *Infrequent:* sciatica, joint and muscle stiffness

Nervous System/Psychiatric: *Less common:* paresthesia; *Infrequent:* depression, anxiety, syncope, peripheral neuropathy, somnolence, migraine, memory impairment; *Rare:* increased intracranial pressure, cerebral edema (including fatalities)

Renal: *Infrequent:* renal failure, urinary frequency, hematuria

Reproductive: *Infrequent:* breast enlargement, menorrhagia, sexual dysfunction

Respiratory: *Rare:* interstitial pneumonitis, pulmonary fibrosis

Special Senses: *Less common:* conjunctivitis, vision blurred; *Infrequent:* conjunctival hemorrhage, dry eye, vertigo, tinnitus; *Rare:* macular edema, papilledema, retinal hemorrhage

OVERDOSAGE

Experience with doses greater than 800 mg is limited. In the event of overdosage, the patient should be observed and appropriate supportive treatment given. An oral dose of 1200 mg/m^2/day, approximately 2.5 times the human dose of 800 mg, based on body surface area, was not lethal to rats following 14 days of administration. A dose of 3600 mg/m^2/day, approximately 7.5 times the human dose of 800 mg, was lethal to rats after 7-10 administrations, due to general deterioration of the animals with secondary degenerative histological changes in many tissues.

DOSAGE AND ADMINISTRATION

Therapy should be initiated by a physician experienced in the treatment of patients with chronic myeloid leukemia or gastrointestinal stromal tumors.

The recommended dosage of Gleevec® (imatinib mesylate) is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis. The recommended Gleevec dosage is 260 mg/m^2/day for children with Ph+ chronic phase CML recurrent after stem cell transplant or who are resistant to interferon alpha therapy. The recommended dosage of Gleevec is 400 mg/day or 600 mg/day for adult patients with unresectable and/or metastatic, malignant GIST.

The prescribed dose should be administered orally, with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day.

In children, Gleevec treatment can be given as a once daily dose or alternatively the daily dose may be split into two – once in the morning and once in the evening. There is no experience with Gleevec treatment in children under 3 years of age.

For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of water or apple juice. The required number of tablets should be placed in the appropriate volume of beverage (approximately 50 mL for a 100-mg tablet, and 200 mL for a 400-mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s).

Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory hematologic response after at least 3 months of treatment; failure to achieve a cytogenetic response after 6-12 months of treatment; or loss of a previously achieved hematologic or cytogenetic response. In children with chronic phase CML, daily doses can be increased under circumstances similar to those leading to an increase in adult chronic phase disease, from 260 mg/m^2/day to 340 mg/m^2/day, as clinically indicated.

Dosage of Gleevec should be increased by at least 50%, and clinical response should be carefully monitored, in patients receiving Gleevec with a potent CYP3A4 inducer such as rifampin or phenytoin.

Dose Adjustment for Hepatotoxicity and Other Non-Hematologic Adverse Reactions

If a severe non-hematologic adverse reaction develops (such as severe hepatotoxicity or severe fluid retention), Gleevec

Table 8
Adverse Experiences Reported in GIST Trial (≥10% of all patients at either dose)[1]

	All CTC Grades Initial Dose (mg/day)		CTC Grade 3/4 Initial Dose (mg/day)	
Preferred Term	400 mg (n=73) %	600 mg (n=74) %	400 mg (n=73) %	600 mg (n=74) %
Fluid retention	71	76	6	3
- Superficial Edema	71	76	4	0
- Pleural Effusion or Ascites	6	4	1	3
Diarrhea	56	60	1	4
Nausea	53	56	3	3
Fatigue	33	38	1	0
Muscle Cramps	30	41	0	0
Abdominal Pain	37	37	7	3
Skin Rash	26	38	3	3
Headache	25	35	0	0
Vomiting	22	23	1	3
Musculoskeletal Pain	19	11	3	0
Flatulence	16	23	0	0
Any Hemorrhage	18	19	5	8
- Tumor Hemorrhage	1	4	1	4
- Cerebral Hemorrhage	1	0	1	0
- GI Tract Hemorrhage	6	4	4	1
Nasopharyngitis	12	14	0	0
Pyrexia	12	5	0	0
Insomnia	11	11	0	0
Back Pain	11	10	1	0
Lacrimation Increased	6	11	0	0
Upper Respiratory Tract Infection	6	11	0	0
Taste Disturbance	1	14	0	0

[1] All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship to treatment.

Table 9
Laboratory Abnormalities in GIST Trial

	400 mg (n=73) %		600 mg (n=74) %	
CTC Grade	Grade 3	Grade 4	Grade 3	Grade 4
Hematology Parameters				
- Anemia	3	0	4	1
- Thrombocytopenia	0	0	1	0
- Neutropenia	3	3	5	4
Biochemistry Parameters				
- Elevated Creatinine	0	1	3	0
- Reduced Albumin	3	0	4	0
- Elevated Bilirubin	1	0	1	3
- Elevated Alkaline Phosphatase	0	0	1	0
- Elevated SGOT (AST)	3	0	1	1
- Elevated SGPT (ALT)	3	0	4	0

CTC grades: neutropenia (grade 3 ≥0.5-1.0 × 10^9/L, grade 4 <0.5 × 10^9/L), thrombocytopenia (grade 3 ≥10-50 × 10^9/L, grade 4 <10 × 10^9/L), anemia (grade 3 ≥65-80 g/L, grade 4 <65 g/L), elevated creatinine (grade 3 >3-6 × upper limit normal range [ULN], grade 4 >6 × ULN), elevated bilirubin (grade 3 >3-10 × ULN, grade 4 >10 × ULN), elevated alkaline phosphatase, SGOT or SGPT (grade 3 >5-20 × ULN, grade 4 >20 × ULN), albumin (grade 3 <20 g/L)

Table 10
Dose Adjustments for Neutropenia and Thrombocytopenia

Chronic Phase CML (starting dose 400 mg[1]) or GIST (starting dose either 400 mg or 600 mg)	ANC <1.0 × 10^9/L and/or Platelets <50 × 10^9/L	1. Stop Gleevec until ANC ≥1.5 × 10^9/L and platelets ≥75 × 10^9/L 2. Resume treatment with Gleevec at the original starting dose of 400 mg[1] or 600 mg 3. If recurrence of ANC <1.0 × 10^9/L and/or platelets <50 × 10^9/L, repeat step 1 and resume Gleevec at a reduced dose (300 mg[2] if starting dose was 400 mg[1], 400 mg if starting dose was 600 mg)
Accelerated Phase CML and Blast Crisis (starting dose 600 mg)	[3]ANC <0.5 × 10^9/L and/or Platelets <10 × 10^9/L	1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy) 2. If cytopenia is unrelated to leukemia, reduce dose of Gleevec to 400 mg 3. If cytopenia persist 2 weeks, reduce further to 300 mg 4. If cytopenia persist 4 weeks and is still unrelated to leukemia, stop Gleevec until ANC ≥1 × 10^9/L and platelets ≥20 × 10^9/L and then resume treatment at 300 mg

[1] or 260 mg/m^2 in children
[2] or 200 mg/m^2 in children
[3] occurring after at least 1 month of treatment

should be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event.
If elevations in bilirubin >3 × institutional upper limit of normal (IULN) or in liver transaminases >5 × IULN occur, Gleevec should be withheld until bilirubin levels have returned to a <1.5 × IULN and transaminase levels to <2.5 × IULN. In adults, treatment with Gleevec may then be continued at a reduced daily dose (i.e., 400 mg to 300 mg or 600 mg to 400 mg). In children, daily doses can be reduced under the same circumstances from 260 mg/m²/day to 200 mg/m²/day or from 340 mg/m²/day to 260 mg/m²/day, respectively.

Dose Adjustment for Hematologic Adverse Reactions

Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in Table 10.

[See table 10 on previous page]

HOW SUPPLIED

Each film-coated tablet contains 100 mg or 400 mg of imatinib free base.

100 mg Tablets

Very dark yellow to brownish orange film-coated tablets, round, biconvex with bevelled edges debossed with "NVR" on one side and "SA" with score on the other side.
Bottles of 100 tablets ..... NDC 0078-0401-05

400 mg Tablets

Very dark yellow to brownish orange film-coated tablets, ovaloid, biconvex with bevelled edges, debossed with "NVR" on one side and "SL" on the other side.
Bottles of 30 tablets ..... NDC 0078-0402-15

Storage

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature]. Protect from moisture.
Dispense in a tight container, USP.

T2003-09
REV: MAY 2003 89019001
Manufactured by:
Novartis Pharma Stein AG
Stein, Switzerland
Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936
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Shown in Product Identification Guide, page 326

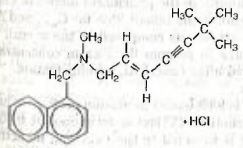
LAMISIL® ℞

[la'mə'sɔl]
(terbinafine hydrochloride tablets)
Tablets
Rx only

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

DESCRIPTION

LAMISIL® (terbinafine hydrochloride tablets) Tablets contain the synthetic allylamine antifungal compound terbinafine hydrochloride.
Chemically, terbinafine hydrochloride is (E)-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-*N*-methyl-1-naphthalenemethanamine hydrochloride. The empirical formula $C_{21}H_{26}ClN$ with a molecular weight of 327.90, and the following structural formula:



Terbinafine hydrochloride is a white to off-white fine crystalline powder. It is freely soluble in methanol and methylene chloride, soluble in ethanol, and slightly soluble in water.

Each tablet contains:

Active Ingredients: terbinafine hydrochloride (equivalent to 250 mg base)
Inactive Ingredients: colloidal silicon dioxide, NF; hydroxypropyl methylcellulose, USP; magnesium stearate, NF; microcrystalline cellulose, NF; sodium starch glycolate, NF

CLINICAL PHARMACOLOGY

Pharmacokinetics

Following oral administration, terbinafine is well absorbed (>70%) and the bioavailability of LAMISIL® (terbinafine hydrochloride tablets) Tablets as a result of first-pass metabolism is approximately 40%. Peak plasma concentrations of 1 µg/mL appear within 2 h after a single 250 mg dose; the AUC (area under the curve) is approximately 4.56 µg·h/mL. An increase in the AUC of terbinafine of less than 20% is observed when LAMISIL® is administered with food. No clinically relevant age-dependent changes in steady-state plasma concentrations of terbinafine have been reported. In patients with renal impairment (creatinine clearance ≤ 50 mL/min) or hepatic cirrhosis, the clearance of terbinafine is decreased by approximately 50% compared to normal volunteers. No effect of gender on the blood levels of terbinafine was detected in clinical trials. In plasma, terbinafine is >99% bound to plasma proteins and there are no specific binding sites. At steady-state, in comparison to a single dose, the peak concentration of terbinafine is 25% higher and plasma AUC increases by a factor of 2.5; the increase in plasma AUC is consistent with an effective half-life of ~36 hours. Terbinafine is distributed to the sebum and skin. A terminal half-life of 200-400 h may represent the slow elimination of terbinafine from tissues such as skin and adipose. Prior to excretion, terbinafine is extensively metabolized. No metabolites have been identified that have antifungal activity similar to terbinafine. Approximately 70% of the administered dose is eliminated in the urine.

Microbiology

Terbinafine hydrochloride is a synthetic allylamine derivative. Terbinafine hydrochloride is hypothesized to act by inhibiting squalene epoxidase, thus blocking the biosynthesis of ergosterol, an essential component of fungal cell membranes. *In vitro*, mammalian squalene epoxidase is only inhibited at higher (4000 fold) concentrations than is needed for inhibition of the dermatophyte enzyme. Depending on the concentration of the drug and the fungal species test *in vitro*, terbinafine hydrochloride may be fungicidal. However, the clinical significance of *in vitro* data is unknown.
Terbinafine has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the *INDICATIONS AND USAGE* section:

Trichophyton mentagrophytes
Trichophyton rubrum

The following *in vitro* data are available, but their clinical significance is unknown. *In vitro*, terbinafine exhibits satisfactory MIC's against most strains of the following microorganisms; however, the safety and efficacy of terbinafine in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials:

Candida albicans
Epidermophyton floccosum
Scopulariopsis brevicaulis

CLINICAL STUDIES

The efficacy of LAMISIL® (terbinafine hydrochloride tablets) Tablets in the treatment of onychomycosis is illustrated by the response of patients with toenail and/or fingernail infections who participated in three US/Canadian placebo-controlled clinical trials.
Results of the first toenail study, as assessed at week 48 (12 weeks of treatment with 36 weeks follow-up after completion of therapy), demonstrated mycological cure, defined as simultaneous occurrence of negative KOH plus negative culture, in 70% of patients. Fifty-nine percent (59%) of patients experienced effective treatment (mycological cure plus 0% nail involvement or >5mm of new unaffected nail growth); 38% of patients demonstrated mycological cure plus clinical cure (0% nail involvement).
In a second toenail study of dermatophytic onychomycosis, in which non-dermatophytes were also cultured, similar efficacy against the dermatophytes was demonstrated. The pathogenic role of the non-dermatophytes cultured in the presence of dermatophytic onychomycosis has not been established. The clinical significance of this association is unknown.
Results of the fingernail study, as assessed at week 24 (6 weeks of treatment with 18 weeks follow-up after completion of therapy), demonstrated mycological cure in 79% of patients, effective treatment in 75% of the patients, and mycological cure plus clinical cure in 59% of the patients.
The mean time to overall success was approximately 10 months for the first toenail study and 4 months for the fingernail study. In the first toenail study, for patients evaluated at least six months after achieving clinical cure and at least one year after completing LAMISIL® therapy, the clinical relapse rate was approximately 15%.

INDICATIONS AND USAGE

LAMISIL® (terbinafine hydrochloride tablets) Tablets are indicated for the treatment of onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium) *(see DOSAGE AND ADMINISTRATION* and *CLINICAL STUDIES)*.
Prior to initiating treatment, appropriate nail specimens for laboratory testing (KOH preparation, fungal culture, or nail biopsy) should be obtained to confirm the diagnosis of onychomycosis.

CONTRAINDICATIONS

LAMISIL® (terbinafine hydrochloride tablets) Tablets are contraindicated in individuals with hypersensitivity to terbinafine or to any other ingredients of the formulation.

WARNINGS

Rare cases of liver failure, some leading to death or liver transplant, have occurred with the use of LAMISIL® Tablets for the treatment of onychomycosis in individuals with and without pre-existing liver disease.
In the majority of liver cases reported in association with LAMISIL® use, the patients had serious underlying systemic conditions and an uncertain causal association with LAMISIL®. The severity of hepatic events and/or their outcome may be worse in patients with active or chronic liver disease *(see PRECAUTIONS)*. Treatment with LAMISIL® Tablets should be discontinued if biochemical or clinical evidence of liver injury develops *(see PRECAUTIONS* below).
There have been isolated reports of serious skin reactions (e.g., Stevens-Johnson Syndrome and toxic epidermal necrolysis). If progressive skin rash occurs, treatment with LAMISIL® should be discontinued.

PRECAUTIONS

General

LAMISIL® is not recommended for patients with chronic or active liver disease. Before prescribing LAMISIL® Tablets, pre-existing liver disease should be assessed. Hepatotoxicity may occur in patients with and without pre-existing liver disease. Pretreatment serum transaminase (ALT and AST) tests are advised for all patients before taking LAMISIL® Tablets. Patients prescribed LAMISIL® (terbinafine hydrochloride tablets) Tablets should be warned to report immediately to their physician any symptoms of persistent nausea, anorexia, fatigue, vomiting, right upper abdominal pain or jaundice, dark urine or pale stools *(see WARNINGS)*. Patients with these symptoms should discontinue taking oral terbinafine, and the patient's liver function should be immediately evaluated.
In patients with renal impairment (creatinine clearance ≤ 50 mL/min), the use of LAMISIL® has not been adequately studied, and therefore, is not recommended *(see CLINICAL PHARMACOLOGY, Pharmacokinetics)*.
Changes in the ocular lens and retina have been reported following the use of LAMISIL® (terbinafine hydrochloride tablets) Tablets in controlled trials. The clinical significance of these changes is unknown.
Transient decreases in absolute lymphocyte counts (ALC) have been observed in controlled clinical trials. In placebo-controlled trials, 8/465 LAMISIL®-treated patients (1.7%) and 3/137 placebo-treated patients (2.2%) had decreases in ALC to below 1000/mm³ on two or more occasions. The clinical significance of this observation is unknown. However, in patients with known or suspected immunodeficiency, physicians should consider monitoring complete blood counts in individuals using LAMISIL® therapy for greater than six weeks.
Isolated cases of severe neutropenia have been reported. These were reversible upon discontinuation of LAMISIL®, with or without supportive therapy. If clinical signs and symptoms suggestive of secondary infection occur, a complete blood count should be obtained. If the neutrophil count is ≤ 1,000 cells/mm³, LAMISIL® should be discontinued and supportive management started.

Drug Interactions

In vitro studies with human liver microsomes showed that terbinafine does not inhibit the metabolism of tolbutamide, ethinylestradiol, ethoxycoumarin, and cyclosporine. *In vitro* studies have also shown that terbinafine inhibits CYP2D6-mediated metabolism. This may be of clinical relevance for compounds predominantly metabolized by this enzyme, such as tricyclic antidepressants, β-blockers, selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAO-Is) Type B, if they have a narrow therapeutic window.
In vivo drug-drug interaction studies conducted in the normal volunteer subjects showed that terbinafine does not affect the clearance of antipyrine or digoxin. Terbinafine decreases the clearance of caffeine by 19%. Terbinafine increases the clearance of cyclosporine by 15%.
There have been spontaneous reports of increase or decrease in prothrombin times in patients concomitantly taking oral terbinafine and warfarin, however, a causal relationship between LAMISIL® Tablets and these changes has not been established.
Terbinafine clearance is increased 100% by rifampin, a CyP450 enzyme inducer, and decreased 33% by cimetidine, a CyP450 enzyme inhibitor. Terbinafine clearance is unaffected by cyclosporine.
There is no information available from adequate drug-drug interaction studies with the following classes of drugs: oral contraceptives, hormone replacement therapies, hypoglycemics, theophyllines, phenytoins, thiazide diuretics, beta blockers, and calcium channel blockers.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 28-month oral carcinogenicity study in rats, an increase in the incidence of liver tumors was observed in males at the highest dose tested, 69 mg/kg/day [2× the Maximum Recommended Human Dose (MRHD) based on AUC comparisons of the parent terbinafine]; however, even though dose-limiting toxicity was not achieved at the highest tested dose, higher doses were not tested.
The results of a variety of *in vitro* (mutations in *E. coli* and *S. typhimurium*, DNA repair in rat hepatocytes, mutagenicity in Chinese hamster fibroblasts, chromosome aberration and sister chromatid exchanges in Chinese hamster lung cells), and *in vivo* (chromosome aberration in Chinese hamsters, micronucleus test in mice) genotoxicity tests gave no evidence of a mutagenic or clastogenic potential. Oral reproduction studies in rats at doses up to 300 mg/kg/day (approximately 12× the MRHD based on body surface area comparisons, BSA) did not reveal any specific effects on fertility or other reproductive parameters. Intravaginal application of terbinafine hydrochloride at 150 mg/day in pregnant rabbits did not increase the incidence of abortions or premature deliveries nor affect fetal parameters.

Pregnancy

Pregnancy Category B: Oral reproduction studies have been performed in rabbits and rats at doses up to 300 mg/kg/day (12× to 23× the MRHD, in rabbits and rats, respectively, based on BSA) and have revealed no evidence of impaired fertility or harm to the fetus due to terbinafine. There are, however, no adequate and well-controlled studies

Continued on next page

dose of 5-10 mg/kg/day. Some centers have successfully tapered the maintenance dose to as low as 3 mg/kg/day in selected *renal* transplant patients without an apparent rise in rejection rate.
(See Blood Level Monitoring below)
In pediatric usage, the same dose and dosing regimen may be used as in adults although in several studies children have required and tolerated higher doses than those used in adults.
Adjunct therapy with adrenal corticosteroids is recommended. Different tapering dosage schedules of prednisone appear to achieve similar results. A dosage schedule based on the patient's weight started with 2.0 mg/kg/day for the first 4 days tapered to 1.0 mg/kg/day by 1 week, 0.6 mg/kg/day by 2 weeks, 0.3 mg/kg/day by 1 month, and 0.15 mg/kg/day by 2 months and thereafter as a maintenance dose. Another center started with an initial dose of 200 mg tapered by 40 mg/day until reaching 20 mg/day. After 2 months at this dose, a further reduction to 10 mg/day was made. Adjustments in dosage of prednisone must be made according to the clinical situation.
To make Sandimmune® Oral Solution (cyclosporine oral solution, USP) more palatable, the oral solution may be diluted with milk, chocolate milk, or orange juice preferably at room temperature. Patients should avoid switching diluents frequently. Sandimmune® Soft Gelatin Capsules and Oral Solution should be administered on a consistent schedule with regard to time of day and relation to meals.
Take the prescribed amount of Sandimmune® (cyclosporine) from the container using the dosage syringe supplied after removal of the protective cover, and transfer the solution to a glass of milk, chocolate milk, or orange juice. Stir well and drink at once. Do not allow to stand before drinking. It is best to use a glass container and rinse it with more diluent to ensure that the total dose is taken. After use, replace the dosage syringe in the protective cover. Do not rinse the dosage syringe with water or other cleaning agents either before or after use. If the dosage syringe requires cleaning, it must be completely dry before resuming use. Introduction of water into the product by any means will cause variation in dose.
Sandimmune® Injection (cyclosporine injection, USP)
FOR INFUSION ONLY
Note: Anaphylactic reactions have occurred with Sandimmune® Injection (cyclosporine injection, USP). *(See WARNINGS)*
Patients unable to take Sandimmune® Soft Gelatin Capsules or Oral Solution pre- or postoperatively may be treated with the I.V. concentrate. **Sandimmune® Injection (cyclosporine injection, USP) is administered at 1/3 the oral dose.** The initial dose of Sandimmune® Injection (cyclosporine injection, USP) should be given 4-12 hours prior to transplantation as a single I.V. dose of 5-6 mg/kg/day. This daily single dose is continued postoperatively until the patient can tolerate the soft gelatin capsules or oral solution. Patients should be switched to Sandimmune® Soft Gelatin Capsules or Oral Solution as soon as possible after surgery. In pediatric usage, the same dose and dosing regimen may be used, although higher doses may be required. Adjunct steroid therapy is to be used. *(See aforementioned)*
Immediately before use, the I.V. concentrate should be diluted 1 mL Sandimmune® Injection (cyclosporine injection, USP) in 20 mL-100 mL 0.9% Sodium Chloride Injection or 5% Dextrose Injection and given in a slow intravenous infusion over approximately 2-6 hours.
Diluted infusion solutions should be discarded after 24 hours.
The Cremophor® EL (polyoxyethylated castor oil) contained in the concentrate for intravenous infusion can cause phthalate stripping from PVC.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
Blood Level Monitoring
Several study centers have found blood level monitoring of cyclosporine useful in patient management. While no fixed relationships have yet been established, in one series of 375 consecutive cadaveric renal transplant recipients, dosage was adjusted to achieve specific whole blood 24-hour trough levels of 100-200 ng/mL as determined by high-pressure liquid chromatography (HPLC).
Of major importance to blood level analysis is the type of assay used. The above levels are specific to the parent cyclosporine molecule and correlate directly to the new monoclonal specific radioimmunoassays (mRIA-sp). Nonspecific assays are also available which detect the parent compound molecule and various of its metabolites. Older studies often cited levels using a nonspecific assay which were roughly twice those of specific assays. Assay results are not interchangeable and their use should be guided by their approved labeling. If plasma specimens are employed, levels will vary with the temperature at the time of separation from whole blood. Plasma levels may range from 1/2–1/5 of whole blood levels. Refer to individual assay labeling for complete instructions. In addition, *Transplantation Proceedings* (June 1990) contains position papers and a broad consensus generated at the Cyclosporine Therapeutic Drug Monitoring conference that year. Blood level monitoring is not a replacement for renal function monitoring or tissue biopsies.

HOW SUPPLIED

Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP)
25 mg: Oblong, pink, branded "⚠ 78/240". Unit dose packages of 30 capsules,
3 blister cards of 10 capsules ..... NDC 0078-0240-15
100 mg: Oblong, dusty rose, branded "⚠ 78/241". Unit dose packages of 30 capsules,
3 blister cards of 10 capsules ..... NDC 0078-0241-15
Store and Dispense: Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). [See USP Controlled Room Temperature]
An odor may be detected upon opening the unit dose container, which will dissipate shortly thereafter. This odor does not affect the quality of the product.
Sandimmune® Oral Solution (cyclosporine oral solution, USP)
Supplied in 50 mL bottles containing 100 mg of cyclosporine per mL ..... NDC 0078-0110-22.
A dosage syringe is provided for dispensing.
Store and Dispense: In the original container at temperatures below 30°C (86°F). Do not store in the refrigerator. Protect from freezing. Once opened, the contents must be used within 2 months.
Sandimmune® Injection (cyclosporine injection, USP)
FOR INTRAVENOUS INFUSION
Supplied as a 5 mL sterile ampul containing 50 mg of cyclosporine per mL,
in boxes of 10 ampuls ..... NDC 0078-0109-01
Store and Dispense: At temperatures below 30°C (86°F) and protected from light.
Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP)
Manufactured by:
R.P. Scherer GmbH, Eberbach/Baden, Germany
Distributed by:
Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936
Sandimmune® Oral Solution (cyclosporine oral solution, USP)
Manufactured by:
Novartis Pharma S.A., Huningue, France
Distributed by:
Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936
Sandimmune® Injection (cyclosporine injection, USP)
FOR INFUSION ONLY
Manufactured by:
Novartis Pharma Stein AG,
Stein, Switzerland
Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2002-89
REV: DECEMBER 2002 8901610

Shown in Product Identification Guide, page 327

SANDOSTATIN®

Rx

[săn-dō-stă-tĭn]
(octreotide acetate)
Injection
Rx only

The following prescribing information is base on official labeling in effect July 2003.

DESCRIPTION

Sandostatin® (octreotide acetate) Injection, a cyclic octapeptide prepared as a clear sterile solution of octreotide, acetate salt, in a buffered lactic acid solution for administration by deep subcutaneous (intrafat) or intravenous injection. Octreotide acetate, known chemically as L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2→7)-disulfide; [R-(R*, R*)] acetate salt, is a long-acting octapeptide with pharmacologic actions mimicking those of the natural hormone somatostatin.
Sandostatin® (octreotide acetate) Injection is available as: sterile 1 mL ampuls in 3 strengths, containing 50, 100, or 500 mcg octreotide (as acetate), and sterile 5 mL multi-dose vials in 2 strengths, containing 200 and 1000 mcg/mL of octreotide (as acetate).
Each ampul also contains:

lactic acid, USP	3.4 mg
mannitol, USP	45 mg
sodium bicarbonate, USP	qs to pH 4.2 ± 0.3
water for injection, USP	qs to 1 mL

Each mL of the multi-dose vials also contains:

lactic acid, USP	3.4 mg
mannitol, USP	45 mg
phenol, USP	5.0 mg
sodium bicarbonate, USP	qs to pH 4.2 ± 0.3
water for injection, USP	qs to 1 mL

Lactic acid and sodium bicarbonate are added to provide a buffered solution, pH to 4.2 ± 0.3.
The molecular weight of octreotide acetate is 1019.3 (free peptide, $C_{49}H_{66}N_{10}O_{10}S_2$) and its amino acid sequence is:

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol,
x CH_3COOH where x = 1.4 to 2.5

CLINICAL PHARMACOLOGY

Sandostatin® (octreotide acetate) exerts pharmacologic actions similar to the natural hormone, somatostatin. It is an even more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Like somatostatin, it also suppresses LH response to GnRH, decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.
By virtue of these pharmacological actions, Sandostatin® (octreotide acetate) has been used to treat the symptoms associated with metastatic carcinoid tumors (flushing and diarrhea), and Vasoactive Intestinal Peptide (VIP) secreting adenomas (watery diarrhea).
Sandostatin® (octreotide acetate) substantially reduces growth hormone and/or IGF-I (somatomedin C) levels in patients with acromegaly.
Single doses of Sandostatin® (octreotide acetate) have been shown to inhibit gallbladder contractility and to decrease bile secretion in normal volunteers. In controlled clinical trials the incidence of gallstone or biliary sludge formation was markedly increased (see *WARNINGS*).
Sandostatin® (octreotide acetate) suppresses secretion of thyroid stimulating hormone (TSH).
Pharmacokinetics
After subcutaneous injection, octreotide is absorbed rapidly and completely from the injection site. Peak concentrations of 5.2 ng/mL (100 mcg dose) were reached 0.4 hours after dosing. Using a specific radioimmunoassay, intravenous and subcutaneous doses were found to be bioequivalent. Peak concentrations and area under the curve values were dose proportional after intravenous single doses up to 200 mcg and subcutaneous single doses up to 500 mcg and after subcutaneous multiple doses up to 500 mcg t.i.d. (1500 mcg/day).
In healthy volunteers the distribution of octreotide from plasma was rapid ($t_{\alpha 1/2}$ = 0.2 h), the volume of distribution (Vdss) was estimated to be 13.6 L, and the total body clearance ranged from 7 L/hr to 10 L/hr. In blood, the distribution into the erythrocytes was found to be negligible and about 65% was bound in the plasma in a concentration-independent manner. Binding was mainly to lipoprotein and, to a lesser extent, to albumin.
The elimination of octreotide from plasma had an apparent half-life of 1.7 to 1.9 hours compared with 1-3 minutes with the natural hormone. The duration of action of Sandostatin® (octreotide acetate) is variable but extends up to 12 hours depending upon the type of tumor. About 32% of the dose is excreted unchanged into the urine. In an elderly population, dose adjustments may be necessary due to a significant increase in the half-life (46%) and a significant decrease in the clearance (26%) of the drug.
In patients with acromegaly, the pharmacokinetics differ somewhat from those in healthy volunteers. A mean peak concentration of 2.8 ng/mL (100 mcg dose) was reached in 0.7 hours after subcutaneous dosing. The volume of distribution (Vdss) was estimated to be 21.6 ± 8.5 L and the total body clearance was increased to 18 L/h. The mean percent of the drug bound was 41.2%. The disposition and elimination half-lives were similar to normals.
In patients with renal impairment the elimination of octreotide from plasma was prolonged and total body clearance reduced. In mild renal impairment (Cl_{CR} 40-60 mL/min) octreotide $t_{\frac{1}{2}}$ was 2.4 hours and total body clearance was 8.8 L/hr, in moderate impairment (Cl_{CR} 10-39 mL/min) $t_{\frac{1}{2}}$ was 3.0 hours and total body clearance 7.3 L/hr, and in severely renally impaired patients not requiring dialysis (Cl_{CR} <10 mL/min) $t_{\frac{1}{2}}$ was 3.1 hours and total body clearance was 7.6 L/hr. In patients with severe renal failure requiring dialysis, total body clearance was reduced to about half that found in healthy subjects (from approximately 10 L/hr to 4.5 L/hr).
Patients with liver cirrhosis showed prolonged elimination of drug, with octreotide $t_{\frac{1}{2}}$ increasing to 3.7 hr and total body clearance decreasing to 5.9 L/hr, whereas patients with fatty liver disease showed $t_{\frac{1}{2}}$ increased to 3.4 hr and total body clearance of 8.2 L/hr.

INDICATIONS AND USAGE

Acromegaly
Sandostatin® (octreotide acetate) is indicated to reduce blood levels of growth hormone and IGF-I (somatomedin C) in acromegaly patients who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, and bromocriptine mesylate at maximally tolerated doses. The goal is to achieve normalization of growth hormone and IGF-I (somatomedin C) levels (*see DOSAGE AND ADMINISTRATION*). In patients with acromegaly, Sandostatin® (octreotide acetate) reduces growth hormone to within normal ranges in 50% of patients and reduces IGF-I (somatomedin C) to within normal ranges in 50%-60% of patients. Since the effects of pituitary irradiation may not become maximal for several years, adjunctive therapy with Sandostatin® (octreotide acetate) to reduce blood levels of growth hormone and IGF-I (somatomedin C) offers potential benefit before the effects of irradiation are manifested.
Improvement in clinical signs and symptoms or reduction in tumor size or rate of growth were not shown in clinical trials performed with Sandostatin® (octreotide acetate); these trials were not optimally designed to detect such effects.
Carcinoid Tumors
Sandostatin® (octreotide acetate) is indicated for the symptomatic treatment of patients with metastatic carcinoid tumors where it suppresses or inhibits the severe diarrhea and flushing episodes associated with the disease.

Continued on next page

Sandostatin—Cont.

Sandostatin® (octreotide acetate) studies were not designed to show an effect on the size, rate of growth or development of metastases.

Vasoactive Intestinal Peptide Tumors (VIPomas)

Sandostatin® (octreotide acetate) is indicated for the treatment of the profuse watery diarrhea associated with VIP-secreting tumors. Sandostatin® (octreotide acetate) studies were not designed to show an effect on the size, rate of growth or development of metastases.

CONTRAINDICATIONS

Sensitivity to this drug or any of its components.

WARNINGS

Single doses of Sandostatin® (octreotide acetate) have been shown to inhibit gallbladder contractility and decrease bile secretion in normal volunteers. In clinical trials (primarily patients with acromegaly or psoriasis), the incidence of biliary tract abnormalities was 63% (27% gallstones, 24% sludge without stones, 12% biliary duct dilatation). The incidence of stones or sludge in patients who received Sandostatin® (octreotide acetate) for 12 months or longer was 52%. Less than 2% of patients treated with Sandostatin® (octreotide acetate) for 1 month or less developed gallstones. The incidence of gallstones did not appear related to age, sex or dose. Like patients without gallbladder abnormalities, the majority of patients developing gallbladder abnormalities on ultrasound had gastrointestinal symptoms. The symptoms were not specific for gallbladder disease. A few patients developed acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, or pancreatitis during Sandostatin® (octreotide acetate) therapy or following its withdrawal. One patient developed ascending cholangitis during Sandostatin® (octreotide acetate) therapy and died.

PRECAUTIONS

General

Sandostatin® (octreotide acetate) alters the balance between the counter-regulatory hormones, insulin, glucagon and growth hormone, which may result in hypoglycemia or hyperglycemia. Sandostatin® (octreotide acetate) also suppresses secretion of thyroid stimulating hormone, which may result in hypothyroidism. Cardiac conduction abnormalities have also occurred during treatment with Sandostatin® (octreotide acetate). However, the incidence of these adverse events during long-term therapy was determined vigorously only in acromegaly patients who, due to their underlying disease and/or the subsequent treatment they receive, are at an increased risk for the development of diabetes mellitus, hypothyroidism, and cardiovascular disease. Although the degree to which these abnormalities are related to Sandostatin® (octreotide acetate) therapy is not clear, new abnormalities of glycemic control, thyroid function and ECG developed during Sandostatin® (octreotide acetate) therapy as described below.

The hypoglycemia or hyperglycemia which occurs during Sandostatin® (octreotide acetate) therapy is usually mild, but may result in overt diabetes mellitus or necessitate dose changes in insulin or other hypoglycemic agents. Hypoglycemia and hyperglycemia occurred on Sandostatin® (octreotide acetate) in 3% and 16% of acromegalic patients, respectively. Severe hyperglycemia, subsequent pneumonia, and death following initiation of Sandostatin® (octreotide acetate) therapy was reported in one patient with no history of hyperglycemia.

In acromegalic patients, 12% developed biochemical hypothyroidism only, 8% developed goiter, and 4% required initiation of thyroid replacement therapy while receiving Sandostatin® (octreotide acetate). Baseline and periodic assessment of thyroid function (TSH, total and/or free T_4) is recommended during chronic therapy.

In acromegalics, bradycardia (<50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias occurred in 9% of patients during Sandostatin® (octreotide acetate) therapy. Other EKG changes observed included QT prolongation, axis shifts, early repolarization, low voltage, R/S transition, and early R wave progression. These ECG changes are not uncommon in acromegalic patients. Dose adjustments in drugs such as beta-blockers that have bradycardia effects may be necessary. In one acromegalic patient with severe congestive heart failure, initiation of Sandostatin® (octreotide acetate) therapy resulted in worsening of CHF with improvement when drug was discontinued. Confirmation of a drug effect was obtained with a positive rechallenge.

Several cases of pancreatitis have been reported in patients receiving Sandostatin® (octreotide acetate) therapy.

Sandostatin® (octreotide acetate) may alter absorption of dietary fats in some patients.

In patients with severe renal failure requiring dialysis, the half-life of Sandostatin® (octreotide acetate) may be increased, necessitating adjustment of the maintenance dosage.

Depressed vitamin B_{12} levels and abnormal Schilling's tests have been observed in some patients receiving Sandostatin® (octreotide acetate) therapy, and monitoring of vitamin B_{12} levels is recommended during chronic Sandostatin® (octreotide acetate) therapy.

Information for Patients

Careful instruction in sterile subcutaneous injection technique should be given to the patients and to other persons who may administer Sandostatin® (octreotide acetate) Injection.

Laboratory Tests

Laboratory tests that may be helpful as biochemical markers in determining and following patient response depend on the specific tumor. Based on diagnosis, measurement of the following substances may be useful in monitoring the progress of therapy:

Acromegaly: Growth Hormone, IGF-I (somatomedin C) Responsiveness to Sandostatin® (octreotide acetate) may be evaluated by determining growth hormone levels at 1-4 hour intervals for 8-12 hours post dose. Alternatively, a single measurement of IGF-I (somatomedin C) level may be made two weeks after drug initiation or dosage change.

Carcinoid: 5-HIAA (urinary 5-hydroxyindole acetic acid), plasma serotonin, plasma Substance P

VIPoma: VIP (plasma vasoactive intestinal peptide)

Baseline and periodic total and/or free T_4 measurements should be performed during chronic therapy *(see PRECAUTIONS — General)*.

Drug Interactions

Sandostatin® (octreotide acetate) has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs. Concomitant administration of Sandostatin® (octreotide acetate) with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection.

Patients receiving insulin, oral hypoglycemic agents, beta blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may require dose adjustments of these therapeutic agents.

Drug Laboratory Test Interactions

No known interference exists with clinical laboratory tests, including amine or peptide determinations.

Carcinogenesis/Mutagenesis/Impairment of Fertility

Studies in laboratory animals have demonstrated no mutagenic potential of Sandostatin® (octreotide acetate).

No carcinogenic potential was demonstrated in mice treated subcutaneously for 85-99 weeks at doses up to 2000 mcg/kg/day (8× the human exposure based on body surface area). In a 116-week subcutaneous study in rats, a 27% and 12% incidence of injection site sarcomas or squamous cell carcinomas was observed in males and females, respectively, at the highest dose level of 1250 mcg/kg/day (10× the human exposure based on body surface area) compared to an incidence of 8%-10% in the vehicle-control groups. The increased incidence of injection site tumors was most probably caused by irritation and the high sensitivity of the rat to repeated subcutaneous injections at the same site. Rotating injection sites would prevent chronic irritation in humans. There have been no reports of injection site tumors in patients treated with Sandostatin® (octreotide acetate) for up to 5 years. There was also a 15% incidence of uterine adenocarcinomas in the 1250 mcg/kg/day females compared to 7% in the saline-control females and 0% in the vehicle-control females. The presence of endometritis coupled with the absence of corpora lutea, the reduction in mammary fibroadenomas, and the presence of uterine dilatation suggest that the uterine tumors were associated with estrogen dominance in the aged female rats which does not occur in humans.

Sandostatin® (octreotide acetate) did not impair fertility in rats at doses up to 1000 mcg/kg/day, which represents 7× the human exposure based on body surface area.

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses up to 16 times the highest human dose based on body surface area and have revealed no evidence of impaired fertility or harm to the fetus due to Sandostatin® (octreotide acetate). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in milk, caution should be exercised when Sandostatin® (octreotide acetate) is administered to a nursing woman.

Pediatric Use

Experience with Sandostatin® (octreotide acetate) in the pediatric population is limited. Although formal controlled clinical trials have not been performed to evaluate safety and effectiveness in this age group, there are reports of 49 cases in the literature of neonates and infants with congenital hyperinsulinism [also called familial hyperinsulinism (HI), persistent hyperinsulinemic hypoglycemia of infancy (PHHI), or nesidioblastosis] who have received Sandostatin® as an inhibitor of insulin release. The following efficacy and safety information is derived from these 49 patients.

Sandostatin® has been used to stabilize plasma glucose levels prior to pancreatectomy and to treat recurrent postoperative hypoglycemia. Although most use of octreotide in this setting is short-term, a few reports in the literature have documented longer-term therapy in pediatric patients (2.2-5.5 years). Octreotide is an alternative medical treatment to diazoxide for control of hypoglycemia in this disorder. Of 31 pediatric patients who received Sandostatin® as prescribed for congenital hyperinsulinism and for which long-term follow-up was available, octreotide obviated the need for surgery in 3 patients (10%) and was replaced by diazoxide in 4 patients (13%) due to uncontrolled hypoglycemia. Although the remainder of these patients required surgery, there have been a few reports in the literature of patients who have responded to octreotide after failing treatment with surgery and/or diazoxide. Doses of 3-40 mcg/kg/day have been used. At these doses, the majority of side effects were gastrointestinal; diarrhea, steatorrhea, vomiting, and abdominal distention, each reported in 22%-35% (n = 11-17) of patients. However, they were generally short-lived – with resolution of vomiting and distention in 2-4 days, and diarrhea/steatorrhea, within 2-4 weeks. Steatorrhea was controlled in most patients with pancreatic enzyme supplements. Poor growth was reported in 37% of patients (n = 7) who received Sandostatin® for 1-4.33 years. It was associated with low serum growth hormone and/or IGF-1 levels in 4/6 patients in whom these parameters were measured. Catch-up growth occurred in 3/3 patients who were followed after Sandostatin® was discontinued. Poor weight gain was reported in 32% of patients (n = 6). Tachyphylaxis was reported in 35% (n = 17) of patients. Asymptomatic gallstones with sludge was reported in one infant after one year of therapy and was treated with ursodeoxycholic acid. There has been a single report of an infant with nesidioblastosis who experienced a seizure thought to be independent of Sandostatin® therapy. A single death has been reported in a 16-month-old male with enterocutaneous fistula who developed sudden abdominal pain and increased nasogastric drainage and expired 8 hours after receiving a single 100 mcg subcutaneous dose of Sandostatin®.

ADVERSE REACTIONS

Gallbladder Abnormalities

Gallbladder abnormalities, especially stones and/or biliary sludge, frequently develop in patients on chronic Sandostatin® (octreotide acetate) therapy *(see WARNINGS)*.

Cardiac

In acromegalics, sinus bradycardia (<50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias developed in 9% of patients during Sandostatin® (octreotide acetate) therapy *(see PRECAUTIONS—General)*.

Gastrointestinal

Diarrhea, loose stools, nausea and abdominal discomfort were each seen in 34%-61% of acromegalic patients in U.S. studies although only 2.6% of the patients discontinued therapy due to these symptoms. These symptoms were seen in 5%-10% of patients with other disorders.

The frequency of these symptoms was not dose-related, but diarrhea and abdominal discomfort generally resolved more quickly in patients treated with 300 mcg/day than in those treated with 750 mcg/day. Vomiting, flatulence, abnormal stools, abdominal distention, and constipation were each seen in less than 10% of patients.

Hypo/Hyperglycemia

Hypoglycemia and hyperglycemia occurred in 3% and 16% of acromegalic patients, respectively, but only in about 1.5% of other patients. Symptoms of hypoglycemia were noted in approximately 2% of patients.

Hypothyroidism

In acromegalics, biochemical hypothyroidism alone occurred in 12% while goiter occurred in 6% during Sandostatin® (octreotide acetate) therapy *(see PRECAUTIONS—General)*. In patients without acromegaly, hypothyroidism has only been reported in several isolated patients and goiter has not been reported.

Other Adverse Events

Pain on injection was reported in 7.7%, headache in 6% and dizziness in 5%. Pancreatitis was also observed *(see WARNINGS* and *PRECAUTIONS)*.

Other Adverse Events 1%-4%

Other events (relationship to drug not established), each observed in 1%-4% of patients, included fatigue, weakness, pruritus, joint pain, backache, urinary tract infection, cold symptoms, flu symptoms, injection site hematoma, bruise, edema, flushing, blurred vision, pollakiuria, fat malabsorption, hair loss, visual disturbance and depression.

Other Adverse Events <1%

Events reported in less than 1% of patients and for which relationship to drug is not established are listed: *Gastrointestinal*: hepatitis, jaundice, increase in liver enzymes, GI bleeding, hemorrhoids, appendicitis, gastric/peptic ulcer, gallbladder polyp; *Integumentary*: rash, cellulitis, petechiae, urticaria, basal cell carcinoma; *Musculoskeletal*: arthritis, joint effusion, muscle pain, Raynaud's phenomenon; *Cardiovascular*: chest pain, shortness of breath, thrombophlebitis, ischemia, congestive heart failure, hypertension, hypertensive reaction, palpitations, orthostatic BP decrease, tachycardia; *CNS*: anxiety, libido decrease, syncope, tremor, seizure, vertigo, Bell's Palsy, paranoia, pituitary apoplexy, increased intraocular pressure, amnesia, hearing loss, neuritis; *Respiratory*: pneumonia, pulmonary nodule, status asthmaticus; *Endocrine*: galactorrhea, hypoadrenalism, diabetes insipidus, gynecomastia, amenorrhea, polymenorrhea, oligomenorrhea, vaginitis; *Urogenital*: nephrolithiasis, hematuria; *Hematologic*: anemia, iron deficiency, epistaxis; *Miscellaneous*: otitis, allergic reaction, increased CK, weight loss.

Evaluation of 20 patients treated for at least 6 months has failed to demonstrate titers of antibodies exceeding background levels. However, antibody titers to Sandostatin® (octreotide acetate) were subsequently reported in three patients and resulted in prolonged duration of drug action in two patients. Anaphylactoid reactions, including anaphylactic shock, have been reported in several patients receiving Sandostatin® (octreotide acetate).

OVERDOSAGE

No frank overdose has occurred in any patient to date. Intravenous bolus doses of 1 mg (1000 mcg) given to healthy volunteers and of 30 mg (30,000 mcg) IV over 20 minutes and of 120 mg (120,000 mcg) IV over 8 hours to research patients have not resulted in serious ill effects.

Up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Regional Poison Control Centers are listed in the Physicians' Desk Reference®.*

Mortality occurred in mice and rats given 72 mg/kg and 18 mg/kg IV, respectively.

Drug Abuse and Dependence

There is no indication that Sandostatin® (octreotide acetate) has potential for drug abuse or dependence. Sandostatin® (octreotide acetate) levels in the central nervous system are negligible, even after doses up to 30,000 mcg.

DOSAGE AND ADMINISTRATION

Sandostatin® (octreotide acetate) may be administered subcutaneously or intravenously. Subcutaneous injection is the usual route of administration of Sandostatin® (octreotide acetate) for control of symptoms. Pain with subcutaneous administration may be reduced by using the smallest volume that will deliver the desired dose. Multiple subcutaneous injections at the same site within short periods of time should be avoided. Sites should be rotated in a systematic manner.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. **Do not use if particulates and/or discoloration are observed.** Proper sterile technique should be used in the preparation of parenteral admixtures to minimize the possibility of microbial contamination. **Sandostatin® (octreotide acetate) is not compatible in Total Parenteral Nutrition (TPN) solutions because of the formation of a glycosyl octreotide conjugate which may decrease the efficacy of the product.**

Sandostatin® (octreotide acetate) is stable in sterile isotonic saline solutions or sterile solutions of dextrose 5% in water for 24 hours. It may be diluted in volumes of 50-200 mL and infused intravenously over 15-30 minutes or administered by IV push over 3 minutes. In emergency situations (e.g.: carcinoid crisis) it may be given by rapid bolus.

The initial dosage is usually 50 mcg administered twice or three times daily. Upward dose titration is frequently required. Dosage information for patients with specific tumors follows.

Acromegaly

Dosage may be initiated at 50 mcg t.i.d. Beginning with this low dose may permit adaptation to adverse gastrointestinal effects for patients who will require higher doses. IGF-I (somatomedin C) levels every 2 weeks can be used to guide titration. Alternatively, multiple growth hormone levels at 0-8 hours after Sandostatin® (octreotide acetate) administration permit more rapid titration of dose. The goal is to achieve growth hormone levels less than 5 ng/mL or IGF-I (somatomedin C) levels less than 1.9 U/mL in males and less than 2.2 U/mL in females. The dose most commonly found to be effective is 100 mcg t.i.d., but some patients require up to 500 mcg t.i.d. for maximum effectiveness. Doses greater than 300 mcg/day seldom result in additional biochemical benefit, and if an increase in dose fails to provide additional benefit, the dose should be reduced. IGF-I (somatomedin C) or growth hormone levels should be reevaluated at 6-month intervals.

Sandostatin® (octreotide acetate) should be withdrawn yearly for approximately 4 weeks from patients who have received irradiation to assess disease activity. If growth hormone or IGF-I (somatomedin C) levels increase and signs and symptoms recur, Sandostatin® (octreotide acetate) therapy may be resumed.

Carcinoid Tumors

The suggested daily dosage of Sandostatin® (octreotide acetate) during the first 2 weeks of therapy ranges from 100-600 mcg/day in 2-4 divided doses (mean daily dosage is 300 mcg). In the clinical studies, the median daily maintenance dosage was approximately 450 mcg, but clinical and biochemical benefits were obtained in some patients with as little as 50 mcg, while others required doses up to 1500 mcg/day. However, experience with doses above 750 mcg/day is limited.

VIPomas

Daily dosages of 200-300 mcg in 2-4 divided doses are recommended during the initial 2 weeks of therapy (range 150-750 mcg) to control symptoms of the disease. On an individual basis, dosage may be adjusted to achieve a therapeutic response, but usually doses above 450 mcg/day are not required.

HOW SUPPLIED

Sandostatin® (octreotide acetate) Injection is available in 1 mL ampuls and 5 mL multi-dose vials as follows:

Ampuls

50 mcg/mL octreotide (as acetate)
Package of 10 ampuls ..... (NDC 0078-0180-01)
100 mcg/mL octreotide (as acetate)
Package of 10 ampuls ..... (NDC 0078-0181-01)
500 mcg/mL octreotide (as acetate)
Package of 10 ampuls ..... (NDC 0078-0182-01)

Multi-Dose Vials

200 mcg/mL octreotide (as acetate)
Box of one ..... (NDC 0078-0183-25)
1000 mcg/mL octreotide (as acetate)
Box of one ..... (NDC 0078-0184-25)

Storage

For prolonged storage, Sandostatin® (octreotide acetate) ampuls and multi-dose vials should be stored at refrigerated temperatures 2°C-8°C (36°F-46°F) and protected from light. At room temperature, (20°C-30°C or 70°F-86°F), Sandostatin® (octreotide acetate) is stable for 14 days if protected from light. The solution can be allowed to come to room temperature prior to administration. Do not warm artificially. After initial use, multiple-dose vials should be discarded within 14 days. Ampuls should be opened just prior to administration and the unused portion discarded.

*Medical Economics Company, Inc.

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Shown in Product Identification Guide, page 327

SANDOSTATIN LAR® DEPOT ℞

[săn-dō-stă-tĭn]

(octreotide acetate for injectable suspension)

℞ only

Prescribing Information

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

DESCRIPTION

Octreotide is the acetate salt of a cyclic octapeptide. It is a long-acting octapeptide with pharmacologic properties mimicking those of the natural hormone somatostatin. Octreotide is known chemically as L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl- L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl) propyl]-, cyclic (2→7)-disulfide; [R-(R*,R*)].

Sandostatin LAR® Depot (octreotide acetate for injectable suspension) is available in a vial containing the sterile drug product, which when mixed with diluent, becomes a suspension that is given as a monthly intragluteal injection. The octreotide is uniformly distributed within the microspheres which are made of a biodegradeable glucose star polymer, D,L-lactic and glycolic acids copolymer. Sterile mannitol is added to the microspheres to improve suspendability.

Sandostatin LAR® Depot is available as: sterile 5 mL vials in 3 strengths delivering 10 mg, 20 mg or 30 mg octreotide free peptide. Each vial of Sandostatin LAR® Depot delivers:

[See first table at top of next page]

Each vial of diluent contains:

carboxymethylcellulose sodium	10.0 mg
mannitol	12.0 mg
water for injection	2.0 mL

The molecular weight of octreotide is 1019.3 (free peptide, $C_{49}H_{66}N_{10}O_{10}S_2$) and its amino acid sequence is:

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol•xCH_3COOH
where x = 1.4 to 2.5

CLINICAL PHARMACOLOGY

Sandostatin LAR® Depot (octreotide acetate for injectable suspension) is a long-acting dosage form consisting of microspheres of the biodegradable glucose star polymer, D,L-lactic and glycolic acids copolymer, containing octreotide. It maintains all of the clinical and pharmacological characteristics of the immediate-release dosage form Sandostatin® (octreotide acetate) Injection with the added feature of slow release of octreotide from the site of injection, reducing the need for frequent administration. This slow release occurs as the polymer biodegrades, primarily through hydrolysis. Sandostatin LAR® Depot is designed to be injected intramuscularly (intragluteally) once every four weeks.

Octreotide exerts pharmacologic actions similar to the natural hormone, somatostatin. It is an even more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Like somatostatin, it also suppresses LH response to GnRH, decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.

By virtue of these pharmacological actions, octreotide has been used to treat the symptoms associated with metastatic carcinoid tumors (flushing and diarrhea), and Vasoactive Intestinal Peptide (VIP) secreting adenomas (watery diarrhea).

Octreotide substantially reduces and in many cases can normalize growth hormone and/or IGF-1 (somatomedin C) levels in patients with acromegaly.

Single doses of Sandostatin® Injection given subcutaneously have been shown to inhibit gallbladder contractility and to decrease bile secretion in normal volunteers. In controlled clinical trials the incidence of gallstone or biliary sludge formation was markedly increased *(see WARNINGS)*.

Octreotide may cause clinically significant suppression of thyroid stimulating hormone (TSH).

Pharmacokinetics

The magnitude and duration of octreotide serum concentrations after an intramuscular injection of the long-acting depot formulation Sandostatin LAR® Depot reflect the release of drug from the microsphere polymer matrix. Drug release is governed by the slow biodegradation of the microspheres in the muscle, but once present in the systemic circulation, octreotide distributes and is eliminated according to its known pharmacokinetic properties which are as follows:

1. Pharmacokinetics of Octreotide Acetate

According to data obtained with the immediate-release formulation, Sandostatin® Injection solution, after subcutaneous injection, octreotide is absorbed rapidly and completely from the injection site. Peak concentrations of 5.2 ng/mL (100 mcg dose) were reached 0.4 hours after dosing. Using a specific radioimmunoassay, intravenous and subcutaneous doses were found to be bioequivalent. Peak concentrations and area-under-the-curve values were dose proportional both after subcutaneous or intravenous single doses up to 400 mcg and with multiple doses of 200 mcg t.i.d. (600 mcg/day). Clearance was reduced by about 66% suggesting nonlinear kinetics of the drug at daily doses of 600 mcg/day as compared to 150 mcg/day. The relative decrease in clearance with doses above 600 mcg/day is not defined.

In healthy volunteers the distribution of octreotide from plasma was rapid ($t_{\alpha 1/2}$ = 0.2 h), the volume of distribution (Vdss) was estimated to be 13.6 L and the total body clearance was 10 L/h.

In blood, the distribution of octreotide into the erythrocytes was found to be negligible and about 65% was bound in the plasma in a concentration-independent manner. Binding was mainly to lipoprotein and, to a lesser extent, to albumin.

The elimination of octreotide from plasma had an apparent half-life of 1.7 hours, compared with the 1-3 minutes with the natural hormone, somatostatin. The duration of action of subcutaneously administered Sandostatin® Injection solution is variable but extends up to 12 hours depending upon the type of tumor, necessitating multiple daily dosing with this immediate-release dosage form. About 32% of the dose is excreted unchanged into the urine. In an elderly population, dose adjustments may be necessary due to a significant increase in the half-life (46%) and a significant decrease in the clearance (26%) of the drug.

In patients with acromegaly, the pharmacokinetics differ somewhat from those in healthy volunteers. A mean peak concentration of 2.8 ng/mL (100 mcg dose) was reached in 0.7 hours after subcutaneous dosing. The volume of distribution (Vdss) was estimated to be 21.6 ± 8.5 L and the total body clearance was increased to 18 L/h. The mean percent of the drug bound was 41.2%. The disposition and elimination half-lives were similar to normals.

In patients with severe renal failure requiring dialysis, clearance was reduced to about half that found in healthy subjects (from approximately 10 L/h to 4.5 L/h).

The effect of hepatic diseases on the disposition of octreotide is unknown.

2. Pharmacokinetics of Sandostatin LAR® Depot

After a single IM injection of the long-acting depot dosage form Sandostatin LAR® Depot in healthy volunteer subjects, the serum octreotide concentration reached a transient initial peak of about 0.03 ng/mL/mg within 1 hour after administration progressively declining over the following 3 to 5 days to a nadir of <0.01 ng/mL/mg, then slowly increasing and reaching a plateau about two to three weeks post injection. Plateau concentrations were maintained over a period of nearly 2-3 weeks, showing dose proportional peak concentrations of about 0.07 ng/mL/mg. After about 6 weeks post injection, octreotide concentration slowly decreased, to <0.01 ng/mL/mg by weeks 12 to 13, concomitant with the terminal degradation phase of the polymer matrix of the dosage form. The relative bioavailability of the long-acting release Sandostatin LAR® Depot compared to immediate-release Sandostatin® Injection solution given subcutaneously was 60-63%.

In patients with acromegaly, the octreotide concentrations after single doses of 10 mg, 20 mg and 30 mg Sandostatin LAR® Depot were dose proportional. The transient day 1 peak, amounting to 0.3 ng/mL, 0.8 ng/mL, and 1.3 ng/mL, respectively, was followed by plateau concentrations of 0.5 ng/mL, 1.3 ng/mL, and 2.0 ng/mL, respectively, achieved about 3 weeks post injection. These plateau concentrations were maintained for nearly two weeks.

Following multiple doses of Sandostatin LAR® Depot given every 4 weeks, steady-state octreotide serum concentrations were achieved after the third injection. Concentrations were dose proportional and higher by a factor of approximately 1.6 to 2.0 compared to the concentrations after a single dose. The steady-state octreotide concentrations were 1.2 ng/mL and 2.1 ng/mL, respectively, at trough and 1.6 ng/mL and 2.6 ng/mL, respectively, at peak with 20 mg and 30 mg Sandostatin LAR® Depot given every 4 weeks. No accumulation of octreotide beyond that expected from the overlapping release profiles occurred over a duration of up to 28 monthly injections of Sandostatin LAR® Depot. With the long-acting depot formulation Sandostatin LAR® Depot administered IM every 4 weeks the peak-to-trough variation in octreotide concentrations ranged from 44%-68%, compared to the 163%-209% variation encountered with the daily subcutaneous t.i.d. regimen of Sandostatin® Injection solution.

Continued on next page

Sandostatin LAR—Cont.

In patients with carcinoid tumors, the mean octreotide concentrations after 6 doses of 10 mg, 20 mg and 30 mg Sandostatin LAR® Depot administered by IM injection every four weeks were 1.2 ng/mL, 2.5 ng/mL, and 4.2 ng/mL, respectively. Concentrations were dose proportional and steady-state concentrations were reached after two injections of 20 mg and 30 mg and after three injections of 10 mg. Sandostatin LAR® Depot has not been studied in patients with renal impairment.

Sandostatin LAR® Depot has not been studied in patients with hepatic impairment.

CLINICAL TRIALS

The clinical trials of Sandostatin LAR® Depot (octreotide acetate for injectable suspension) were performed in patients who had been receiving Sandostatin® (octreotide acetate) Injection for a period of weeks to as long as 10 years. The acromegaly studies with Sandostatin LAR® Depot described below were performed in patients who achieved GH levels of <10 ng/mL (and, in most cases <5 ng/mL) while on subcutaneous Sandostatin® Injection. However, some patients enrolled were partial responders to subcutaneous Sandostatin® Injection, i.e., GH levels were reduced by >50% on subcutaneous Sandostatin® Injection compared to the untreated state, although not suppressed to <5 ng/mL.

Acromegaly

Sandostatin LAR® Depot was evaluated in three clinical trials in acromegalic patients.

In two of the clinical trials, a total of 101 patients were entered who had, in most cases, achieved a GH level <5 ng/mL on Sandostatin® Injection given in doses of 100 mcg or 200 mcg t.i.d. Most patients were switched to 20 mg or 30 mg doses of Sandostatin LAR® Depot given once every 4 weeks for up to 27 to 28 injections. A few patients received doses of 10 mg and a few required doses of 40 mg. Growth hormone and IGF-1 levels were at least as well controlled with Sandostatin LAR® Depot as they had been on Sandostatin® Injection and this level of control remained for the entire duration of the trials.

A third trial was a 12-month study that enrolled 151 patients who had a GH level <10 ng/mL after treatment with Sandostatin® Injection (most had levels <5 ng/mL). The starting dose of Sandostatin LAR® Depot was 20 mg every 4 weeks for 3 doses. Thereafter, patients received 10 mg, 20 mg or 30 mg every 4 weeks, depending upon the degree of GH suppression. (The recommended regimen for these dosage changes is described under DOSAGE AND ADMINISTRATION). Growth hormone and IGF-1 were at least as well controlled on Sandostatin LAR® Depot as they had been on Sandostatin® Injection.

Table 1 summarizes the data on hormonal control (GH and IGF-1) for those patients in the first two clinical trials who received all 27-28 injections of Sandostatin LAR® Depot.

[See table 1 at right]

For the 88 patients in Table 1, a mean GH level of <2.5 ng/mL was observed in 47% receiving Sandostatin LAR® Depot. Over the course of the trials 42% of patients maintained mean growth hormone levels of <2.5 ng/mL and mean normal IGF-1 levels.

Table 2 summarizes the data on hormonal control (GH and IGF-1) for those patients in the third clinical trial who received all 12 injections of Sandostatin LAR® Depot.

[See table 2 at right]

For the 122 patients in Table 2, who received all 12 injections in the third trial, a mean GH level of <2.5 ng/mL was observed in 66% receiving Sandostatin LAR® Depot. Over the course of the trial 57% of patients maintained mean growth hormone levels of <2.5 ng/mL and mean normal IGF-1 levels. In comparing the hormonal response in these trials, note that a higher percentage of patients in the third trial suppressed their mean GH to <5 ng/mL on subcutaneous Sandostatin® Injection, 95%, compared to 78% across the two previous trials.

In all three trials, GH, IGF-1, and clinical symptoms were similarly controlled on Sandostatin LAR® Depot as they had been on Sandostatin® Injection.

Of the 25 patients who completed the trials and were partial responders to Sandostatin® Injection (GH >5.0 ng/mL but reduced by >50% relative to untreated levels), 1 patient (4%) responded to Sandostatin LAR® Depot with a reduction of GH to <2.5 ng/mL and 8 patients (32%) responded with a reduction of GH to <5.0 ng/mL.

Carcinoid Syndrome

A 6-month clinical trial of malignant carcinoid syndrome was performed in 93 patients who had previously been shown to be responsive to Sandostatin® Injection. Sixty-seven patients were randomized at baseline to receive, double-blind, doses of 10 mg, 20 mg or 30 mg Sandostatin LAR® Depot every 28 days and 26 patients continued, unblinded, on their previous Sandostatin® Injection regimen (100-300 mcg t.i.d.).

In any given month after steady-state levels of octreotide were reached, approximately 35%-40% of the patients who received Sandostatin LAR® Depot required supplemental subcutaneous Sandostatin® Injection therapy usually for a few days, to control exacerbation of carcinoid symptoms. In any given month the percentage of patients randomized to subcutaneous Sandostatin® Injection, who required supplemental treatment with an increased dose of Sandostatin® Injection, was similar to the percentage of patients randomized to Sandostatin LAR® Depot. Over the six-month treatment period approximately 50%-70% of patients who completed the trial on Sandostatin LAR® Depot required subcutaneous Sandostatin® Injection supplemental therapy to control exacerbation of carcinoid symptoms although steady-state serum Sandostatin LAR® Depot levels had been reached.

Table 3 presents the average number of daily stools and flushing episodes in malignant carcinoid patients.

[See table 3 above]

Overall, mean daily stool frequency was as well controlled on Sandostatin LAR® Depot as on Sandostatin® Injection (approximately 2 to 2.5 stools/day).

Mean daily flushing episodes were similar at all doses of Sandostatin LAR® Depot and on Sandostatin® Injection (approximately 0.5 to 1 episode/day).

In a subset of patients with variable severity of disease, median 24 hour urinary 5-HIAA (5-hydroxyindole acetic acid) levels were reduced by 38-50% in the groups randomized to Sandostatin LAR® Depot.

The reductions are within the range reported in the published literature for patients treated with octreotide (about 10%-50%).

Seventy-eight patients with malignant carcinoid syndrome who had participated in this 6-month trial, subsequently participated in a 12-month extension study in which they received 12 injections of Sandostatin LAR® Depot at 4-week intervals. For those who remained in the extension trial, diarrhea and flushing were as well controlled as during the 6-month trial. Because malignant carcinoid disease is progressive, as expected, a number of deaths (8 patients: 10%) occurred due to disease progression or complications from the underlying disease. An additional 22% of patients prematurely discontinued Sandostatin LAR® Depot due to disease progression or worsening of carcinoid symptoms.

Name of Ingredient	10 mg	20 mg	30 mg
octreotide acetate	11.2 mg*	22.4 mg*	33.6 mg*
D,L-lactic and glycolic acids copolymer	188.8 mg	377.6 mg	566.4 mg
mannitol	41.0 mg	81.9 mg	122.9 mg

*Equivalent to 10/20/30 mg octreotide base.

Table 1
Hormonal Response in Acromegalic Patients Receiving 27-28 Injections During[1] Treatment with Sandostatin LAR® Depot

Mean Hormone Level	Sandostatin® Injection S.C. N	Sandostatin® Injection S.C. %	Sandostatin LAR® Depot N	Sandostatin LAR® Depot %
GH <5.0 ng/mL	69/88	78	73/88	83
<2.5 ng/mL	44/88	50	41/88	47
<1.0 ng/mL	6/88	7	10/88	11
IGF-1 normalized	36/88	41	45/88	51
GH <5.0 ng/mL + IGF-1 normalized	36/88	41	45/88	51
<2.5 ng/mL + IGF-1 normalized	30/88	34	37/88	42
<1.0 ng/mL + IGF-1 normalized	5/88	6	10/88	11

[1]Average of monthly levels of GH and IGF-1 over the course of the trials

Table 2
Hormonal Response in Acromegalic Patients Receiving 12 Injections During[1] Treatment with Sandostatin LAR® Depot

Mean Hormone Level	Sandostatin® Injection S.C. N	Sandostatin® Injection S.C. %	Sandostatin LAR® Depot N	Sandostatin LAR® Depot %
GH <5.0 ng/mL	116/122	95	118/122	97
<2.5 ng/mL	84/122	69	80/122	66
<1.0 ng/mL	25/122	21	28/122	23
IGF-1 normalized	82/122	67	82/122	67
GH <5.0 ng/mL + IGF-1 normalized	80/122	66	82/122	67
<2.5 ng/mL + IGF-1 normalized	65/122	53	70/122	57
<1.0 ng/mL + IGF-1 normalized	23/122	19	27/122	22

[1]Average of monthly levels of GH and IGF-1 over the course of the trial

Table 3
Average No. of Daily Stools and Flushing Episodes in Patients with Malignant Carcinoid Syndrome

Treatment	N	Daily Stools (Average No.) Baseline	Daily Stools (Average No.) Last Visit	Daily Flushing Episodes (Average No.) Baseline	Daily Flushing Episodes (Average No.) Last Visit
Sandostatin® Injection S.C.	26	3.7	2.6	3.0	0.5
Sandostatin LAR® Depot					
10 mg	22	4.6	2.8	3.0	0.9
20 mg	20	4.0	2.1	5.9	0.6
30 mg	24	4.9	2.8	6.1	1.0

INDICATIONS AND USAGE

Acromegaly

Sandostatin LAR® Depot (octreotide acetate for injectable suspension) is indicated for long-term maintenance therapy in acromegalic patients for whom medical treatment is appropriate and who have been shown to respond to and can tolerate Sandostatin® (octreotide acetate) Injection. The goal of treatment in acromegaly is to reduce GH and IGF-1 levels to normal. Sandostatin LAR® Depot can be used in patients who have had an inadequate response to surgery or in those for whom surgical resection is not an option. It may also be used in patients who have received radiation and have had an inadequate therapeutic response (see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

Carcinoid Tumors

Sandostatin LAR® Depot is indicated for long-term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors in patients in whom initial treatment with Sandostatin® Injection has been shown to be effective and tolerated.

Vasoactive Intestinal Peptide Tumors (VIPomas)

Sandostatin LAR® Depot is indicated for long-term treatment of the profuse watery diarrhea associated with VIP-secreting tumors in patients in whom initial treatment with Sandostatin® Injection has been shown to be effective and tolerated.

In patients with acromegaly, carcinoid syndrome and VIPomas, the effect of Sandostatin® Injection and Sandostatin LAR® Depot on tumor size, rate of growth and development of metastases, has not been determined.

CONTRAINDICATIONS

Sensitivity to this drug or any of its components.

WARNINGS

Adverse events that have been reported in patients receiving Sandostatin® (octreotide acetate) Injection can also be expected in patients receiving Sandostatin LAR® Depot (octreotide acetate for injectable suspension). Incidence figures in the WARNINGS and ADVERSE REACTIONS sections, below, are those obtained in clinical trials of Sandostatin® Injection and Sandostatin LAR® Depot.

Gallbladder and Related Events

Single doses of Sandostatin® Injection have been shown to inhibit gallbladder contractility and decrease bile secretion in normal volunteers. In clinical trials with Sandostatin® Injection (primarily patients with acromegaly or psoriasis) in patients who had not previously received octreotide, the

incidence of biliary tract abnormalities was 63% (27% gallstones, 24% sludge without stones, 12% biliary duct dilatation). The incidence of stones or sludge in patients who received Sandostatin® Injection for 12 months or longer was 52%. The incidence of gallbladder abnormalities did not appear to be related to age, sex or dose but was related to duration of exposure.

In clinical trials 52% of acromegalic patients, most of whom received Sandostatin LAR® Depot for 12 months or longer, developed new biliary abnormalities including gallstones, microlithiasis, sediment, sludge and dilatation. The incidence of new cholelithiasis was 22%, of which 7% were microstones.

In clinical trials 62% of malignant carcinoid patients who received Sandostatin LAR® Depot for up to 18 months developed new biliary abnormalities including gallstones, sludge and dilatation. New gallstones occurred in a total of 24% of patients.

Across all trials, a few patients developed acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, or pancreatitis during octreotide therapy or following its withdrawal. One patient developed ascending cholangitis during Sandostatin® Injection therapy and died. Despite the high incidence of new gallstones in patients receiving octreotide, 1% of patients developed acute symptoms requiring cholecystectomy.

PRECAUTIONS (See ADVERSE REACTIONS).

General

Growth hormone secreting tumors may sometimes expand and cause serious complications (e.g., visual field defects). Therefore, all patients with these tumors should be carefully monitored.

Octreotide alters the balance between the counter-regulatory hormones, insulin, glucagon and growth hormone, which may result in hypoglycemia or hyperglycemia. Octreotide also suppresses secretion of thyroid stimulating hormone, which may result in hypothyroidism. Cardiac conduction abnormalities have also occurred during treatment with octreotide.

Glucose Metabolism

The hypoglycemia or hyperglycemia which occurs during octreotide therapy is usually mild, but may result in overt diabetes mellitus or necessitate dose changes in insulin or other hypoglycemic agents. Severe hyperglycemia, subsequent pneumonia, and death following initiation of Sandostatin® (octreotide acetate) Injection therapy was reported in one patient with no history of hyperglycemia (see ADVERSE REACTIONS).

Thyroid Function

Hypothyroidism has been reported in acromegaly and carcinoid patients receiving octreotide therapy. Baseline and periodic assessment of thyroid function (TSH, total and/or free T_4) is recommended during chronic octreotide therapy *(see ADVERSE REACTIONS).*

Cardiac Function

In both acromegalic and carcinoid syndrome patients, bradycardia, arrhythmias and conduction abnormalities have been reported during octreotide therapy. Other EKG changes were observed such as QT prolongation, axis shifts, early repolarization, low voltage, R/S transition, early R wave progression, and non-specific ST-T wave changes. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease (see PRECAUTIONS). Dose adjustments in drugs such as beta-blockers that have bradycardia effects may be necessary. In one acromegalic patient with severe congestive heart failure, initiation of Sandostatin® Injection therapy resulted in worsening of CHF with improvement when drug was discontinued. Confirmation of a drug effect was obtained with a positive rechallenge (see ADVERSE REACTIONS).

Nutrition

Octreotide may alter absorption of dietary fats in some patients.

Depressed vitamin B_{12} levels and abnormal Schilling's tests have been observed in some patients receiving octreotide therapy, and monitoring of vitamin B_{12} levels is recommended during therapy with Sandostatin LAR® Depot (octreotide acetate for injectable suspension).

Octreotide has been investigated for the reduction of excessive fluid loss from the G.I. tract in patients with conditions producing such a loss. If such patients are receiving total parenteral nutrition (TPN), serum zinc may rise excessively when the fluid loss is reversed. Patients on TPN and octreotide should have periodic monitoring of zinc levels.

Information for Patients

Patients with carcinoid tumors and VIPomas should be advised to adhere closely to their scheduled return visits for reinjection in order to minimize exacerbation of symptoms. Patients with acromegaly should also be urged to adhere to their return visit schedule to help assure steady control of GH and IGF-1 levels.

Laboratory Tests

Laboratory tests that may be helpful as biochemical markers in determining and following patient response depend on the specific tumor. Based on diagnosis, measurement of the following substances may be useful in monitoring the progress of therapy:

Acromegaly: Growth Hormone, IGF-1 (somatomedin C)

Responsiveness to octreotide may be evaluated by determining growth hormone levels at 1-4 hour intervals for 8-12 hours after subcutaneous injection of Sandostatin® Injection (not Sandostatin LAR® Depot). Alternatively, a single measurement of IGF-1 (somatomedin C) level may be made two weeks after initiation of Sandostatin® Injection or dosage change. After patients are switched from Sandostatin® Injection to Sandostatin LAR® Depot, GH and IGF-1 determinations may be made after 3 monthly injections of Sandostatin LAR® Depot. (Steady-state serum levels of octreotide are reached only after a period of 3 months of monthly injections.) Growth hormone can be determined using the mean of 4 assays taken at 1 hour intervals. Somatomedin C can be determined with a single assay. All GH and IGF-1 determinations should be made 4 weeks after the previous Sandostatin LAR® Depot.

Carcinoid: 5-HIAA (urinary 5-hydroxyindole acetic acid), plasma serotonin, plasma Substance P

VIPoma: VIP (plasma vasoactive intestinal peptide)

Baseline and periodic total and/or free T_4 measurements should be performed during chronic therapy (see PRECAUTIONS—General).

Drug Interactions

Octreotide has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs. Concomitant administration of octreotide injection with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection.

Patients receiving insulin, oral hypoglycemic agents, beta-blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may require dose adjustments of these therapeutic agents.

Drug Laboratory Test Interactions

No known interference exists with clinical laboratory tests, including amine or peptide determinations.

Carcinogenesis/Mutagenesis/Impairment of Fertility

Studies in laboratory animals have demonstrated no mutagenic potential of Sandostatin®. No mutagenic potential of the polymeric carrier in Sandostatin LAR® Depot, D,L-lactic and glycolic acids copolymer, was observed in the Ames mutagenicity test.

No carcinogenic potential was demonstrated in mice treated subcutaneously with octreotide for 85-99 weeks at doses up to 2000 mcg/kg/day (8× the human exposure based on body surface area). In a 116-week subcutaneous study in rats administered octreotide, a 27% and 12% incidence of injection site sarcomas or squamous cell carcinomas was observed in males and females, respectively, at the highest dose level of 1250 mcg/kg/day (10× the human exposure based on body surface area) compared to an incidence of 8-10% in the vehicle-control groups. The increased incidence of injection site tumors was most probably caused by irritation and the high sensitivity of the rat to repeated subcutaneous injections at the same site. Rotating injection sites would prevent chronic irritation in humans. There have been no reports of injection site tumors in patients treated with Sandostatin® Injection for at least 5 years. There was also a 15% incidence of uterine adenocarcinomas in the 1250 mcg/kg/day females compared to 7% in the saline-control females and 0% in the vehicle-control females. The presence of endometritis coupled with the absence of corpora lutea, the reduction in mammary fibroadenomas, and the presence of uterine dilatation suggest that the uterine tumors were associated with estrogen dominance in the aged female rats which does not occur in humans.

Octreotide did not impair fertility in rats at doses up to 1000 mcg/kg/day, which represents 7× the human exposure based on body surface area.

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses up to 16 times the highest human dose based on body surface area and have revealed no evidence of impaired fertility or harm to the fetus due to octreotide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in milk, caution should be exercised when Sandostatin LAR® Depot is administered to a nursing woman.

Pediatric Use

Sandostatin LAR® Depot has not been studied in pediatric patients.

Experience with Sandostatin® Injection in the pediatric population is limited. Its use has been primarily in patients with congenital hyperinsulinism (also called nesidioblastosis). The youngest patient to receive the drug was 1 month old. At doses of 1-40 mcg/kg body weight/day, the majority of side effects observed were gastrointestinal-steatorrhea, diarrhea, vomiting and abdominal distention. Poor growth has been reported in several patients treated with Sandostatin® Injection for more than 1 year; catch-up growth occurred after Sandostatin® Injection was discontinued. A 16-month-old male with enterocutaneous fistula developed sudden abdominal pain and increased nasogastric drainage and died 8 hours after receiving a single 100 mcg subcutaneous dose of Sandostatin® Injection.

Table 4
Number (%) of Acromegalic Patients with Common G.I. Adverse Events

Adverse Event	Sandostatin® Injection S.C. t.i.d. n=114		Sandostatin LAR® Depot q. 28 days n=261	
	N	%	N	%
Diarrhea	66	(57.9)	95	(36.4)
Abdominal Pain or Discomfort	50	(43.9)	76	(29.1)
Flatulence	15	(13.2)	67	(25.7)
Constipation	10	(8.8)	49	(18.8)
Nausea	34	(29.8)	27	(10.3)
Vomiting	5	(4.4)	17	(6.5)

ADVERSE REACTIONS (See WARNINGS and PRECAUTIONS).

Gallbladder abnormalities, especially stones and/or biliary sludge, frequently develop in patients on chronic octreotide therapy *(see WARNINGS).* Few patients, however, develop acute symptoms requiring cholecystectomy.

Cardiac

In acromegalics, sinus bradycardia (<50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias developed in 9% of patients during Sandostatin® (octreotide acetate) Injection therapy. Electrocardiograms were performed only in carcinoid patients receiving Sandostatin LAR® Depot (octreotide acetate for injectable suspension). In carcinoid syndrome patients sinus bradycardia developed in 19%; conduction abnormalities occurred in 9%, and arrhythmias developed in 3%. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease (see PRECAUTIONS).

Gastrointestinal

The most common symptoms are gastrointestinal. The overall incidence of the most frequent of these symptoms in clinical trials of acromegalic patients treated for approximately 1 to 4 years is shown in Table 4.

[See table 4 above]

Only 2.6% of the patients on Sandostatin® (octreotide acetate) Injection in U.S. clinical trials discontinued therapy due to these symptoms. No acromegalic patient receiving Sandostatin LAR® Depot discontinued therapy for a G.I. event.

In patients receiving Sandostatin LAR® Depot the incidence of diarrhea was dose-related. Diarrhea, abdominal pain, and nausea developed primarily during the first month of treatment with Sandostatin LAR® Depot. Thereafter, new cases of these events were uncommon. The vast majority of these events were mild-to-moderate in severity.

In rare instances gastrointestinal adverse effects may resemble acute intestinal obstruction, with progressive abdominal distention, severe epigastric pain, abdominal tenderness, and guarding.

Dyspepsia, steatorrhea, discoloration of feces, and tenesmus were reported in 4%-6% of patients.

In a clinical trial of carcinoid syndrome, nausea, abdominal pain, and flatulence were reported in 27%-38% and constipation or vomiting in 15%-21% of patients treated with Sandostatin LAR® Depot. Diarrhea was reported as an adverse event in 14% of patients but since most of the patients had diarrhea as a symptom of carcinoid syndrome, it is difficult to assess the actual incidence of drug-related diarrhea.

Hypo/Hyperglycemia

In acromegaly patients treated with either Sandostatin® Injection or Sandostatin LAR® Depot, hypoglycemia occurred in approximately 2% and hyperglycemia in approximately 15% of patients. In carcinoid patients, hypoglycemia occurred in 4% and hyperglycemia in 27% of patients treated with Sandostatin LAR® Depot *(see PRECAUTIONS).*

Hypothyroidism

In acromegaly patients receiving Sandostatin® Injection, 12% developed biochemical hypothyroidism, 8% developed goiter, and 4% required initiation of thyroid replacement therapy while receiving Sandostatin® Injection. In acromegalics treated with Sandostatin LAR® Depot hypothyroidism was reported as an adverse event in 2% and goiter in 2%. Two patients receiving Sandostatin LAR® Depot, required initiation of thyroid hormone replacement therapy. In carcinoid patients, hypothyroidism has only been reported in isolated patients and goiter has not been reported *(see PRECAUTIONS).*

Pain At the Injection Site

Pain on injection, which is generally mild-to-moderate, and short-lived (usually about 1 hour) is dose-related, being reported by 2%, 9%, and 11% of acromegalics receiving doses of 10 mg, 20 mg and 30 mg, respectively, of Sandostatin LAR® Depot. In carcinoid patients, where a diary was kept, pain at the injection site was reported by about 20%-25% at a 10-mg dose and about 30%-50% at the 20-mg and 30-mg dose.

Continued on next page

Sandostatin LAR—Cont.

Other Adverse Events 16%-20%
Other adverse events (relationship to drug not established) in acromegalic and/or carcinoid syndrome patients receiving Sandostatin LAR® Depot were upper respiratory infection, flu-like symptoms, fatigue, dizziness, headache, malaise, fever, dyspnea, back pain, chest pain, arthropathy.

Other Adverse Events 5%-15%
Other adverse events (relationship to drug not established) occurring in an incidence of 5%-15% in patients receiving Sandostatin LAR® Depot were:
Body As a Whole: asthenia, rigors, allergy
Cardiovascular: hypertension, peripheral edema
Central and Peripheral Nervous System: paresthesia, hypoesthesia
Gastrointestinal: dyspepsia, anorexia, hemorrhoids
Hearing and Vestibular: earache
Heart Rate and Rhythm: palpitations
Hematologic: anemia
Metabolic and Nutritional: dehydration, weight decrease
Musculoskeletal System: myalgia, leg cramps, arthralgia
Psychiatric: depression, anxiety, confusion, insomnia
Resistance Mechanism: viral infection, otitis media
Respiratory System: coughing, pharyngitis, rhinitis, sinusitis
Skin and Appendages: rash, pruritus, increased sweating
Urinary System: urinary tract infection, renal calculus

Other Adverse Events 1%-4%
Other events (relationship to drug not established), each occurring in an incidence of 1%-4% in patients receiving Sandostatin LAR® Depot and reported by at least 2 patients were:
Application Site: injection site inflammation
Body As a Whole: syncope, ascites, hot flushes
Cardiovascular: cardiac failure, angina pectoris, hypertension aggravated
Central and Peripheral Nervous System: vertigo, abnormal gait, neuropathy, neuralgia, tremor, dysphonia, hyperkinesia, hypertonia
Gastrointestinal: rectal bleeding, melena, gastritis, gastroenteritis, colitis, gingivitis, taste perversion, stomatitis, glossitis, dry mouth, dysphagia, steatorrhea, diverticulitis
Hearing and Vestibular: tinnitus
Heart Rate and Rhythm: tachycardia
Liver and Biliary: jaundice
Metabolic and Nutritional: hypokalemia, cachexia, gout, hypoproteinemia
Platelet, Bleeding, Clotting: pulmonary embolism, epistaxis
Psychiatric: amnesia, somnolence, nervousness, hallucinations
Reproductive, Female: menstrual irregularities, breast pain
Reproductive, Male: impotence
Resistance Mechanism: cellulitis, renal abcess, moniliasis, bacterial infection
Respiratory System: bronchitis, pneumonia, pleural effusion
Skin and Appendages: alopecia, urticaria, acne
Urinary System: incontinence, albuminuria
Vascular: cerebral vascular disorder, phlebitis, hematoma
Vision: abnormal vision

Rare Adverse Events
Other events (relationship to drug not established) of potential clinical significance occurring rarely (<1%) in clinical trials of octreotide either as Sandostatin® Injection or Sandostatin LAR® Depot, or reported post-marketing in patients with acromegaly, carcinoid syndrome, or other disorders include:
Body As a Whole: anaphylactoid reactions, including anaphylactic shock, facial edema, generalized edema, abdomen enlarged, malignant hyperpyrexia
Cardiovascular: aneurysm, myocardial infarction, angina pectoris, aggravated, pulmonary hypertension, cardiac arrest, orthostatic hypotension
Central and Peripheral Nervous System: hemiparesis, paresis, convulsions, paranoia, pituitary apoplexy, visual field defect, migraine, aphasia, scotoma, Bell's palsy
Endocrine Disorders: hypoadrenalism, diabetes insipidus, gynecomastia, galactorrhea
Gastrointestinal: G.I. hemorrhage, intestinal obstruction, hepatitis, increase in liver enzymes, fatty liver, peptic/gastric ulcer, gallbladder polyp, appendicitis, pancreatitis
Hearing and Vestibular: deafness
Heart Rate and Rhythm: atrial fibrillation
Hematologic: pancytopenia, thrombocytopenia
Metabolic and Nutritional: renal insufficiency, creatinine increased, CK increased, diabetes mellitus
Musculoskeletal: Raynaud's syndrome, arthritis, joint effusion
Neoplasms: breast carcinoma, basal cell carcinoma
Platelet, Bleeding, and Clotting: arterial thrombosis of the arm
Psychiatric: suicide attempt, libido decrease
Reproductive, Female: lactation, nonpuerperal
Respiratory: pulmonary nodule, status asthmaticus, pneumothorax
Skin and Appendages: cellulitis, petechiae, urticaria
Urinary System: renal failure, hematuria
Vascular: intracranial hemorrhage, retinal vein thrombosis
Vision: glaucoma

Antibodies to Octreotide
Studies to date have shown that antibodies to octreotide develop in up to 25% of patients treated with octreotide acetate. These antibodies do not influence the degree of efficacy response to octreotide; however, in two acromegalic patients who received Sandostatin® Injection, the duration of GH suppression following each injection was about twice as long as in patients without antibodies. It has not been determined whether octreotide antibodies will also prolong the duration of GH suppression in patients being treated with Sandostatin LAR® Depot.

OVERDOSAGE

No frank overdose has occurred in any patient to date. Sandostatin® (octreotide acetate) Injection given in intravenous bolus doses of 1 mg (1000 mcg) to healthy volunteers did not result in serious ill effects, nor did doses of 30 mg (30,000 mcg) given IV over 20 minutes and of 120 mg (120,000 mcg) given IV over 8 hours to research patients. Doses of 2.5 mg (2500 mcg) of Sandostatin® Injection subcutaneously have, however, caused hypoglycemia, flushing, dizziness, and nausea.
Up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Regional Poison Control Centers are listed in the Physicians' Desk Reference®*.
Mortality occurred in mice and rats given 72 mg/kg and 18 mg/kg IV, respectively, of octreotide.

Drug Abuse and Dependence
There is no indication that octreotide has potential for drug abuse or dependence. Octreotide levels in the central nervous system are negligible, even after doses up to 30,000 mcg.

DOSAGE AND ADMINISTRATION

Sandostatin LAR® Depot (octreotide acetate for injectable suspension) must be administered under the supervision of a physician. It is important to closely follow the mixing instructions included in the packaging. Sandostatin LAR® Depot must be administered immediately after mixing. Sandostatin LAR® Depot should be administered intragluteally at four-week intervals. Administration of Sandostatin LAR® Depot at intervals greater than 4 weeks is not recommended because there is no adequate information on whether such patients could be satisfactorily controlled. Deltoid injections are to be avoided because of significant discomfort at the injection site when given in that area. **Sandostatin LAR® Depot should never be administered by the IV or S.C. routes.** The following dosage regimens are recommended.

Acromegaly
1. Patients Not Currently Receiving Octreotide Acetate
Patients not currently receiving octreotide acetate should begin therapy with Sandostatin® (octreotide acetate) Injection given subcutaneously in an initial dose of 50 mcg t.i.d. Beginning with this low dose may permit adaptation to adverse gastrointestinal effects for patients who require higher doses. Multiple growth hormone (GH) determinations at 0-8 hours after a subcutaneous Sandostatin® Injection will guide dosage titration. The goal is to attempt to normalize GH and IGF-1 (somatomedin C) levels. Most patients require doses of 100 mcg to 200 mcg t.i.d. for maximum effect but some patients require up to 500 mcg t.i.d. Injection sites should be rotated in a systematic manner to avoid irritation.
Although responsiveness of GH to octreotide acetate can be ascertained quickly, patients should be maintained on Sandostatin® Injection s.c. for at least 2 weeks to determine tolerance to octreotide.
The most common adverse events are gastrointestinal, which usually begin within the first few days of administration and usually subside within 2 to 8 weeks. In clinical trials, <3% of patients discontinued Sandostatin® Injection because of G.I. symptoms.
Patients who are considered to be "responders" to the drug, based on GH and IGF-1 levels, and who tolerate the drug, can then be switched to Sandostatin LAR® Depot in the dosage scheme described under 2, below [Patients Currently Receiving Sandostatin® Injection].
2. Patients Currently Receiving Sandostatin® (octreotide acetate) Injection
Patients currently receiving Sandostatin® Injection can be switched directly to Sandostatin LAR® Depot in a dose of 20 mg given IM intragluteally at 4-week intervals for 3 months. **(Deltoid injections are to be avoided because of significant discomfort at the injection site when given in that area.)** Gluteal injection sites should be alternated to avoid irritation.
At the end of 3 months Sandostatin LAR® Depot dosage may be continued at the same level or increased or decreased based on the following regimen:
GH ≤2.5 ng/mL, IGF-1 normal and clinical symptoms controlled: maintain Sandostatin LAR® Depot dosage at 20 mg every 4 weeks.
GH >2.5 ng/mL, IGF-1 elevated, and/or clinical symptoms uncontrolled, increase Sandostatin LAR® Depot dosage to 30 mg every 4 weeks.
GH ≤1 ng/mL, IGF-1 normal and clinical symptoms controlled, reduce Sandostatin LAR® Depot dosage to 10 mg every 4 weeks.
Patients whose GH, IGF-1, and symptoms are not adequately controlled at a dose of 30 mg may have the dose increased to 40 mg every 4 weeks. Doses higher than 40 mg are not recommended.
Administration of Sandostatin LAR® Depot at intervals greater than 4 weeks is not recommended because there is no adequate information on whether such patients could be satisfactorily controlled.
In patients who have received pituitary irradiation, Sandostatin LAR® Depot should be withdrawn yearly for approximately 8 weeks to assess disease activity. If GH or IGF-1 levels increase and signs and symptoms recur, Sandostatin LAR® Depot therapy may be resumed.
3. Special Populations: Renal Failure
In patients with renal failure requiring dialysis, the half-life of octreotide may be increased, necessitating adjustment of the maintenance dosage (see CLINICAL PHARMACOLOGY and Pharmacokinetics of Octreotide).

Carcinoid Tumors and VIPomas
1. Patients Not Currently Receiving Octreotide Acetate
Patients not currently receiving octreotide acetate should begin therapy with Sandostatin® Injection given subcutaneously. The suggested daily dosage for carcinoid tumors during the first 2 weeks of therapy ranges from 100-600 mcg/day in 2-4 divided doses (mean daily dosage is 300 mcg). Some patients may require doses up to 1500 mcg/day. The suggested daily dosage for VIPomas is 200-300 mcg in 2-4 divided doses (range 150-750 mcg); dosage may be adjusted on an individual basis to control symptoms but usually doses above 450 mcg/day are not required.
Sandostatin® Injection should be continued for at least 2 weeks. Thereafter, patients who are considered "responders" to octreotide acetate and who tolerate the drug may be switched to Sandostatin LAR® Depot in the dosage regimen described under 2, below [Patients Currently Receiving Sandostatin® Injection].
2. Patients Currently Receiving Sandostatin® (octreotide acetate) Injection
Patients currently receiving Sandostatin® Injection can be switched to Sandostatin LAR® Depot in a dosage of 20 mg given IM intragluteally at 4-week intervals for 2 months. **Deltoid injections are to be avoided because of significant discomfort at the injection site when given in that area.** Gluteal injection sites should be alternated to avoid irritation. Because of the need for serum octreotide to reach therapeutically effective levels following initial injection of Sandostatin LAR® Depot, carcinoid tumor and VIPoma patients should continue to receive Sandostatin® Injection s.c. for at least 2 weeks in the same dosage they were taking before the switch. Failure to continue subcutaneous injections for this period may result in exacerbation of symptoms. (Some patients may require 3 or 4 weeks of such therapy.)
After two months of a 20 mg dosage of Sandostatin LAR® Depot, dosage may be increased to 30 mg every 4 weeks if symptoms are not adequately controlled. Patients who achieve good control on a 20-mg dose may have their dose lowered to 10 mg for a trial period. If symptoms recur, dosage should then be increased to 20 mg every 4 weeks. Many patients can, however, be satisfactorily maintained at a 10 mg dosage every 4 weeks. A dose of 10 mg is not recommended as a starting dose, however, because therapeutically effective levels of octreotide are reached more rapidly with a 20-mg dose.
Dosages higher than 30 mg are not recommended because there is no information on their usefulness.
Despite good overall control of symptoms, patients with carcinoid tumors and VIPomas often experience periodic exacerbation of symptoms (regardless of whether they are being maintained on Sandostatin® Injection or Sandostatin LAR® Depot). During these periods they may be given Sandostatin® Injection s.c. for a few days at the dosage they were receiving prior to switch to Sandostatin LAR® Depot. When symptoms are again controlled, the Sandostatin® Injection s.c. can be discontinued.
Administration of Sandostatin LAR® Depot at intervals greater than 4 weeks is not recommended because there is no adequate information on whether such patients could be adequately controlled.
3. Special Populations: Renal Failure
In patients with renal failure requiring dialysis, the half-life of octreotide may be increased, necessitating adjustment of the maintenance dosage (see CLINICAL PHARMACOLOGY and Pharmacokinetics of Octreotide).

HOW SUPPLIED

Sandostatin LAR® Depot (octreotide acetate for injectable suspension) is available in single-use kits containing a 5 mL vial of 10 mg, 20 mg or 30 mg strength, a 2 mL vial of diluent, a 5 mL sterile plastic syringe, two sterile 1 1/2" 19 gauge needles, and three alcohol wipes. An instruction booklet for the preparation of drug suspension for injection is also included with each kit.

Drug Product Kits

10 mg kit	NDC 0078-0340-84
20 mg kit	NDC 0078-0341-84
30 mg kit	NDC 0078-0342-84
Demonstration kit	NDC 0078-0340-97

Storage
For prolonged storage, Sandostatin LAR® Depot should be stored at refrigerated temperatures between 2°C and 8°C (36°-46°F) and protected from light until the time of use. Sandostatin LAR® Depot drug product kit should remain at room temperature for 30-60 minutes prior to preparation of the drug suspension. However, after preparation the drug suspension must be administered immediately.
*Trademark of Medical Economics Company, Inc.
REV: SEPTEMBER 2002 T2002-38
89015802

Sandostatin LAR® Depot vials are manufactured by:
Biochemie GmbH, Schaftenau, Austria
(Subsidiary of Novartis Pharma AG, Basle, Switzerland)
The diluent vials are manufactured by:
Novartis Pharma AG, Basle, Switzerland
Distributed by:
Novartis Pharmaceuticals Corporation
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 about 50% compared to adult renal transplantation patients. The volume of distribution at steady state was 4.8 ± 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 the percentage of patients by treatment group experiencing the primary efficacy endpoint during the first 12 months 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.

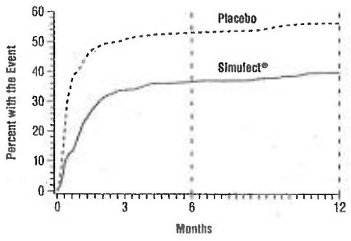
[See table 1 above]

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.

Continued on next page

shock); angioedema (Quincke's edema); anterior ischemic optic neuropathy; severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal); hepatocellular damage leading to jaundice and hepatic failure; interstitial nephritis; pancreatitis; pancytopenia; and rhabdomyolysis. In addition, also observed have been confusion, hypokinesia, speech disorder, increased salivation, vertigo, nausea, tinnitus, and blurred vision.

Laboratory Values

In U.S. clinical trials of patients having GERD with a history of erosive esophagitis and international clinical trials of patients with erosive esophagitis associated with GERD, the overall percentages of transaminase elevations did not increase during treatment with intravenous pantoprazole. For other laboratory parameters, there were no clinically important changes identified.

In two U.S. controlled trials of oral pantoprazole in patients with erosive esophagitis associated with GERD, 0.4% of the patients on 40 mg oral pantoprazole experienced SGPT elevations of greater than three times the upper limit of normal at the final treatment visit. Except in those patients where there was a clear alternative explanation for a laboratory value change, such as intercurrent illness, the elevations tended to be mild and sporadic. The following changes in laboratory parameters were reported as adverse events: creatinine increased, hypercholesterolemia, and hyperuricemia.

OVERDOSAGE

Experience in patients taking very high doses of pantoprazole is limited. There have been spontaneous reports of overdosage with pantoprazole, including a suicide in which pantoprazole 560 mg and undetermined amounts of chloroquine and zopiclone were also ingested. There have also been spontaneous reports of patients taking similar amounts of pantoprazole (400 and 600 mg) with no adverse effects.

Pantoprazole is not removed by hemodialysis. In case of overdose, treatment should be symptomatic and supportive. Single intravenous doses of pantoprazole at 378, 230, and 266 mg/kg (38, 46, and 177 times the recommended human dose based on body surface area) were lethal to mice, rats and dogs, respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

DOSAGE AND ADMINISTRATION

PROTONIX I.V. for Injection admixtures should be administered intravenously through a dedicated line, using the in-line filter provided. **The filter must be used** to remove the precipitate that may form when the reconstituted drug product is mixed with I.V. solutions. Studies have shown that filtration does not alter the amount of drug that is available for administration. If administration through a Y-site is desirable, the in-line filter must be positioned below the Y-site that is closest to the patient. The intravenous line should be flushed before and after administration of PROTONIX I.V. for Injection with either 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP. PROTONIX I.V. for Injection should not be simultaneously administered through the same line with other intravenous solutions.

Treatment with PROTONIX I.V. for Injection should be discontinued as soon as the patient is able to resume treatment with PROTONIX Delayed-Release Tablets. Also, data on the safe and effective dosing for conditions other than those described in **INDICATIONS AND USAGE**, such as life-threatening upper gastrointestinal bleeds, are not available. PROTONIX I.V. 40 mg once daily does not raise gastric pH to levels sufficient to contribute to the treatment of such life-threatening conditions.

Parenteral routes of administration other than intravenous are not recommended.

No dosage adjustment is necessary in patients with renal impairment, hepatic impairment, or for elderly patients. Doses higher than 40 mg/day have not been studied in hepatically-impaired patients. No dosage adjustment is necessary in patients undergoing hemodialysis.

Treatment of Gastroesophageal Reflux Disease Associated With a History of Erosive Esophagitis

The recommended adult dose, **as an alternative to continued oral therapy**, is 40-mg pantoprazole given once daily by intravenous infusion for 7 to 10 days. Safety and efficacy of PROTONIX I.V. for Injection as a treatment of patients having GERD with a history of erosive esophagitis for more than 10 days have not been demonstrated (see **INDICATIONS AND USAGE**).

PROTONIX I.V. for Injection should be reconstituted with 10 mL of 0.9% Sodium Chloride Injection, USP, and further diluted (admixed) with 100 mL of 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP, to a final concentration of approximately 0.4 mg/mL. The reconstituted solution may be stored for up to 2 hours at room temperature prior to further dilution; the admixed solution may be stored for up to 12 hours at room temperature prior to intravenous infusion. Neither the reconstituted solution nor the admixed solution need to be protected from light.

PROTONIX I.V. for Injection admixtures should be administered intravenously over a period of approximately 15 minutes at a rate not greater than 3 mg/min (7 mL/min).

Pathological Hypersecretion Associated with Zollinger-Ellison Syndrome

The dosage of PROTONIX I.V. for Injection in patients with pathological hypersecretory conditions associated with Zollinger-Ellison Syndrome or other neoplastic conditions varies with individual patients. The recommended adult dosage is 80 mg q12h. The frequency of dosing can be adjusted to individual patient needs based on acid output measurements. In those patients who need a higher dosage, 80 mg q8h is expected to maintain acid output below 10 mEq/h. Daily doses higher than 240 mg or administered for more than 6 days have not been studied. (See **Clinical Studies** section.) Transition from oral to I.V. and from I.V. to oral formulations of gastric acid inhibitors should be performed in such a manner to ensure continuity of effect of suppression of acid secretion. Patients with Zollinger-Ellison Syndrome may be vulnerable to serious clinical complications of increased acid production even after a short period of loss of effective inhibition.

Each vial of PROTONIX I.V. for Injection should be reconstituted with 10 mL of 0.9% Sodium Chloride Injection, USP. The contents of the two vials should be combined and further diluted (admixed) with 80 mL of 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP, to a total volume of 100 mL with a final concentration of approximately 0.8 mg/mL. The reconstituted solution may be stored for up to 2 hours at room temperature prior to further dilution; the admixed solution may be stored for up to 12 hours at room temperature prior to intravenous infusion. Neither the reconstituted solution nor the admixed solution need to be protected from light.

PROTONIX I.V. for Injection should be administered intravenously over a period of approximately 15 minutes at a rate not greater than 6 mg/min (7 mL/min).

HOW SUPPLIED

PROTONIX® I.V. (pantoprazole sodium) for Injection is supplied as a freeze-dried powder containing 40 mg of pantoprazole per vial.

PROTONIX I.V. for Injection is available as follows:

NDC 0008-0923-03 One carton containing 25 vials of PROTONIX I.V. for Injection (each vial containing 40-mg pantoprazole) and 25 required in-line filters (1.2 µm pore size).

Storage

Store PROTONIX I.V. for Injection vials at 2°C - 8°C (36°F - 46°F) and protect from light.

Caution: the reconstituted product should not be frozen.

Store the provided in-line filters at room temperature.

℞ only

U.S. Patent No. 4,758,579

Marketed by Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101
under license from
ALTANA Pharma
D78467 Konstanz, Germany

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ET01
Rev 03/03

Shown in Product Identification Guide, page 340

RAPAMUNE®

℞

[răp-ă-mūn]

(sirolimus)

Oral Solution and Tablets

℞ **only**

WARNING:

Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of renal transplant patients should use Rapamune®. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

DESCRIPTION

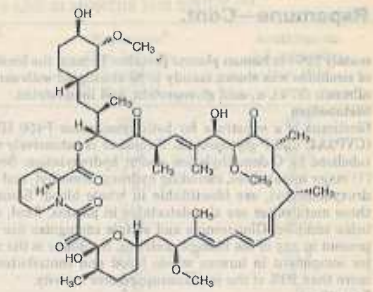
Rapamune® (sirolimus) is an immunosuppressive agent. Sirolimus is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. The chemical name of sirolimus (also known as rapamycin) is (3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34, 34a-hexadecahydro-9,27-dihydroxy-3-[(1*R*)-2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-c][1,4]oxaazacyclohentriacontine-1, 5,11,28,29 (4*H*,6*H*,31*H*)-pentone. Its molecular formula is $C_{51}H_{79}NO_{13}$ and its molecular weight is 914.2. The structural formula of sirolimus is shown below.

[See chemical structure at top of next column]

Sirolimus is a white to off-white powder and is insoluble in water, but freely soluble in benzyl alcohol, chloroform, acetone, and acetonitrile.

Rapamune® is available for administration as an oral solution containing 1 mg/mL sirolimus. Rapamune is also available as a white, triangular-shaped tablet containing 1-mg sirolimus, and as a yellow to beige triangular-shaped tablet containing 2-mg sirolimus.

The inactive ingredients in Rapamune® Oral Solution are Phosal 50 PG® (phosphatidylcholine, propylene glycol, mono- and di-glycerides, ethanol, soy fatty acids, and ascorbyl palmitate) and polysorbate 80. Rapamune Oral Solution contains 1.5%-2.5% ethanol.



The inactive ingredients in Rapamune® Tablets include sucrose, lactose, polyethylene glycol 8000, calcium sulfate, microcrystalline cellulose, pharmaceutical glaze, talc, titanium dioxide, magnesium stearate, povidone, poloxamer 188, polyethylene glycol 20,000, glyceryl monooleate, carnauba wax, and other ingredients. The 2 mg dosage strength also contains iron oxide yellow 10 and iron oxide brown 70.

CLINICAL PHARMACOLOGY

Mechanism of Action

Sirolimus inhibits T lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (Interleukin [IL]-2, IL-4, and IL-15) stimulation by a mechanism that is distinct from that of other immunosuppressants. Sirolimus also inhibits antibody production. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. The sirolimus:FKBP-12 complex has no effect on calcineurin activity. This complex binds to and inhibits the activation of the mammalian Target Of Rapamycin (mTOR), a key regulatory kinase. This inhibition suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G_1 to the S phase of the cell cycle.

Studies in experimental models show that sirolimus prolongs allograft (kidney, heart, skin, islet, small bowel, pancreatico-duodenal, and bone marrow) survival in mice, rats, pigs, and/or primates. Sirolimus reverses acute rejection of heart and kidney allografts in rats and prolonged the graft survival in presensitized rats. In some studies, the immunosuppressive effect of sirolimus lasted up to 6 months after discontinuation of therapy. This tolerization effect is alloantigen specific.

In rodent models of autoimmune disease, sirolimus suppresses immune-mediated events associated with systemic lupus erythematosus, collagen-induced arthritis, autoimmune type I diabetes, autoimmune myocarditis, experimental allergic encephalomyelitis, graft-versus-host disease, and autoimmune uveoretinitis.

Pharmacokinetics

Sirolimus pharmacokinetic activity has been determined following oral administration in healthy subjects, pediatric dialysis patients, hepatically-impaired patients, and renal transplant patients.

Absorption

Following administration of Rapamune® (sirolimus) Oral Solution, sirolimus is rapidly absorbed, with a mean time-to-peak concentration (t_{max}) of approximately 1 hour after a single dose in healthy subjects and approximately 2 hours after multiple oral doses in renal transplant recipients. The systemic availability of sirolimus was estimated to be approximately 14% after the administration of Rapamune Oral Solution. The mean bioavailability of sirolimus after administration of the tablet is about 27% higher relative to the oral solution. Sirolimus oral tablets are not bioequivalent to the oral solution; however, clinical equivalence has been demonstrated at the 2-mg dose level. (See **Clinical Studies** and **DOSAGE AND ADMINISTRATION**). Sirolimus concentrations, following the administration of Rapamune Oral Solution to stable renal transplant patients, are dose proportional between 3 and 12 mg/m^2.

Food effects: In 22 healthy volunteers receiving Rapamune Oral Solution, a high-fat meal (861.8 kcal, 54.9% kcal from fat) altered the bioavailability characteristics of sirolimus. Compared with fasting, a 34% decrease in the peak blood sirolimus concentration (C_{max}), a 3.5-fold increase in the time-to-peak concentration (t_{max}), and a 35% increase in total exposure (AUC) was observed. After administration of Rapamune Tablets and a high-fat meal in 24 healthy volunteers, C_{max}, t_{max}, and AUC showed increases of 65%, 32%, and 23%, respectively. To minimize variability, both Rapamune Oral Solution and Tablets should be taken consistently with or without food (See **DOSAGE AND ADMINISTRATION**).

Distribution

The mean (± SD) blood-to-plasma ratio of sirolimus was 36 ± 17.9 in stable renal allograft recipients, indicating that sirolimus is extensively partitioned into formed blood elements. The mean volume of distribution (V_d/F) of sirolimus is 12 ± 7.52 L/kg. Sirolimus is extensively bound (approxi-

Continued on next page

Rapamune—Cont.

mately 92%) to human plasma proteins. In man, the binding of sirolimus was shown mainly to be associated with serum albumin (97%), α_1-acid glycoprotein, and lipoproteins.

Metabolism

Sirolimus is a substrate for both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein. Sirolimus is extensively metabolized by O-demethylation and/or hydroxylation. Seven (7) major metabolites, including hydroxy, demethyl, and hydroxydemethyl, are identifiable in whole blood. Some of these metabolites are also detectable in plasma, fecal, and urine samples. Glucuronide and sulfate conjugates are not present in any of the biologic matrices. Sirolimus is the major component in human whole blood and contributes to more than 90% of the immunosuppressive activity.

Excretion

After a single dose of [^{14}C]sirolimus in healthy volunteers, the majority (91%) of radioactivity was recovered from the feces, and only a minor amount (2.2%) was excreted in urine.

Pharmacokinetics in renal transplant patients

Rapamune Oral Solution: Pharmacokinetic parameters for sirolimus oral solution given daily in combination with cyclosporine and corticosteroids in renal transplant patients are summarized below based on data collected at months 1, 3, and 6 after transplantation (Studies 1 and 2; see **CLINICAL STUDIES**). There were no significant differences in any of these parameters with respect to treatment group or month.

[See first table at right]

Whole blood sirolimus trough concentrations (mean ± SD), as measured by immunoassay, for the 2 mg/day and 5 mg/day dose groups were 8.6 ± 4.0 ng/mL (n = 226) and 17.3 ± 7.4 ng/mL (n = 219), respectively. Whole blood trough sirolimus concentrations, as measured by LC/MS/MS, were significantly correlated (r^2 = 0.96) with $AUC_{\tau,ss}$. Upon repeated twice daily administration without an initial loading dose in a multiple-dose study, the average trough concentration of sirolimus increases approximately 2 to 3-fold over the initial 6 days of therapy at which time steady state is reached. A loading dose of 3 times the maintenance dose will provide near steady-state concentrations within 1 day in most patients. The mean ± SD terminal elimination half life ($t_{½}$) of sirolimus after multiple dosing in stable renal transplant patients was estimated to be about 62 ± 16 hours.

Rapamune Tablets: Pharmacokinetic parameters for sirolimus tablets administered daily in combination with cyclosporine and corticosteroids in renal transplant patients are summarized below based on data collected at months 1 and 3 after transplantation (Study 3; see **CLINICAL STUDIES**).

[See second table at right]

Whole blood sirolimus trough concentrations (mean ± SD), as measured by immunoassay, for 2 mg of oral solution and 2 mg of tablets over 6 months, were 8.9 ± 4.4 ng/mL (n = 172) and 9.5 ± 3.9 ng/mL (n = 179), respectively. Whole blood trough sirolimus concentrations, as measured by LC/MS/MS, were significantly correlated (r^2 = 0.85) with $AUC_{\tau,ss}$. Mean whole blood sirolimus trough concentrations in patients receiving either Rapamune Oral Solution or Rapamune Tablets with a loading dose of three times the maintenance dose achieved steady-state concentrations within 24 hours after the start of dose administration.

Average Rapamune doses and sirolimus whole blood trough concentrations for tablets administered daily in combination with cyclosporine and following cyclosporine withdrawal, in combination with corticosteroids in renal transplant patients (Study 4; see **CLINICAL STUDIES**) are summarized in the table below.

[See third table at right]

The withdrawal of cyclosporine and concurrent increases in sirolimus trough concentrations to steady-state required approximately 6 weeks. Larger Rapamune® doses were required due to the absence of the inhibition of sirolimus metabolism and transport by cyclosporine and to achieve higher target concentrations during concentration-controlled administration following cyclosporine withdrawal.

Special Populations

Hepatic impairment: Sirolimus (15 mg) was administered as a single oral dose to 18 subjects with normal hepatic function and to 18 patients with Child-Pugh classification A or B hepatic impairment, in which hepatic impairment was primary and not related to an underlying systemic disease. Shown below are the mean ± SD pharmacokinetic parameters following the administration of sirolimus oral solution.

[See fourth table at right]

Compared with the values in the normal hepatic group, the hepatic impairment group had higher mean values for sirolimus AUC (61%) and $t_{½}$ (43%) and had lower mean values for sirolimus CL/F/WT (33%). The mean $t_{1/2}$ increased from 79 ± 12 hours in subjects with normal hepatic function to 113 ± 41 hours in patients with impaired hepatic function. The rate of absorption of sirolimus was not altered by hepatic disease, as evidenced by C_{max} and t_{max} values. However, hepatic diseases with varying etiologies may show different effects and the pharmacokinetics of sirolimus in patients with severe hepatic dysfunction is unknown. Dosage adjustment is recommended for patients with mild to moderate hepatic impairment (see **DOSAGE AND ADMINISTRATION**).

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN RENAL TRANSPLANT PATIENTS (MULTIPLE DOSE ORAL SOLUTION)[a,b]

N	Dose	$C_{max,ss}$[c] (ng/mL)	$t_{max,ss}$ (h)	$AUC_{\tau,ss}$[c] (ng•h/mL)	CL/F/WT[d] (mL/h/kg)
19	2 mg	12.2 ± 6.2	3.01 ± 2.40	158 ± 70	182 ± 72
23	5 mg	37.4 ± 21	1.84 ± 1.30	396 ± 193	221 ± 143

a: Sirolimus administered four hours after cyclosporine oral solution (MODIFIED) (e.g., Neoral® Oral Solution) and/or cyclosporine capsules (MODIFIED) (e.g., Neoral® Soft Gelatin Capsules).
b: As measured by the Liquid Chromatographic/Tandem Mass Spectrometric Method (LC/MS/MS).
c: These parameters were dose normalized prior to the statistical comparison.
d: CL/F/WT = oral dose clearance.

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN RENAL TRANSPLANT PATIENTS (MULTIPLE DOSE TABLETS)[a,b]

n	Dose (2 mg/day)	$C_{max,ss}$[c] (ng/mL)	$t_{max,ss}$ (h)	$AUC_{\tau,ss}$[c] (ng•h/mL)	CL/F/WT[d] (mL/h/kg)
17	Oral solution	14.4 ± 5.3	2.12 ± 0.84	194 ± 78	173 ± 50
13	Tablets	15.0 ± 4.9	3.46 ± 2.40	230 ± 67	139 ± 63

a: Sirolimus administered four hours after cyclosporine oral solution (MODIFIED) (e.g., Neoral® Oral Solution) and/or cyclosporine capsules (MODIFIED) (e.g., Neoral® Soft Gelatin Capsules).
b: As measured by the Liquid Chromatographic/Tandem Mass Spectrometric Method (LC/MS/MS).
c: These parameters were dose normalized prior to the statistical comparison.
d: CL/F/WT = oral dose clearance.

AVERAGE RAPAMUNE DOSES AND SIROLIMUS TROUGH CONCENTRATIONS (MEAN ± SD) IN RENAL TRANSPLANT PATIENTS AFTER MULTIPLE DOSE TABLET ADMINISTRATION

	Rapamune with Cyclosporine Therapy[a]	Rapamune Following Cyclosporine Withdrawal[a]
Rapamune Dose (mg/day)		
Months 4 to 12	2.1 ± 0.7	8.2 ± 4.2
Months 12 to 24	2.0 ± 0.8	6.4 ± 3.0
Sirolimus C_{min}, (ng/mL)[b]		
Months 4 to 12	10.7 ± 3.8	23.3 ± 5.0
Months 12 to 24	11.2 ± 4.1	22.5 ± 4.8

a: 215 patients were randomized to each group.
b: Expressed by immunoassay and equivalence.

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN 18 HEALTHY SUBJECTS AND 18 PATIENTS WITH HEPATIC IMPAIRMENT (15 MG SINGLE DOSE – ORAL SOLUTION)

Population	$C_{max,ss}$[a] (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng•h/mL)	CL/F/WT (mL/h/kg)
Healthy subjects	78.2 ± 18.3	0.82 ± 0.17	970 ± 272	215 ± 76
Hepatic impairment	77.9 ± 23.1	0.84 ± 0.17	1567 ± 616	144 ± 62

a: As measured by (LC/MS/MS).

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN PEDIATRIC PATIENTS WITH STABLE CHRONIC RENAL FAILURE MAINTAINED ON HEMODIALYSIS OR PERITONEAL DIALYSIS (1, 3, 9, 15 MG/M^2 SINGLE DOSE)

Age Group (y)	n	t_{max} (h)	$t_{1/2}$ (h)	CL/F/WT (mL/h/kg)
5-11	9	1.1 ± 0.5	71 ± 40	580 ± 450
12-18	11	0.79 ± 0.17	55 ± 18	450 ± 232

Renal impairment: The effect of renal impairment on the pharmacokinetics of sirolimus is not known. However, there is minimal (2.2%) renal excretion of the drug or its metabolites.

Pediatric: Limited pharmacokinetic data are available in pediatric patients. The table below summarizes pharmacokinetic data obtained in pediatric dialysis patients with chronically impaired renal function.

[See fifth table at right]

Geriatric: Clinical studies of Rapamune did not include a sufficient number of patients >65 years of age to determine whether they will respond differently than younger patients. After the administration of Rapamune Oral Solution, sirolimus trough concentration data in 35 renal transplant patients >65 years of age were similar to those in the adult population (n = 822) 18 to 65 years of age. Similar results were obtained after the administration of Rapamune Tablets to 12 renal transplant patients >65 years of age compared with adults (n = 167) 18 to 65 years of age.

Gender: After the administration of Rapamune Oral Solution, sirolimus oral dose clearance in males was 12% lower than that in females; male subjects had a significantly longer $t_{1/2}$ than did female subjects (72.3 hours versus 61.3 hours). A similar trend in the effect of gender on sirolimus oral dose clearance and $t_{1/2}$ was observed after the administration of Rapamune Tablets. Dose adjustments based on gender are not recommended.

Race: In large phase 3 trials (Studies 1 and 2) using Rapamune Oral Solution and cyclosporine oral solution (MODIFIED) (e.g., Neoral® Oral Solution) and/or cyclosporine capsules (MODIFIED) (e.g., Neoral® Soft Gelatin Capsules), there were no significant differences in mean trough sirolimus concentrations over time between black (n = 139) and non-black (n = 724) patients during the first 6 months after transplantation at sirolimus doses of 2 mg/day and 5 mg/day. Similarly, after administration of Rapamune Tablets (2 mg/day) in a phase III trial, mean sirolimus trough concentrations over 6 months were not significantly different among black (n = 51) and non-black (n = 128) patients.

CLINICAL STUDIES

Rapamune® (sirolimus) Oral Solution: The safety and efficacy of Rapamune® Oral Solution for the prevention of organ rejection following renal transplantation were assessed in two randomized, double-blind, multicenter, controlled trials. These studies compared two dose levels of Rapamune Oral Solution (2 mg and 5 mg, once daily) with azathioprine (Study 1) or placebo (Study 2) when administered in combination with cyclosporine and corticosteroids. Study 1 was conducted in the United States at 38 sites. Seven hundred nineteen (719) patients were enrolled in this trial and randomized following transplantation; 284 were randomized to receive Rapamune Oral Solution 2 mg/day, 274 were randomized to receive Rapamune Oral Solution 5 mg/day, and 161 to receive azathioprine 2-3 mg/kg/day. Study 2 was conducted in Australia, Canada, Europe, and the United States, at a total of 34 sites. Five hundred seventy-six (576) patients were enrolled in this trial and randomized before transplantation; 227 were randomized to receive Rapamune Oral Solution 2 mg/day, 219 were randomized to receive Rapamune Oral Solution 5 mg/day, and 130 to receive placebo. In both studies, the use of antilymphocyte antibody induction therapy was prohibited. In both studies, the primary efficacy endpoint was the rate of efficacy failure in the first 6 months after transplantation. Efficacy failure was defined as the first occurrence of an acute rejection episode (confirmed by biopsy), graft loss, or death.

The tables below summarize the results of the primary efficacy analyses from these trials. Rapamune Oral Solution, at doses of 2 mg/day and 5 mg/day, significantly reduced the incidence of efficacy failure (statistically significant at the <0.025 level; nominal significance level adjusted for multiple [2] dose comparisons) at 6 months following transplantation compared with both azathioprine and placebo.

[See first table at right]
[See second table at right]
Patient and graft survival at 1 year were co-primary endpoints. The table below shows graft and patient survival at 1 and 2 years in Study 1 and 1 and 3 years in Study 2. The graft and patient survival rates were similar in patients treated with Rapamune and comparator-treated patients.
[See third table at right]
The reduction in the incidence of first biopsy-confirmed acute rejection episodes in patients treated with Rapamune compared with the control groups included a reduction in all grades of rejection.
In Study 1, which was prospectively stratified by race within center, efficacy failure was similar for Rapamune Oral Solution 2 mg/day and lower for Rapamune Oral Solution 5 mg/day compared with azathioprine in black patients. In Study 2, which was not prospectively stratified by race, efficacy failure was similar for both Rapamune Oral Solution doses compared with placebo in black patients. The decision to use the higher dose of Rapamune Oral Solution in black patients must be weighed against the increased risk of dose-dependent adverse events that were observed with the Rapamune Oral Solution 5-mg dose (see **ADVERSE REACTIONS**).
[See first table at top of next page]
Mean glomerular filtration rates (GFR) post transplant were calculated by using the Nankivell equation at 12 and 24 months for Study 1, and 12 and 36 months for Study 2. Mean GFR was lower in patients treated with cyclosporine and Rapamune Oral Solution compared with those treated with cyclosporine and the respective azathioprine or placebo control.
[See second table at top of next page]
Within each treatment group in Studies 1 and 2, mean GFR at one year post transplant was lower in patients who experienced at least 1 episode of biopsy-proven acute rejection, compared with those who did not.
Renal function should be monitored and appropriate adjustment of the immunosuppression regimen should be considered in patients with elevated or increasing serum creatinine levels (see **PRECAUTIONS**).
Rapamune® Tablets: The safety and efficacy of Rapamune Oral Solution and Rapamune Tablets for the prevention of organ rejection following renal transplantation were compared in a randomized multicenter controlled trial (Study 3). This study compared a single dose level (2 mg, once daily) of Rapamune Oral Solution and Rapamune Tablets when administered in combination with cyclosporine and corticosteroids. The study was conducted at 30 centers in Australia, Canada, and the United States. Four hundred seventy-seven (477) patients were enrolled in this study and randomized before transplantation; 238 patients were randomized to receive Rapamune Oral Solution 2 mg/day and 239 patients were randomized to receive Rapamune Tablets 2 mg/day. In this study, the use of antilymphocyte antibody induction therapy was prohibited. The primary efficacy endpoint was the rate of efficacy failure in the first 3 months after transplantation. Efficacy failure was defined as the first occurrence of an acute rejection episode (confirmed by biopsy), graft loss, or death.
The table below summarizes the result of the efficacy failure analysis at 3 and 6 months from this trial. The overall rate of efficacy failure at 3 months, the primary endpoint, in the tablet treatment group was equivalent to the rate in the oral solution treatment group.
[See third table on next page]
Graft and patient survival at 12 months were co-primary endpoints. There was no significant difference between the oral solution and tablet formulations for both graft and patient survival. Graft survival was 92.0% and 88.7% for the oral solution and tablet treatment groups, respectively. The patient survival rates in the oral solution and tablet treatment groups were 95.8% and 96.2%, respectively.
The mean GFR at 12 months, calculated by the Nankivell equation, were not significantly different for the oral solution group and for the tablet group.
The table below summarizes the mean GFR at one-year post-transplantation for all patients in Study 3 who had serum creatinine measured at 12 months.

OVERALL CALCULATED GLOMERULAR FILTRATION RATES (CC/MIN) BY NANKIVELL EQUATION AT 12 MONTHS POST TRANSPLANT: STUDY 3[a,b]

	Rapamune® Oral Solution	Rapamune® Tablets
Mean ± SEM	53.1 ± 1.7 (n = 229)	51.7 ± 1.7 (n = 225)

a: Includes patients who prematurely discontinued treatment.
b: Patients who had a graft loss were included in the analysis with GFR set to 0.0.

In Study 4, the safety and efficacy of Rapamune as a maintenance regimen were assessed following cyclosporine withdrawal at 3 to 4 months post renal transplantation. Study 4 was a randomized, multicenter, controlled trial conducted at 57 centers in Australia, Canada, and Europe. Five hundred twenty-five (525) patients were enrolled. All patients in this study received the tablet formulation. This study compared patients who were administered Rapamune, cyclosporine, and corticosteroids continuously with patients who received the same standardized therapy for the first 3 months after transplantation (prerandomization period) followed by the withdrawal of cyclosporine. During cyclosporine withdrawal the Rapamune dosages were adjusted to achieve targeted sirolimus whole blood trough concentration ranges (20 to 30 ng/mL, experimental immunoassay). At 3 months, 430 patients were equally randomized to either Rapamune with cyclosporine therapy or Rapamune as a maintenance regimen following cyclosporine withdrawal. Eligibility for randomization included no Banff Grade 3 acute rejection episode or vascular rejection in the 4 weeks before random assignment; serum creatinine ≤ 4.5 mg/dL; and adequate renal function to support cyclosporine withdrawal (in the opinion of the investigator). The primary efficacy endpoint was graft survival at 12 months after transplantation. Secondary efficacy endpoints were the rate of biopsy-confirmed acute rejection, patient survival, incidence of efficacy failure (defined as the first occurrence of either biopsy-proven acute rejection, graft loss, or death), and treatment failure (defined as the first occurrence of either discontinuation, acute rejection, graft loss, or death).
The safety and efficacy of cyclosporine withdrawal in high-risk patients have not been adequately studied and it is therefore not recommended. This includes patients with Banff grade III acute rejection or vascular rejection prior to cyclosporine withdrawal, those who are dialysis-dependent, serum creatinine > 4.5 mg/dL, black patients, re-transplants, multi-organ transplants, or patients with high panel of reactive antibodies (See **INDICATIONS AND USAGE**).

INCIDENCE (%) OF EFFICACY FAILURE AT 6 AND 24 MONTHS FOR STUDY 1[a,b]

Parameter	Rapamune® Oral Solution 2 mg/day (n = 284)	Rapamune® Oral Solution 5 mg/day (n = 274)	Azathioprine 2-3 mg/kg/day (n = 161)
Efficacy failure at 6 months[c]	18.7	16.8	32.3
Components of efficacy failure			
Biopsy-proven acute rejection	16.5	11.3	29.2
Graft loss	1.1	2.9	2.5
Death	0.7	1.8	0
Lost to follow-up	0.4	0.7	0.6
Efficacy failure at 24 months	32.8	25.9	36.0
Components of efficacy failure			
Biopsy-proven acute rejection	23.6	17.5	32.3
Graft loss	3.9	4.7	3.1
Death	4.2	3.3	0
Lost to follow-up	1.1	0.4	0.6

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c: Primary endpoint.

INCIDENCE (%) OF EFFICACY FAILURE AT 6 AND 36 MONTHS FOR STUDY 2[a,b]

Parameter	Rapamune® Oral Solution 2 mg/day (n = 227)	Rapamune® Oral Solution 5 mg/day (n = 219)	Placebo (n = 130)
Efficacy failure at 6 months[c]	30.0	25.6	47.7
Components of efficacy failure			
Biopsy-proven acute rejection	24.7	19.2	41.5
Graft loss	3.1	3.7	3.9
Death	2.2	2.7	2.3
Lost to follow-up	0	0	0
Efficacy failure at 36 months	44.1	41.6	54.6
Components of efficacy failure			
Biopsy-proven acute rejection	32.2	27.4	43.9
Graft loss	6.2	7.3	4.6
Death	5.7	5.9	5.4
Lost to follow-up	0	0.9	0.8

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c: Primary endpoint.

GRAFT AND PATIENT SURVIVAL (%) FOR STUDY 1 (12 AND 24 MONTHS) AND STUDY 2 (12 AND 36 MONTHS)[a,b]

Parameter	Rapamune® Oral Solution 2 mg/day	Rapamune® Oral Solution 5 mg/day	Azathioprine 2-3 mg/kg/day	Placebo
Study 1	(n = 284)	(n = 274)	(n = 161)	
Graft survival				
Month 12	94.7	92.7	93.8	
Month 24	85.2	89.1	90.1	
Patient survival				
Month 12	97.2	96.0	98.1	
Month 24	92.6	94.9	96.3	
Study 2	(n = 227)	(n = 219)		(n = 130)
Graft survival				
Month 12	89.9	90.9		87.7
Month 36	81.1	79.9		80.8
Patient survival				
Month 12	96.5	95.0		94.6
Month 36	90.3	89.5		90.8

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.

The table below summarizes the resulting graft and patient survival at 12, 24, and 36 months for this trial. At 12, 24, and 36 months, graft and patient survival were similar for both groups.

GRAFT AND PATIENT SURVIVAL (%): STUDY 4[a]

Parameter	Rapamune with Cyclosporine Therapy (n = 215)	Rapamune Following Cyclosporine Withdrawal (n = 215)
Graft Survival		
Month 12[b]	95.8	97.2
Month 24	91.2	93.5
Month 36	85.1	91.2
Patient Survival		
Month 12	97.2	98.1
Month 24	94.0	95.3
Month 36	88.4	93.5

a: Includes patients who prematurely discontinued treatment.
b: Primary efficacy endpoint.

The table below summarizes the results of first biopsy-proven acute rejection at 12 and 36 months. There was a significant difference in first biopsy-proven rejection be-

Continued on next page

Rapamune—Cont.

tween the two groups during post-randomization through 12 months. Most of the post-randomization acute rejections occurred in the first 3 months following randomization.

INCIDENCE OF FIRST BIOPSY-PROVEN ACUTE REJECTION (%) BY TREATMENT GROUP AT 36 MONTHS: STUDY 4[a]

Period	Rapamune with Cyclosporine Therapy (n = 215)	Rapamune Following Cyclosporine Withdrawal (n = 215)
Prerandomization[b]	9.3	10.2
Postrandomization through 12 months[b]	4.2	9.8
Postrandomization from 12 to 36 months	1.4	0.5
Postrandomization through 36 months	5.6	10.2
Total at 36 months	14.9	20.5

a: Includes patients who prematurely discontinued treatment.
b: Randomization occurred at 3 months ± 2 weeks.

Patients receiving renal allografts with ≥ 4 HLA mismatches experienced significantly higher rates of acute rejection following randomization to the cyclosporine withdrawal group compared with patients who continued cyclosporine (15.3% vs 3.0%). Patients receiving renal allografts with ≤ 3 HLA mismatches, demonstrated similar rates of acute rejection between treatment groups (6.8% vs 7.7%) following randomization.
The table below summarizes the mean calculated GFR in Study 4.

CALCULATED GLOMERULAR FILTRATION RATES (mL/min) BY NANKIVELL EQUATION AT 12, 24, AND 36 MONTHS POST TRANSPLANT: STUDY 4[a,b]

Parameter	Rapamune with Cyclosporine Therapy	Rapamune Following Cyclosporine Withdrawal
Month 12		
Mean ± SEM	53.2 ± 1.5	59.3 ± 1.5
	n = 208	n = 203
Month 24		
Mean ± SEM	48.4 ± 1.7	58.4 ± 1.6
	n = 203	n = 201
Month 36		
Mean ± SEM	47.3 ± 1.8	59.4 ± 1.8
	(n = 194)	(n = 194)

a: Includes patients who prematurely discontinued treatment.
b: Patients who had a graft loss were included in the analysis and had their GFR set to 0.0.

The mean GFR at 12, 24, and 36 months, calculated by the Nankivell equation, was significantly higher for patients receiving Rapamune as a maintenance regimen following cyclosporine withdrawal than for those in the Rapamune with cyclosporine therapy group. Patients who had an acute rejection prior to randomization had a significantly higher GFR following cyclosporine withdrawal compared to those in the Rapamune with cyclosporine group. There was no significant difference in GFR between groups for patients who experienced acute rejection postrandomization.

INDICATIONS AND USAGE

Rapamune® (sirolimus) is indicated for the prophylaxis of organ rejection in patients receiving renal transplants. It is recommended that Rapamune be used initially in a regimen with cyclosporine and corticosteroids. In patients at low to moderate immunologic risk cyclosporine should be withdrawn 2 to 4 months after transplantation and Rapamune® dose should be increased to reach recommended blood concentrations (See **DOSAGE AND ADMINISTRATION**).
The safety and efficacy of cyclosporine withdrawal in high-risk patients have not been adequately studied and it is therefore not recommended. This includes patients with Banff grade III acute rejection or vascular rejection prior to cyclosporine withdrawal, those who are dialysis-dependent, or with serum creatinine > 4.5 mg/dL, black patients, re-transplants, multi-organ transplants, patients with high panel of reactive antibodies (See **CLINICAL STUDIES**).

CONTRAINDICATIONS

Rapamune is contraindicated in patients with a hypersensitivity to sirolimus or its derivatives or any component of the drug product.

WARNINGS

Increased susceptibility to infection and the possible development of lymphoma and other malignancies, particularly of the skin, may result from immunosuppression (see **ADVERSE REACTIONS**). Oversuppression of the immune system can also increase susceptibility to infection including opportunistic infections, fatal infections, and sepsis. Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should use Rapamune. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.
Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, have been associated with the administration of sirolimus (see **ADVERSE REACTIONS**).
As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.
Increased serum cholesterol and triglycerides, that may require treatment, occurred more frequently in patients treated with Rapamune compared with azathioprine or placebo controls (see **PRECAUTIONS**).
In Studies 1 and 2, from month 6 through months 24 and 36, respectively, mean serum creatinine was increased and mean glomerular filtration rate was decreased in patients treated with Rapamune and cyclosporine compared with those treated with cyclosporine and placebo or azathioprine controls. The rate of decline in renal function was greater in patients receiving Rapamune and cyclosporine compared with control therapies (see **CLINICAL STUDIES**).
Renal function should be closely monitored during the administration of Rapamune® in combination with cyclosporine since long-term administration can be associated with deterioration of renal function. Appropriate adjustment of the immunosuppression regimen, including discontinuation of Rapamune and/or cyclosporine, should be considered in patients with elevated or increasing serum creatinine levels. Caution should be exercised when using other drugs which are known to impair renal function. In patients at low to moderate immunologic risk continuation of combination therapy with cyclosporine beyond 4 months following transplantation should only be considered when the benefits outweigh the risks of this combination for the individual patients (see **PRECAUTIONS**).
In clinical trials, Rapamune has been administered concurrently with corticosteroids and with the following formulations of cyclosporine:
Sandimmune® Injection (cyclosporine injection)
Sandimmune® Oral Solution (cyclosporine oral solution)
Sandimmune® Soft Gelatin Capsules (cyclosporine capsules)
Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED])
Neoral® Oral Solution (cyclosporine oral solution [MODIFIED])
The efficacy and safety of the use of Rapamune in combination with other immunosuppressive agents has not been determined.

PERCENTAGE OF EFFICACY FAILURE BY RACE AT 6 MONTHS[a,b]

Parameter	Rapamune® Oral Solution 2 mg/day	Rapamune® Oral Solution 5 mg/day	Azathioprine 2-3 mg/kg/day	Placebo
Study 1				
Black (n = 166)	34.9 (n = 63)	18.0 (n = 61)	33.3 (n = 42)	
Non-black (n = 553)	14.0 (n = 221)	16.4 (n = 213)	31.9 (n = 119)	
Study 2				
Black (n = 66)	30.8 (n = 26)	33.7 (n = 27)		38.5 (n = 13)
Non-black (n = 510)	29.9 (n = 201)	24.5 (n = 192)		48.7 (n = 117)

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.

OVERALL CALCULATED GLOMERULAR FILTRATION RATES (Mean ± SEM, cc/min) BY NANKIVELL EQUATION POST TRANSPLANT[a,b]

Parameter	Rapamune® Oral Solution 2 mg/day	Rapamune® Oral Solution 5 mg/day	Azathioprine 2-3 mg/kg/day	Placebo
Study 1				
Month 12	57.4 ± 1.3 (n = 269)	54.6 ± 1.3 (n = 245)	64.1 ± 1.6 (n = 149)	
Month 24	58.4 ± 1.5 (n = 221)	52.6 ± 1.5 (n = 222)	62.4 ± 1.9 (n = 132)	
Study 2				
Month 12	52.4 ± 1.5 (n = 211)	51.5 ± 1.5 (n = 199)		58.0 ± 2.1 (n = 117)
Month 36	48.1 ± 1.8 (n = 183)	46.1 ± 2.0 (n = 177)		53.4 ± 2.7 (n = 102)

a: Includes patients who prematurely discontinued treatment.
b: Patients who had a graft loss were included in the analysis with GFR set to 0.0.

INCIDENCE (%) OF EFFICACY FAILURE AT 3 AND 6 MONTHS: STUDY 3[a,b]

	Rapamune® Oral Solution (n = 238)	Rapamune® Tablets (n = 239)
Efficacy Failure at 3 months[c]	23.5	24.7
Components of efficacy failure		
Biopsy-proven acute rejection	18.9	17.6
Graft loss	3.4	6.3
Death	1.3	0.8
Efficacy Failure at 6 months	26.1	27.2
Components of efficacy failure		
Biopsy-proven acute rejection	21.0	19.2
Graft loss	3.4	6.3
Death	1.7	1.7

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c: Efficacy failure at 3 months was the primary endpoint.

Liver Transplantation – Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis (HAT):
The use of sirolimus in combination with tacrolimus was associated with excess mortality and graft loss in a study in de novo liver transplant recipients. Many of these patients had evidence of infection at or near the time of death.
In this and another study in de novo liver transplant recipients, the use of sirolimus in combination with cyclosporine or tacrolimus was associated with an increase in HAT; most cases of HAT occurred within 30 days post-transplantation and most led to graft loss or death.
Lung Transplantation – Bronchial Anastomotic Dehiscence:
Cases of bronchial anastomotic dehiscence, most fatal, have been reported in de novo lung transplant patients when sirolimus has been used as part of an immunosuppressive regimen.
The safety and efficacy of Rapamune® (sirolimus) as immunosuppressive therapy have not been established in liver or lung transplant patients, and therefore, such use is not recommended.

PRECAUTIONS

General
Rapamune is intended for oral administration only.
Lymphocele, a known surgical complication of renal transplantation, occurred significantly more often in a dose-related fashion in patients treated with Rapamune. Appropriate operative measures should be considered to minimize this complication.

Lipids

The use of Rapamune® (sirolimus) in renal transplant patients was associated with increased serum cholesterol and triglycerides that may require treatment.

In Studies 1 and 2, in *de novo* renal transplant recipients who began the study with normal, fasting, total serum cholesterol (<200 mg/dL) or normal, fasting, total serum triglycerides (<200 mg/dL), there was an increased incidence of hypercholesterolemia (fasting serum cholesterol >240 mg/dL) or hypertriglyceridemia (fasting serum triglycerides >500 mg/dL), respectively, in patients receiving both Rapamune® 2 mg and Rapamune® 5 mg compared with azathioprine and placebo controls.

Treatment of new-onset hypercholesterolemia with lipid-lowering agents was required in 42-52% of patients enrolled in the Rapamune arms of Studies 1 and 2 compared with 16% of patients in the placebo arm and 22% of patients in the azathioprine arm.

In Study 4 during the prerandomization period, mean fasting serum cholesterol and triglyceride values rapidly increased, and peaked at 2 months with mean cholesterol values > 240 mg/dL and triglycerides > 250 mg/dL. After randomization mean cholesterol and triglyceride values remained higher in the cyclosporine withdrawal arm compared to the Rapamune® and cyclosporine combination.

Renal transplant patients have a higher prevalence of clinically significant hyperlipidemia. Accordingly, the risk/benefit should be carefully considered in patients with established hyperlipidemia before initiating an immunosuppressive regimen including Rapamune.

Any patient who is administered Rapamune should be monitored for hyperlipidemia using laboratory tests and if hyperlipidemia is detected, subsequent interventions such as diet, exercise, and lipid-lowering agents, as outlined by the National Cholesterol Education Program guidelines, should be initiated.

In clinical trials, the concomitant administration of Rapamune and HMG-CoA reductase inhibitors and/or fibrates appeared to be well tolerated.

During Rapamune therapy with cyclosporine, patients administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects as described in the respective labeling for these agents.

Renal Function

Patients treated with cyclosporine and Rapamune were noted to have higher serum creatinine levels and lower glomerular filtration rates compared with patients treated with cyclosporine and placebo or azathioprine controls (Studies 1 and 2). The rate of decline in renal function in these studies was greater in patients receiving Rapamune and cyclosporine compared with control therapies. In patients at low to moderate immunologic risk (See **CLINICAL STUDIES**) continuation of combination therapy with cyclosporine beyond 4 months following transplantation should only be considered when the benefits outweigh the risks of this combination for the individual patients (see **WARNINGS**).

Renal function should be monitored during the administration of Rapamune® in combination with cyclosporine. Appropriate adjustment of the immunosuppression regimen, including discontinuation of Rapamune and/or cyclosporine, should be considered in patients with elevated or increasing serum creatinine levels. Caution should be exercised when using agents (e.g., aminoglycosides, and amphotericin B) that are known to have a deleterious effect on renal function.

Antimicrobial Prophylaxis

Cases of *Pneumocystis carinii* pneumonia have been reported in patients not receiving antimicrobial prophylaxis. Therefore, antimicrobial prophylaxis for *Pneumocystis carinii* pneumonia should be administered for 1 year following transplantation.

Cytomegalovirus (CMV) prophylaxis is recommended for 3 months after transplantation, particularly for patients at increased risk for CMV disease.

Interstitial Lung Disease

Cases of interstitial lung disease (including pneumonitis, and infrequently bronchiolitis obliterans organizing pneumonia [BOOP] and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including Rapamune. In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of Rapamune. The risk may be increased as the trough Rapamune concentration increases (see **ADVERSE REACTIONS**).

Information for Patients

Patients should be given complete dosage instructions (see **Patient Instructions**). Women of childbearing potential should be informed of the potential risks during pregnancy and that they should use effective contraception prior to initiation of Rapamune therapy, during Rapamune therapy and for 12 weeks after Rapamune therapy has been stopped (see **PRECAUTIONS: Pregnancy**).

Patients should be told that exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor because of the increased risk for skin cancer (see **WARNINGS**).

Laboratory Tests

Whole blood sirolimus concentrations should be monitored in patients receiving concentration-controlled Rapamune. Monitoring is also necessary in patients likely to have altered drug metabolism, in patients ≥13 years who weigh less than 40 kg, in patients with hepatic impairment, and during concurrent administration of potent CYP3A4 inducers and inhibitors (see **PRECAUTIONS: Drug Interactions**).

Drug Interactions

Sirolimus is known to be a substrate for both cytochrome CYP3A4 and P-glycoprotein. The pharmacokinetic interaction between sirolimus and concomitantly administered drugs is discussed below. Drug interaction studies have not been conducted with drugs other than those described below.

Cyclosporine capsules MODIFIED:

Rapamune Oral Solution: In a single dose drug-drug interaction study, 24 healthy volunteers were administered 10 mg sirolimus either simultaneously or 4 hours after a 300 mg dose of Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). For simultaneous administration, the mean C_{max} and AUC of sirolimus were increased by 116% and 230%, respectively, relative to administration of sirolimus alone. However, when given 4 hours after Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]) administration, sirolimus C_{max} and AUC were increased by 37% and 80%, respectively, compared with administration of sirolimus alone.

Mean cyclosporine C_{max} and AUC were not significantly affected when sirolimus was given simultaneously or when administered 4 hours after Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). However, after multiple-dose administration of sirolimus given 4 hours after Neoral® in renal post-transplant patients over 6 months, cyclosporine oral-dose clearance was reduced, and lower doses of Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]) were needed to maintain target cyclosporine concentration.

Rapamune (sirolimus) Tablets: In a single-dose drug-drug interaction study, 24 healthy volunteers were administered 10 mg sirolimus (Rapamune Tablets) either simultaneously or 4 hours after a 300-mg dose of Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). For simultaneous administration, mean C_{max} and AUC were increased by 512% and 148%, respectively, relative to administration of sirolimus alone. However, when given 4 hours after cyclosporine administration, sirolimus C_{max} and AUC were both increased by only 33% compared with administration of sirolimus alone.

Because of the effect of cyclosporine capsules (MODIFIED), it is recommended that sirolimus should be taken 4 hours after administration of cyclosporine oral solution (MODIFIED) and/or cyclosporine capsules (MODIFIED), (see DOSAGE AND ADMINISTRATION).

Cyclosporine oral solution: In a multiple-dose study in 150 psoriasis patients, sirolimus 0.5, 1.5, and 3 mg/m²/day was administered simultaneously with Sandimmune® Oral Solution (cyclosporine Oral Solution) 1.25 mg/kg/day. The increase in average sirolimus trough concentrations ranged between 67% to 86% relative to when sirolimus was administered without cyclosporine. The intersubject variability (%CV) for sirolimus trough concentrations ranged from 39.7% to 68.7%. There was no significant effect of multiple-dose sirolimus on cyclosporine trough concentrations following Sandimmune® Oral Solution (cyclosporine oral solution) administration. However, the %CV was higher (range 85.9%-165%) than those from previous studies.

Sandimmune® Oral Solution (cyclosporine oral solution) is not bioequivalent to Neoral® Oral Solution (cyclosporine oral solution MODIFIED), and should not be used interchangeably. Although there is no published data comparing Sandimmune® Oral Solution (cyclosporine oral solution) to SangCya® Oral Solution (cyclosporine oral solution [MODIFIED]), they should not be used interchangeably. Likewise, Sandimmune® Soft Gelatin Capsules (cyclosporine capsules) are not bioequivalent to Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]) and should not be used interchangeably.

Diltiazem: The simultaneous oral administration of 10 mg of sirolimus oral solution and 120 mg of diltiazem to 18 healthy volunteers significantly affected the bioavailability of sirolimus. Sirolimus C_{max}, t_{max}, and AUC were increased 1.4-, 1.3-, and 1.6-fold, respectively. Sirolimus did not affect the pharmacokinetics of either diltiazem or its metabolites desacetyldiltiazem and desmethyldiltiazem. If diltiazem is administered, sirolimus should be monitored and a dose adjustment may be necessary.

Ketoconazole: Multiple-dose ketoconazole administration significantly affected the rate and extent of absorption and sirolimus exposure after administration of Rapamune® (sirolimus) Oral Solution, as reflected by increases in sirolimus C_{max}, t_{max}, and AUC of 4.3-fold, 38%, and 10.9-fold, respectively. However, the terminal $t_{1/2}$ of sirolimus was not changed. Single-dose sirolimus did not affect steady-state 12-hour plasma ketoconazole concentrations. It is recommended that sirolimus oral solution and oral tablets should not be administered with ketoconazole.

Rifampin: Pretreatment of 14 healthy volunteers with multiple doses of rifampin, 600 mg daily for 14 days, followed by a single 20-mg dose of sirolimus, greatly increased sirolimus oral-dose clearance by 5.5-fold (range = 2.8 to 10), which represents mean decreases in AUC and C_{max} of about 82% and 71%, respectively. In patients where rifampin is indicated, alternative therapeutic agents with less enzyme induction potential should be considered.

Drugs which may be coadministered without dose adjustment

Clinically significant pharmacokinetic drug-drug interactions were not observed in studies of drugs listed below. A synopsis of the type of study performed for each drug is provided. Sirolimus and these drugs may be coadministered without dose adjustments.

Acyclovir: Acyclovir, 200 mg, was administered once daily for 3 days followed by a single 10-mg dose of sirolimus oral solution on day 3 in 20 adult healthy volunteers.

Digoxin: Digoxin, 0.25 mg, was administered daily for 8 days and a single 10-mg dose of sirolimus oral solution was given on day 8 to 24 healthy volunteers.

Glyburide: A single 5-mg dose of glyburide and a single 10-mg dose of sirolimus oral solution were administered to 24 healthy volunteers. Sirolimus did not affect the hypoglycemic action of glyburide.

Nifedipine: A single 60-mg dose of nifedipine and a single 10-mg dose of sirolimus oral solution were administered to 24 healthy volunteers.

Norgestrel/ethinyl estradiol (Lo/Ovral®): Sirolimus oral solution, 2 mg, was given daily for 7 days to 21 healthy female volunteers on norgestrel/ethinyl estradiol.

Prednisolone: Pharmacokinetic information was obtained from 42 stable renal transplant patients receiving daily doses of prednisone (5-20 mg/day) and either single or multiple doses of sirolimus oral solution (0.5-5 mg/m² q 12h).

Sulfamethoxazole/trimethoprim (Bactrim®): A single oral dose of sulfamethoxazole (400 mg)/trimethoprim (80 mg) was given to 15 renal transplant patients receiving daily oral doses of sirolimus (8 to 25 mg/m²).

Other drug interactions

Sirolimus is extensively metabolized by the CYP3A4 isoenzyme in the gut wall and liver. Therefore, absorption and the subsequent elimination of systemically absorbed sirolimus may be influenced by drugs that affect this isoenzyme. Inhibitors of CYP3A4 may decrease the metabolism of sirolimus and increase sirolimus concentrations, while inducers of CYP3A4 may increase the metabolism of sirolimus and decrease sirolimus concentrations.

Drugs that may increase sirolimus blood concentrations include:

Calcium channel blockers: nicardipine, verapamil.

Antifungal agents: clotrimazole, fluconazole, itraconazole.

Macrolide antibiotics: clarithromycin, erythromycin, troleandomycin.

Gastrointestinal prokinetic agents: cisapride, metoclopramide.

Other drugs: bromocriptine, cimetidine, danazol, HIV-protease inhibitors (e.g., ritonavir, indinavir).

Drugs that may decrease sirolimus concentrations include:

Anticonvulsants: carbamazepine, phenobarbital, phenytoin.

Antibiotics: rifabutin, rifapentine.

This list is not all inclusive.

Care should be exercised when drugs or other substances that are metabolized by CYP3A4 are administered concomitantly with Rapamune. Grapefruit juice reduces CYP3A4-mediated metabolism of Rapamune and must not be used for dilution (see **DOSAGE AND ADMINISTRATION**).

Herbal Preparations

St. John's Wort (*hypericum perforatum*) induces CYP3A4 and P-glycoprotein. Since sirolimus is a substrate for both cytochrome CYP3A4 and P-glycoprotein, there is the potential that the use of St. John's Wort in patients receiving Rapamune could result in reduced sirolimus concentrations.

Vaccination

Immunosuppressants may affect response to vaccination. Therefore, during treatment with Rapamune, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid.

Drug-Laboratory Test Interactions

There are no studies on the interactions of sirolimus in commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Sirolimus was not genotoxic in the in vitro bacterial reverse mutation assay, the Chinese hamster ovary cell chromosomal aberration assay, the mouse lymphoma cell forward mutation assay, or the in vivo mouse micronucleus assay.

Carcinogenicity studies were conducted in mice and rats. In an 86-week female mouse study at dosages of 0, 12.5, 25 and 50/6 (dosage lowered from 50 to 6 mg/kg/day at week 31 due to infection secondary to immunosuppression) there was a statistically significant increase in malignant lymphoma at all dose levels (approximately 16 to 135 times the clinical doses adjusted for body surface area) compared with controls. In a second mouse study at dosages of 0, 1, 3 and 6 mg/kg (approximately 3 to 16 times the clinical dose adjusted for body surface area), hepatocellular adenoma and carcinoma (males), were considered Rapamune related. In the 104-week rat study at dosages of 0, 0.05, 0.1, and 0.2 mg/kg/day (approximately 0.4 to 1 times the clinical dose adjusted for body surface area), there was a statistically significant increased incidence of testicular adenoma in the 0.2 mg/kg/day group.

There was no effect on fertility in female rats following the administration of sirolimus at dosages up to 0.5 mg/kg (approximately 1 to 3 times the clinical doses adjusted for body surface area). In male rats, there was no significant difference in fertility rate compared to controls at a dosage of 2 mg/kg (approximately 4 to 11 times the clinical doses adjusted for body surface area). Reductions in testicular

Continued on next page

Rapamune—Cont.

weights and/or histological lesions (e.g., tubular atrophy and tubular giant cells) were observed in rats following dosages of 0.65 mg/kg (approximately 1 to 3 times the clinical doses adjusted for body surface area) and above and in a monkey study at 0.1 mg/kg (approximately 0.4 to 1 times the clinical doses adjusted for body surface area) and above. Sperm counts were reduced in male rats following the administration of sirolimus for 13 weeks at a dosage of 6 mg/kg (approximately 12 to 32 times the clinical doses adjusted for body surface area), but showed improvement by 3 months after dosing was stopped.

Pregnancy

Pregnancy Category C: Sirolimus was embryo/feto toxic in rats at dosages of 0.1 mg/kg and above (approximately 0.2 to 0.5 the clinical doses adjusted for body surface area). Embryo/feto toxicity was manifested as mortality and reduced fetal weights (with associated delays in skeletal ossification). However, no teratogenesis was evident. In combination with cyclosporine, rats had increased embryo/feto mortality compared with Rapamune alone. There were no effects on rabbit development at the maternally toxic dosage of 0.05 mg/kg (approximately 0.3 to 0.8 times the clinical doses adjusted for body surface area). There are no adequate and well controlled studies in pregnant women. Effective contraception must be initiated before Rapamune therapy, during Rapamune therapy, and for 12 weeks after Rapamune therapy has been stopped. Rapamune should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo/fetus.

Use during lactation

Sirolimus is excreted in trace amounts in milk of lactating rats. It is not known whether sirolimus is excreted in human milk. The pharmacokinetic and safety profiles of sirolimus in infants are not known. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from sirolimus, 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 efficacy of Rapamune in pediatric patients below the age of 13 years have not been established.

Geriatric use

Clinical studies of Rapamune Oral Solution or Tablets did not include sufficient numbers of patients aged 65 years and over to determine whether safety and efficacy differ in this population from younger patients. Data pertaining to sirolimus trough concentrations suggest that dose adjustments based upon age in geriatric renal patients are not necessary.

ADVERSE REACTIONS

Rapamune® Oral Solution: The incidence of adverse reactions was determined in two randomized, double-blind, multicenter controlled trials in which 499 renal transplant patients received Rapamune Oral Solution 2 mg/day, 477 received Rapamune Oral Solution 5 mg/day, 160 received azathioprine, and 124 received placebo. All patients were treated with cyclosporine and corticosteroids. Data (≥ 12 months post-transplant) presented in the table below show the adverse reactions that occurred in any treatment group with an incidence of ≥ 20%.

Specific adverse reactions associated with the administration of Rapamune (sirolimus) Oral Solution occurred at a significantly higher frequency than in the respective control group. For both Rapamune Oral Solution 2 mg/day and 5 mg/day these include hypercholesterolemia, hyperlipemia, hypertension, and rash; for Rapamune Oral Solution 2 mg/day acne; and for Rapamune Oral Solution 5 mg/day anemia, arthralgia, diarrhea, hypokalemia, and thrombocytopenia. The elevations of triglycerides and cholesterol and decreases in platelets and hemoglobin occurred in a dose-related manner in patients receiving Rapamune.

Patients maintained on Rapamune Oral Solution 5 mg/day, when compared with patients on Rapamune Oral Solution 2 mg/day, demonstrated an increased incidence of the following adverse events: anemia, leukopenia, thrombocytopenia, hypokalemia, hyperlipemia, fever, and diarrhea.

In general, adverse events related to the administration of Rapamune were dependent on dose/concentration.

[See first table at right]

With longer term follow-up, the adverse event profile remained similar. Some new events became significantly different among the treatment groups. For events which occurred at a frequency of ≥ 20% by 24 months for Study 1 and 36 months for Study 2, only the incidence of edema became significantly higher in both Rapamune groups as compared with the control group. The incidence of headache became significantly more common in the Rapamune 5 mg/day group as compared with control therapy.

At 24 months for Study 1, the following treatment-emergent infections were significantly different among the treatment groups: bronchitis, Herpes simplex, pneumonia, pyelonephritis, and upper respiratory infections. In each instance, the incidence was highest in the Rapamune 5 mg/day group, lower in the Rapamune 2 mg/day group and lowest in the azathioprine group. Except for upper respiratory infections in the Rapamune 5 mg/day cohort, the remainder of events occurred with a frequency of < 20%.

At 36 months in Study 2 only the incidence of treatment-emergent Herpes simplex was significantly different among the treatment groups, being higher in the Rapamune 5 mg/day group than either of the other groups.

ADVERSE EVENTS OCCURRING AT A FREQUENCY OF ≥ 20% IN ANY TREATMENT GROUP IN PREVENTION OF ACUTE RENAL REJECTION TRIALS (%) AT ≥ 12 MONTHS POST-TRANSPLANTATION FOR STUDIES 1 AND 2[a]

Body System	Rapamune® Oral Solution 2 mg/day		Rapamune® Oral Solution 5 mg/day		Azathioprine 2-3 mg/kg/day	Placebo
Adverse Event	Study 1 (n = 281)	Study 2 (n = 218)	Study 1 (n = 269)	Study 2 (n = 208)	Study 1 (n = 160)	Study 2 (n = 124)
Body As A Whole						
Abdominal pain	28	29	30	36	29	30
Asthenia	38	22	40	28	37	28
Back pain	16	23	26	22	23	20
Chest pain	16	18	19	24	16	19
Fever	27	23	33	34	33	35
Headache	23	34	27	34	21	31
Pain	24	33	29	29	30	25
Cardiovascular System						
Hypertension	43	45	39	49	29	48
Digestive System						
Constipation	28	36	34	38	37	31
Diarrhea	32	25	42	35	28	27
Dyspepsia	17	23	23	25	24	34
Nausea	31	25	36	31	39	29
Vomiting	21	19	25	25	31	21
Hemic And Lymphatic System						
Anemia	27	23	37	33	29	21
Leukopenia	9	9	15	13	20	8
Thrombocytopenia	13	14	20	30	9	9
Metabolic And Nutritional						
Creatinine increased	35	39	37	40	28	38
Edema	24	20	16	18	23	15
Hypercholesteremia (See **WARNINGS** and **PRECAUTIONS**)	38	43	42	46	33	23
Hyperkalemia	15	17	12	14	24	27
Hyperlipemia (See **WARNINGS** and **PRECAUTIONS**)	38	45	44	57	28	23
Hypokalemia	17	11	21	17	11	9
Hypophosphatemia	20	15	23	19	20	19
Peripheral edema	60	54	64	58	58	48
Weight gain	21	11	15	8	19	15
Musculoskeletal System						
Arthralgia	25	25	27	31	21	18
Nervous System						
Insomnia	14	13	22	14	18	8
Tremor	31	21	30	22	28	19
Respiratory System						
Dyspnea	22	24	28	30	23	30
Pharyngitis	17	16	16	21	17	22
Upper respiratory infection	20	26	24	23	13	23
Skin And Appendages						
Acne	31	22	20	22	17	19
Rash	12	10	13	20	6	6
Urogenital System						
Urinary tract infection	20	26	23	33	31	26

a: Patients received cyclosporine and corticosteroids.

INCIDENCE (%) OF MALIGNANCIES IN STUDY 1 (24 MONTHS) AND STUDY 2 (36 MONTHS) POST-TRANSPLANT[a,b]

	Rapamune® Oral Solution 2 mg/day		Rapamune® Oral Solution 5 mg/day		Azathioprine 2-3 mg/kg/day	Placebo
Malignancy	Study 1 (n = 284)	Study 2 (n = 227)	Study 1 (n = 274)	Study 2 (n = 219)	Study 1 (n = 161)	Study 2 (n = 130)
Lymphoma /lymphoproliferative disease	**0.7**	**1.8**	**1.1**	**3.2**	**0.6**	**0.8**
Skin Carcinoma						
Any Squamous Cell[c]	0.4	2.7	2.2	0.9	3.8	3.0
Any Basal Cell[c]	0.7	2.2	1.5	1.8	2.5	5.3
Melanoma	0.0	0.4	0.0	1.4	0.0	0.0
Miscellaneous/Not Specified	0.0	0.0	0.0	0.0	0.0	0.8
Total	**1.1**	**4.4**	**3.3**	**4.1**	**4.3**	**7.7**
Other Malignancy	**1.1**	**2.2**	**1.5**	**1.4**	**0.6**	**2.3**

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c: Patients may be counted in more than one category.

The table below summarizes the incidence of malignancies in the two controlled trials for the prevention of acute rejection. At 24 (Study 1) and 36 months (Study 2) there were no significant differences among treatment groups.

[See second table at right]

Among the adverse events that were reported at a rate of ≥3% and <20% at 12 months, the following were more prominent in patients maintained on Rapamune 5 mg/day, when compared with patients on Rapamune 2 mg/day: epistaxis, lymphocele, insomnia, thrombotic thrombocytopenic purpura (hemolytic-uremic syndrome), skin ulcer, increased LDH, hypotension, facial edema.

The following adverse events were reported with ≥3% and <20% incidence in patients in any Rapamune treatment group in the two controlled clinical trials for the prevention of acute rejection, BODY AS A WHOLE: abdomen enlarged, abscess, ascites, cellulitis, chills, face edema, flu syndrome, generalized edema, hernia, *Herpes zoster* infection, lymphocele, malaise, pelvic pain, peritonitis, sepsis; CARDIOVASCULAR SYSTEM: atrial fibrillation, congestive heart failure, hemorrhage, hypervolemia, hypotension, palpitation, peripheral vascular disorder, postural hypotension, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation, venous thromboembolism; DIGESTIVE SYSTEM: anorexia, dysphagia, eructation, esophagitis, flatulence, gastritis, gastroenteritis, gingivitis, gum hyperplasia, ileus, liver function tests abnormal, mouth ulceration, oral moniliasis, stomatitis; ENDOCRINE SYSTEM: Cushing's syndrome, diabetes mellitus, glycosuria; HEMIC AND LYMPHATIC SYSTEM: ecchymosis, leukocytosis, lymphadenopathy, polycythemia, thrombotic thrombocytopenic purpura (hemolytic-uremic syndrome); METABOLIC AND NUTRITIONAL: acidosis, alkaline phosphatase increased, BUN increased, creatine phosphokinase increased, dehydration, healing abnormal, hypercalcemia, hyperglycemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypomagnesemia, hyponatremia, lactic dehydrogenase in-

creased, AST/SGOT increased, ALT/SGPT increased, weight loss; MUSCULOSKELETAL SYSTEM: arthrosis, bone necrosis, leg cramps, myalgia, osteoporosis, tetany; NERVOUS SYSTEM: anxiety, confusion, depression, dizziness, emotional lability, hypertonia, hypesthesia, hypotonia, insomnia, neuropathy, paresthesia, somnolence; RESPIRATORY SYSTEM: asthma, atelectasis, bronchitis, cough increased, epistaxis, hypoxia, lung edema, pleural effusion, pneumonia, rhinitis, sinusitis; SKIN AND APPENDAGES: fungal dermatitis, hirsutism, pruritus, skin hypertrophy, skin ulcer, sweating; SPECIAL SENSES: abnormal vision, cataract, conjunctivitis, deafness, ear pain, otitis media, tinnitus; UROGENITAL SYSTEM: albuminuria, bladder pain, dysuria, hematuria, hydronephrosis, impotence, kidney pain, kidney tubular necrosis, nocturia, oliguria, pyelonephritis, pyuria, scrotal edema, testis disorder, toxic nephropathy, urinary frequency, urinary incontinence, urinary retention.

Less frequently occurring adverse events included: mycobacterial infections, Epstein-Barr virus infections, and pancreatitis.

Among the events which were reported at an incidence of ≥ 3% and < 20% by 24 months for Study 1 and 36 months for Study 2, tachycardia and Cushing's syndrome were reported significantly more commonly in both Rapamune groups as compared with the control therapy. Events that were reported more commonly in the Rapamune 5 mg/day group than either the Rapamune 2 mg/day group and/or control group were: abnormal healing, bone necrosis, chills, congestive heart failure, dysuria, hernia, hirsutism, urinary frequency, and lymphadenopathy.

Rapamune® Tablets: The safety profile of the tablet did not differ from that of the oral solution formulation. The incidence of adverse reactions up to 12 months was determined in a randomized, multicenter controlled trial (Study 3) in which 229 renal transplant patients received Rapamune Oral Solution 2 mg once daily and 228 patients received Rapamune Tablets 2 mg once daily. All patients were treated with cyclosporine and corticosteroids. The adverse reactions that occurred in either treatment group with an incidence of ≥ 20% in Study 3 are similar to those reported for Studies 1 and 2. There was no notable difference in the incidence of these adverse events between treatment groups (oral solution versus tablets) in Study 3, with the exception of acne, which occurred more frequently in the oral solution group, and tremor which occurred more frequently in the tablet group, particularly in Black patients. The adverse events that occurred in patients with an incidence of ≥3% and <20% in either treatment group in Study 3 were similar to those reported in Studies 1 and 2. There was no notable difference in the incidence of these adverse events between treatment groups (oral solution versus tablets) in Study 3, with the exception of hypertonia, which occurred more frequently in the oral solution group and diabetes mellitus which occurred more frequently in the tablet group. Hispanic patients in the tablet group experienced hyperglycemia more frequently than Hispanic patients in the oral solution group. In Study 3 alone, menorrhagia, metrorrhagia, and polyuria occurred with an incidence of ≥3% and <20%.

The clinically important opportunistic or common transplant-related infections were identical in all three studies and the incidences of these infections were similar in Study 3 compared with Studies 1 and 2. The incidence rates of these infections were not significantly different between the oral solution and tablet treatment groups in Study 3.

In Study 3 (at 12 months), there were two cases of lymphoma/lymphoproliferative disorder in the oral solution treatment group (0.8%) and two reported cases of lymphoma/lymphoproliferative disorder in the tablet treatment group (0.8%). These differences were not statistically significant and were similar to the incidences observed in Studies 1 and 2.

Rapamune following cyclosporine withdrawal: The incidence of adverse reactions was determined through 36 months in a randomized, multicenter controlled trial (Study 4) in which 215 renal transplant patients received Rapamune as a maintenance regimen following cyclosporine withdrawal and 215 patients received Rapamune with cyclosporine therapy. All patients were treated with corticosteroids. The safety profile prior to randomization (start of cyclosporine withdrawal) was similar to that of the 2-mg Rapamune groups in Studies 1, 2, and 3. Following randomization (at 3 months) patients who had cyclosporine eliminated from their therapy experienced significantly higher incidences of abnormal liver function tests (including increased AST/SGOT and increased ALT/SGPT), hypokalemia, thrombocytopenia, abnormal healing, ileus, and rectal disorder. Conversely, the incidence of hypertension, cyclosporine toxicity, increased creatinine, abnormal kidney function, toxic nephropathy, edema, hyperkalemia, hyperuricemia, and gum hyperplasia was significantly higher in patients who remained on cyclosporine than those who had cyclosporine withdrawn from therapy. Mean systolic and diastolic blood pressure improved significantly following cyclosporine withdrawal.

In Study 4, at 36 months, the incidence of Herpes zoster infection was significantly lower in patients receiving Rapamune following cyclosporine withdrawal compared with patients who continued to receive Rapamune and cyclosporine.

The incidence of malignancies in Study 4 is presented in the table below. In Study 4, the incidence of lymphoma/lymphoproliferative disease was similar in all treatment groups. The overall incidence of malignancy was higher in patients receiving Rapamune plus cyclosporine compared with patients who had cyclosporine withdrawn.

INCIDENCE (%) OF MALIGNANCIES IN STUDY 4 AT 36 MONTHS POST-TRANSPLANT[a,b]

Malignancy	Nonrandomized (n = 95)	Rapamune with Cyclosporine Therapy (n = 215)	Rapamune Following Cyclosporine Withdrawal (n = 215)
Lymphoma/lymphoproliferative disease	**1.1**	**1.4**	**0.5**
Skin Carcinoma			
Any Squamous Cell[c]	1.1	1.9	2.3
Any Basal Cell[c]	3.2	4.7	2.3
Melanoma	0.0	0.5	0.0
Miscellaneous/Not Specified	1.1	0.9	0.0
Total	**4.2**	**6.5**	**3.7**
Other Malignancy	**1.1**	**3.3**	**1.4**

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c: Patients may be counted in more than one category.

[See table above]

Other clinical experience: Cases of interstitial lung disease (including pneumonitis, and infrequently bronchiolitis obliterans organizing pneumonia [BOOP] and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including Rapamune. In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of Rapamune. The risk may be increased as the sirolimus trough concentration increases (see **PRECAUTIONS**). There have been reports of neutropenia and rare reports of pancytopenia. Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, have been associated with the administration of sirolimus (see **WARNINGS**). Hepatotoxicity has been reported, including fatal hepatic necrosis with elevated sirolimus trough concentrations. Abnormal healing following transplant surgery has been reported, including fascial dehiscence and anastomotic disruption (e.g., wound, vascular, airway, ureteral, biliary).

OVERDOSAGE

Reports of overdose with Rapamune have been received; however, experience has been limited. In general, the adverse effects of overdose are consistent with those listed in the **ADVERSE REACTIONS** section (see **ADVERSE REACTIONS**).

General supportive measures should be followed in all cases of overdose. Based on the poor aqueous solubility and high erythrocyte and plasma protein binding of sirolimus, it is anticipated that sirolimus is not dialyzable to any significant extent. In mice and rats, the acute oral lethal dose was greater than 800 mg/kg.

DOSAGE AND ADMINISTRATION

It is recommended that Rapamune Oral Solution and Tablets be used initially in a regimen with cyclosporine and corticosteroids. Cyclosporine withdrawal is recommended 2 to 4 months after transplantation in patients at low to moderate immunologic risk.

The safety and efficacy of cyclosporine withdrawal in high-risk patients have not been adequately studied and it is therefore not recommended. This includes patients with Banff grade III acute rejection or vascular rejection prior to cyclosporine withdrawal, those who are dialysis-dependent, or with serum creatinine > 4.5 mg/dL, black patients, re-transplants, multi-organ transplants, patients with high panel of reactive antibodies (See **INDICATIONS AND USAGE** and **CLINICAL STUDIES**).

Two-mg of Rapamune oral solution has been demonstrated to be clinically equivalent to 2-mg Rapamune oral tablets and hence, are interchangeable on a mg to mg basis. However, it is not known if higher doses of Rapamune oral solution are clinically equivalent to higher doses of tablets on a mg to mg basis. (See **CLINICAL PHARMACOLOGY: Absorption**). Rapamune is to be administered orally once daily.

Rapamune and cyclosporine combination therapy: The initial dose of Rapamune should be administered as soon as possible after transplantation. For *de novo* transplant recipients, a loading dose of Rapamune of 3 times the maintenance dose should be given. A daily maintenance dose of 2-mg is recommended for use in renal transplant patients, with a loading dose of 6 mg. Although a daily maintenance dose of 5 mg, with a loading dose of 15 mg was used in clinical trials of the oral solution and was shown to be safe and effective, no efficacy advantage over the 2-mg dose could be established for renal transplant patients. Patients receiving 2 mg of Rapamune Oral Solution per day demonstrated an overall better safety profile than did patients receiving 5 mg of Rapamune Oral Solution per day.

Rapamune following cyclosporine withdrawal: Initially, patients considered for cyclosporine withdrawal should be receiving Rapamune and cyclosporine combination therapy. At 2 to 4 months following transplantation, cyclosporine should be progressively discontinued over 4 to 8 weeks and the Rapamune® dose should be adjusted to obtain whole blood trough concentrations within the range of 12 to 24 ng/mL (chromatographic method). Therapeutic drug monitoring should not be the sole basis for adjusting Rapamune therapy. Careful attention should be made to clinical signs/symptoms, tissue biopsy, and laboratory parameters. Cyclosporine inhibits the metabolism and transport of sirolimus, and consequently, sirolimus concentrations will decrease when cyclosporine is discontinued unless the Rapamune dose is increased. The Rapamune® dose will need to be approximately 4-fold higher to account for both the absence of the pharmacokinetic interaction (approximately 2-fold increase) and the augmented immunosuppressive requirement in the absence of cyclosporine (approximately 2-fold increase).

Frequent Rapamune® dose adjustments based on non-steady-state sirolimus concentrations can lead to overdosing or underdosing because sirolimus has a long half-life. Once Rapamune® maintenance dose is adjusted, patients should be retained on the new maintenance dose at least for 7 to 14 days before further dosage adjustment with concentration monitoring. In most patients dose adjustments can be based on simple proportion: new Rapamune® dose = current dose x (target concentration/current concentration). A loading dose should be considered in addition to a new maintenance dose when it is necessary to considerably increase sirolimus trough concentrations: Rapamune® loading dose = 3 x (new maintenance dose - current maintenance dose). The maximum Rapamune® dose administered on any day should not exceed 40 mg. If an estimated daily dose exceeds 40 mg due to the addition of a loading dose, the loading dose should be administered over 2 days. Sirolimus trough concentrations should be monitored at least 3 to 4 days after a loading dose(s).

To minimize the variability of exposure to Rapamune, this drug should be taken consistently with or without food. Grapefruit juice reduces CYP3A4-mediated metabolism of Rapamune and must not be administered with Rapamune or used for dilution.

It is recommended that sirolimus be taken 4 hours after administration of cyclosporine oral solution (MODIFIED) and/or cyclosporine capsules (MODIFIED).

Dosage Adjustments

The initial dosage in patients ≥13 years who weigh less than 40 kg should be adjusted, based on body surface area, to 1 mg/m²/day. The loading dose should be 3 mg/m².

It is recommended that the maintenance dose of Rapamune be reduced by approximately one third in patients with hepatic impairment. It is not necessary to modify the Rapamune loading dose. Dosage need not be adjusted because of impaired renal function.

Blood Concentration Monitoring

Whole blood trough concentrations of sirolimus should be monitored in patients receiving concentration-controlled Rapamune®. Monitoring is also necessary in pediatric patients, in patients with hepatic impairment, during concurrent administration of strong CYP3A4 and/or p-glycoprotein inducers and inhibitors, and/or if cyclosporine dosage is markedly changed or discontinued (see **DOSAGE AND ADMINISTRATION**).

In controlled clinical trials with concomitant cyclosporine (Studies 1 and 2), mean sirolimus whole blood trough concentrations through month 12 following transplantation, as measured by immunoassay, were 9 ng/mL (range 4.5-14 ng/mL [10th to 90th percentile]) for the 2 mg/day treatment group, and 17 ng/mL (range 10-28 ng/mL [10th to 90th percentile]) for the 5 mg/day dose.

In a controlled clinical trial with cyclosporine withdrawal (Study 4), the mean sirolimus whole blood trough concentrations during months 4 through 12 following transplantation, as measured by immunoassay, were 10.7 ng/mL (range 6.3-16.0 ng/mL [10th to 90th percentile]) in the concomitant Rapamune and cyclosporine treatment group (n = 205) and were 23.3 ng/mL (range 17.0-29.0 ng/mL [10th to 90th percentile]) in the cyclosporine withdrawal treatment group (n = 200).

Results from other assays may differ from those with an immunoassay. On average, chromatographic methods (HPLC UV or LC/MS/MS) yield results that are approximately 20% lower than the immunoassay for whole blood concentration determinations. Adjustments to the targeted range should be made according to the assay utilized to determine sirolimus trough concentrations. 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. A discussion of the different assay methods is contained in *Clinical Therapeutics*, Volume 22, Supplement B, April 2000.

Instructions for Dilution and Administration of Rapamune® Oral Solution

Bottles

The amber oral dose syringe should be used to withdraw the prescribed amount of Rapamune® Oral Solution from the

Continued on next page

Rapamune—Cont.

bottle. Empty the correct amount of Rapamune from the syringe into only a glass or plastic container holding at least two (2) ounces (1/4 cup, 60 mL) of water or orange juice. No other liquids, including grapefruit juice, should be used for dilution. Stir vigorously and drink at once. Refill the container with an additional volume (minimum of four [4] ounces [1/2 cup, 120 mL]) of water or orange juice, stir vigorously, and drink at once.

Pouches

When using the pouch, squeeze the entire contents of the pouch into only a glass or plastic container holding at least two (2) ounces (1/4 cup, 60 mL) of water or orange juice. No other liquids, including grapefruit juice, should be used for dilution. Stir vigorously and drink at once. Refill the container with an additional volume (minimum of four [4] ounces [1/2 cup, 120 mL]) of water or orange juice, stir vigorously, and drink at once.

Handling and Disposal

Since Rapamune is not absorbed through the skin, there are no special precautions. However, if direct contact with the skin or mucous membranes occurs, wash thoroughly with soap and water; rinse eyes with plain water.

HOW SUPPLIED

Rapamune® (sirolimus) Oral Solution is supplied at a concentration of 1 mg/mL in:

1. Cartons:
   NDC # 0008-1030-06, containing a 2 oz (60 mL fill) amber glass bottle.
   NDC # 0008-1030-15, containing a 5 oz (150 mL fill) amber glass bottle.

In addition to the bottles, each carton is supplied with an oral syringe adapter for fitting into the neck of the bottle, sufficient disposable amber oral syringes and caps for daily dosing, and a carrying case.

2. Cartons:
   NDC # 0008-1030-03, containing 30 unit-of-use laminated aluminum pouches of 1 mL.
   NDC # 0008-1030-07, containing 30 unit-of-use laminated aluminum pouches of 2 mL.
   NDC # 0008-1030-08, containing 30 unit-of-use laminated aluminum pouches of 5 mL.

Rapamune® (sirolimus) Tablets are available as follows:

1 mg, white, triangular-shaped tablets marked "RAPAMUNE 1 mg" on one side.
   NDC # 0008-1031-05, bottle of 100 tablets.
   NDC # 0008-1031-10, Redipak® cartons of 100 tablets (10 blister cards of 10 tablets each).

2 mg, yellow to beige triangular-shaped tablets marked "RAPAMUNE 2 mg" on one side.
   NDC # 0008-1032-05, bottle of 100 tablets.
   NDC # 0008-1032-10, Redipak® cartons of 100 tablets (10 blister cards of 10 tablets each [2 x 5]).

Storage

Rapamune® Oral Solution bottles and pouches should be stored protected from light and refrigerated at 2°C to 8°C (36°F to 46°F). Once the bottle is opened, the contents should be used within one month. If necessary, the patient may store both the pouches and the bottles at room temperatures up to 25°C (77°F) for a short period of time (e.g., up to 24 hours for the pouches and not more than 15 days for the bottles).

An amber syringe and cap are provided for dosing and the product may be kept in the syringe for a maximum of 24 hours at room temperatures up to 25°C (77°F) or refrigerated at 2°C to 8°C (36°F to 46°F). The syringe should be discarded after one use. After dilution, the preparation should be used immediately.

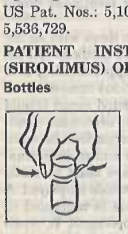
Rapamune Oral Solution provided in bottles may develop a slight haze when refrigerated. If such a haze occurs allow the product to stand at room temperature and shake gently until the haze disappears. The presence of this haze does not affect the quality of the product.

Rapamune® Tablets should be stored at 20° to 25°C (USP Controlled Room Temperature) (68° to 77°F). Use cartons to protect blister cards and strips from light. Dispense in a tight, light-resistant container as defined in the USP.

US Pat. Nos.: 5,100,899; 5,212,155; 5,308,647; 5,403,833; 5,536,729.

PATIENT INSTRUCTIONS FOR RAPAMUNE® (SIROLIMUS) ORAL SOLUTION ADMINISTRATION

Bottles



1. Open the solution bottle. Remove the safety cap by squeezing the tabs on the cap and twisting counterclockwise.

2. On first use, insert the adapter assembly (plastic tube with stopper) tightly into the bottle until it is even with the top of the bottle. Do not remove the adapter assembly from the bottle once inserted.

3. For each use, tightly insert one of the amber syringes with the plunger fully depressed into the opening in the adapter.

4. Withdraw the prescribed amount of Rapamune® (sirolimus) Oral Solution by gently pulling out the plunger of the syringe until the bottom of the black line of the plunger is even with the appropriate mark on the syringe. Always keep the bottle in an upright position. If bubbles form in the syringe, empty the syringe into the bottle and repeat the procedure.

5. You may have been instructed to carry your medication with you. If it is necessary to carry the filled syringe, place a cap securely on the syringe – the cap should snap into place.

6. Then place the capped syringe in the enclosed carrying case. Once in the syringe, the medication may be kept at room temperature or refrigerated and should be used within 24 hours. Extreme temperatures (below 36°F and above 86°F) should be avoided. Remember to keep this medication out of the reach of children.

7. Empty the syringe into a glass or plastic cup containing at least 2 ounces (1/4 cup, 60 mL) of water or orange juice, stir vigorously for one (1) minute and drink immediately. Refill the container with at least 4 ounces (1/2 cup, 120 mL) of water or orange juice, stir vigorously again and drink the rinse solution. Apple juice, grapefruit juice, or other liquids are NOT to be used. Only glass or plastic cups should be used to dilute Rapamune® Oral Solution. The syringe and cap should be used once and then discarded.

8. Always store the bottles of medication in the refrigerator. When refrigerated, a slight haze may develop in the solution. The presence of a haze does not affect the quality of the product. If this happens, bring the Rapamune® Oral Solution to room temperature and shake until the haze disappears. If it is necessary to wipe clean the mouth of the bottle before returning the product to the refrigerator, wipe with a dry cloth to avoid introducing water, or any other liquid, into the bottle.

PATIENT INSTRUCTIONS FOR RAPAMUNE® (SIROLIMUS) ORAL SOLUTION ADMINISTRATION

Pouches

1. Before opening the pouch, squeeze the pouch from the neck area to push the contents into the lower part of the pouch.

2. Carefully open the pouch by folding the marked area and then cutting with a scissors along the marked line near the top of the pouch.

3. Squeeze the entire contents of the pouch into a glass or plastic cup containing at least 2 ounces (1/4 cup, 60 mL) of water or orange juice, stir vigorously for one (1) minute and drink immediately. Refill the container with at least 4 ounces (1/2 cup, 120 mL) of water or orange juice, stir vigorously again and drink the rinse solution. Apple juice, grapefruit juice, or other liquids are NOT to be used. Only glass or plastic cups should be used to dilute Rapamune® Oral Solution.
4. Unused pouches should be stored in the refrigerator.

Wyeth Laboratories
Division of Wyeth-Ayerst Pharmaceuticals Inc.
Philadelphia, PA 19101

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ET02
Rev 04/03

Shown in Product Identification Guide, page 340

REFACTO® Ⓑ

[rē-făk'tō]

Antihemophilic Factor, Recombinant

Ⓑ only

DESCRIPTION

ReFacto® Antihemophilic Factor (Recombinant) is a purified protein produced by recombinant DNA technology for use in therapy of factor VIII deficiency. ReFacto is a glycoprotein with an approximate molecular mass of 170 kDa consisting of 1438 amino acids. It has an amino acid sequence that is comparable to the 90 + 80 kDa form of factor VIII, and post-translational modifications that are similar to those of the plasma-derived molecule. ReFacto has *in vitro* functional characteristics comparable to those of endogenous factor VIII.

ReFacto is produced by a genetically engineered Chinese hamster ovary (CHO) cell line. The CHO cell line secretes B-domain deleted recombinant factor VIII into a defined cell culture medium that contains human serum albumin and recombinant insulin, but does not contain any proteins derived from animal sources. The protein is purified by a chromatography purification process that yields a high-purity, active product. The potency expressed in international units (IU) is determined using the European Pharmacopoeial chromogenic assay against the WHO standard. The specific activity of ReFacto is 11,200-15,500 IU per milligram of protein. ReFacto is not purified from human blood and contains no preservatives or added human components in the final formulation.

ReFacto is formulated as a sterile, nonpyrogenic, lyophilized powder preparation for intravenous (IV) injection. It is available in single-use vials containing the labeled amount of factor VIII activity (IU). Each vial contains nominally 250, 500, 1000 or 2000 IU of ReFacto per vial. The formulated product is a clear colorless solution upon reconstitution and contains sodium chloride, sucrose, L-histidine, calcium chloride, and polysorbate 80.

CLINICAL PHARMACOLOGY

Factor VIII is the specific clotting factor deficient in patients with hemophilia A (classical hemophilia). The administration of ReFacto® Antihemophilic Factor (Recombinant) increases plasma levels of factor VIII activity and can temporarily correct the *in vitro* coagulation defect in these patients.

Activated factor VIII acts as a cofactor for activated factor IX accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot is formed. Factor VIII activity is greatly reduced in patients with hemophilia A and therefore replacement therapy is necessary.

In a crossover pharmacokinetic study of eighteen (18) previously treated patients **using the chromogenic assay,** the circulating mean half-life for ReFacto was 14.5 ± 5.3 hours (ranged from 7.6-27.7 hours), which was not statistically significantly different from plasma-derived Antihemophilic Factor (Human) (pdAHF), which had a mean half-life of 13.7 ± 3.4 hours (ranged from 8.8-23.7 hours). Mean incremental recovery (K-value) of ReFacto in plasma was 2.4 ± 0.4 IU/dL per IU/kg (ranged from 1.9-3.3 IU/dL per IU/kg). This was comparable to the mean incremental recovery observed in plasma for pdAHF which was 2.3 ± 0.3 IU/dL per IU/kg (ranged from 1.7-2.9 IU/dL per IU/kg). **Results obtained from this controlled pharmacokinetic study, which used a central laboratory for the analysis of all plasma samples, showed that the one-stage factor VIII clotting assay gave results which were approximately 50% of the values obtained with the chromogenic assay** (see **DOSAGE AND ADMINISTRATION**).

In two additional clinical studies, pharmacokinetic parameters were evaluated for previously treated patients [PTPs] and previously untreated patients [PUPs]. In PTPs (n=87) ReFacto had a mean incremental recovery of 2.4 ± 0.4 IU/dL per IU/kg (ranged from 1.1-3.8 IU/dL per IU/kg) and an elimination half-life (n=67) of 10.7 ± 2.8 hours. In PUPs (n=45) ReFacto had a lower mean incremental recovery of 1.7 ± 0.4 IU/dL per IU/kg (ranged from 0.2-2.8 IU/dL per IU/kg) as compared to PTPs. Population pharmacokinetic modeling using data from 44 PUPs led to a mean estimated half-life of ReFacto in PUPs of 8.0 ± 2.2 hours. These parameters did not change over time (12 months) for PTPs or PUPs.