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Physician's Desk Reference for Prescription Drugs

Agenerase Capsules(GlaxoSmithKline)

BODY:

Because of the potential risk of toxicity from the large amount of the excipient, propylene glycol, contained in AGENERASE Oral Solution , that formulation is contraindicated in infants and children below the age of 4 years and certain other patient populations and should be used with caution in others. Consult the complete prescribing information for AGENERASE Oral Solution for full information.

DESCRIPTION

AGENERASE (amprenavir) is an inhibitor of the human immunodeficiency virus (HIV) protease. The chemical name of amprenavir is (3 *S*)-tetrahydro-3-furyl *N* - (1 *S* ,2 *R*)-3-(4-amino-*N*-isobutylbenzenesulfonamido)-1-benzyl-2-hydroxypropyl carbamate. Amprenavir is a single stereoisomer with the (3 *S*)(1 *S* ,2 *R*) configuration. It has a molecular formula of C[25] H[35] N[3] O[6] S and a molecular weight of 505.64.

Amprenavir is a white to cream-colored solid with a solubility of approximately 0.04 mg/mL in water at 25 deg. C.

AGENERASE Capsules are available for oral administration. Each 50-mg capsule contains the inactive ingredients d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), polyethylene glycol 400 (PEG 400) 246.7 mg, and propylene glycol 19 mg. The capsule shell contains the inactive ingredients d-sorbitol and sorbitans solution, gelatin, glycerin, and titanium dioxide. The soft gelatin capsules are printed with edible red ink. Each 50-mg AGENERASE Capsule contains 36.3 IU vitamin E in the form of TPGS. The total amount of vitamin E in the recommended daily adult dose of AGENERASE is 1,744 IU.

MICROBIOLOGY

Mechanism of Action: Amprenavir is an inhibitor of HIV-1 protease. Amprenavir binds to the active site of HIV-1 protease and thereby prevents the processing of viral gag and gag-pol polyprotein precursors, resulting in the formation of immature non-infectious viral particles.

Antiviral Activity in Vitro: The in vitro antiviral activity of amprenavir was evaluated against HIV-1 IIIB in both acutely and chronically infected lymphoblastic cell lines (MT-4, CEM-CCRF, H9) and in peripheral blood lymphocytes. The 50% inhibitory concentration (IC[50]) of amprenavir ranged from 0.012 to 0.08 micro M in acutely infected cells and was 0.41 micro M in chronically infected cells (1 micro M = 0.50 mcg/mL). Amprenavir exhibited synergistic anti-HIV-1 activity in combination with abacavir, zidovudine, didanosine, or saquinavir, and additive anti-HIV-1 activity in combination with indinavir, nelfinavir, and ritonavir in vitro. These drug combinations have not been adequately studied in humans. The relationship between in vitro anti-HIV-1 activity of amprenavir and the inhibition of HIV-1 replication in humans has not been defined.

Resistance: HIV-1 isolates with a decreased susceptibility to amprenavir have been selected in vitro and obtained from patients treated with amprenavir. Genotypic analysis of isolates from amprenavir-treated patients showed mutations in the HIV-1 protease gene resulting in amino acid substitutions primarily at positions V32I, M46I/L, I47V, I50V, I54L/M, and I84V as well as mutations in the p7/p1 and p1/p6 gag cleavage sites. Phenotypic analysis of HIV-1 isolates from 21 nucleoside reverse transcriptase inhibitor-(NRTI-) experienced, protease inhibitor-naive patients treated with amprenavir in combination with NRTIs for 16 to 48 weeks identified isolates from 15 patients who exhibited a 4-to 17-fold decrease in susceptibility to amprenavir in vitro compared to wild-type virus. Clinical isolates that exhibited a decrease in amprenavir susceptibility harbored one or more amprenavir-associated mutations. The

clinical relevance of the genotypic and phenotypic changes associated with amprenavir therapy is under evaluation.

Cross-Resistance: Varying degrees of HIV-1 cross-resistance among protease inhibitors have been observed. Five of 15 amprenavir-resistant isolates exhibited 4-to 8-fold decrease in susceptibility to ritonavir. However, amprenavir-resistant isolates were susceptible to either indinavir or saquinavir.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults: The pharmacokinetic properties of amprenavir have been studied in asymptomatic, HIV-infected adult patients after administration of single oral doses of 150 to 1,200 mg and multiple oral doses of 300 to 1,200 mg twice daily.

Absorption and Bioavailability: Amprenavir was rapidly absorbed after oral administration in HIV-1-infected patients with a time to peak concentration (T[max]) typically between 1 and 2 hours after a single oral dose. The absolute oral bioavailability of amprenavir in humans has not been established.

Increases in the area under the plasma concentration versus time curve (AUC) after single oral doses between 150 and 1,200 mg were slightly greater than dose proportional.

Increases in AUC were dose proportional after 3 weeks of dosing with doses from 300 to 1,200 mg twice daily. The pharmacokinetic parameters after administration of amprenavir 1,200 mg twice daily for 3 weeks to HIV-infected subjects are shown in Table 1.

Table 1. Average (%CV) Pharmacokinetic Parameters After 1,200 mg Twice Daily of Amprenavir Capsules (n = 54)

C[max] (mcg/mL)	T[max] (hours)	AUC[0-12] (mcg*hr/mL)	C[avg] (mcg/mL)	C[min] (mcg/mL)	CL/F (mL/min/kg)
7.66 (54%)	1.0 (42%)	17.7 (47%)	1.48 (47%)	0.32 (77%)	19.5 (46%)

The relative bioavailability of AGENERASE Capsules and Oral Solution was assessed in healthy adults. AGENERASE Oral Solution was 14% less bioavailable compared to the capsules.

Effects of Food on Oral Absorption: The relative bioavailability of AGENERASE Capsules was assessed in the fasting and fed states in healthy volunteers (standardized high-fat meal: 967 kcal, 67 grams fat, 33 grams protein, 58 grams carbohydrate). Administration of a single 1,200-mg dose of amprenavir in the fed state compared to the fasted state was associated with changes in C[max] (fed: 6.18 +/-2.92 mcg/mL, fasted: 9.72 +/-2.75 mcg/mL), T[max] (fed: 1.51 +/-0.68, fasted: 1.05 +/-0.63), and AUC[0-(infinity)] (fed: 22.06 +/-11.6 mcg*hr/mL, fasted: 28.05 +/-10.1 mcg*hr/mL). AGENERASE may be taken with or without food, but should not be taken with a high-fat meal (see DOSAGE AND ADMINISTRATION).

Distribution: The apparent volume of distribution (V[z] /F) is approximately 430 L in healthy adult subjects. In vitro binding is approximately 90% to plasma proteins. The highaffinity binding protein for amprenavir is alpha[1]-acid glycoprotein (AAG). The partitioning of amprenavir into erythrocytes is low, but increases as amprenavir concentrations increase, reflecting the higher amount of unbound drug at higher concentrations.

Metabolism: Amprenavir is metabolized in the liver by the cytochrome P450 3A4 (CYP3A4) enzyme system. The 2 major metabolites result from oxidation of the tetrahydrofuran and aniline moieties. Glucuronide conjugates of oxidized metabolites have been identified as minor metabolites in urine and feces.

Elimination: Excretion of unchanged amprenavir in urine and feces is minimal. Approximately 14% and 75% of an administered single dose of[14] C-amprenavir can be accounted for as radiocarbon in urine and feces, respectively. Two metabolites accounted for >90% of the radiocarbon in fecal samples. The plasma elimination half-life of amprenavir ranged from 7.1 to 10.6 hours.

Special Populations: *Hepatic Insufficiency:* AGENERASE has been studied in adult patients with impaired hepatic function using a single 600-mg oral dose. The AUC[0-(infinity)] was significantly greater in patients with moderate cirrhosis (25.76 +/-14.68 mcg*hr/mL) compared with healthy volunteers (12.00 +/-4.38 mcg*hr/mL). The AUC[0-(infinity)] and C[max] were significantly greater in patients with severe cirrhosis (AUC[0-(infinity)] : 38.66 +/-16.08 mcg*hr/mL; C[max] : 9.43 +/-2.61 mcg/mL) compared with healthy volunteers (AUC[0-(infinity)] : 12.00 +/-4.38 mcg*hr/mL; C[max] : 4.90 +/-1.39 mcg/mL). Patients with impaired hepatic function require dosage adjustment (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency: The impact of renal impairment on amprenavir elimination in adult patients has not been studied. The renal elimination of unchanged amprenavir represents <3% of the administered dose.

Pediatric Patients: The pharmacokinetics of amprenavir have been studied after either single or repeat doses of AGENERASE Capsules or Oral Solution in 84 pediatric patients. Twenty HIV-1-infected children ranging in age from 4 to 12 years received single doses from 5 mg/kg to 20 mg/kg using 25-mg or 150-mg capsules. The C[max] of amprenavir increased less than proportionally with dose. The AUC[0-(infinity)] increased proportionally at doses between 5 and 20 mg/kg. Amprenavir is 14% less bioavailable from the liquid formulation than from the capsules; therefore AGENERASE Capsules and AGENERASE Oral Solution are not interchangeable on a milligram-per-milligram basis.

AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years due to the potential risk of toxicity from the large amount of the excipient, propylene glycol. Please see the complete prescribing information for AGENERASE Oral Solution for full information.

Table 2. Average (%CV) Pharmacokinetic Parameters in Children Ages 4 to 12 Years Receiving 20 mg/kg Twice Daily or 15 mg/kg Three Times Daily of AGENERASE Oral Solution

Dose	n	C[max] (mcg/mL)	T[max] (hours)	AUC[ss]* (mcg*hr/mL)	C[avg] (mcg/mL)	C[min] (mcg/mL)	CL/F (mL/min/kg)
20 mg/kg b.i.d.	20	6.77 (51%)	1.1 (21%)	15.46 (59%)	1.29 (59%)	0.24 (98%)	29 (58%)
15 mg/kg t.i.d.	17	3.99 (37%)	1.4 (90%)	8.73 (36%)	1.09 (36%)	0.27 (95%)	32 (34%)

*AUC is 0 to 12 hours for b.i.d. and 0 to 8 hours for t.i.d., therefore the C[avg] is a better comparison of the exposures.

Geriatric Patients: The pharmacokinetics of amprenavir have not been studied in patients over 65 years of age.

Gender: The pharmacokinetics of amprenavir do not differ between males and females.

Race: The pharmacokinetics of amprenavir do not differ between blacks and non-blacks.

Drug Interactions: See also CONTRAINDICATIONS , WARNINGS , and PRECAUTIONS : Drug Interactions .

Amprenavir is metabolized in the liver by the cytochrome P450 enzyme system. Amprenavir inhibits CYP3A4. Caution should be used when coadministering medications that are substrates, inhibitors, or inducers of CYP3A4, or potentially toxic medications that are metabolized by CYP3A4. Amprenavir does not inhibit CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2E1, or uridine glucuronosyltransferase (UDPGT).

Drug interaction studies were performed with amprenavir capsules and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration of amprenavir on the AUC, C[max] , and C[min] are summarized in Table 3 (effect of other drugs on amprenavir) and Table 4 (effect of amprenavir on other drugs). For information regarding clinical recommendations, see PRECAUTIONS .

Table 3. Drug Interactions: Pharmacokinetic Parameters for Amprenavir in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministered Drug	Dose of AGENERASE	C[min]	% Change in Amprenavir Pharmacokinetic Parameters * (90% CI)		
				n	C[max]	AUC
Abacavir	300 mg b.i.d. for 3 weeks	900 mg b.i.d. for 3 weeks	4	up 47 (down 15 to up154)	up 29 (down 18 to up103)	up 27 (down 46 to up197)
Clarithromycin	500 mg b.i.d. for 4 days	1,200 mg b.i.d. for 4 days	12	up15 (up1 to up31)	up18 (up 8 to up 29)	up39 (up31 to up 47)
Delavirdine	600 mg b.i.d. for 10 days	600 mg b.i.d. for 10 days	9	up 40[#]	up130[#]	up125[#]
Ethinyl estradiol/ Norethindrone	0.035 mg/1 mg for 1 cycle	1,200 mg b.i.d. for 28 days	10	<-> (down 20 to up 3)	down 22 (down 35 to down 8)	down 20 (down 41 to up 8)
Indinavir	800 mg t.i.d. for 2 weeks (fasted)	750 or 800 mg t.i.d. for 2 weeks (fasted)	9	up18 (down 13 to up 58)	up33 (up2 to up73)	up 25 (down 27 to up116)
Ketoconazole	400 mg single dose	1,200 mg single dose	12	down 16 (down 25 to down 6)	up31 (up20 to up42)	NA
Lamivudine	150 mg single dose	600 mg single dose	11	<-> (down 17 to up 9)	<-> (down 15 to up14)	NA
Nelfinavir	750 mg t.i.d. for 2 weeks	750 or 800 mg t.i.d. for 2	6	down 14 (down 38 to up20)	<-> (down 19 to up 47)	up189 (up52 to up 448)

Table 3. Drug Interactions: Pharmacokinetic Parameters for Amprenavir in the Presence of the Coadministered Drug

	(fed)	weeks (fed)				
Rifabutin	300 mg q.d. for 10 days	1,200 mg b.i.d. for 10 days	5	<-> (down 21 to up10)	down 15 (down 28 to 0)	down 15 (down 38 to up17)
Rifampin	300 mg q.d. for 4 days	1,200 mg b.i.d. for 4 days	11	down 70 (down 76 to down 62)	down 82 (down 84 to down 78)	down 92 (down 95 to down 89)
Ritonavir	100 mg b.i.d. for 2 to 4 weeks	600 mg b.i.d.	18	down 30[**/*] (down 44 to down 14)	up 64[**/*] (up37 to up 97)	up 508[**/*] (up394 to up 649)
Ritonavir	200 mg q.d. for 2 to 4 weeks	1,200 mg q.d.	12	<->[**/*] (down 17 to up30)	up 62[**/*] (up35 to up 94)	up 319[**/*] (up190 to up508)
Saquinavir	800 mg t.i.d. for 2 weeks (fed)	750 or 800 mg t.i.d. for 2 weeks (fed)	7	down 37 (down 54 to down 14)	down 32 (down 49 to down 9)	down 14 (down 52 to up54)
Zidovudine	300 mg single dose	600 mg single dose	12	<-> (down 5 to up 24)	up13 (down 2 to up 31)	NA

*Based on total-drug concentrations.
[**/*] Compared to amprenavir 1,200 mg b.i.d. in the same patients.
[#] Median percent change; confidence interval not reported.
up = Increase; down =Decrease; <-> = No change (up or down <10%); NA = C[min] not calculated for single-dose study.

Table 4. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Amprenavir

Coadministered Drug	Dose of Coadministered Drug	Dose of AGENERASE	n	% Change in Pharmacokinetic Parameters of Coadministered Drug (90% CI)		
				C[max]	AUC	C[min]
Clarithromycin	500 mg b.i.d. for 4 days	1,200 mg b.i.d. for 4 days	12	down 10 (down 24 to up 7)	<-> (down 17 to up 11)	<-> (down 13 to up 20)
Delavirdine	600 mg b.i.d. for 10	600 mg b.i.d. for 10	9	down 47 *	down 61 *	down 88 *

Table 4. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Amprenavir

	days	days				
Ethinyl estradiol	0.035 mg for 1 cycle	1,200 mg b.i.d. for 28 days	10	<-> (down 25 to up 15)	<-> (down 14 to up 38)	up 32 (down 3 to up 79)
Norethindrone	1.0 mg for 1 cycle	1,200 mg b.i.d. for 28 days	10	<-> (down 20 to up 18)	up 18 (up 1 to up 38)	up 45 (up 13 to up 88)
Ketoconazole	400 mg single dose	1,200 mg single dose	12	up 19 (up 8 to up 33)	up 44 (up 31 to up 59)	NA
Lamivudine	150 mg single dose	600 mg single dose	11	<-> (down 17 to up 3)	<-> (down 11 to 0)	NA
Methadone	44 to 100 mg q.d. for >30 days	1,200 mg b.i.d. for 10 days	16		R-Methadone (active)	
				down 25 (down 32 to down 18)	down 13 (down 21 to down 5)	down 21 (down 32 to down 9)
					S-Methadone (inactive)	
				down 48 (down 55 to down 40)	down 40 (down 46 to down 32)	down 53 (down 60 to down 43)
Rifabutin	300 mg q.d. for 10 days	1,200 mg b.i.d. for 10 days	5	up 119 (up 82 to up 164)	up 193 (up 156 to up 235)	up 271 (up 171 to up 409)
Rifampin	300 mg q.d. for 4 days	1,200 mg b.i.d. for 4 days	11	<-> (down 13 to up 12)	<-> (down 10 to up 13)	ND
Zidovudine	300 mg single dose	600 mg single dose	12	up 40 (up 14 to up 71)	up 31 (up 19 to up 45)	NA

*Median percent change; confidence interval not reported.
up = Increase; down = Decrease; <-> = No change (up or down <10%); NA = C[min] not calculated for single-dose study; ND = Interaction cannot be determined as C[min] was below the lower limit of quantitation.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs): There was no effect of amprenavir on abacavir in subjects receiving both agents based on historical data.

HIV Protease Inhibitors: The effect of amprenavir on total drug concentrations of other HIV protease inhibitors in

subjects receiving both agents was evaluated using comparisons to historical data. Indinavir steady-state C[max] , AUC, and C[min] were decreased by 22%, 38%, and 27%, respectively, by concomitant amprenavir. Similar decreases in C[max] and AUC were seen after the first dose. Saquinavir steady-state C[max] , AUC, and C[min] were increased 21%, decreased 19%, and decreased 48%, respectively, by concomitant amprenavir. Nelfinavir steady-state C[max] , AUC, and C[min] were increased by 12%, 15%, and 14%, respectively, by concomitant amprenavir.

Methadone: Coadministration of amprenavir and methadone can decrease plasma levels of methadone.

Coadministration of amprenavir and methadone as compared to a non-matched historical control group resulted in a 30%, 27%, and 25% decrease in serum amprenavir AUC, C[max] , and C[min] , respectively.

For information regarding clinical recommendations, see PRECAUTIONS : Drug Interactions .

INDICATIONS AND USAGE

AGENERASE (amprenavir) is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

The following points should be considered when initiating therapy with AGENERASE:

In a study of NRTI-experienced, protease inhibitor-naive patients, AGENERASE was found to be significantly less effective than indinavir (see Description of Clinical Studies).

Mild to moderate gastrointestinal adverse events led to discontinuation of AGENERASE primarily during the first 12 weeks of therapy (see ADVERSE REACTIONS).

There are no data on response to therapy with AGENERASE in protease inhibitor-experienced patients.

Description of Clinical Studies: *Therapy-Naive Adults:* PROAB3001, a randomized, double-blind, placebo-controlled, multicenter study, compared treatment with AGENERASE Capsules (1,200 mg twice daily) plus lamivudine (150 mg twice daily) plus zidovudine (300 mg twice daily) versus lamivudine (150 mg twice daily) plus zidovudine (300 mg twice daily) in 232 patients. Through 24 weeks of therapy, 53% of patients assigned to AGENERASE/zidovudine/lamivudine achieved HIV-1 RNA <400 copies/mL. Through week 48, the antiviral response was 41%. Through 24 weeks of therapy, 11% of patients assigned to zidovudine/lamivudine achieved HIV-1 RNA <400 copies/mL. Antiviral response beyond week 24 is not interpretable because the majority of patients discontinued or changed their antiretroviral therapy.

NRTI-Experienced Adults: PROAB3006, a randomized, open-label multicenter study, compared treatment with AGENERASE Capsules (1,200 mg twice daily) plus NRTIs versus indinavir (800 mg every 8 hours) plus NRTIs in 504 NRTI-experienced, protease inhibitor-naive patients, median age 37 years (range 20 to 71 years), 72% Caucasian, 80% male, with a median CD4 cell count of 404 cells/mm[3] (range 9 to 1,706 cells/mm[3]) and a median plasma HIV-1 RNA level of 3.93 log[10] copies/mL (range 2.60 to 7.01 log[10] copies/mL) at baseline. Through 48 weeks of therapy, the median CD4 cell count increase from baseline in the amprenavir group was significantly lower than in the indinavir group, 97 cells/mm[3] versus 144 cells/mm[3] , respectively. There was also a significant difference in the proportions of patients with plasma HIV-1 RNA levels <400 copies/mL through 48 weeks (see Figure 1 and Table 5).

See Image

HIV-1 RNA status and reasons for discontinuation of randomized treatment at 48 weeks are summarized (Table 5).

Table 5. Outcomes of Randomized Treatment Through Week 48 (PROAB3006)

Outcome	AGENERASE	Indinavir

Table 5. Outcomes of Randomized Treatment Through Week 48 (PROAB3006)

	(n = 254)	(n = 250)
HIV-1 RNA <400 copies/mL *	30%	49%
HIV-1 RNA >/=400 copies/mL[**/*,][#]	38%	26%
Discontinued due to adverse events *[,#]	16%	12%
Discontinued due to other reasons[#,][§]	16%	13%

*Corresponds to rates at Week 48 in Figure 1.
[**/*] Virological failures at or before Week 48.
[#] Considered to be treatment failure in the analysis.
[§] Includes discontinuations due to consent withdrawn, loss to follow-up, protocol violations, non-compliance, pregnancy, never treated, and other reasons.

CONTRAINDICATIONS

Coadministration of AGENERASE is contraindicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in Table 6.

Table 6. Drugs That Are Contraindicated With AGENERASE

Drug Class	Drugs Within Class That Are CONTRAINDICATED with AGENERASE
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedatives/hypnotics	Midazolam, triazolam

If AGENERASE is coadministered with ritonavir, the antiarrhythmic agents flecainide and propafenone are also contraindicated.

Because of the potential toxicity from the large amount of the excipient, propylene glycol, contained in AGENERASE Oral Solution , that formulation is contraindicated in certain patient populations and should be used with caution in others. Consult the complete prescribing information for AGENERASE Oral Solution for full information.

AGENERASE is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of this product.

WARNINGS

ALERT: Find out about medicines that should not be taken with AGENERASE.

Serious and/or life-threatening drug interactions could occur between amprenavir and amiodarone, lidocaine (systemic), tricyclic antidepressants, and quinidine. Concentration monitoring of these agents is recommended if these agents are used concomitantly with AGENERASE (see CONTRAINDICATIONS).

Rifampin should not be used in combination with amprenavir because it reduces plasma concentrations and AUC of

amprenavir by about 90%.

A drug interaction study in healthy subjects has shown that ritonavir significantly increases plasma fluticasone propionate exposures, resulting in significantly decreased serum cortisol concentrations. Concomitant use of AGENERASE with ritonavir and fluticasone propionate is expected to produce the same effects. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Therefore, coadministration of fluticasone propionate and AGENERASE/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (see PRECAUTIONS : Drug Interactions).

Concomitant use of AGENERASE and St. John's wort (hypericum perforatum) or products containing St. John's wort is not recommended. Coadministration of protease inhibitors, including AGENERASE, with St. John's wort is expected to substantially decrease protease inhibitor concentrations and may result in suboptimal levels of amprenavir and lead to loss of virologic response and possible resistance to AGENERASE or to the class of protease inhibitors.

Concomitant use of AGENERASE with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including AGENERASE, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin). The risk of myopathy, including rhabdomyolysis, may be increased when HIV protease inhibitors, including amprenavir, are used in combination with these drugs.

Particular caution should be used when prescribing sildenafil in patients receiving amprenavir. Coadministration of AGENERASE with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism (see PRECAUTIONS : Drug Interactions and Information for Patients , and the complete prescribing information for sildenafil).

Because of the potential toxicity from the large amount of the excipient, propylene glycol, contained in AGENERASE Oral Solution , that formulation is contraindicated in certain patient populations and should be used with caution in others. Consult the complete prescribing information for AGENERASE Oral Solution for full information.

Severe and life-threatening skin reactions, including Stevens-Johnson syndrome, have occurred in patients treated with AGENERASE (see ADVERSE REACTIONS). Acute hemolytic anemia has been reported in a patient treated with AGENERASE.

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and causal relationships between protease inhibitor therapy and these events have not been established.

PRECAUTIONS

General: AGENERASE Capsules and AGENERASE Oral Solution are not interchangeable on a milligram-per-milligram basis (see CLINICAL PHARMACOLOGY : Pediatric Patients).

Amprenavir is a sulfonamide. The potential for cross-sensitivity between drugs in the sulfonamide class and amprenavir is unknown. AGENERASE should be used with caution in patients with a known sulfonamide allergy.

AGENERASE is principally metabolized by the liver. AGENERASE, when used alone and in combination with low-dose ritonavir, has been associated with elevations of SGOT (AST) and SGPT (ALT) in some patients. Caution should be exercised when administering AGENERASE to patients with hepatic impairment (see DOSAGE AND ADMINISTRATION). Appropriate laboratory testing should be conducted prior to initiating therapy with AGENERASE and at periodic intervals during treatment.

Formulations of AGENERASE provide high daily doses of vitamin E (see Information for Patients , DESCRIPTION , and DOSAGE AND ADMINISTRATION). The effects of long-term, high-dose vitamin E administration in humans is not well characterized and has not been specifically studied in HIV-infected individuals. High vitamin E doses may exacerbate the blood coagulation defect of vitamin K deficiency caused by anticoagulant therapy or malabsorption.

Patients with Hemophilia: There have been reports of spontaneous bleeding in patients with hemophilia A and B treated with protease inhibitors. In some patients, additional factor VIII was required. In many of the reported cases, treatment with protease inhibitors was continued or restarted. A causal relationship between protease inhibitor therapy and these episodes has not been established.

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including AGENERASE. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia PCP , or tuberculosis), which may necessitate further evaluation and treatment.

Fat Redistribution: Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance," have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Lipid Elevations: Treatment with AGENERASE alone or in combination with ritonavir has resulted in increases in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing should be performed prior to initiation of therapy with AGENERASE and at periodic intervals during treatment. Lipid disorders should be managed as clinically appropriate. See PRECAUTIONS Table 8: Established and Other Potentially Significant Drug Interactions for additional information on potential drug interactions with AGENERASE and HMG-CoA reductase inhibitors.

Resistance/Cross-Resistance: Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored, it is unknown what effect amprenavir therapy will have on the activity of subsequently administered protease inhibitors. It is also unknown what effect previous treatment with other protease inhibitors will have on the activity of amprenavir (see MICROBIOLOGY).

Information for Patients: A statement to patients and healthcare providers is included on the product's bottle label: ALERT: Find out about medicines that should NOT be taken with AGENERASE. A Patient Package Insert (PPI) for AGENERASE Capsules is available for patient information.

Patients treated with AGENERASE Capsules should be cautioned against switching to AGENERASE Oral Solution because of the increased risk of adverse events from the large amount of propylene glycol in AGENERASE Oral Solution . Please see the complete prescribing information for AGENERASE Oral Solution for full information.

Patients should be informed that AGENERASE is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of AGENERASE (amprenavir) are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with AGENERASE can reduce the risk of transmitting HIV to others through sexual contact.

Patients should remain under the care of a physician while using AGENERASE. Patients should be advised to take AGENERASE every day as prescribed. AGENERASE must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting their physician. If a dose is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped, the patient should not double the next dose.

Patients should inform their doctor if they have a sulfa allergy. The potential for cross-sensitivity between drugs in the

sulfonamide class and amprenavir is unknown.

AGENERASE may interact with many drugs; therefore, patients should be advised to report to their doctor the use of any other prescription or nonprescription medication or herbal products, particularly St. John's wort.

Patients taking antacids (or the buffered formulation of didanosine) should take AGENERASE at least 1 hour before or after antacid (or the buffered formulation of didanosine) use.

Patients receiving sildenafil should be advised that they may be at an increased risk of sildenafil-associated adverse events, including hypotension, visual changes, and priapism, and should promptly report any symptoms to their doctor.

Patients taking AGENERASE should be instructed not to use hormonal contraceptives because some birth control pills (those containing ethinyl estradiol/norethindrone) have been found to decrease the concentration of amprenavir. Therefore, patients receiving hormonal contraceptives should be instructed to use alternate contraceptive measures during therapy with AGENERASE.

High-fat meals may decrease the absorption of AGENERASE and should be avoided. AGENERASE may be taken with meals of normal fat content.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Adult and pediatric patients should be advised not to take supplemental vitamin E since the vitamin E content of AGENERASE Capsules and Oral Solution exceeds the Reference Daily Intake (adults 30 IU, pediatrics approximately 10 IU).

Laboratory Tests: The combination of AGENERASE and low-dose ritonavir has been associated with elevations of cholesterol and triglycerides, SGOT (AST), and SGPT (ALT) in some patients. Appropriate laboratory testing should be considered prior to initiating combination therapy with AGENERASE and ritonavir and at periodic intervals or if any clinical signs or symptoms of hyperlipidemia or elevated liver function tests occur during therapy. For comprehensive information concerning laboratory test alterations associated with ritonavir, physicians should refer to the complete prescribing information for NORVIR(R) (ritonavir).

Drug Interactions: See also CONTRAINDICATIONS , WARNINGS , and CLINICAL PHARMACOLOGY : Drug Interactions .

AGENERASE is an inhibitor of cytochrome P450 3A4 metabolism and therefore should not be administered concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4. There are other agents that may result in serious and/or life-threatening drug interactions (see CONTRAINDICATIONS and WARNINGS).

Table 7. Drugs That Should Not Be Coadministered With AGENERASE

Drug Class/Drug Name	Clinical Comment
Antimycobacterials: Rifampin *	May lead to loss of virologic response and possible resistance to AGENERASE or to the class of protease inhibitors.
Ergot derivatives: Dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.

Table 7. Drugs That Should Not Be Coadministered With AGENERASE

GI motility agents: Cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to AGENERASE or to the class of protease inhibitors.
HMG Co-reductase inhibitors: Lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: Pimozide	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Non-nucleoside reverse transcriptase inhibitor: Delavirdine *	May lead to loss of virologic response and possible resistance to delavirdine.
Oral contraceptives: Ethinyl estradiol/norethindrone	May lead to loss of virologic response and possible resistance to AGENERASE. Alternative methods of non-hormonal contraception are recommended.
Sedative/hypnotics: Midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

*See CLINICAL PHARMACOLOGY for magnitude of interaction, Tables 3 and 4.

Table 8. Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Amprenavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitors: Efavirenz, nevirapine	down Amprenavir	Appropriate doses of the combinations with respect to safety and efficacy have not been established.
Nucleoside reverse transcriptase inhibitor: Didanosine (buffered formulation only)	down Amprenavir	Take AGENERASE at least 1 hour before or after the buffered formulation of didanosine.
HIV protease inhibitors:	up Amprenavir	Appropriate doses of the combinations with

Table 8. Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Indinavir *, lopinavir/ritonavir, nelfinavir *	Amprenavir's effect on other protease inhibitors is not well established.	respect to safety and efficacy have not been established.
HIV protease inhibitor: Ritonavir *	up Amprenavir	The dose of amprenavir should be reduced when used in combination with ritonavir (see Dosage and Administration). Also, see the full prescribing information for NORVIR for additional drug interaction information.
HIV protease inhibitor: Saquinavir *	down Amprenavir	Appropriate doses of the combination with respect to safety and efficacy have not been established.
	Amprenavir's effect on saquinavir is not well established.	
Other Agents		
Antacids	down Amprenavir	Take AGENERASE at least 1 hour before or after antacids.
Antiarrhythmics: Amiodarone, lidocaine (systemic), and quinidine	up Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when coadministered with AGENERASE, if available.
Antiarrhythmic: Bepridil	up Bepridil	Use with caution. Increased bepridil exposure may be associated with life-threatening reactions such as cardiac arrhythmias.
Anticoagulant: Warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio)

Table 8. Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

		be monitored.
Anticonvulsants: Carbamazepine, phenobarbital, phenytoin	down Amprenavir	Use with caution. AGENERASE may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.
Antidepressant: Trazodone	up Trazodone	Concomitant use of trazodone and AGENERASE with or without ritonavir may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension, and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as AGENERASE, the combination should be used with caution and a lower dose of trazodone should be considered.
Antifungals: Ketoconazole, itraconazole	up Ketoconazole up Itraconazole	Increase monitoring for adverse events due to ketoconazole or itraconazole. Dose reduction of ketoconazole or itraconazole may be needed for patients receiving more than 400 mg ketoconazole or itraconazole per day.
Antimycobacterial: Rifabutin *	up Rifabutin and rifabutin metabolite	A dosage reduction of rifabutin to at least half the recommended dose is required when AGENERASE and rifabutin are coadministered. * A complete blood count should be performed weekly and as clinically indicated in order to monitor for

Table 8. Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

		neutropenia in patients receiving amprenavir and rifabutin.
Benzodiazepines: Alprazolam, clorazepate, diazepam, flurazepam	up Benzodiazepines	Clinical significance is unknown; however, a decrease in benzodiazepine dose may be needed.
Calcium channel blockers: Diltiazem, felodipine, nifedipine, nicardipine, nimodipine, verapamil, amlodipine, nisoldipine, isradipine	up Calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: Dexamethasone	down Amprenavir	Use with caution. AGENERASE may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.
Erectile dysfunction agent: Sildenafil	up Sildenafil	Use with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events.
HMG-CoA reductase inhibitors: Atorvastatin	up Atorvastatin	Use lowest possible dose of atorvastatin with careful monitoring or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with AGENERASE.
Immunosuppressants: Cyclosporine, tacrolimus, rapamycin	up Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with AGENERASE.
Inhaled/nasal steroid: Fluticasone	AGENERASE up Fluticasone	Concomitant use of fluticasone propionate

Table 8. Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

		and AGENERASE (without ritonavir) may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use.
	AGENERASE/ ritonavir up Fluticasone	Concomitant use of fluticasone propionate and AGENERASE/ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Coadministration of fluticasone propionate and AGENERASE/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (see WARNINGS).
Narcotic analgesics: Methadone *	down Amprenavir	AGENERASE may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly. Alternative antiretroviral therapy should be considered.
	down Methadone	Dosage of methadone may need to be increased when coadministered with AGENERASE.
Tricyclic antidepressants: Amitriptyline, imipramine	up Tricyclics	Therapeutic concentration monitoring is recommended for tricyclic antidepressants when

Table 8. Established and Other Potentially Significant Drug Interactions:
Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction
Studies or Predicted Interaction

coadministered with
AGENERASE.

*See CLINICAL PHARMACOLOGY for magnitude of interaction, Tables 3 and 4.

Carcinogenesis and Mutagenesis: Amprenavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to 104 weeks. Daily doses of 50, 275 to 300, and 500 to 600 mg/kg/day were administered to mice and doses of 50, 190, and 750 mg/kg/day were administered to rats. Results showed an increase in the incidence of benign hepatocellular adenomas and an increase in the combined incidence of hepatocellular adenomas plus carcinoma in males of both species at the highest doses tested. Female mice and rats were not affected. These observations were made at systemic exposures equivalent to approximately 2 times (mice) and 4 times (rats) the human exposure (based on AUC[0-24 hr] measurement) at the recommended dose of 1,200 mg twice daily. Administration of amprenavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. It is not known how predictive the results of rodent carcinogenicity studies may be for humans. However, amprenavir was not mutagenic or genotoxic in a battery of in vitro and in vivo assays including bacterial reverse mutation (Ames), mouse lymphoma, rat micronucleus, and chromosome aberrations in human lymphocytes.

Fertility: The effects of amprenavir on fertility and general reproductive performance were investigated in male rats (treated for 28 days before mating at doses producing up to twice the expected clinical exposure based on AUC comparisons) and female rats (treated for 15 days before mating through day 17 of gestation at doses producing up to 2 times the expected clinical exposure). Amprenavir did not impair mating or fertility of male or female rats and did not affect the development and maturation of sperm from treated rats. The reproductive performance of the F1 generation born to female rats given amprenavir was not different from control animals.

Pregnancy and Reproduction: Pregnancy Category C. Embryo/fetal development studies were conducted in rats (dosed from 15 days before pairing to day 17 of gestation) and rabbits (dosed from day 8 to day 20 of gestation). In pregnant rabbits, amprenavir administration was associated with abortions and an increased incidence of 3 minor skeletal variations resulting from deficient ossification of the femur, humerus trochlea, and humerus. Systemic exposure at the highest tested dose was approximately one twentieth of the exposure seen at the recommended human dose. In rat fetuses, thymic elongation and incomplete ossification of bones were attributed to amprenavir. Both findings were seen at systemic exposures that were one half of that associated with the recommended human dose.

Pre-and post-natal developmental studies were performed in rats dosed from day 7 of gestation to day 22 of lactation. Reduced body weights (10% to 20%) were observed in the offspring. The systemic exposure associated with this finding was approximately twice the exposure in humans following administration of the recommended human dose. The subsequent development of these offspring, including fertility and reproductive performance, was not affected by the maternal administration of amprenavir.

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

AGENERASE Oral Solution is contraindicated during pregnancy due to the potential risk of toxicity to the fetus from the high propylene glycol content.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to AGENERASE, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Although it is not known if amprenavir is excreted in human milk, amprenavir is secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to

breastfeed if they are receiving AGENERASE.

Pediatric Use: Two hundred fifty-one patients aged 4 and above have received amprenavir as single or multiple doses in studies. An adverse event profile similar to that seen in adults was seen in pediatric patients.

AGENERASE Capsules have not been evaluated in pediatric patients below the age of 4 years (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years due to the potential risk of toxicity from the large amount of the excipient, propylene glycol. Please see the complete prescribing information for AGENERASE Oral Solution for full information.

Geriatric Use: Clinical studies of AGENERASE did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger adults. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

In clinical studies, adverse events leading to amprenavir discontinuation occurred primarily during the first 12 weeks of therapy, and were mostly due to gastrointestinal events (nausea, vomiting, diarrhea, and abdominal pain/discomfort), which were mild to moderate in severity.

Skin rash occurred in 22% of patients treated with amprenavir in studies PROAB3001 and PROAB3006. Rashes were usually maculopapular and of mild or moderate intensity, some with pruritus. Rashes had a median onset of 11 days after amprenavir initiation and a median duration of 10 days. Skin rashes led to amprenavir discontinuation in approximately 3% of patients. In some patients with mild or moderate rash, amprenavir dosing was often continued without interruption; if interrupted, reintroduction of amprenavir generally did not result in rash recurrence.

Severe or life-threatening rash (Grade 3 or 4), including cases of Stevens-Johnson syndrome, occurred in approximately 1% of recipients of AGENERASE (see WARNINGS). Amprenavir therapy should be discontinued for severe or life-threatening rashes and for moderate rashes accompanied by systemic symptoms.

Table 9. Selected Clinical Adverse Events of All Grades Reported in >5% of Adult Patients

	PROAB3001 Therapy-Naive Patients		PROAB3006 NRTI-Experienced Patients	
Adverse Event	AGENERASE/ Lamivudine/ Zidovudine (n = 113)	Lamivudine/ Zidovudine (n = 109)	AGENERASE/ NRTI (n = 245)	Indinavir/NRTI (n = 241)
Digestive				
Nausea	74%	50%	43%	35%
Vomiting	34%	17%	24%	20%
Diarrhea or loose stools	39%	35%	60%	41%
Taste disorders	10%	6%	2%	8%
Skin				
Rash	27%	6%	20%	15%
Nervous				

Table 9. Selected Clinical Adverse Events of All Grades Reported in >5% of Adult Patients

Paresthesia, oral/perioral	26%	6%	31%	2%
Paresthesia, peripheral	10%	4%	14%	10%
Psychiatric				
Depressive or mood disorders	16%	4%	9%	13%

Among amprenavir-treated patients in Phase 3 studies, 2 patients developed de novo diabetes mellitus, 1 patient developed a dorsocervical fat enlargement (buffalo hump), and 9 patients developed fat redistribution.

In studies PROAB3001 and PROAB3006, no increased frequency of Grade 3 or 4 AST, ALT, amylase, or bilirubin elevations was seen compared to controls.

Pediatric Patients: An adverse event profile similar to that seen in adults was seen in pediatric patients.

Concomitant Therapy with Ritonavir: Tables 10 and 11 present adverse clinical events and laboratory abnormalities observed in subjects who received AGENERASE plus ritonavir. Since the trials were small, open-label, of varying duration, and often included different patient populations, direct comparisons to the frequency of events with AGENERASE alone (see Table 9) cannot be made.

Table 10. Selected Clinical Adverse Events of All Grades Reported in Adult Patients in Open-Label Clinical Trials of AGENERASE in Combination With Ritonavir

Adverse Event	AGENERASE 1,200 mg plus Ritonavir 200 mg q.d. * (n = 101)	AGENERASE 600 mg plus Ritonavir 100 mg b.i.d.[**/*] (n = 239)
Nausea	31%	23%
Diarrhea/loose stools	30%	28%
Headache	16%	12%
Abdominal symptoms	14%	14%
Vomiting	11%	9%
Rash	10%	9%
Paresthesias	9%	11%
Fatigue	7%	14%
Depressive & mood disorders	4%	9%

*Data from 2 open-label studies in treatment-naive patients also receiving abacavir/lamivudine.
[**/*] Data from 3 open-label studies in treatment-naive and treatment-experienced patients receiving combination antiretroviral therapy.

Table 11. Grade 3/4 Laboratory Abnormalities Reported in >/=2% of Adult Patients in Open-Label Clinical Trials of AGENERASE in Combination With Ritonavir

Laboratory Abnormality (non-fasting specimens)	AGENERASE 1,200 mg plus Ritonavir 200 mg q.d. * (n = 101)	AGENERASE 600 mg plus Ritonavir 100 mg b.i.d.[**/*] (n = 239)
Hypertriglyceridemia (>750 mg/dL)	8%	13%
Hyperglycemia (>251 mg/dL)	2%	3%
AST (>5 x ULN)	3%	5%
ALT (>5 x ULN)	4%	4%
Amylase (>2 x ULN)	4%	3%

*Data from 2 open-label studies in treatment-naive patients also receiving abacavir/lamivudine.
[**/*] Data from 3 open-label studies in treatment-naive and treatment-experienced patients receiving combination antiretroviral therapy.

OVERDOSAGE

There is no known antidote for AGENERASE. It is not known whether amprenavir can be removed by peritoneal dialysis or hemodialysis. If overdosage occurs, the patient should be monitored for evidence of toxicity and standard supportive treatment applied as necessary.

DOSAGE AND ADMINISTRATION

AGENERASE may be taken with or without food; however, a high-fat meal decreases the absorption of amprenavir and should be avoided (see CLINICAL PHARMACOLOGY : Effects of Food on Oral Absorption). Adult and pediatric patients should be advised not to take supplemental vitamin E since the vitamin E content of AGENERASE Capsules exceeds the Reference Daily Intake (adults 30 IU, pediatrics approximately 10 IU) (see DESCRIPTION).

Adults: The recommended oral dose of AGENERASE Capsules for adults is 1,200 mg (twenty-four 50-mg capsules) twice daily in combination with other antiretroviral agents.

Concomitant Therapy: If AGENERASE and ritonavir are used in combination, the recommended dosage regimens are: AGENERASE 1,200 mg with ritonavir 200 mg once daily or AGENERASE 600 mg with ritonavir 100 mg twice daily.

Pediatric Patients: For adolescents (13 to 16 years), the recommended oral dose of AGENERASE Capsules is 1,200 mg (twenty-four 50-mg capsules) twice daily in combination with other antiretroviral agents. For patients between 4 and 12 years of age or for patients 13 to 16 years of age with weight of <50 kg, the recommended oral dose of AGENERASE Capsules is 20 mg/kg twice daily or 15 mg/kg 3 times daily (to a maximum daily dose of 2,400 mg) in combination with other antiretroviral agents. The recommended dose of AGENERASE for use in combination with ritonavir has not been established in pediatric patients.

Before using AGENERASE Oral Solution , the complete prescribing information should be consulted.

AGENERASE Capsules and AGENERASE Oral Solution are not interchangeable on a milligram-per-milligram basis (see CLINICAL PHARMACOLOGY).

Patients with Hepatic Impairment: AGENERASE Capsules should be used with caution in patients with moderate or

severe hepatic impairment. Patients with a Child-Pugh score ranging from 5 to 8 should receive a reduced dose of AGENERASE Capsules of 450 mg twice daily, and patients with a Child-Pugh score ranging from 9 to 12 should receive a reduced dose of AGENERASE Capsules of 300 mg twice daily (see CLINICAL PHARMACOLOGY : Hepatic Insufficiency).

HOW SUPPLIED

AGENERASE Capsules, 50 mg, are oblong, opaque, off-white to cream-colored soft gelatin capsules printed with "GX CC1" on one side.

Bottles of 480 with child-resistant closures (NDC 0173-0679-00).

Store at controlled room temperature of 25 deg. C (77 deg. F) (see USP).

AGENERASE Capsules are manufactured by

R.P. Scherer, Beinheim, France

for GlaxoSmithKline, Research Triangle Park, NC 27709

Licensed from Vertex Pharmaceuticals Incorporated

Cambridge, MA 02139

AGENERASE is a registered trademark of GlaxoSmithKline.

May 2005/ RL-2194

PRODUCT PHOTO(S): NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

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See Image

LANGUAGE: ENGLISH

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Serial Number: 73195625 Assignment Information

Registration Number: 1144669 Assignment Information

Mark (words only): AUGMENTIN

Standard Character claim: No

Current Status: This registration has been renewed.

Date of Status: 2001-02-19

Filing Date: 1978-12-04

Transformed into a National Application: No

Registration Date: 1980-12-30

Register: Principal

Law Office Assigned: (NOT AVAILABLE)

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LAST APPLICANT(S)/OWNER(S) OF RECORD

1. SMITHKLINE BEECHAM CORPORATION

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United States
Legal Entity Type: Corporation
State or Country of Incorporation: Pennsylvania

GOODS AND/OR SERVICES

International Class: 005
Class Status: Active

Antibiotic Preparations
Basis: 1(a)
First Use Date: 1978-06-30
First Use in Commerce Date: 1978-06-30

ADDITIONAL INFORMATION

(NOT AVAILABLE)

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2001-02-19 - First renewal 10 year

2001-02-19 - Section 8 (10-year) accepted/ Section 9 granted

2000-08-30 - Combined Section 8 (10-year)/Section 9 filed

1989-10-06 - Section 15 acknowledged

1989-08-25 - Section 15 affidavit received

1986-10-20 - Section 8 (6-year) accepted

1986-07-07 - Section 8 (6-year) filed

1980-12-30 - Registered - Principal Register

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Serial Number: 73746157 Assignment Information

Registration Number: 1533895 Assignment Information

Mark

(words only): AUGMENTIN

Standard Character claim: No

Current Status: Section 8 and 15 affidavits have been accepted and acknowledged.

Date of Status: 1995-11-19

Filing Date: 1988-08-15

Transformed into a National Application: No

Registration Date: 1989-04-11

Register: Principal

Law Office Assigned: (NOT AVAILABLE)

If you are the applicant or applicant's attorney and have questions about this file, please contact the Trademark Assistance Center at TrademarkAssistanceCenter@uspto.gov

Current Location: 900 -File Repository (Franconia)

Date In Location: 1995-12-11

LAST APPLICANT(S)/OWNER(S) OF RECORD

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United States
Legal Entity Type: Corporation
State or Country of Incorporation: Pennsylvania

GOODS AND/OR SERVICES

International Class: 005
Class Status: Active
ANTIBIOTIC PREPARATIONS
Basis: 1(a)
First Use Date: 1984-08-00
First Use in Commerce Date: 1984-08-00

ADDITIONAL INFORMATION

Design Search Code(s):
26.05.02 - Plain single line triangles; Triangles, plain single line
27.03.01 - Geometric figures forming letters or numerals

Prior Registration Number(s):
1144669

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

1995-11-19 - Section 8 (6-year) accepted & Section 15 acknowledged

1995-03-22 - Section 8 (6-year) and Section 15 Filed

1989-04-11 - Registered - Principal Register

1989-01-17 - Published for opposition

1988-12-20 - Notice of publication

1988-12-17 - Notice of publication

1988-10-17 - Approved for Pub - Principal Register (Initial exam)

1988-10-11 - Assigned To Examiner

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16 of 201 DOCUMENTS

Physician's Desk Reference for Prescription Drugs

Augmentin Tablets(GlaxoSmithKline)

BODY:

To reduce the development of drug-resistant bacteria and maintain the effectiveness of AUGMENTIN (amoxicillin/clavulanate potassium) and other antibacterial drugs, AUGMENTIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

AUGMENTIN is an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the (beta)-lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid). Amoxicillin is an analog of ampicillin, derived from the basic penicillin nucleus, 6-aminopenicillanic acid. The amoxicillin molecular formula is C[16] H[19] N[3] O[5] S*3H[2] O, and the molecular weight is 419.46. Chemically, amoxicillin is (2 *S* ,5 *R* ,6 *R*)-6-(*R*)-(-)-2-Amino-2-(*p*-hydroxyphenyl)acetamido-3,3-dimethyl-7-oxo-4-thia-1- azabicyclo 3.2.0 heptane-2-carboxylic acid trihydrate.

Clavulanic acid is produced by the fermentation of *Streptomyces clavuligerus* . It is a (beta)-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of (beta)-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid-mediated (beta)-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins. The clavulanate potassium molecular formula is C[8] H[8] KNO[5] , and the molecular weight is 237.25. Chemically, clavulanate potassium is potassium (*Z*)-(2 *R* ,5 *R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo 3.2.0-heptane-2-carboxylate.

Inactive Ingredients: Colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide.

Each tablet of AUGMENTIN contains 0.63 mEq potassium.

CLINICAL PHARMACOLOGY

Amoxicillin and clavulanate potassium are well absorbed from the gastrointestinal tract after oral administration of AUGMENTIN. Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. While AUGMENTIN can be given without regard to meals, absorption of clavulanate potassium when taken with food is greater relative to the fasted state. In 1 study, the relative bioavailability of clavulanate was reduced when AUGMENTIN was dosed at 30 and 150 minutes after the start of a high-fat breakfast. The safety and efficacy of AUGMENTIN have been established in clinical trials where AUGMENTIN was taken without regard to meals.

Mean * amoxicillin and clavulanate potassium pharmacokinetic parameters are shown in the table below:

Dose[**] and regimen amoxicillin/ clavulanate potassium	AUC[0-24] (mcg*hr/mL)		C[max] (mcg/mL)	
	amoxicillin (+/-S.D.)	clavulanate potassium (+/-S.D.)	amoxicillin (+/-S.D.)	clavulanate potassium (+/-S.D.)

250/125 mg q8h	26.7 +/-4.56	12.6 +/-3.25	3.3 +/-1.12	1.5 +/-0.70
500/125 mg q12h	33.4 +/-6.76	8.6 +/-1.95	6.5 +/-1.41	1.8 +/-0.61
500/125 mg q8h	53.4 +/-8.87	15.7 +/-3.86	7.2 +/-2.26	2.4 +/-0.83
875/125 mg q12h	53.5 +/-12.31	10.2 +/-3.04	11.6 +/-2.78	2.2 +/-0.99

* Mean values of 14 normal volunteers (n = 15 for clavulanate potassium in the low-dose regimens). Peak concentrations occurred approximately 1.5 hours after the dose.
[**] Administered at the start of a light meal.

Amoxicillin serum concentrations achieved with AUGMENTIN are similar to those produced by the oral administration of equivalent doses of amoxicillin alone. The half-life of amoxicillin after the oral administration of AUGMENTIN is 1.3 hours and that of clavulanic acid is 1.0 hour.

Approximately 50% to 70% of the amoxicillin and approximately 25% to 40% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of a single 250-mg or 500-mg tablet of AUGMENTIN.

Concurrent administration of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.

Neither component in AUGMENTIN is highly protein-bound; clavulanic acid has been found to be approximately 25% bound to human serum and amoxicillin approximately 18% bound.

Amoxicillin diffuses readily into most body tissues and fluids with the exception of the brain and spinal fluid. The results of experiments involving the administration of clavulanic acid to animals suggest that this compound, like amoxicillin, is well distributed in body tissues.

Microbiology: Amoxicillin is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Amoxicillin is, however, susceptible to degradation by (beta)-lactamases, and therefore, the spectrum of activity does not include organisms which produce these enzymes. Clavulanic acid is a (beta)-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of (beta)-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid-mediated (beta)-lactamases frequently responsible for transferred drug resistance.

The formulation of amoxicillin and clavulanic acid in AUGMENTIN protects amoxicillin from degradation by (beta)-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other (beta)-lactam antibiotics. Thus, AUGMENTIN possesses the properties of a broad-spectrum antibiotic and a (beta)-lactamase inhibitor.

Amoxicillin/clavulanic acid has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in INDICATIONS AND USAGE .

Gram-Positive Aerobes:

Staphylococcus aureus ((beta)-lactamase and non-(beta)-lactamase producing)[***]

[***] Staphylococci which are resistant to methicillin/oxacillin must be considered resistant to amoxicillin/clavulanic acid.

Gram-Negative Aerobes:

Enterobacter species (Although most strains of *Enterobacter* species are resistant in vitro, clinical efficacy has been

demonstrated with AUGMENTIN in urinary tract infections caused by these organisms.)

Escherichia coli ((beta)-lactamase and non-(beta)-lactamase-producing)

Haemophilus influenzae ((beta)-lactamase and non-(beta)-lactamase-producing)

Klebsiella species (All known strains are (beta)-lactamase-producing.)

Moraxella catarrhalis ((beta)-lactamase and non-(beta)-lactamase-producing)

The following in vitro data are available, but their clinical significance is unknown.

Amoxicillin/clavulanic acid exhibits in vitro minimal inhibitory concentrations (MICs) of 2 mcg/mL or less against most (>/=90%) strains of *Streptococcus pneumoniae* [§] ; MICs of 0.06 mcg/mL or less against most (>/=90%) strains of *Neisseria gonorrhoeae* ; MICs of 4 mcg/mL or less against most (>/=90%) strains of staphylococci and anaerobic bacteria; and MICs of 8 mcg/mL or less against most (>/=90%) strains of other listed organisms. However, with the exception of organisms shown to respond to amoxicillin alone, the safety and effectiveness of amoxicillin/clavulanic acid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

[§] Because amoxicillin has greater in vitro activity against *S. pneumoniae* than does ampicillin or penicillin, the majority of *S. pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin.

Gram-Positive Aerobes:

Enterococcus faecalis [|| para.]

Staphylococcus epidermidis ((beta)-lactamase and non-(beta)-lactamase-producing)

Staphylococcus saprophyticus ((beta)-lactamase and non-(beta)-lactamase-producing)

Streptococcus pneumoniae || [para.]

Streptococcus pyogenes || [para.]

viridans group *Streptococcus* || [para.]

Gram-Negative Aerobes:

Eikenella corrodens ((beta)-lactamase and non-(beta)-lactamase-producing)

Neisseria gonorrhoeae [||] ((beta)-lactamase and non-(beta)-lactamase-producing)

Proteus mirabilis [||] ((beta)-lactamase and non-(beta)-lactamase-producing)

Anaerobic Bacteria:

Bacteroides species, including *Bacteroides fragilis* ((beta)-lactamase and non-(beta)-lactamase-producing)

Fusobacterium species ((beta)-lactamase and non-(beta)-lactamase-producing)

Peptostreptococcus species[para.]

[| |] Adequate and well-controlled clinical trials have established the effectiveness of amoxicillin alone in treating certain clinical infections due to these organisms.

[para.] These are non-(beta)-lactamase-producing organisms, and therefore, are susceptible to amoxicillin alone.

Susceptibility Testing: *Dilution Techniques:* Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of amoxicillin/clavulanate potassium powder.

The recommended dilution pattern utilizes a constant amoxicillin/clavulanate potassium ratio of 2 to 1 in all tubes with varying amounts of amoxicillin. MICs are expressed in terms of the amoxicillin concentration in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid. The MIC values should be interpreted according to the following criteria:

RECOMMENDED RANGES FOR AMOXICILLIN/CLAVULANIC ACID SUSCEPTIBILITY TESTING

For Gram-Negative Enteric Aerobes:

MIC (mcg/mL)	Interpretation
</=8/4	Susceptible (S)
16/8	Intermediate (I)
>/=32/16	Resistant (R)

For Staphylococcus ** and
Haemophilus species:

MIC (mcg/mL)	Interpretation
</=4/2	Susceptible (S)
>/=8/4	Resistant (R)

**Staphylococci which are susceptible to amoxicillin/clavulanic acid but resistant to methicillin/oxacillin must be considered as resistant.

For *S. pneumoniae* from non-meningitis sources: Isolates should be tested using amoxicillin/clavulanic acid and the following criteria should be used:

MIC (mcg/mL)	Interpretation
</=2.1	Susceptible (S)
4/2	Intermediate (I)
>/=8/4	Resistant (R)

Note: These interpretive criteria are based on the recommended doses for respiratory tract infections.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the

blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard amoxicillin/clavulanate potassium powder should provide the following MIC values:

Microorganism	MIC Range (mcg/mL)[**]
Escherichia coli ATCC 25922	2 to 8
Escherichia coli ATCC 35218	4 to 16
Enterococcus faecalis ATCC 29212	0.25 to 1.0
Haemophilus influenzae ATCC 49247	2 to 16
Staphylococcus aureus ATCC 29213	0.12 to 0.5
Streptococcus pneumoniae ATCC 49619	0.03 to 0.12

[**] Expressed as concentration of amoxicillin in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 mcg of amoxicillin/clavulanate potassium (20 mcg amoxicillin plus 10 mcg clavulanate potassium) to test the susceptibility of microorganisms to amoxicillin/clavulanic acid.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-mcg amoxicillin/clavulanate acid (20 mcg amoxicillin plus 10 mcg clavulanate potassium) disk should be interpreted according to the following criteria:

RECOMMENDED RANGES FOR AMOXICILLIN/CLAVULANIC ACID SUSCEPTIBILITY TESTING

For *Staphylococcus* [**/*] species and *H. influenzae* [a] :

Zone Diameter (mm)	Interpretation
>/=20	Susceptible (S)
</=19	Resistant (R)

For Other Organisms Except *S. pneumoniae* [b] and *N. gonorrhoeae* [c] :

Zone Diameter (mm)	Interpretation
>/=18	Susceptible (S)

14 to 17	Intermediate (I)
</=13	Resistant (R)

[**/*] Staphylococci which are resistant to methicillin/oxacillin must be considered as resistant to amoxicillin/clavulanic acid.
[a] A broth microdilution method should be used for testing H. influenzae. Beta-lactamase-negative, ampicillin-resistant strains must be considered resistant to amoxicillin/clavulanic acid.
[b] Susceptibility of S. pneumoniae should be determined using a 1 mcg oxacillin disk. Isolates with oxacillin zone sizes of >/=20 mm are susceptible to amoxicillin/clavulanic acid. An amoxicillin/clavulanic acid MIC should be determined on isolates of S. pneumoniae with oxacillin zone sizes of </=19 mm.
[c] A broth microdilution method should be used for testing N. gonorrhoeae and interpreted according to penicillin breakpoints.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for amoxicillin/clavulanic acid.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30-mcg amoxicillin/clavulanate potassium (20-mcg amoxicillin plus 10-mcg clavulanate potassium) disk should provide the following zone diameters in these laboratory quality control strains:

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 25922	19 to 25
Escherichia coli ATCC 35218	18 to 22
Staphylococcus aureus ATCC 25923	28 to 36

INDICATIONS AND USAGE

AUGMENTIN is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower Respiratory Tract Infections - caused by (beta)-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*.

Otitis Media - caused by (beta)-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*.

Sinusitis - caused by (beta)-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*.

Skin and Skin Structure Infections - caused by (beta)-lactamase-producing strains of *S. aureus, E. coli,* and *Klebsiella* spp.

Urinary Tract Infections - caused by (beta)-lactamase-producing strains of *E. coli, Klebsiella* spp., and *Enterobacter* spp.

While AUGMENTIN is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with AUGMENTIN due to its amoxicillin content; therefore, mixed infections caused by ampicillin-susceptible organisms and (beta)-lactamase-producing organisms susceptible to AUGMENTIN should not require the addition of another antibiotic. Because amoxicillin has greater in vitro activity against *S. pneumoniae* than does ampicillin or penicillin, the majority of *S. pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin and AUGMENTIN. (See Microbiology .)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of AUGMENTIN and other antibacterial drugs, AUGMENTIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Bacteriological studies, to determine the causative organisms and their susceptibility to AUGMENTIN, should be performed together with any indicated surgical procedures.

CONTRAINDICATIONS

AUGMENTIN is contraindicated in patients with a history of allergic reactions to any penicillin. It is also contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with AUGMENTIN.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH AUGMENTIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AUGMENTIN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including AUGMENTIN, and has ranged in severity from mild to life-threatening; therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

AUGMENTIN should be used with caution in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with the use of AUGMENTIN is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. (See CONTRAINDICATIONS and ADVERSE REACTIONS - Liver .)

PRECAUTIONS

General: While AUGMENTIN possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin-class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Prescribing AUGMENTIN in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with AUGMENTIN may result in increased and prolonged blood levels of amoxicillin. Co-administration of probenecid cannot be recommended.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with AUGMENTIN and allopurinol administered concurrently.

In common with other broad-spectrum antibiotics, AUGMENTIN may reduce the efficacy of oral contra-ceptives.

Drug/Laboratory Test Interactions: Oral administration of AUGMENTIN will result in high urine concentrations of amoxicillin. High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using CLINITEST(R), Benedict's Solution, or Fehling's Solution. Since this effect may also occur with amoxicillin and therefore AUGMENTIN, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as CLINISTIX(R)) be used.

Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone and estradiol has been noted. This effect may also occur with amoxicillin and therefore AUGMENTIN.

Information for Patients: Patients should be counseled that antibacterial drugs including AUGMENTIN, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When AUGMENTIN is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by AUGMENTIN or other antibacterial drugs in the future.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenesis: The mutagenic potential of AUGMENTIN was investigated in vitro with an Ames test, a human lymphocyte cytogenetic assay, a yeast test and a mouse lymphoma forward mutation assay, and in vivo with mouse micronucleus tests and a dominant lethal test. All were negative apart from the in vitro mouse lymphoma assay where weak activity was found at very high, cytotoxic con-centrations.

Impairment of Fertility: AUGMENTIN at oral doses of up to 1,200 mg/kg/day (5.7 times the maximum human dose, 1,480 mg/m[2] /day, based on body surface area) was found to have no effect on fertility and reproductive performance in rats, dosed with a 2:1 ratio formulation of amoxicillin:clavulanate.

Teratogenic effects: Pregnancy (Category B). Reproduction studies performed in pregnant rats and mice given AUGMENTIN at oral dosages up to 1,200 mg/kg/day, equivalent to 7,200 and 4,080 mg/m[2] /day, respectively (4.9 and 2.8 times the maximum human oral dose based on body surface area), revealed no evidence of harm to the fetus due to AUGMENTIN. 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.

Labor and Delivery: Oral ampicillin-class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions; however, it is not known whether the use of AUGMENTIN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary. In a single study in women with premature rupture of fetal membranes, it was reported that prophylactic treatment with AUGMENTIN may be associated with an increased risk of necrotizing enterocolitis in neonates.

Nursing Mothers: Ampicillin-class antibiotics are excreted in the milk; therefore, caution should be exercised when AUGMENTIN is administered to a nursing woman.

ADVERSE REACTIONS

AUGMENTIN is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: Abdominal discomfort, flatulence, and headache.

The following adverse reactions have been reported for ampicillin-class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, mucocutaneous candidiasis, enterocolitis, and hemorrhagic/pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS .)

Hypersensitivity Reactions: Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson syndrome), acute generalized exanthematous pustulosis, and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis) have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin. (See WARNINGS .)

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin-class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin, and/or alkaline phosphatase, has been infrequently reported with AUGMENTIN. It has been reported more commonly in the elderly, in males, or in patients on prolonged treatment. The

histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications.

Renal: Interstitial nephritis and hematuria have been reported rarely. Crystalluria has also been reported (see OVERDOSAGE).

Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with AUGMENTIN. There have been reports of increased prothrombin time in patients receiving AUGMENTIN and anticoagulant therapy concomitantly.

Central Nervous System: Agitation, anxiety, behavioral changes, confusion, convulsions, dizziness, insomnia, and reversible hyperactivity have been reported rarely.

Miscellaneous: Tooth discoloration (brown, yellow, or gray staining) has been rarely reported. Most reports occurred in pediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

OVERDOSAGE

Following overdosage, patients have experienced primarily gastrointestinal symptoms including stomach and abdominal pain, vomiting, and diarrhea. Rash, hyperactivity, or drowsiness have also been observed in a small number of patients.

In the case of overdosage, discontinue AUGMENTIN, treat symptomatically, and institute supportive measures as required. If the overdosage is very recent and there is no contraindication, an attempt at emesis or other means of removal of drug from the stomach may be performed. A prospective study of 51 pediatric patients at a poison center suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.[3]

Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin.

Crystalluria, in some cases leading to renal failure, has also been reported after amoxicillin overdosage in adult and pediatric patients. In cases of overdosage, adequate fluid intake and diuresis should be maintained to reduce the risk of amoxicillin crystalluria.

Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of both amoxicillin and clavulanate. Both amoxicillin and clavulanate are removed from the circulation by hemodialysis. (See DOSAGE AND ADMINISTRATION for recommended dosing for patients with impaired renal function.)

DOSAGE AND ADMINISTRATION

Since both the 250-mg and 500-mg tablets of AUGMENTIN contain the same amount of clavulanic acid (125 mg, as the potassium salt), two 250-mg tablets of AUGMENTIN are not equivalent to one 500-mg tablet of AUGMENTIN; therefore, two 250-mg tablets of AUGMENTIN should not be substituted for one 500-mg tablet of AUGMENTIN.

Dosage

Adults: The usual adult dose is one 500-mg tablet of AUGMENTIN every 12 hours or one 250-mg tablet of AUGMENTIN every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be

one 875-mg tablet of AUGMENTIN every 12 hours or one 500-mg tablet of AUGMENTIN every 8 hours.

Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with a glomerular filtration rate of <30 mL/min. should not receive the 875-mg tablet. Patients with a glomerular filtration rate of 10 to 30 mL/min. should receive 500 mg or 250 mg every 12 hours, depending on the severity of the infection. Patients with a less than 10 mL/min. glomerular filtration rate should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection.

Hemodialysis patients should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection. They should receive an additional dose both during and at the end of dialysis.

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals. (See WARNINGS .)

Pediatric Patients: Pediatric patients weighing 40 kg or more should be dosed according to the adult recommendations.

Due to the different amoxicillin to clavulanic acid ratios in the 250-mg tablet of AUGMENTIN (250/125) versus the 250-mg chewable tablet of AUGMENTIN (250/62.5), the 250-mg tablet of AUGMENTIN should not be used until the pediatric patient weighs at least 40 kg or more.

Administration: AUGMENTIN may be taken without regard to meals; however, absorption of clavulanate potassium is enhanced when AUGMENTIN is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, AUGMENTIN should be taken at the start of a meal.

HOW SUPPLIED

AUGMENTIN 250-mg Tablets: Each white oval filmcoated tablet, debossed with AUGMENTIN on 1 side and 250/125 on the other side, contains 250 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the potassium salt.

NDC 0029-6075-27 bottles of 30

NDC 0029-6075-31 Unit Dose (10 x 10) 100 tablets

AUGMENTIN 500-mg TABLETS: Each white oval filmcoated tablet, debossed with AUGMENTIN on 1 side and 500/125 on the other side, contains 500 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the potassium salt.

NDC 0029-6080-12 bottles of 20

NDC 0029-6080-31 Unit Dose (10 x 10) 100 tablets

AUGMENTIN 875-mg Tablets: Each scored white capsule-shaped tablet, debossed with AUGMENTIN 875 on 1 side and scored on the other side, contains 875 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the potassium salt.

NDC 0029-6086-12 bottles of 20

NDC 0029-6086-21 Unit Dose (10 x 10) 100 tablets

AUGMENTIN is Also Supplied as:

AUGMENTIN 125 mg/5 mL (125 mg amoxicillin/31.25 mg clavulanic acid) For Oral Suspension:

NDC 0029-6085-39 75 mL bottle

NDC 0029-6085-23 100 mL bottle

NDC 0029-6085-22 150 mL bottle

AUGMENTIN 200 mg/5 mL (200 mg amoxicillin/28.5 mg clavulanic acid) For Oral Suspension:

NDC 0029-6087-29 50 mL bottle

NDC 0029-6087-39 75 mL bottle

NDC 0029-6087-51 100 mL bottle

AUGMENTIN 250 mg/5 mL (250 mg amoxicillin/62.5 mg clavulanic acid) For Oral Suspension:

NDC 0029-6090-39 75 mL bottle

NDC 0029-6090-23 100 mL bottle

NDC 0029-6090-22 150 mL bottle

AUGMENTIN 400 mg/5 mL (400 mg amoxicillin/57 mg clavulanic acid) For Oral Suspension:

NDC 0029-6092-29 50 mL bottle

NDC 0029-6092-39 75 mL bottle

NDC 0029-6092-51 100 mL bottle

AUGMENTIN 125 mg (125 mg amoxicillin/31.25 mg clavulanic acid) Chewable Tablets:

NDC 0029-6073-47 carton of 30 (5 x 6) tablets

AUGMENTIN 200 mg (200 mg amoxicillin/28.5 mg clavulanic acid) Chewable Tablets:

NDC 0029-6071-12 carton of 20 tablets

AUGMENTIN 250 mg (250 mg amoxicillin/62.5 mg clavulanic acid) Chewable Tablets:

NDC 0029-6074-47 carton of 30 (5 x 6) tablets

AUGMENTIN 400 mg (400 mg amoxicillin/57.0 mg clavulanic acid) Chewable Tablets:

NDC 0029-6072-12 carton of 20 tablets

Store tablets and dry powder at or below 25 deg. C (77 deg. F). Dispense in original container.

CLINICAL STUDIES

Data from 2 pivotal studies in 1,191 patients treated for either lower respiratory tract infections or complicated urinary tract infections compared a regimen of 875-mg tablets of AUGMENTIN q12h to 500-mg tablets of AUGMENTIN dosed q8h (584 and 607 patients, respectively). Comparable efficacy was demonstrated between the q12h and q8h dosing regimens. There was no significant difference in the percentage of adverse events in each group. The most

frequently reported adverse event was diarrhea; incidence rates were similar for the 875-mg q12h and 500-mg q8h dosing regimens (14.9% and 14.3%, respectively); however, there was a statistically significant difference ($p<0.05$) in rates of severe diarrhea or withdrawals with diarrhea between the regimens: 1.0% for 875-mg q12h dosing versus 2.5% for the 500-mg q8h dosing.

In 1 of these pivotal studies, 629 patients with either pyelonephritis or a complicated urinary tract infection (i.e., patients with abnormalities of the urinary tract that predispose to relapse of bacteriuria following eradication) were randomized to receive either 875-mg tablets of AUGMENTIN q12h or 500-mg tablets of AUGMENTIN q8h in the following distribution:

	875 mg q12h	500 mg q8h
Pyelonephritis	173 patients	188 patients
Complicated UTI	135 patients	133 patients
Total patients	308	321

The number of bacteriologically evaluable patients was comparable between the 2 dosing regimens. AUGMENTIN produced comparable bacteriological success rates in patients assessed 2 to 4 days immediately following end of therapy. The bacteriologic efficacy rates were comparable at 1 of the follow-up visits (5 to 9 days post-therapy) and at a late post-therapy visit (in the majority of cases, this was 2 to 4 weeks post-therapy), as seen in the table below:

	875 mg q12h	500 mg q8h
2 to 4 days	81%, n = 58	80%, n = 54
5 to 9 days	58.5%, n = 41	51.9%, n = 52
2 to 4 weeks	52.5%, n = 101	54.8%, n = 104

As noted before, though there was no significant difference in the percentage of adverse events in each group, there was a statistically significant difference in rates of severe diarrhea or withdrawals with diarrhea between the regimens.

REFERENCES

National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25. NCCLS, Villanova, PA, December 1993.

National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests—Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24. NCCLS, Villanova, PA, December 1993.

Swanson-Biearman B, Dean BS, Lopez G, Krenzelok EP. The effects of penicillin and cephalosporin ingestions in children less than six years of age. *Vet Hum Toxicol* 1988;30:66-67.

AUGMENTIN is a registered trademark of

GlaxoSmithKline.

CLINITEST is a registered trademark of Miles, Inc.

CLINISTIX is a registered trademark of Bayer Corporation.

GlaxoSmithKline, Research Triangle Park, NC 27709

June 2004/AG:AL13

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See Image

LANGUAGE: ENGLISH

LOAD-DATE: March 9, 2006

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This page was generated by the TARR system on 2006-06-27 20:11:29 ET

Serial Number: 73368678 Assignment Information

Registration Number: 1269595 Assignment Information

Mark (words only): BACTROBAN

Standard Character claim: No

Current Status: This registration has been renewed.

Date of Status: 2004-03-18

Filing Date: 1982-06-09

Transformed into a National Application: No

Registration Date: 1984-03-13

Register: Principal

Law Office Assigned: (NOT AVAILABLE)

If you are the applicant or applicant's attorney and have questions about this file, please contact the Trademark Assistance Center at TrademarkAssistanceCenter@uspto.gov

Current Location: 900 -File Repository (Franconia)

Date In Location: 2004-03-19

LAST APPLICANT(S)/OWNER(S) OF RECORD

1. SMITHKLINE BEECHAM CORPORATION

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ONE FRANKLIN PLAZA
PHILADELPHIA, PA 19101
United States
Legal Entity Type: Corporation
State or Country of Incorporation: Pennsylvania

GOODS AND/OR SERVICES

International Class: 005
Class Status: Active

Antibiotic Preparations for Topical Use
Basis: 1(a)
First Use Date: 1982-05-11
First Use in Commerce Date: 1982-05-11

ADDITIONAL INFORMATION

(NOT AVAILABLE)

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2004-03-18 - First renewal 10 year

2004-03-18 - Section 8 (10-year) accepted/ Section 9 granted

2004-01-22 - Combined Section 8 (10-year)/Section 9 filed

2004-01-22 - TEAS Section 8 & 9 Received

1989-09-15 - Section 8 (6-year) accepted

1989-07-24 - Section 8 (6-year) filed

1984-03-13 - Registered - Principal Register

1983-08-16 - Published for opposition

1983-08-16 - Published for opposition

1983-07-27 - Notice of publication

1983-07-22 - Notice of publication

1983-07-21 - Notice of publication

1983-07-20 - Notice of publication

1983-07-19 - Notice of publication

1983-06-06 - Approved for Pub - Principal Register (Initial exam)

1983-05-12 - Communication received from applicant

1983-04-29 - Non-final action mailed

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22 of 201 DOCUMENTS

Physician's Desk Reference for Prescription Drugs

Bactroban Cream(GlaxoSmithKline)

BODY:

DESCRIPTION

BACTROBAN CREAM (mupirocin calcium cream), 2% contains the dihydrate crystalline calcium hemi-salt of the antibiotic mupirocin. Chemically, it is ((alpha) *E* ,2 *S* ,3 *R* ,4 *R* ,5 *S*)-5-(2 *S* ,3 *S* ,4 *S* ,5 *S*)-2,3-Epoxy-5-hydroxy-4-methylhexyl tetra-hydro-3,4-dihydroxy-(beta)-methyl-2 *H*-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid, calcium salt (2:1), dihydrate.

The molecular formula of mupirocin calcium is (C[26] H[43] O[9])[2] Ca*2H[2] O, and the molecular weight is 1075.3. The molecular weight of mupirocin free acid is 500.6.

BACTROBAN CREAM is a white cream that contains 2.15% w/w mupirocin calcium (equivalent to 2.0% mupirocin free acid) in an oil and water-based emulsion. The inactive ingredients are benzyl alcohol, cetomacrogol 1000, cetyl alcohol, mineral oil, phenoxyethanol, purified water, stearyl alcohol, and xanthan gum.

CLINICAL PHARMACOLOGY

Pharmacokinetics: Systemic absorption of mupirocin through intact human skin is minimal. The systemic absorption of mupirocin was studied following application of BACTROBAN CREAM three times daily for 5 days to various skin lesions (greater than 10 cm in length or 100 cm[2] in area) in 16 adults (aged 29 to 60 years) and 10 children (aged 3 to 12 years). Some systemic absorption was observed as evidenced by the detection of the metabolite, monic acid, in urine. Data from this study indicated more frequent occurrence of percutaneous absorption in children (90% of patients) compared to adults (44% of patients); however, the observed urinary concentrations in children (0.07 - 1.3 mcg/mL 1 pediatric patient had no detectable level) are within the observed range (0.08 - 10.03 mcg/mL 9 adults had no detectable level) in the adult population. In general, the degree of percutaneous absorption following multiple dosing appears to be minimal in adults and children. Any mupirocin reaching the systemic circulation is rapidly metabolized, predominantly to inactive monic acid, which is eliminated by renal excretion.

Microbiology: Mupirocin is an antibacterial agent produced by fermentation using the organism *Pseudomonas fluorescens* . It is active against a wide range of gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA). It is also active against certain gram-negative bacteria. Mupirocin inhibits bacterial protein synthesis by reversibly and specifically binding to bacterial isoleucyl transfer-RNA synthetase. Due to this unique mode of action, mupirocin demonstrates no in vitro cross-resistance with other classes of antimicrobial agents.

Resistance occurs rarely; however, when mupirocin resistance does occur, it appears to result from the production of a modified isoleucyl-tRNA synthetase. High-level plasmid-mediated resistance (MIC >1024 mcg/mL) has been reported in some strains of *Staphylococcus aureus* and coagulase-negative staphylococci.

Mupirocin is bactericidal at concentrations achieved by topical application. The minimum bactericidal concentration (MBC) against relevant pathogens is generally 8-fold to 30-fold higher than the minimum inhibitory concentration (MIC). In addition, mupirocin is highly protein bound (>97%), and the effect of wound secretions on the MICs of mupirocin has not been determined.

Mupirocin has been shown to be active against most strains of *S. aureus* and *Streptococcus pyogenes* , both in vitro and in clinical studies. (See INDICATIONS AND USAGE .) The following in vitro data are available, BUT THEIR

CLINICAL SIGNIFICANCE IS UNKNOWN. Mupirocin is active against most strains of *Staphylococcus epidermidis* and *Staphylococcus saprophyticus* .

INDICATIONS AND USAGE

BACTROBAN CREAM is indicated for the treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm[2] in area) due to susceptible strains of *S. aureus* and *S. pyogenes* .

CONTRAINDICATIONS

BACTROBAN CREAM is contraindicated in patients with known hypersensitivity to any of the constituents of the product.

WARNINGS

Avoid contact with the eyes.

In the event of a sensitization or severe local irritation from BACTROBAN CREAM, usage should be discontinued, and appropriate alternative therapy for the infection instituted.

PRECAUTIONS

General: As with other antibacterial products, prolonged use may result in overgrowth of nonsusceptible microorganisms, including fungi. (See DOSAGE AND ADMINISTRATION .)

BACTROBAN CREAM is not formulated for use on mucosal surfaces.

Information for Patients:

Use this medication only as directed by your healthcare provider. It is for external use only. Avoid contact with the eyes.The treated area may be covered by gauze dressing if desired.Report to your healthcare provider any signs of local adverse reactions. The medication should be stopped and your healthcare provider contacted if irritation, severe itching, or rash occurs.If no improvement is seen in 3 to 5 days, contact your healthcare provider.

Drug Interactions: The effect of the concurrent application of topical mupirocin calcium cream and other topical products has not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate carcinogenic potential of mupirocin calcium have not been conducted.

Results of the following studies performed with mupirocin calcium or mupirocin sodium in vitro and in vivo did not indicate a potential for mutagenicity: Rat primary hepatocyte unscheduled DNA synthesis, sediment analysis for DNA strand breaks, *Salmonella* reversion test (Ames), *Escherichia coli* mutation assay, metaphase analysis of human lymphocytes, mouse lymphoma assay, and bone marrow micronuclei assay in mice.

Fertility studies were performed in rats with mupirocin administered subcutaneously at doses up to 49 times a human topical dose of 1 gram/day (approximately 20 mg mupirocin per day) on a mg/m[2] basis and revealed no evidence of impaired fertility from mupirocin sodium.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B. Teratology studies have been performed in rats and rabbits with mupirocin administered subcutaneously at doses up to 78 and 154 times, respectively, a human topical dose of 1 gram/day (approximately 20 mg mupirocin per day) on a mg/m[2] basis and revealed no evidence of harm to the fetus due to mupirocin. 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 human milk, caution should be exercised when BACTROBAN CREAM is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of BACTROBAN CREAM have been established in the age groups 3 months to 16 years. Use of BACTROBAN CREAM in these age groups is supported by evidence from adequate and well-controlled studies of BACTROBAN CREAM in adults with additional data from 93 pediatric patients studied as part of the pivotal trials in adults. (See CLINICAL STUDIES .)

Geriatric Use: In 2 well-controlled studies, 30 patients older than 65 years were treated with BACTROBAN CREAM. No overall difference in the efficacy or safety of BACTROBAN CREAM was observed in this patient population when compared to that observed in younger patients.

ADVERSE REACTIONS

In 2 randomized, double-blind, double-dummy trials, 339 patients were treated with topical BACTROBAN CREAM plus oral placebo. Adverse events thought to be possibly or probably drug-related occurred in 28 (8.3%) patients. The incidence of those events that were reported in at least 1% of patients enrolled in these trials were: Headache (1.7%), rash, and nausea (1.1% each).

Other adverse events thought to be possibly or probably drug-related which occurred in less than 1% of patients were: Abdominal pain, burning at application site, cellulitis, dermatitis, dizziness, pruritus, secondary wound infection, and ulcerative stomatitis.

In a supportive study in the treatment of secondarily infected eczema, 82 patients were treated with BACTROBAN CREAM. The incidence of adverse events thought to be possibly or probably drug-related was as follows: Nausea (4.9%), headache, and burning at application site (3.6% each), pruritus (2.4%) and 1 report each of abdominal pain, bleeding secondary to eczema, pain secondary to eczema, hives, dry skin, and rash.

OVERDOSAGE

Intravenous infusions of 252 mg, as well as single oral doses of 500 mg of mupirocin, have been well tolerated in healthy adult subjects. There is no information regarding overdose of BACTROBAN CREAM.

DOSAGE AND ADMINISTRATION

A small amount of BACTROBAN CREAM should be applied to the affected area three times daily for 10 days. The area treated may be covered with gauze dressing if desired. Patients not showing a clinical response within 3 to 5 days should be re-evaluated.

CLINICAL STUDIES

The efficacy of topical BACTROBAN CREAM for the treatment of secondarily infected traumatic skin lesions (e.g., lacerations, sutured wounds, and abrasions not more than 10 cm in length or 100 cm[2] in total area) was compared to that of oral cephalexin in 2 randomized, double-blind, double-dummy clinical trials. Clinical efficacy rates at follow-up in the per protocol populations (adults and pediatric patients included) were 96.1% for BACTROBAN CREAM (n = 231) and 93.1% for oral cephalexin (n = 219). Pathogen eradication rates at follow-up in the per protocol populations were 100% for both BACTROBAN CREAM and oral cephalexin.

Pediatrics: There were 93 pediatric patients aged 2 weeks to 16 years enrolled per protocol in the secondarily infected skin lesion studies, although only 3 were less than 2 years of age in the population treated with BACTROBAN CREAM. Patients were randomized to either 10 days of topical BACTROBAN CREAM three times daily or 10 days of oral cephalexin (250 mg four times daily for patients >40 kg or 25 mg/kg/day oral suspension in 4 divided doses

for patients </=40 kg). Clinical efficacy at follow-up (7 to 12 days post-therapy) in the per protocol populations was 97.7% (43/44) for BACTROBAN CREAM and 93.9% (46/49) for cephalexin. Only 1 adverse event (headache) was thought to be possibly or probably related to drug therapy with BACTROBAN CREAM in the intent-to-treat pediatric population of 70 children (1.4%).

HOW SUPPLIED

BACTROBAN CREAM is supplied in 15-gram and 30-gram tubes.

NDC 0029-1527-22 (15-gram tube)

NDC 0029-1527-25 (30-gram tube)

Store at or below 25 deg. C (77 deg. F). Do not freeze.

GlaxoSmithKline, Research Triangle Park, NC 27709

BACTROBAN CREAM is a registered trademark of GlaxoSmithKline.

July 2003/BB:L5

PRODUCT PHOTO(S): NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

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LANGUAGE: ENGLISH

LOAD-DATE: March 9, 2006

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Serial Number: 78209524

Registration Number: 2931724

Mark (words only): BONIVA

Standard Character claim: No

Current Status: Registered.

Date of Status: 2005-03-08

Filing Date: 2003-01-31

Transformed into a National Application: No

Registration Date: 2005-03-08

Register: Principal

Law Office Assigned: LAW OFFICE 102

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Current Location: 650 -Publication And Issue Section

Date In Location: 2005-01-27

LAST APPLICANT(S)/OWNER(S) OF RECORD

1. Roche Therapeutics Inc.

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United States
Legal Entity Type: Corporation
State or Country of Incorporation: Delaware
Phone Number: 973-235-2122
Fax Number: 973-235-5450

GOODS AND/OR SERVICES

International Class: 005
Class Status: Active
pharmaceutical preparation for the prevention and treatment of bone diseases
Basis: 1(a)
First Use Date: 2004-08-24
First Use in Commerce Date: 2004-08-24

ADDITIONAL INFORMATION

Prior Registration Number(s):
2106772

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2005-03-08 - Registered - Principal Register

2004-11-13 - Law Office Registration Review Completed

2004-11-10 - Assigned To LIE

2004-11-08 - Assigned To LIE

2004-10-04 - Assigned To LIE

2004-09-27 - Allowed for Registration - Principal Register (SOU accepted)

2004-09-27 - Assigned To Examiner

2004-09-23 - Statement of use processing complete

2004-09-23 - Extension 2 granted

2004-09-09 - Amendment to Use filed

2004-09-09 - Extension 2 filed

2004-09-09 - TEAS Statement of Use Received

2004-09-09 - TEAS Extension Received

2004-04-29 - Extension 1 granted

2004-04-22 - Extension 1 filed

2004-04-22 - TEAS Extension Received

2003-12-16 - Notice of allowance - mailed

2003-09-23 - Published for opposition

2003-09-03 - Notice of publication

2003-07-21 - Approved for Pub - Principal Register (Initial exam)

2003-07-21 - Assigned To Examiner

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Physician's Desk Reference for Prescription Drugs

Boniva Tablets(Roche Laboratories)

BODY:

DESCRIPTION

BONIVA (ibandronate sodium) is a nitrogen-containing bisphosphonate that inhibits osteoclast-mediated bone resorption. The chemical name for ibandronate sodium is 3-(N-methyl-N-pentyl) amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt, monohydrate with the molecular formula C[9] H[22] NO[7] P[2] Na*H[2] O and a molecular weight of 359.24. Ibandronate sodium is a white-to off-white powder. It is freely soluble in water and practically insoluble in organic solvents.

BONIVA is available as a white, oblong, 2.5-mg film-coated tablet for daily oral administration or as a white, oblong, 150-mg film-coated tablet for once-monthly oral administration. One 2.5-mg film-coated tablet contains 2.813 mg ibandronate monosodium monohydrate, equivalent to 2.5 mg free acid. One 150-mg film-coated tablet contains 168.75 mg ibandronate monosodium monohydrate, equivalent to 150 mg free acid. BONIVA also contains the following inactive ingredients: lactose monohydrate, povidone, microcrystalline cellulose, crospovidone, purified stearic acid, colloidal silicon dioxide, and purified water. The tablet film coating contains hypromellose, titanium dioxide, talc, polyethylene glycol 6000, and purified water.

CLINICAL PHARMACOLOGY

Mechanism of Action

The action of ibandronate on bone tissue is based on its affinity for hydroxyapatite, which is part of the mineral matrix of bone. Ibandronate inhibits osteoclast activity and reduces bone resorption and turnover. In postmenopausal women, it reduces the elevated rate of bone turnover, leading to, on average, a net gain in bone mass.

Pharmacokinetics

Absorption

The absorption of oral ibandronate occurs in the upper gastrointestinal tract. Plasma concentrations increase in a dose-linear manner up to 50 mg oral intake and increases nonlinearly above this dose.

Following oral dosing, the time to maximum observed plasma ibandronate concentrations ranged from 0.5 to 2 hours (median 1 hour) in fasted healthy post-menopausal women. The mean oral bioavailability of 2.5 mg ibandronate was about 0.6% compared to intravenous dosing. The extent of absorption is impaired by food or beverages (other than plain water). The oral bioavailability of ibandronate is reduced by about 90% when BONIVA is administered concomitantly with a standard breakfast in comparison with bioavailability observed in fasted subjects. There is no meaningful reduction in bioavailability when ibandronate is taken at least 60 minutes before a meal. However, both bioavailability and the effect on bone mineral density (BMD) are reduced when food or beverages are taken less than 60 minutes following an ibandronate dose.

Distribution

After absorption, ibandronate either rapidly binds to bone or is excreted into urine. In humans, the apparent terminal volume of distribution is at least 90 L, and the amount of dose removed from the circulation via the bone is estimated

to be 40% to 50% of the circulating dose. In vitro protein binding in human serum was 99.5% to 90.9% over an ibandronate concentration range of 2 to 10 ng/mL in one study and approximately 85.7% over a concentration range of 0.5 to 10 ng/mL in another study.

Metabolism

There is no evidence that ibandronate is metabolized in humans.

Elimination

The portion of ibandronate that is not removed from the circulation via bone absorption is eliminated unchanged by the kidney (approximately 50% to 60% of the absorbed dose). Unabsorbed ibandronate is eliminated unchanged in the feces.

The plasma elimination of ibandronate is multiphasic. Its renal clearance and distribution into bone accounts for a rapid and early decline in plasma concentrations, reaching 10% of the C[max] within 3 or 8 hours after intravenous or oral administration, respectively. This is followed by a slower clearance phase as ibandronate redistributes back into the blood from bone. The observed apparent terminal half-life for ibandronate is generally dependent on the dose studied and on assay sensitivity. The observed apparent terminal half-life for the 150 mg ibandronate tablet upon oral administration to healthy postmenopausal women ranges from 37 to 157 hours.

Total clearance of ibandronate is low, with average values in the range 84 to 160 mL/min. Renal clearance (about 60 mL/min in healthy postmenopausal females) accounts for 50% to 60% of total clearance and is related to creatinine clearance. The difference between the apparent total and renal clearances likely reflects bone uptake of the drug.

Special Populations

Pediatrics

The pharmacokinetics of ibandronate has not been studied in patients <18 years of age.

Gender

The bioavailability and pharmacokinetics of ibandronate are similar in both men and women.

Geriatric

Since ibandronate is not known to be metabolized, the only difference in ibandronate elimination for geriatric patients versus younger patients is expected to relate to progressive age-related changes in renal function (see Special Populations : Renal Impairment).

Race

Pharmacokinetic differences due to race have not been studied.

Renal Impairment

Renal clearance of ibandronate in patients with various degrees of renal impairment is linearly related to creatinine clearance (CLcr).

Following a single dose of 0.5 mg ibandronate by intravenous administration, patients with CLcr 40 to 70 mL/min had 55% higher exposure (AUC[(infinity)]) than the exposure observed in subjects with CLcr >90 mL/min. Patients with CLcr <30 mL/min had more than a two-fold increase in exposure compared to the exposure for healthy subjects (see DOSAGE AND ADMINISTRATION : Patients with Renal Impairment).

Hepatic Impairment

No studies have been performed to assess the pharmacokinetics of ibandronate in patients with hepatic impairment since ibandronate is not metabolized in the human liver.

Drug Interactions

Ibandronate does not undergo hepatic metabolism and does not inhibit the hepatic cytochrome P450 system. Ibandronate is eliminated by renal excretion. Based on a rat study, the ibandronate secretory pathway does not appear to include known acidic or basic transport systems involved in the excretion of other drugs.

Products containing calcium and other multivalent cations (such as aluminum, magnesium, iron), including milk, food, and antacids are likely to interfere with absorption of ibandronate, which is consistent with findings in animal studies.

H2 Blockers and Proton Pump Inhibitors (PPIs)

A pharmacokinetic interaction study in healthy volunteers demonstrated that 75 mg ranitidine (25 mg injected intravenously 90 and 15 minutes before and 30 minutes after ibandronate administration) increased the oral bioavailability of 10 mg ibandronate by about 20%. This degree of increase is not considered to be clinically relevant.

Tamoxifen

A pharmacokinetic interaction study in healthy postmenopausal women demonstrated that there was no interaction between oral 30 mg tamoxifen and intravenous 2 mg ibandronate.

Pharmacodynamics

Osteoporosis is characterized by decreased bone mass and increased fracture risk, most commonly at the spine, hip, and wrist. The diagnosis can be confirmed by a finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis indicative of vertebral fracture. While osteoporosis occurs in both men and women, it is most common among women following menopause. In healthy humans, bone formation and resorption are closely linked; old bone is resorbed and replaced by newly formed bone. In postmenopausal osteoporosis, bone resorption exceeds bone formation, leading to bone loss and increased risk of fracture. After menopause, the risk of fractures of the spine and hip increases; approximately 40% of 50-year-old women will experience an osteoporosis-related fracture during their remaining lifetimes.

BONIVA produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases of biochemical markers of bone collagen degradation (such as deoxypyridinoline, and cross-linked C-telopeptide of Type I collagen) in the daily dose range of 0.25 to 5.0 mg and once-monthly doses from 100 mg to 150 mg in postmenopausal women.

Treatment with 2.5 mg daily BONIVA resulted in decreases in biochemical markers of bone turnover, including urinary C-terminal telopeptide of Type I collagen (uCTX) and serum osteocalcin, to levels similar to those in premenopausal women. Changes in markers of bone formation were observed later than changes in resorption markers, as expected, due to the coupled nature of bone resorption and formation. Treatment with 2.5 mg daily BONIVA decreased levels of uCTX within 1 month of starting treatment and decreased levels of osteocalcin within 3 months. Bone turnover markers reached a nadir of approximately 64% below baseline values by 6 months of treatment and remained stable with continued treatment for up to 3 years. Following treatment discontinuation, there is a return to pretreatment baseline rates of elevated bone resorption associated with postmenopausal osteoporosis.

In a 1-year, Phase 3 study comparing once-monthly vs. once-daily oral dosing regimens, the median decrease from baseline in serum CTX values was-76% for patients treated with the 150 mg once-monthly regimen and-67% for

patients treated with the 2.5 mg daily regimen.

CLINICAL STUDIES

Treatment of Postmenopausal Osteoporosis

The effectiveness and safety of BONIVA were demonstrated in a randomized, double-blind, placebo-controlled, multinational study (Treatment Study) of 2946 women aged 55 to 80 years, who were on average 21 years post-menopause, who had lumbar spine BMD 2 to 5 SD below the premenopausal mean (T-score) in at least one vertebra L1-L4 , and who had 1 to 4 prevalent vertebral fractures. BONIVA was evaluated at oral doses of 2.5 mg daily and 20 mg intermittently. The main outcome measure was the occurrence of new radiographically diagnosed vertebral fractures after 3 years of treatment. The diagnosis of an incident vertebral fracture was based on both qualitative diagnosis by the radiologist and quantitative morphometric criterion. The morphometric criterion required the dual occurrence of 2 events: a relative height ratio or relative height reduction in a vertebral body of at least 20%, together with at least a 4 mm absolute decrease in height. All women received 400 IU vitamin D and 500 mg calcium supplementation per day.

The effectiveness and safety of BONIVA once monthly were demonstrated in a randomized, double-blind, multinational, noninferiority trial in 1602 women aged 54 to 81 years, who were on average 18 years postmenopause, and had L2-L4 lumbar spine BMD T-score below-2.5 SD at baseline. The main outcome measure was the comparison of the percentage change from baseline in lumbar spine BMD after 1 year of treatment with once-monthly ibandronate (100 mg, 150 mg) to daily ibandronate (2.5 mg). All patients received 400 IU vitamin D and 500 mg calcium supplementation per day.

Effect on Vertebral Fracture

BONIVA 2.5 mg daily significantly reduced the incidence of new vertebral and of new and worsening vertebral fractures. Over the course of the 3-year study, the risk for vertebral fracture was 9.6% in the placebo-treated women and 4.7% in the women treated with BONIVA 2.5 mg ($p<0.001$) (see Table 1).

Table 1 Effect of BONIVA on the Incidence of Vertebral Fracture in the 3-Year Osteoporosis Treatment Study *

	Proportion of Patients with Fracture (%)			
	Placebo n=975	BONIVA 2.5 mg Daily n=977	Absolute Risk Reduction (%) 95% CI	Relative Risk Reduction (%) 95% CI
New Vertebral Fracture 0-3 Year	9.6	4.7	4.9 (2.3, 7.4)	52 ** (29, 68)
New and Worsening Vertebral Fracture 0-3 Year	10.4	5.1	5.3 (2.6, 7.9)	52 (30, 67)
Clinical (Symptomatic) Vertebral Fracture 0-3 Year	5.3	2.8	2.5 (0.6, 4.5)	49 (14, 69)

*The endpoint value is the value at the study's last time point, 3 years, for all patients who had a fracture identified at that time; otherwise, the last post-baseline value prior to the study's last time point is used.

Table 1 Effect of BONIVA on the Incidence of Vertebral Fracture in the 3-Year Osteoporosis Treatment Study *

**p=0.0003 vs. placebo

Effect on Nonvertebral Fractures

There was a similar number of nonvertebral osteoporotic fractures at 3 years reported in women treated with BONIVA 2.5 mg daily 9.1%, (95% CI: 7.1%, 11.1%) and placebo 8.2%, (95% CI: 6.3%, 10.2%) . The two treatment groups were also similar with regard to the number of fractures reported at the individual nonvertebral sites: pelvis, femur, wrist, forearm, rib, and hip.

Effect on Bone Mineral Density (BMD)

BONIVA significantly increased BMD at the lumbar spine and hip relative to treatment with placebo. In the 3-year osteoporosis treatment study, BONIVA 2.5 mg daily produced increases in lumbar spine BMD that were progressive over 3 years of treatment and were statistically significant relative to placebo at 6 months and at all later time points. Lumbar spine BMD increased by 6.4% after 3 years of treatment with 2.5 mg daily BONIVA compared with 1.4% in the placebo group. Table 2 displays the significant increases in BMD seen at the lumbar spine, total hip, femoral neck, and trochanter compared to placebo. Thus, overall BONIVA reverses the loss of BMD, a central factor in the progression of osteoporosis.

Table 2 Mean Percent Change in BMD from Baseline to Endpoint in Patients Treated Daily with BONIVA 2.5 mg or Placebo in the 3-Year Osteoporosis Treatment Study *

	Placebo	BONIVA 2.5 mg Daily
Lumbar Spine	1.4	6.4
	(n=693)	(n=712)
Total Hip	-0.7	3.1
	(n=638)	(n=654)
Femoral Neck	-0.7	2.6
	(n=683)	(n=699)
Trochanter	0.2	5.3
	(n=683)	(n=699)

*The endpoint value is the value at the study's last time point, 3 years, for all patients who had BMD measured at that time; otherwise, the last postbaseline value prior to the study's last time point is used.

BONIVA 150 mg once-monthly (n=327) was shown to be noninferior to BONIVA 2.5 mg daily (n=318) in lumbar spine BMD in a 1-year, double-blind, multicenter study of women with postmenopausal osteoporosis. In the primary efficacy analysis (per-protocol population), the mean increases from baseline in lumbar spine BMD at 1 year were 3.86% (95% CI: 3.40%, 4.32%) in the 2.5-mg daily group and 4.85% (95% CI: 4.41%, 5.29%) in the 150-mg once-monthly group; the mean difference between 2.5 mg daily and 150 mg once monthly was 0.99% (95% CI: 0.38%, 1.60%), which was statistically significant (p=0.002). The results of the intent-to-treat analysis were consistent with the primary efficacy analysis. The 150 mg once-monthly group also had consistently higher BMD increases at the other skeletal sites compared to the 2.5 mg daily group.

Bone Histology

The effects of BONIVA 2.5 mg daily on bone histology were evaluated in iliac crest biopsies from 16 women after 22

months of treatment and 20 women after 34 months of treatment.

The histological analysis of bone biopsies showed bone of normal quality and no indication of osteomalacia or a mineralization defect.

Prevention of Postmenopausal Osteoporosis

BONIVA 2.5 mg daily prevented bone loss in a majority of women in a randomized, double-blind, placebo-controlled 2-year study (Prevention Study) of 653 postmenopausal women without osteoporosis at baseline. Women were aged 41 to 82 years, were on average 8.5 years postmenopause, and had lumbar spine BMD T-scores >-2.5. Women were stratified according to time since menopause (1 to 3 years, >3 years) and baseline lumbar spine BMD (T-score: >-1,-1 to-2.5). The study compared daily BONIVA at three dose levels (0.5 mg, 1.0 mg, 2.5 mg) with placebo. All women received 500 mg of supplemental calcium per day.

The primary efficacy measure was the change in BMD of lumbar spine after 2 years of treatment. BONIVA 2.5 mg daily resulted in a mean increase in lumbar spine BMD of 3.1% compared with placebo following 2 years of treatment (see Figure 1). Increases in BMD were seen at 6 months and at all later time points. Irrespective of the time since menopause or the degree of pre-existing bone loss, treatment with BONIVA resulted in a higher BMD response at the lumbar spine compared with placebo across all four baseline strata time since menopause (1 to 3 years, >3 years) and baseline lumbar spine BMD (T-score: >-1,-1 to-2.5) . Compared with placebo, treatment with BONIVA 2.5 mg daily increased BMD of the total hip by 1.8%, the femoral neck by 2.0%, and the trochanter by 2.1% (see Figure 1).

See Image

The safety and efficacy of once-monthly BONIVA 150 mg in postmenopausal women without osteoporosis are currently being studied, but data are not yet available.

Animal Pharmacology

Animal studies have shown that ibandronate is an inhibitor of osteoclast-mediated bone resorption. In the Schenk assay in growing rats, ibandronate inhibited bone resorption and increased bone volume, based on histologic examination of the tibial metaphyses. There was no evidence of impaired mineralization at the highest dose of 5 mg/kg/day (subcutaneously), which is 1000 times the lowest antiresorptive dose of 0.005 mg/kg/day in this model, and 5000 times the optimal antiresorptive dose of 0.001 mg/kg/day in the aged ovariectomized rat. This indicates that BONIVA administered at therapeutic doses is unlikely to induce osteomalacia.

Long-term daily or once-monthly intermittent administration of ibandronate to ovariectomized rats or monkeys was associated with suppression of bone turnover and increases in bone mass. In both rats and monkeys, vertebral BMD, trabecular density, and biomechanical strength were increased dose-dependently at doses up to 15 times the recommended human daily oral dose of 2.5 mg, or cumulative monthly doses up to 8 times (rat) or 6 times (monkey) the recommended human once-monthly oral dose of 150 mg, based on body surface area (mg/m[2]) or AUC comparison. In monkeys, ibandronate maintained the positive correlation between bone mass and strength at the ulna and femoral neck. New bone formed in the presence of ibandronate had normal histologic structure and did not show mineralization defects.

INDICATIONS AND USAGE

BONIVA is indicated for the treatment and prevention of osteoporosis in postmenopausal women.

Treatment of Postmenopausal Osteoporosis

In postmenopausal women with osteoporosis, BONIVA increases BMD and reduces the incidence of vertebral fractures (see CLINICAL STUDIES). Osteoporosis may be confirmed by the presence or history of osteoporotic fracture or by a finding of low bone mass (BMD more than 2 standard deviations below the premenopausal mean ie, T-score).

Prevention of Postmenopausal Osteoporosis

BONIVA may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of fracture.

Factors such as family history of osteoporosis, early menopause, previous fracture, high bone turnover, reduced BMD (at least 1.0 SD below the premenopausal mean), thin body frame, Caucasian or Asian race, and smoking, are associated with an increased risk of developing osteoporosis and fractures. The presence of these risk factors may be important when considering the use of BONIVA for preventing osteoporosis.

CONTRAINDICATIONS

Known hypersensitivity to BONIVA or to any of its excipientsUncorrected hypocalcemia (see PRECAUTIONS : General)Inability to stand or sit upright for at least 60 minutes (see DOSAGE AND ADMINISTRATION)

WARNINGS

BONIVA, like other bisphosphonates administered orally may cause upper gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcer (see PRECAUTIONS).

PRECAUTIONS

General

Mineral Metabolism

Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting BONIVA therapy. Adequate intake of calcium and vitamin D is important in all patients.

Upper Gastrointestinal Effects

Bisphosphonates administered orally have been associated with dysphagia, esophagitis, and esophageal or gastric ulcers. This association has been reported for bisphosphonates in postmarketing experience but has not been found in most preapproval clinical trials, including those conducted with BONIVA. Therefore, patients should be advised to pay particular attention to and be able to comply with the dosing instructions to minimize the risk of these effects (see DOSAGE AND ADMINISTRATION).

Severe Renal Impairment

BONIVA is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min).

Jaw Osteonecrosis

Osteonecrosis, primarily in the jaw, has been reported in patients treated with bisphosphonates. Most cases have been in cancer patients undergoing dental procedures, but some have occurred in patients with postmenopausal osteoporosis or other diagnoses. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (eg, chemotherapy, radiotherapy, corticosteroids), and co-morbid disorders (eg, anemia, coagulopathy, infection, pre-existing dental disease). Most reported cases have been in patients treated with bisphosphonates intravenously but some have been in patients treated orally.

For patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should

guide the management plan of each patient based on individual benefit/risk assessment.

Musculoskeletal Pain

In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see ADVERSE REACTIONS). However, such reports have been infrequent. This category of drugs include BONIVA (ibandronate sodium) Tablets. Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

In placebo-controlled studies with BONIVA, the percentages of patients with these symptoms were similar in the BONIVA and placebo groups.

Information for Patients

Patients should be instructed to read the Patient Information Leaflet carefully before taking BONIVA, to re-read it each time the prescription is renewed and to pay particular attention to the dosing instructions in order to maximize absorption and clinical benefit.

BONIVA should be taken at least 60 minutes before the first food or drink (other than water) of the day and before taking any oral medications containing multivalent cations (including antacids, supplements or vitamins).To facilitate delivery to the stomach, and thus reduce the potential for esophageal irritation, BONIVA tablets should be swallowed whole with a full glass of plain water (6 to 8 oz) while the patient is standing or sitting in an upright position. Patients should not lie down for 60 minutes after taking BONIVA.Plain water is the only drink that should be taken with BONIVA. Please note that some mineral waters may have a higher concentration of calcium and therefore should not be used.Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration.The BONIVA 150-mg tablet should be taken on the same date each month (ie, the patient's BONIVA day).If the once-monthly dose is missed, and the patient's next scheduled BONIVA day is more than 7 days away, the patient should be instructed to take one BONIVA 150-mg tablet in the morning following the date that it is remembered (see DOSAGE AND ADMINISTRATION). The patient should then return to taking one BONIVA 150-mg tablet every month in the morning of their chosen day, according to their original schedule.The patient must not take two 150-mg tablets within the same week. If the patient's next scheduled BONIVA day is only 1 to 7 days away, the patient must wait until their next scheduled BONIVA day to take their tablet. The patient should then return to taking one BONIVA 150-mg tablet every month in the morning of their chosen day, according to their original schedule.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate. Intake of supplemental calcium and vitamin D should be delayed for at least 60 minutes following oral administration of BONIVA in order to maximize absorption of BONIVA.

Physicians should be alert to signs or symptoms signaling a possible esophageal reaction during therapy, and patients should be instructed to discontinue BONIVA and seek medical attention if they develop symptoms of esophageal irritation such as new or worsening dysphagia, pain on swallowing, retrosternal pain, or heartburn.

Drug Interactions

See CLINICAL PHARMACOLOGY : Pharmacokinetics : Drug Interactions .

Calcium Supplements/Antacids

Products containing calcium and other multivalent cations (such as aluminum, magnesium, iron) are likely to interfere with absorption of BONIVA. BONIVA should be taken at least 60 minutes before any oral medications containing multivalent cations (including antacids, supplements or vitamins) (see PRECAUTIONS : Information for Patients).

H2 Blockers and Proton Pump Inhibitors (PPIs)

Of over 3500 patients enrolled in the BONIVA osteoporosis Treatment and Prevention Studies, 15% used anti-peptic agents (primarily H2 blockers and PPIs). Among these patients, the incidence of upper gastrointestinal adverse experiences in the patients treated with BONIVA was similar to that in placebo-treated patients. Similarly, of over 1600 patients enrolled in a study comparing once-monthly with daily dosing regimens of ibandronate, 14% of patients used anti-peptic agents. Among these patients, the incidence of upper gastrointestinal adverse experiences in the patients treated with BONIVA 150 mg once monthly was similar to that in patients treated with BONIVA 2.5 mg once daily.

Aspirin/Nonsteroidal Antiinflammatory Drugs (NSAIDs)

In the large, placebo-controlled osteoporosis Treatment Study, aspirin and non-steroidal antiinflammatory drugs were taken by 62% of the 2946 patients. Among aspirin or NSAID users, the incidence of upper gastrointestinal adverse events in patients treated with ibandronate 2.5 mg daily (28.9%) was similar to that in placebo-treated patients (30.7%). Similarly, in the 1-year monthly comparison study, aspirin and nonsteroidal antiinflammatory drugs were taken by 39% of the 1602 patients. The incidence of upper gastrointestinal events in patients concomitantly taking aspirin or NSAIDs was similar in patients taking ibandronate 2.5 mg daily (21.7%) and 150 mg once monthly (22.0%). However, since aspirin, NSAIDs, and bisphosphonates are all associated with gastrointestinal irritation, caution should be exercised in the concomitant use of aspirin or NSAIDs with BONIVA.

Drug/Laboratory Test Interactions

Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with ibandronate have not been performed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 104-week carcinogenicity study, doses of 3, 7, or 15 mg/kg/day were administered by oral gavage to male and female Wistar rats (systemic exposures up to 12 and 7 times, respectively, human exposure at the recommended daily oral dose of 2.5 mg, and cumulative exposures up to 3.5 and 2 times, respectively, human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). There were no significant drug-related tumor findings in male or female rats. In a 78-week carcinogenicity study, doses of 5, 20, or 40 mg/kg/day were administered by oral gavage to male and female NMRI mice (exposures up to 475 and 70 times, respectively, human exposure at the recommended daily oral dose of 2.5 mg and cumulative exposures up to 135 and 20 times, respectively, human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). There were no significant drug-related tumor findings in male or female mice. In a 90-week carcinogenicity study, doses of 5, 20, or 80 mg/kg/day were administered in the drinking water to NMRI mice (cumulative monthly exposures in males and females up to 70 and 115 times, respectively, human exposure at the recommended dose of 150 mg, based on AUC comparison). A dose-related increased incidence of adrenal sub-capsular adenoma/carcinoma was observed in female mice, which was statistically significant at 80 mg/kg/day (220 to 400 times human exposure at the recommended daily oral dose of 2.5 mg and 115 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). The relevance of these findings to humans is unknown.

Mutagenesis

There was no evidence for a mutagenic or clastogenic potential of ibandronate in the following assays: in vitro bacterial mutagenesis assay in *Salmonella typhimurium* and *Escherichia coli* (Ames test), mammalian cell mutagenesis assay in Chinese hamster V79 cells, and chromosomal aberration test in human peripheral lymphocytes, each with and without metabolic activation. Ibandronate was not genotoxic in the in vivo mouse micronucleus tests for chromosomal damage.

Impairment of Fertility

In female rats treated from 14 days prior to mating through gestation, decreases in fertility, corpora lutea, and implantation sites were observed at an oral dose of 16 mg/kg/day (45 times human exposure at the recommended daily oral dose of 2.5 mg and 13 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison).

Pregnancy

Pregnancy Category C

In female rats given oral doses of 1, 4, or 16 mg/kg/day beginning 14 days before mating and continuing through lactation, maternal deaths were observed at the time of delivery in all dose groups (>/=3 times human exposure at the recommended daily oral dose of 2.5 mg or >/=1 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). Perinatal pup loss in dams given 16 mg/kg/day (45 times human exposure at the recommended daily oral dose of 2.5 mg and 13 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison) was likely related to maternal dystocia. In pregnant rats given oral doses of 6, 20, or 60 mg/kg/day during gestation, calcium supplementation (32 mg/kg/day by subcutaneous injection from gestation day 18 to parturition) did not completely prevent dystocia and periparturient mortality in any of the treated groups (>/=16 times human exposure at the recommended daily oral dose of 2.5 mg and >/=4.6 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). A low incidence of postimplantation loss was observed in rats treated from 14 days before mating throughout lactation or during gestation, only at doses causing maternal dystocia and periparturient mortality. In pregnant rats dosed orally with 1, 5, or 20 mg/kg/day from gestation day 17 through lactation day 21 (following closure of the hard palate through weaning), maternal toxicity, including dystocia and mortality, fetal perinatal and postnatal mortality, were observed at doses >/=5 mg/kg/day (equivalent to human exposure at the recommended daily oral dose of 2.5 mg and >/=4 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). Periparturient mortality has also been observed with other bisphosphonates and appears to be a class effect related to inhibition of skeletal calcium mobilization resulting in hypocalcemia and dystocia.

Exposure of pregnant rats during the period of organogenesis resulted in an increased fetal incidence of RPU (renal pelvis ureter) syndrome at oral doses >/=10 mg/kg/day (>/=30 times human exposure at the recommended daily oral dose of 2.5 mg and >/=9 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). Impaired pup neuromuscular development (cliff avoidance test) was observed at 16 mg/kg/day when dams were dosed from 14 days before mating through lactation (45 times human exposure at the recommended daily oral dose of 2.5 mg and 13 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison).

In pregnant rabbits given oral doses of 1, 4, or 20 mg/kg/day during gestation, dose-related maternal mortality was observed in all treatment groups (>/=8 times the recommended human daily oral dose of 2.5 mg and >/=4 times the recommended human once-monthly oral dose of 150 mg, based on body surface area comparison, mg/m[2]). The deaths occurred prior to parturition and were associated with lung edema and hemorrhage. No significant fetal anomalies were observed.

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (eg, skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been established.

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

Nursing Mothers

In lactating rats treated with intravenous doses of 0.08 mg/kg, ibandronate was present in breast milk at concentrations of 8.1 to 0.4 ng/mL from 2 to 24 hours after dose administration. Concentrations in milk averaged 1.5 times plasma concentrations. It is not known whether BONIVA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BONIVA is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the patients receiving BONIVA 2.5 mg daily in postmenopausal osteoporosis studies, 52% were over 65 years of age, and 10% were over 75 years of age. Of the patients receiving BONIVA 150 mg once monthly in the postmenopausal osteoporosis 1-year study, 52% were over 65 years of age, and 9% were over 75 years of age. No overall differences in effectiveness or safety were observed between these patients and younger patients but greater sensitivity in some older individuals cannot be ruled out.

ADVERSE REACTIONS

Daily Dosing

Daily treatment with oral BONIVA was studied in over 3900 patients in postmenopausal osteoporosis trials of up to 3 years duration. The overall adverse event profile of BONIVA 2.5 mg once daily in these studies was similar to that of placebo.

Treatment and Prevention of Postmenopausal Osteoporosis

Most adverse events were mild or moderate and did not lead to discontinuation. The incidence of serious adverse events was 20% in the placebo group and 23% in the BONIVA 2.5 mg daily group. The percentage of patients who withdrew from treatment due to adverse events was approximately 17% in both the BONIVA 2.5 mg daily group and the placebo group. Overall, and according to body system, there was no difference between BONIVA and placebo, with adverse events of the digestive system being the most common reason for withdrawal.

Table 3 lists adverse events from the Treatment and Prevention Studies reported in >/=2% of patients and in more patients treated daily with BONIVA than patients treated with placebo. Adverse events are shown without attribution of causality.

Table 3 Adverse Events Occurring at a Frequency >/=2% and in More Patients Treated with BONIVA than in Patients Treated with Placebo Daily in the Osteoporosis Treatment and Prevention Studies

Body System	Placebo % (n=1134)	BONIVA 2.5 mg % (n=1140)
Body as a Whole		
Back Pain	12.2	13.5
Pain in Extremity	6.4	7.8
Infection	3.4	4.3
Asthenia	2.3	3.5
Allergic Reaction	1.9	2.5

Table 3 Adverse Events Occurring at a Frequency >/=2% and in More Patients Treated with BONIVA than in Patients Treated with Placebo Daily in the Osteoporosis Treatment and Prevention Studies

Digestive System		
Dyspepsia	9.8	11.9
Diarrhea	5.0	6.8
Tooth Disorder	2.3	3.5
Vomiting	2.1	2.7
Gastritis	1.9	2.2
Metabolic and Nutritional Disorders		
Hypercholesterolemia	4.2	4.8
Musculoskeletal System		
Myalgia	5.1	5.7
Joint Disorder	3.3	3.6
Arthritis	2.7	3.2
Nervous System		
Headache	5.8	6.5
Dizziness	2.6	3.7
Vertigo	2.5	3.0
Nerve Root Lesion	1.9	2.2
Respiratory System		
Upper Respiratory Infection	33.2	33.7
Bronchitis	6.8	10.0
Pneumonia	4.3	5.9
Pharyngitis	1.5	2.5
Urogenital System		
Urinary Tract Infection	4.2	5.5

Once-Monthly Dosing

In a 1-year, double-blind, multicenter study comparing BONIVA 2.5 mg once daily and BONIVA 150 mg once monthly in women with postmenopausal osteoporosis, the overall safety and tolerability profiles of the two oral dosing regimens were similar. The incidence of serious adverse events was 4.8% in the BONIVA 2.5 mg daily group and 7.1% in the BONIVA 150 mg once-monthly group. The percentage of patients who withdrew from treatment due to adverse events was approximately 8.9% in the BONIVA 2.5 mg daily group and 7.8% in the BONIVA 150 mg once-monthly group. Table 4 lists the adverse events reported in >/=2% of patients without attribution of causality.

Tabl e 4 Adverse Events With an Incidence of at Least 2% in Patients Treated with BONIVA 150 mg Once Monthly or 2.5 mg Daily

Body System/Adverse Event	BONIVA 2.5 mg Daily % (n=395)	BONIVA 150 mg Monthly % (n=396)
Vascular Disorders		
Hypertension	7.3	6.3
Gastrointestinal Disorders		
Dyspepsia	7.1	5.6
Nausea	4.8	5.1
Diarrhea	4.1	5.1
Constipation	2.5	4.0
Abdominal Pain[a]	5.3	7.8

Tabl e 4 Adverse Events With an Incidence of at Least 2% in Patients Treated with BONIVA 150 mg Once Monthly or 2.5 mg Daily

Musculoskeletal and Connective Tissue Disorders		
Arthralgia	3.5	5.6
Back Pain	4.3	4.5
Pain in Extremity	1.3	4.0
Localized	1.3	3.0
Osteoarthritis		
Myalgia	0.8	2.0
Muscle Cramp	2.0	1.8
Infections and Infestations		
Influenza	3.8	4.0
Nasopharyngitis	4.3	3.5
Bronchitis	3.5	2.5
Urinary Tract	1.8	2.3
Infection		
Upper Respiratory	2.0	2.0
Tract		
Infection		
Nervous System Disorders		
Headache	4.1	3.3
Dizziness	1.0	2.3
General Disorders and Administration Site Conditions		
Influenza-like	0.8	3.3
Illness[b]		
Skin and Subcutaneous Tissue Disorders		
Rash[c]	1.3	2.3
Psychiatric Disorders		
Insomnia	0.8	2.0

[a] Combination of abdominal pain and abdominal pain upper
[b] Combination of influenza-like illness and acute phase reaction
[c] Combination of rash pruritic, rash macular, rash papular, rash generalized, rash erythematous, dermatitis, dermatitis allergic, dermatitis medicamentosa, erythema and exanthem

Patients with a previous history of gastrointestinal disease, including patients with peptic ulcer without recent bleeding or hospitalization and patients with dyspepsia or reflux controlled by medication, were included in the once-monthly treatment study. For these patients, there was no difference in upper gastrointestinal adverse events with the 150 mg once-monthly regimen compared to the 2.5 mg once-daily regimen.

Ocular Adverse Events

Reports in the medical literature indicate that bisphosphonates may be associated with ocular inflammation such as uveitis and scleritis. In some cases, these events did not resolve until the bisphosphonate was discontinued. There were no reports of ocular inflammation in studies with BONIVA 2.5 mg daily. Two patients who received BONIVA once monthly experienced ocular inflammation, one was a case of uveitis and the other scleritis.

Laboratory Test Findings

In the 3-year treatment study with BONIVA 2.5 mg daily, there were no clinically significant changes from baseline values or shifts in any laboratory variable for each of the treatment groups. As expected with bisphosphonate treatment, a decrease in total alkaline phosphatase levels was seen in the active treatment groups compared to placebo. There was no difference compared with placebo for laboratory abnormalities indicative of hepatic or renal dysfunction, hypocalcemia, or hypophosphatemia. Similarly, no changes were noted for the 150 mg once-monthly administration

in the 1-year study.

OVERDOSAGE

No specific information is available on the treatment of overdosage with BONIVA. However, based on knowledge of this class of compounds, oral overdosage may result in hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, dyspepsia, esophagitis, gastritis, or ulcer. Milk or antacids should be given to bind BONIVA. Due to the risk of esophageal irritation, vomiting should not be induced, and the patient should remain fully upright. Dialysis would not be beneficial.

DOSAGE AND ADMINISTRATION

The recommended dose of BONIVA for treatment of postmenopausal osteoporosis is one 2.5-mg tablet taken once daily or one 150-mg tablet taken once monthly on the same date each month (see INDICATIONS AND USAGE).

The recommended dose of BONIVA for the prevention of postmenopausal osteoporosis is one 2.5-mg tablet taken once daily. Alternatively, one 150-mg tablet taken once monthly on the same date each month may be considered (see INDICATIONS AND USAGE).

To maximize absorption and clinical benefit, BONIVA should be taken at least 60 minutes before the first food or drink (other than water) of the day or before taking any oral medication or supplementation, including calcium, antacids, or vitamins (see PRECAUTIONS : Information for Patients and Drug Interactions).To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, BONIVA tablets should be swallowed whole with a full glass of plain water (6 to 8 oz) while the patient is standing or sitting in an upright position. Patients should not lie down for 60 minutes after taking BONIVA (see PRECAUTIONS : General and Information for Patients).Plain water is the only drink that should be taken with BONIVA. Please note that some mineral waters may have a higher concentration of calcium and therefore should not be used.Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration.The BONIVA 150-mg tablet should be taken on the same date each month (ie, the patient's BONIVA day).If the once-monthly dose is missed, and the patient's next scheduled BONIVA day is more than 7 days away, the patient should be instructed to take one BONIVA 150-mg tablet in the morning following the date that it is remembered. The patient should then return to taking one BONIVA 150-mg tablet every month in the morning of their chosen day, according to their original schedule.The patient must not take two 150-mg tablets within the same week. If the patient's next scheduled BONIVA day is only 1 to 7 days away, the patient must wait until their next scheduled BONIVA day to take their tablet. The patient should then return to taking one BONIVA 150-mg tablet every month in the morning of their chosen day, according to their original schedule.

Patients should receive supplemental calcium or vitamin D if dietary intake is inadequate (see PRECAUTIONS : Information for Patients).

Patients with Hepatic Impairment

No dose adjustment is necessary (see CLINICAL PHARMACOLOGY : Special Populations).

Patients with Renal Impairment

No dose adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is equal to or greater than 30 mL/min.

BONIVA is not recommended for use in patients with severe renal impairment (creatinine clearance of <30 mL/min) (see CLINICAL PHARMACOLOGY : Special Populations).

Geriatric Patients

No dosage adjustment is necessary in the elderly (see PRECAUTIONS : Geriatric Use).

HOW SUPPLIED

BONIVA 2.5-mg tablets: supplied as white, oblong, film-coated tablets, engraved with "IT" on one side and "L3" on the other side and packaged in bottles of 30 tablets (NDC 0004-0185-23).

BONIVA 150-mg tablets: supplied as white, oblong, film-coated tablets, engraved with "BNVA" on one side and "150" on the other side. Packaged in boxes of 3 blister packs containing 1 tablet each (NDC 0004-0186-82).

Storage

Store at 25 deg. C (77 deg. F); excursions permitted between 15 deg. and 30 deg. C (59 deg. and 86 deg. F) see USP Controlled Room Temperature .

PRODUCT PHOTO(S): NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

The product samples shown here have been supplied by the manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.
See Image

PATIENT INFORMATION

Read this patient information carefully before you start taking BONIVA. Read this patient information each time you get a refill for BONIVA. There may be new information. This information is not everything you need to know about BONIVA. It does not take the place of talking with your health care provider about your condition or your treatment. Talk about BONIVA with your health care provider before you start taking it, and at your regular check-ups.

What is the most important information I should know about BONIVA?

BONIVA may cause serious problems in the stomach and the esophagus (the tube that connects your mouth and stomach) such as trouble swallowing, heartburn, and ulcers (see " What are the possible side effects of BONIVA ? ").

You must take BONIVA exactly as prescribed for BONIVA to work for you and to lower the chance of serious side effects (see " How should I take BONIVA ?").

What is BONIVA?

BONIVA is a prescription medicine used to treat or prevent osteoporosis in women after menopause (see the end of this leaflet for " What is osteoporosis ? ").

BONIVA may reverse bone loss by stopping more loss of bone and increasing bone mass in most women who take it, even though they won't be able to see or feel a difference. BONIVA may help lower the chances of breaking bones (fractures).

For BONIVA to treat or prevent osteoporosis, you have to take it as prescribed. BONIVA will not work if you stop taking it.

Who should not take BONIVA?

Do not take BONIVA if you:

have low blood calcium (hypocalcemia)cannot sit or stand up for at least 1 hour (60 minutes)have kidneys that work very poorlyare allergic to ibandronate sodium or any of the other ingredients of BONIVA (see the end of this leaflet for a list of all the ingredients in BONIVA)

Tell your health care provider before using BONIVA:

if you are pregnant or planning to become pregnant. It is not known if BONIVA can harm your unborn baby.if you are breast-feeding. It is not known if BONIVA passes into your milk and if it can harm your baby.have swallowing problems or other problems with your esophagus (the tube that connects your mouth and stomach)if you have kidney problemsabout all the medicines you take including prescription and non-prescription medicines, vitamins and supplements. Some medicines, especially certain vitamins, supplements, and antacids can stop BONIVA from getting to your bones. This can happen if you take other medicines too close to the time that you take BONIVA (see " How should I take BONIVA ? ").

How should I take BONIVA?

Take BONIVA exactly as instructed by your health care provider.Take BONIVA first thing in the morning at least 1 hour (60 minutes) before you eat, drink anything other than plain water, or take any other oral medicine.Take BONIVA with 6 to 8 ounces (about 1 full cup) of plain water. Do not take it with any other drink besides plain water. Do not take it with other drinks, such as mineral water, sparkling water, coffee, tea, dairy drinks (such as milk), or juice.Swallow BONIVA whole. Do not chew or suck the tablet or keep it in your mouth to melt or dissolve.After taking BONIVA you must wait at least 1 hour (60 minutes) before:
Lying down. You may sit, stand, or do normal activities like read the newspaper or take a walk.Eating or drinking anything except for plain water.Taking other oral medicines including vitamins, calcium, or antacids. Take your vitamins, calcium, and antacids at a different time of the day from the time when you take BONIVA.If you take too much BONIVA, drink a full glass of milk and call your local poison control center or emergency room right away. Do not make yourself vomit. Do not lie down.Keep taking BONIVA for as long as your health care provider tells you. BONIVA will not work if you stop taking it.Your health care provider may tell you to exercise and take calcium and vitamin supplements to help your osteoporosis.Your health care provider may do a test to measure the thickness (density) of your bones or do other tests to check your progress.

What is my BONIVA schedule?

Schedule for taking BONIVA 150 mg once monthly:

Take one BONIVA 150-mg tablet once a month.Choose one date of the month (your BONIVA day) that you will remember and that best fits your schedule to take your BONIVA 150-mg tablet.Take one BONIVA 150-mg tablet in the morning of your chosen day (see " How should I take BONIVA ? ").

What to do if I miss a monthly dose:

If your next scheduled BONIVA day is more than 7 days away, take one BONIVA 150-mg tablet in the morning following the day that you remember (see " How should I take BONIVA ? "). Then return to taking one BONIVA 150-mg tablet every month in the morning of your chosen day, according to your original schedule.Do not take two 150-mg tablets within the same week. If your next scheduled BONIVA day is only 1 to 7 days away, wait until your next scheduled BONIVA day to take your tablet. Then return to taking one BONIVA 150-mg tablet every month in the morning of your chosen day, according to your original schedule.If you are not sure what to do if you miss a dose, contact your health care provider who will be able to advise you.

Schedule for taking BONIVA 2.5 mg once daily:

Take one BONIVA 2.5-mg tablet once a day first thing in the morning at least 1 hour (60 minutes) before you eat, drink anything other than plain water, or take any other oral medicine (see " How should I take BONIVA ? ").

What to do if I miss a daily dose:

If you forget to take your BONIVA 2.5-mg tablet in the morning, do not take it later in the day. Just return to your normal schedule and take 1 tablet the next morning. Do not take two tablets on the same day.If you are not sure what to do if you miss a dose, contact your health care provider who will be able to advise you.

What should I avoid while taking BONIVA?

Do not take other medicines, or eat or drink anything but plain water before you take BONIVA and for at least 1 hour (60 minutes) after you take it.Do not lie down for at least 1 hour (60 minutes) after you take BONIVA.

What are the possible side effects of BONIVA?

Stop taking BONIVA and call your health care provider right away if you have:

pain or trouble with swallowingchest painvery bad heartburn or heartburn that does not get better

BONIVA MAY CAUSE:

pain or trouble swallowing (dysphagia)heartburn (esophagitis)ulcers in your stomach or esophagus (the tube that connects your mouth and stomach)

Common side effects with BONIVA are:

diarrheapain in extremities (arms or legs)dyspepsia (upset stomach)

Less common side effects with BONIVA are short-lasting, mild flu-like symptoms (usually improve after the first dose). These are not all the possible side effects of BONIVA. For more information ask your health care provider or pharmacist.

Rarely, patients have reported severe bone, joint, and/or muscle pain starting within one day to several months after beginning to take, by mouth, bisphosphonate drugs to treat osteoporosis (thin bones). This group of drugs includes BONIVA. Most patients experienced relief after stopping the drug. Contact your health care provider if you develop these symptoms after starting BONIVA.

What is osteoporosis?

Osteoporosis is a disease that causes bones to become thinner. Thin bones can break easily. Most people think of their bones as being solid like a rock. Actually, bone is living tissue, just like other parts of the body, such as your heart, brain, or skin. Bone just happens to be a harder type of tissue. Bone is always changing. Your body keeps your bones strong and healthy by replacing old bone with new bone.

Osteoporosis causes the body to remove more bone than it replaces. This means that bones get weaker. Weak bones are more likely to break. Osteoporosis is a bone disease that is quite common in women after menopause. At first, osteoporosis has no symptoms, but people with osteoporosis may develop loss of height and are more likely to break (fracture) their bones, especially the back (spine), wrist, and hip bones.

Osteoporosis can be prevented, and with proper therapy it can be treated.

Who is at risk for osteoporosis?

Talk to your health care provider about your chances for getting osteoporosis.

Many things put people at risk for osteoporosis. The following people have a higher chance of getting osteoporosis:

Women who:

are going through or who are past menopause ("the change")are white (Caucasian) or Oriental (Asian)

People who:

are thinhave a family member with osteoporosisdo not get enough calcium or vitamin Ddo not exercisesmokedrink alcohol oftentake bone thinning medicines (like prednisone) for a long time

General information about BONIVA

Medicines are sometimes prescribed for conditions that are not mentioned in patient information. Do not use BONIVA for a condition for which it was not prescribed. Do not give BONIVA to other people, even if they have the same symptoms you have. It may harm them.

Store BONIVA at 77 deg. F (25 deg. C) or at room temperature between 59 deg. F and 86 deg. F (15 deg. C and 30 deg. C).

Keep BONIVA and all medicines out of the reach of children.

This summarizes the most important information about BONIVA. If you would like more information, talk with your health care provider. You can ask your health care provider or pharmacist for information about BONIVA that is written for health professionals.

For more information about BONIVA, call 1-888-MY-BONIVA or visit www.myboniva.com.

What are the ingredients of BONIVA?

BONIVA (active ingredient): ibandronate sodium

BONIVA (inactive ingredients): lactose monohydrate, povidone, microcrystalline cellulose, crospovidone, purified stearic acid, colloidal silicon dioxide, and purified water. The tablet film coating contains hypromellose, titanium dioxide, talc, polyethylene glycol 6000 and purified water.

BONIVA is a registered trademark of Roche Therapeutics Inc.

Distributed by:

Roche Laboratories Inc.

340 Kingsland Street

Nutley, New Jersey 07110-1199

Co-promoted by Roche Laboratories Inc. and

GlaxoSmithKline

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Research Triangle Park, NC 27709

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Serial Number: 74389190

Registration Number: 1870977

Mark (words only): FLONASE

Standard Character claim: No

Current Status: This registration has been renewed.

Date of Status: 2005-02-17

Filing Date: 1993-05-11

Transformed into a National Application: No

Registration Date: 1995-01-03

Register: Principal

Law Office Assigned: LAW OFFICE 5

If you are the applicant or applicant's attorney and have questions about this file, please contact the Trademark Assistance Center at TrademarkAssistanceCenter@uspto.gov

Current Location: 834 -Post Registration

Date In Location: 2005-02-17

LAST APPLICANT(S)/OWNER(S) OF RECORD

1. Glaxo Group Limited

Address:
Glaxo Group Limited
Glaxo House, Berkeley Avenue
Greenford, Middlesex UB6 0NN
United Kingdom
Legal Entity Type: Corporation
State or Country of Incorporation: United Kingdom

GOODS AND/OR SERVICES

International Class: 005
Class Status: Active

pharmaceutical preparations and substances for the treatment and/or alleviation of respiratory diseases
Basis: 44(e)
First Use Date: (DATE NOT AVAILABLE)
First Use in Commerce Date: (DATE NOT AVAILABLE)

ADDITIONAL INFORMATION

Foreign Registration Number: A1466284
Foreign Registration Date: 1991-06-04
Country: United Kingdom
Foreign Expiration Date: 1998-06-04

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2005-02-17 - First renewal 10 year

2005-02-17 - Section 8 (10-year) accepted/ Section 9 granted

2004-12-20 - Combined Section 8 (10-year)/Section 9 filed

2004-12-20 - TEAS Section 8 & 9 Received

2004-11-12 - Attorney Revoked And/Or Appointed

2004-11-12 - TEAS Revoke/Appoint Attorney Received

2000-05-16 - Section 8 (6-year) accepted & Section 15 acknowledged

2000-02-14 - Section 8 (6-year) and Section 15 Filed

1995-01-03 - Registered - Principal Register

1994-03-22 - Extension Of Time To Oppose Received

1994-02-22 - Published for opposition

1994-01-21 - Notice of publication

1993-11-24 - Notice of publication

1993-10-18 - Approved for Pub - Principal Register (Initial exam)

1993-09-23 - Communication received from applicant

1993-09-21 - Non-final action mailed

1993-08-31 - Assigned To Examiner

1993-08-26 - Assigned To Examiner

CORRESPONDENCE INFORMATION

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Physician's Desk Reference for Prescription Drugs

Flonase Nasal Spray(GlaxoSmithKline)

BODY:

DESCRIPTION

Fluticasone propionate, the active component of FLONASE Nasal Spray, is a synthetic corticosteroid having the chemical name S-(fluoromethyl)6(alpha),9-difluoro-11(beta)-17-dihydroxy-16(alpha)-methyl-3-oxo androsta-1,4-diene-17(beta)-carbothioate, 17-propionate.

Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and the empirical formula is C[25] H[31] F[3] O[5] S. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

FLONASE Nasal Spray, 50 mcg is an aqueous suspension of microfine fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump. FLONASE Nasal Spray also contains microcrystalline cellulose and carboxymethylcellulose sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, and 0.25% w/w phenylethyl alcohol, and has a pH between 5 and 7.

It is necessary to prime the pump before first use or after a period of non-use (1 week or more). After initial priming (6 actuations), each actuation delivers 50 mcg of fluticasone propionate in 100 mg of formulation through the nasal adapter. Each 16-g bottle of FLONASE Nasal Spray provides 120 metered sprays. After 120 metered sprays, the amount of fluticasone propionate delivered per actuation may not be consistent and the unit should be discarded.

CLINICAL PHARMACOLOGY

Mechanism of Action: Fluticasone propionate is a synthetic, trifluorinated corticosteroid with anti-inflammatory activity. In vitro dose response studies on a cloned human glucocorticoid receptor system involving binding and gene expression afforded 50% responses at 1.25 and 0.17 nM concentrations, respectively. Fluticasone propionate was 3-fold to 5-fold more potent than dexamethasone in these assays. Data from the McKenzie vasoconstrictor assay in man also support its potent glucocorticoid activity.

In preclinical studies, fluticasone propionate revealed progesterone-like activity similar to the natural hormone. However, the clinical significance of these findings in relation to the low plasma levels (see Pharmacokinetics) is not known.

The precise mechanism through which fluticasone propionate affects allergic rhinitis symptoms is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation. In 7 trials in adults, FLONASE Nasal Spray has decreased nasal mucosal eosinophils in 66% (35% for placebo) of patients and basophils in 39% (28% for placebo) of patients. The direct relationship of these findings to long-term symptom relief is not known.

FLONASE Nasal Spray, like other corticosteroids, is an agent that does not have an immediate effect on allergic symptoms. A decrease in nasal symptoms has been noted in some patients 12 hours after initial treatment with FLONASE Nasal Spray. Maximum benefit may not be reached for several days. Similarly, when corticosteroids are discontinued, symptoms may not return for several days.

Pharmacokinetics: *Absorption:* The activity of FLONASE Nasal Spray is due to the parent drug, fluticasone propionate. Indirect calculations indicate that fluticasone propionate delivered by the intranasal route has an absolute bioavailability averaging less than 2%. After intranasal treatment of patients with allergic rhinitis for 3 weeks, fluticasone propionate plasma concentrations were above the level of detection (50 pg/mL) only when recommended doses were exceeded and then only in occasional samples at low plasma levels. Due to the low bioavailability by the intranasal route, the majority of the pharmacokinetic data was obtained via other routes of administration. Studies using oral dosing of radiolabeled drug have demonstrated that fluticasone propionate is highly extracted from plasma and absorption is low. Oral bioavailability is negligible, and the majority of the circulating radioactivity is due to an inactive metabolite.

Distribution: Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averaged 91% with no obvious concentration relationship. Fluticasone propionate is weakly and reversibly bound to erythrocytes and freely equilibrates between erythrocytes and plasma. Fluticasone propionate is not significantly bound to human transcortin.

Metabolism: The total blood clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17(beta)-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 pathway. This inactive metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Elimination: Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations: Fluticasone propionate nasal spray was not studied in any special populations, and no gender-specific pharmacokinetic data have been obtained.

Drug Interactions: Fluticasone propionate is a substrate of cytochrome P450 3A4. Coadministration of fluticasone propionate and the highly potent cytochrome P450 3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (< 10 pg/mL) in most subjects, and when concentrations were detectable peak levels (C[max] averaged 11.9 pg/mL range, 10.8 to 14.1 pg/mL and AUC[(0-tgr)] averaged 8.43 pg*hr/mL range, 4.2 to 18.8 pg*hr/mL). Fluticasone propionate C[max] and AUC[(0-tgr)] increased to 318 pg/mL (range, 110 to 648 pg/mL) and 3,102.6 pg*hr/mL (range, 1,207.1 to 5,662.0 pg*hr/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in plasma cortisol area under the plasma concentration versus time curve (AUC).

Caution should be exercised when other potent cytochrome P450 3A4 inhibitors are coadministered with fluticasone propionate. In a drug interaction study, coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in increased fluticasone propionate exposure and reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol.

In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Pharmacodynamics: In a trial to evaluate the potential systemic and topical effects of FLONASE Nasal Spray on allergic rhinitis symptoms, the benefits of comparable drug blood levels produced by FLONASE Nasal Spray and oral fluticasone propionate were compared. The doses used were 200 mcg of FLONASE Nasal Spray, the nasal spray

vehicle (plus oral placebo), and 5 and 10 mg of oral fluticasone propionate (plus nasal spray vehicle) per day for 14 days. Plasma levels were undetectable in the majority of patients after intranasal dosing, but present at low levels in the majority after oral dosing. FLONASE Nasal Spray was significantly more effective in reducing symptoms of allergic rhinitis than either the oral fluticasone propionate or the nasal vehicle. This trial demonstrated that the therapeutic effect of FLONASE Nasal Spray can be attributed to the topical effects of fluticasone propionate.

In another trial, the potential systemic effects of FLONASE Nasal Spray on the hypothalamic-pituitary-adrenal (HPA) axis were also studied in allergic patients. FLONASE Nasal Spray given as 200 mcg once daily or 400 mcg twice daily was compared with placebo or oral prednisone 7.5 or 15 mg given in the morning. FLONASE Nasal Spray at either dose for 4 weeks did not affect the adrenal response to 6-hour cosyntropin stimulation, while both doses of oral prednisone significantly reduced the response to cosyntropin.

Clinical Trials: A total of 13 randomized, double-blind, parallel-group, multicenter, vehicle placebo-controlled clinical trials were conducted in the United States in adults and pediatric patients (4 years of age and older) to investigate regular use of FLONASE Nasal Spray in patients with seasonal or perennial allergic rhinitis. The trials included 2,633 adults (1,439 men and 1,194 women) with a mean age of 37 (range, 18 to 79 years). A total of 440 adolescents (405 boys and 35 girls), mean age of 14 (range, 12 to 17 years), and 500 children (325 boys and 175 girls), mean age of 9 (range, 4 to 11 years) were also studied. The overall racial distribution was 89% white, 4% black, and 7% other. These trials evaluated the total nasal symptom scores (TNSS) that included rhinorrhea, nasal obstruction, sneezing, and nasal itching in known allergic patients who were treated for 2 to 24 weeks. Subjects treated with FLONASE Nasal Spray exhibited significantly greater decreases in TNSS than vehicle placebo-treated patients. Nasal mucosal basophils and eosinophils were also reduced at the end of treatment in adult studies; however, the clinical significance of this decrease is not known.

There were no significant differences between fluticasone propionate regimens whether administered as a single daily dose of 200 mcg (two 50-mcg sprays in each nostril) or as 100 mcg (one 50-mcg spray in each nostril) twice daily in 6 clinical trials. A clear dose response could not be identified in clinical trials. In 1 trial, 200 mcg/day was slightly more effective than 50 mcg/day during the first few days of treatment; thereafter, no difference was seen.

Two randomized, double-blind, parallel-group, multicenter, vehicle placebo-controlled 28-day trials were conducted in the United States in 732 patients (243 given FLONASE) 12 years of age and older to investigate "as-needed" use of FLONASE Nasal Spray (200 mcg) in patients with seasonal allergic rhinitis. Patients were instructed to take the study medication only on days when they thought they needed the medication for symptom control, not to exceed 2 sprays per nostril on any day, and not more than once daily. "As-needed" use was prospectively defined as average use of study medication no more than 75% of study days. Average use of study medications was 57% to 70% of days for all treatment arms. The studies demonstrated significantly greater reduction in TNSS (sum of nasal congestion, rhinorrhea, sneezing, and nasal itching) with FLONASE Nasal Spray 200 mcg compared to placebo. The relative difference in efficacy with as-needed use as compared to regularly administered doses was not studied.

Three randomized, double-blind, parallel-group, vehicle placebo-controlled trials were conducted in 1,191 patients to investigate regular use of FLONASE Nasal Spray in patients with perennial nonallergic rhinitis. These trials evaluated the patient-rated TNSS (nasal obstruction, postnasal drip, rhinorrhea) in patients treated for 28 days of double-blind therapy and in 1 of the 3 trials for 6 months of open-label treatment. Two of these trials demonstrated that patients treated with FLONASE Nasal Spray at a dose of 100 mcg twice daily exhibited statistically significant decreases in TNSS compared with patients treated with vehicle.

Individualization of Dosage: Patients should use FLONASE Nasal Spray at regular intervals for optimal effect.

Adult patients may be started on a 200-mcg once-daily regimen (two 50-mcg sprays in each nostril once daily). An alternative 200-mcg/day dosage regimen can be given as 100 mcg twice daily (one 50-mcg spray in each nostril twice daily).

Individual patients will experience a variable time to onset and different degree of symptom relief. In 4 randomized, double-blind, vehicle placebo-controlled, parallel-group allergic rhinitis studies and 2 studies of patients in an outdoor

"park" setting (park studies), a decrease in nasal symptoms in treated subjects compared to placebo was shown to occur as soon as 12 hours after treatment with a 200-mcg dose of FLONASE Nasal Spray. Maximum effect may take several days. Regular-use patients who have responded may be able to be maintained (after 4 to 7 days) on 100 mcg/day (1 spray in each nostril once daily).

Some patients (12 years of age and older) with seasonal allergic rhinitis may find as-needed use of FLONASE Nasal Spray (not to exceed 200 mcg daily) effective for symptom control (see Clinical Trials). Greater symptom control may be achieved with scheduled regular use. Efficacy of as-needed use of FLONASE Nasal Spray has not been studied in pediatric patients under 12 years of age with seasonal allergic rhinitis, or patients with perennial allergic or nonallergic rhinitis.

Pediatric patients (4 years of age and older) should be started with 100 mcg (1 spray in each nostril once daily). Treatment with 200 mcg (2 sprays in each nostril once daily or 1 spray in each nostril twice daily) should be reserved for pediatric patients not adequately responding to 100 mcg daily. Once adequate control is achieved, the dosage should be decreased to 100 mcg (1 spray in each nostril) daily.

Maximum total daily doses should not exceed 2 sprays in each nostril (total dose, 200 mcg/day). There is no evidence that exceeding the recommended dose is more effective.

INDICATIONS AND USAGE

FLONASE Nasal Spray is indicated for the management of the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

Safety and effectiveness of FLONASE Nasal Spray in children below 4 years of age have not been adequately established.

CONTRAINDICATIONS

FLONASE Nasal Spray is contraindicated in patients with a hypersensitivity to any of its ingredients.

WARNINGS

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency, and in addition some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

The concomitant use of intranasal corticosteroids with other inhaled corticosteroids could increase the risk of signs or symptoms of hypercorticism and/or suppression of the HPA axis.

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY : Drug Interactions and PRECAUTIONS : Drug Interactions). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In children or adults who have not had these diseases or been properly immunized,

particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known.

If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Avoid spraying in eyes.

PRECAUTIONS

General: Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see PRECAUTIONS : Pediatric Use).

Rarely, immediate hypersensitivity reactions or contact dermatitis may occur after the administration of FLONASE Nasal Spray. Rare instances of wheezing, nasal septum perforation, cataracts, glaucoma, and increased intraocular pressure have been reported following the intranasal application of corticosteroids, including fluticasone propionate.

Use of excessive doses of corticosteroids may lead to signs or symptoms of hypercorticism and/or suppression of HPA function.

Although systemic effects have been minimal with recommended doses of FLONASE Nasal Spray, potential risk increases with larger doses. Therefore, larger than recommended doses of FLONASE Nasal Spray should be avoided.

When used at higher than recommended doses or in rare individuals at recommended doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of FLONASE Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral corticosteroid therapy.

In clinical studies with fluticasone propionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy and discontinuation of treatment with FLONASE Nasal Spray. Patients using FLONASE Nasal Spray over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa.

Intranasal corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated local or systemic fungal or bacterial infections; systemic viral or parasitic infections; or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or nasal trauma should not use a nasal corticosteroid until healing has occurred.

Information for Patients: Patients being treated with FLONASE Nasal Spray should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay.

Patients should use FLONASE Nasal Spray at regular intervals for optimal effect. Some patients (12 years of age and older) with seasonal allergic rhinitis may find as-needed use of 200 mcg once daily effective for symptom control (see Clinical Trials).

A decrease in nasal symptoms may occur as soon as 12 hours after starting therapy with FLONASE Nasal Spray. Results in several clinical trials indicate statistically significant improvement within the first day or two of treatment; however, the full benefit of FLONASE Nasal Spray may not be achieved until treatment has been administered for several days. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.

For the proper use of FLONASE Nasal Spray and to attain maximum improvement, the patient should read and follow carefully the patient's instructions accompanying the product.

Drug Interactions: Fluticasone propionate is a substrate of cytochrome P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY : Drug Interactions). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

In a placebo-controlled, crossover study in 8 healthy volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg; 5 times the maximum daily intranasal dose) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. Caution should be exercised when FLONASE Nasal Spray is coadministered with ketoconazole and other known potent cytochrome P450 3A4 inhibitors.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 20 times the maximum recommended daily intranasal dose in adults and approximately 10 times the maximum recommended daily intranasal dose in children on a mcg/m[2] basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (approximately 2 times the maximum recommended daily intranasal dose in adults and approximately equivalent to the maximum recommended daily intranasal dose in children on a mcg/m[2] basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the mouse micronucleus test.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 2 times the maximum recommended daily intranasal dose in adults on a mcg/m[2] basis). Prostate weight was significantly reduced at a subcutaneous dose of 50 mcg/kg.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg, respectively (approximately equivalent to and 4 times the maximum recommended daily intranasal dose in adults on a mcg/m[2] basis, respectively) revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of 4 mcg/kg (less than the maximum recommended daily intranasal dose in adults on a mcg/m[2] basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg (approximately 25 times the maximum recommended daily intranasal dose in adults on a mcg/m[2] basis) of fluticasone propionate to the rabbit. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY).

Fluticasone propionate crossed the placenta following oral administration of 100 mcg/kg to rats or 300 mcg/kg to rabbits (approximately 4 and 25 times, respectively, the maximum recommended daily intranasal dose in adults on a mcg/m[2] basis).

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

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Nursing Mothers: It is not known whether fluticasone propionate is excreted in human breast milk. However, other corticosteroids have been detected in human milk. Subcutaneous administration to lactating rats of 10 mcg/kg of tritiated fluticasone propionate (less than the maximum recommended daily intranasal dose in adults on a mcg/m[2] basis) resulted in measurable radioactivity in the milk. Since there are no data from controlled trials on the use of intranasal fluticasone propionate by nursing mothers, caution should be exercised when FLONASE Nasal Spray is administered to a nursing woman.

Pediatric Use: Six hundred fifty (650) patients aged 4 to 11 years and 440 patients aged 12 to 17 years were studied in US clinical trials with fluticasone propionate nasal spray. The safety and effectiveness of FLONASE Nasal Spray in children below 4 years of age have not been established.

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including FLONASE Nasal Spray, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks/benefits of treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, including FLONASE Nasal Spray, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

A 1-year placebo-controlled clinical growth study was conducted in 150 pediatric patients (ages 3 to 9 years) to assess the effect of FLONASE Nasal Spray (single daily dose of 200 mcg, the maximum approved dose) on growth velocity. From the primary population of 56 patients receiving FLONASE Nasal Spray and 52 receiving placebo, the point estimate for growth velocity with FLONASE Nasal Spray was 0.14 cm/year lower than that noted with placebo (95% confidence interval ranging from 0.54 cm/year lower than placebo to 0.27 cm/year higher than placebo). Thus, no statistically significant effect on growth was noted compared to placebo. No evidence of clinically relevant changes in HPA axis function or bone mineral density was observed as assessed by 12-hour urinary cortisol excretion and dual-energy x-ray absorptiometry, respectively.

The potential for FLONASE Nasal Spray to cause growth suppression in susceptible patients or when given at higher doses cannot be ruled out.

Geriatric Use: A limited number of patients 65 years of age and older (n = 129) or 75 years of age and older (n = 11) have been treated with FLONASE Nasal Spray in US and non-US clinical trials. While the number of patients is too small to permit separate analysis of efficacy and safety, the adverse reactions reported in this population were similar to those reported by younger patients.

ADVERSE REACTIONS

In controlled US studies, more than 3,300 patients with seasonal allergic, perennial allergic, or perennial nonallergic rhinitis received treatment with intranasal fluticasone propionate. In general, adverse reactions in clinical studies have been primarily associated with irritation of the nasal mucous membranes, and the adverse reactions were reported with

approximately the same frequency by patients treated with the vehicle itself. The complaints did not usually interfere with treatment. Less than 2% of patients in clinical trials discontinued because of adverse events; this rate was similar for vehicle placebo and active comparators.

Systemic corticosteroid side effects were not reported during controlled clinical studies up to 6 months' duration with FLONASE Nasal Spray. If recommended doses are exceeded, however, or if individuals are particularly sensitive or taking FLONASE Nasal Spray in conjunction with administration of other corticosteroids, symptoms of hypercorticism, e.g., Cushing syndrome, could occur.

The following incidence of common adverse reactions (>3%, where incidence in fluticasone propionate-treated subjects exceeded placebo) is based upon 7 controlled clinical trials in which 536 patients (57 girls and 108 boys aged 4 to 11 years, 137 female and 234 male adolescents and adults) were treated with FLONASE Nasal Spray 200 mcg once daily over 2 to 4 weeks and 2 controlled clinical trials in which 246 patients (119 female and 127 male adolescents and adults) were treated with FLONASE Nasal Spray 200 mcg once daily over 6 months. Also included in the table are adverse events from 2 studies in which 167 children (45 girls and 122 boys aged 4 to 11 years) were treated with FLONASE Nasal Spray 100 mcg once daily for 2 to 4 weeks.

Overall Adverse Experiences With >3% Incidence on Fluticasone Propionate in Controlled Clinical Trials With FLONASE Nasal Spray in Patients >/=4 Years With Seasonal or Perennial Allergic Rhinitis

Adverse Experience	Vehicle Placebo (n = 758) %	FLONASE 100 mcg Once Daily (n = 167) %	FLONASE 200 mcg Once Daily (n = 782) %
Headache	14.6	6.6	16.1
Pharyngitis	7.2	6.0	7.8
Epistaxis	5.4	6.0	6.9
Nasal burning/nasal irritation	2.6	2.4	3.2
Nausea/vomiting	2.0	4.8	2.6
Asthma symptoms	2.9	7.2	3.3
Cough	2.8	3.6	3.8

Other adverse events that occurred in </=3% but >/=1% of patients and that were more common with fluticasone propionate (with uncertain relationship to treatment) included: blood in nasal mucus, runny nose, abdominal pain, diarrhea, fever, flu-like symptoms, aches and pains, dizziness, bronchitis.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during postapproval use of intranasal fluticasone propionate in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to fluticasone propionate or a combination of these factors.

General: Hypersensitivity reactions, including angioedema, skin rash, edema of the face and tongue, pruritus, urticaria, bronchospasm, wheezing, dyspnea, and anaphylaxis/anaphylactoid reactions, which in rare instances were severe.

Ear, Nose, and Throat: Alteration or loss of sense of taste and/or smell and, rarely, nasal septal perforation, nasal ulcer, sore throat, throat irritation and dryness, cough, hoarseness, and voice changes.

Eye: Dryness and irritation, conjunctivitis, blurred vision, glaucoma, increased intraocular pressure, and cataracts.

Cases of growth suppression have been reported for intranasal corticosteroids, including FLONASE (see PRECAUTIONS : Pediatric Use).

OVERDOSAGE

Chronic overdosage may result in signs/symptoms of hypercorticism (see PRECAUTIONS). Intranasal administration of 2 mg (10 times the recommended dose) of fluticasone propionate twice daily for 7 days to healthy human volunteers was well tolerated. Single oral doses up to 16 mg have been studied in human volunteers with no acute toxic effects reported. Repeat oral doses up to 80 mg daily for 10 days in volunteers and repeat oral doses up to 10 mg daily for 14 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups. Acute overdosage with this dosage form is unlikely since 1 bottle of FLONASE Nasal Spray contains approximately 8 mg of fluticasone propionate.

The oral and subcutaneous median lethal doses in mice and rats were >1,000 mg/kg (>20,000 and >41,000 times, respectively, the maximum recommended daily intranasal dose in adults and >10,000 and >20,000 times, respectively, the maximum recommended daily intranasal dose in children on a mg/m[2] basis).

DOSAGE AND ADMINISTRATION

Patients should use FLONASE Nasal Spray at regular intervals for optimal effect.

Adults: The recommended starting dosage in adults is 2 sprays (50 mcg of fluticasone propionate each) in each nostril once daily (total daily dose, 200 mcg). The same dosage divided into 100 mcg given twice daily (e.g., 8 a.m. and 8 p.m.) is also effective. After the first few days, patients may be able to reduce their dosage to 100 mcg (1 spray in each nostril) once daily for maintenance therapy. Some patients (12 years of age and older) with seasonal allergic rhinitis may find as-needed use of 200 mcg once daily effective for symptom control (see Clinical Trials). Greater symptom control may be achieved with scheduled regular use.

Adolescents and Children (4 Years of Age and Older): Patients should be started with 100 mcg (1 spray in each nostril once daily). Patients not adequately responding to 100 mcg may use 200 mcg (2 sprays in each nostril). Once adequate control is achieved, the dosage should be decreased to 100 mcg (1 spray in each nostril) daily.

The maximum total daily dosage should not exceed 2 sprays in each nostril (200 mcg/day). (See Individualization of Dosage and Clinical Trials sections).

FLONASE Nasal Spray is not recommended for children under 4 years of age.

Directions for Use: Illustrated patient's instructions for proper use accompany each package of FLONASE Nasal Spray.

HOW SUPPLIED

FLONASE Nasal Spray 50 mcg is supplied in an amber glass bottle fitted with a white metering atomizing pump, white nasal adapter, and green dust cover in a box of 1 (NDC 0173-0453-01) with patient's instructions for use. Each bottle contains a net fill weight of 16 g and will provide 120 actuations. Each actuation delivers 50 mcg of fluticasone propionate in 100 mg of formulation through the nasal adapter. The correct amount of medication in each spray cannot be assured after 120 sprays even though the bottle is not completely empty. The bottle should be discarded when the labeled number of actuations has been used.

Store between 4 deg. and 30 deg. C (39 deg. and 86 deg. F).

GlaxoSmithKline Research Triangle Park, NC 27709

March 2004/RL-2066

PRODUCT PHOTO(S): NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

The product samples shown here have been supplied by the manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.
See Image

LANGUAGE: ENGLISH

LOAD-DATE: March 9, 2006

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This page was generated by the TARR system on 2006-06-27 20:15:00 ET

Serial Number: 74081658

Registration Number: 1787324

Mark (words only): IMITREX

Standard Character claim: No

Current Status: This registration has been renewed.

Date of Status: 2003-11-24

Filing Date: 1990-07-25

Transformed into a National Application: No

Registration Date: 1993-08-10

Register: Principal

Law Office Assigned: LAW OFFICE 11

If you are the applicant or applicant's attorney and have questions about this file, please contact the Trademark Assistance Center at TrademarkAssistanceCenter@uspto.gov

Current Location: 900 -File Repository (Franconia)

Date In Location: 2003-11-26

LAST APPLICANT(S)/OWNER(S) OF RECORD

1. GLAXO GROUP LIMITED

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United Kingdom
Legal Entity Type: Corporation
State or Country of Incorporation: United Kingdom

GOODS AND/OR SERVICES

International Class: 005
Class Status: Active

pharmaceutical preparations and substances for the prevention, treatment and/or alleviation of diseases of the central nervous system; migraine and other forms of headache which are distributed by prescription only
Basis: 1(a)
First Use Date: 1993-03-17
First Use in Commerce Date: 1993-03-29

ADDITIONAL INFORMATION

(NOT AVAILABLE)

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2003-11-24 - First renewal 10 year

2003-11-24 - Section 8 (10-year) accepted/ Section 9 granted

2003-08-08 - Combined Section 8 (10-year)/Section 9 filed

2003-08-08 - TEAS Section 8 & 9 Received

1999-08-05 - Section 8 (6-year) accepted & Section 15 acknowledged

1999-02-24 - Section 8 (6-year) and Section 15 Filed

1993-08-10 - Registered - Principal Register

1993-06-09 - Allowed for Registration - Principal Register (SOU accepted)

1993-05-28 - Statement of use processing complete

1993-05-28 - Extension 2 granted

1993-04-15 - Amendment to Use filed

1993-04-15 - Extension 2 filed

1992-08-27 - Extension 1 granted

1992-08-13 - Extension 1 filed

1992-08-07 - Extension 1 Denial letter mailed

1992-08-07 - Extension 1 Denial letter

1992-07-27 - Extension 1 filed

1992-05-26 - Notice of allowance - mailed

1991-03-26 - Published for opposition

1991-02-22 - Notice of publication

1990-12-05 - Approved for Pub - Principal Register (Initial exam)

1990-11-27 - Assigned To Examiner

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Serial Number: 74590264

Registration Number: 1946573

Mark

(words only): IMITREX

Standard Character claim: No

Current Status: Section 8 and 15 affidavits have been accepted and acknowledged.

Date of Status: 2002-01-30

Filing Date: 1994-10-25

Transformed into a National Application: No

Registration Date: 1996-01-09

Register: Principal

Law Office Assigned: LAW OFFICE 105

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Current Location: 900 -File Repository (Franconia)

Date In Location: 2002-01-30

LAST APPLICANT(S)/OWNER(S) OF RECORD

1. GLAXO GROUP LIMITED

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State or Country of Incorporation: United Kingdom

GOODS AND/OR SERVICES

International Class: 005
Class Status: Active
pharmaceutical preparations and substances for the prevention, treatment, and/or alleviation of diseases of the central nervous system, gastro-intestinal disorders, migraine and other forms of headache
Basis: 1(a)
First Use Date: 1993-03-00
First Use in Commerce Date: 1993-03-00

ADDITIONAL INFORMATION

Lining and Stippling: The mark is lined for the colors blue and yellow.

Design Search Code(s):
26.09.01 - Squares as carriers or squares as single or multiple line borders
26.11.21 - Rectangles that are completely or partially shaded

Prior Registration Number(s):
1787324

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2002-01-30 - Section 8 (6-year) accepted & Section 15 acknowledged

2001-12-07 - Section 8 (6-year) and Section 15 Filed

1996-01-09 - Registered - Principal Register

1995-10-17 - Published for opposition

1995-09-15 - Notice of publication

1995-03-24 - Approved for Pub - Principal Register (Initial exam)

1995-03-21 - Examiner's amendment mailed

1995-03-13 - Assigned To Examiner

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SMITHKLINE BEECHAM CORPORATION

98 of 201 DOCUMENTS

Physician's Desk Reference for Prescription Drugs

Imitrex Tablets(GlaxoSmithKline)

BODY:

DESCRIPTION

IMITREX Tablets contain sumatriptan (as the succinate), a selective 5-hydroxytryptamine[1] receptor subtype agonist. Sumatriptan succinate is chemically designated as 3-2-(dimethylamino)ethyl-N-methyl-indole-5-methanesulfonamide succinate (1:1).

The empirical formula is C[14] H[21] N[3] O[2] S*C[4] H[6] O[4] , representing a molecular weight of 413.5. Sumatriptan succinate is a white to off-white powder that is readily soluble in water and in saline. Each IMITREX Tablet for oral administration contains 35, 70, or 140 mg of sumatriptan succinate equivalent to 25, 50, or 100 mg of sumatriptan, respectively. Each tablet also contains the inactive ingredients croscarmellose sodium, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, and sodium bicarbonate. Each 100-mg tablet also contains hypromellose, iron oxide, titanium dioxide, and triacetin.

CLINICAL PHARMACOLOGY

Mechanism of Action: Sumatriptan is an agonist for a vascular 5-hydroxytryptamine[1] receptor subtype (probably a member of the 5-HT[1D] family) having only a weak affinity for 5-HT[1A] , 5-HT[5A] , and 5-HT[7] receptors and no significant affinity (as measured using standard radioligand binding assays) or pharmacological activity at 5-HT[2] , 5-HT[3] , or 5-HT[4] receptor subtypes or at alpha[1]-, alpha[2]-, or beta-adrenergic; dopamine[1] ; dopamine[2] ; muscarinic; or benzodiazepine receptors.

The vascular 5-HT[1] receptor subtype that sumatriptan activates is present on cranial arteries in both dog and primate, on the human basilar artery, and in the vasculature of human dura mater and mediates vasoconstriction. This action in humans correlates with the relief of migraine headache. In addition to causing vasoconstriction, experimental data from animal studies show that sumatriptan also activates 5-HT[1] receptors on peripheral terminals of the trigeminal nerve innervating cranial blood vessels. Such an action may also contribute to the antimigrainous effect of sumatriptan in humans.

In the anesthetized dog, sumatriptan selectively reduces the carotid arterial blood flow with little or no effect on arterial blood pressure or total peripheral resistance. In the cat, sumatriptan selectively constricts the carotid arteriovenous anastomoses while having little effect on blood flow or resistance in cerebral or extracerebral tissues.

Pharmacokinetics: The mean maximum concentration following oral dosing with 25 mg is 18 ng/mL (range, 7 to 47 ng/mL) and 51 ng/mL (range, 28 to 100 ng/mL) following oral dosing with 100 mg of sumatriptan. This compares with a C[max] of 5 and 16 ng/mL following dosing with a 5-and 20-mg intranasal dose, respectively. The mean C[max] following a 6-mg subcutaneous injection is 71 ng/mL (range, 49 to 110 ng/mL). The bioavailability is approximately 15%, primarily due to presystemic metabolism and partly due to incomplete absorption. The C[max] is similar during a migraine attack and during a migraine-free period, but the T[max] is slightly later during the attack, approximately 2.5 hours compared to 2.0 hours. When given as a single dose, sumatriptan displays dose proportionality in its extent of absorption (area under the curve AUC) over the dose range of 25 to 200 mg, but the C[max] after 100 mg is approximately 25% less than expected (based on the 25-mg dose).

A food effect study involving administration of IMITREX Tablets 100 mg to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C[max] and AUC were increased by 15% and 12%, respectively, when

administered in the fed state.

Plasma protein binding is low (14% to 21%). The effect of sumatriptan on the protein binding of other drugs has not been evaluated, but would be expected to be minor, given the low rate of protein binding. The apparent volume of distribution is 2.4 L/kg.

The elimination half-life of sumatriptan is approximately 2.5 hours. Radiolabeled[14] C-sumatriptan administered orally is largely renally excreted (about 60%) with about 40% found in the feces. Most of the radiolabeled compound excreted in the urine is the major metabolite, indole acetic acid (IAA), which is inactive, or the IAA glucuronide. Only 3% of the dose can be recovered as unchanged sumatriptan.

In vitro studies with human microsomes suggest that sumatriptan is metabolized by monoamine oxidase (MAO), predominantly the A isoenzyme, and inhibitors of that enzyme may alter sumatriptan pharmacokinetics to increase systemic exposure. No significant effect was seen with an MAO-B inhibitor (see CONTRAINDICATIONS , WARNINGS , and PRECAUTIONS : Drug Interactions).

Special Populations: *Renal Impairment:* The effect of renal impairment on the pharmacokinetics of sumatriptan has not been examined, but little clinical effect would be expected as sumatriptan is largely metabolized to an inactive substance.

Hepatic Impairment: The liver plays an important role in the presystemic clearance of orally administered sumatriptan. Accordingly, the bioavailability of sumatriptan following oral administration may be markedly increased in patients with liver disease. In 1 small study of hepatically impaired patients (N = 8) matched for sex, age, and weight with healthy subjects, the hepatically impaired patients had an approximately 70% increase in AUC and C[max] and a T[max] 40 minutes earlier compared to the healthy subjects (see DOSAGE AND ADMINISTRATION).

Age: The pharmacokinetics of oral sumatriptan in the elderly (mean age, 72 years; 2 males and 4 females) and in patients with migraine (mean age, 38 years; 25 males and 155 females) were similar to that in healthy male subjects (mean age, 30 years) (see PRECAUTIONS : Geriatric Use).

Gender: In a study comparing females to males, no pharmacokinetic differences were observed between genders for AUC, C[max] , T[max] , and half-life.

Race: The systemic clearance and C[max] of sumatriptan were similar in black (N = 34) and Caucasian (N = 38) healthy male subjects.

Drug Interactions: *Monoamine Oxidase Inhibitors:* Treatment with MAO-A inhibitors generally leads to an increase of sumatriptan plasma levels (see CONTRAINDICATIONS and PRECAUTIONS).

Due to gut and hepatic metabolic first-pass effects, the increase of systemic exposure after coadministration of an MAO-A inhibitor with oral sumatriptan is greater than after coadministration of the monoamine oxidase inhibitors (MAOI) with subcutaneous sumatriptan. In a study of 14 healthy females, pretreatment with an MAO-A inhibitor decreased the clearance of subcutaneous sumatriptan. Under the conditions of this experiment, the result was a 2-fold increase in the area under the sumatriptan plasma concentration x time curve (AUC), corresponding to a 40% increase in elimination half-life. This interaction was not evident with an MAO-B inhibitor.

A small study evaluating the effect of pretreatment with an MAO-A inhibitor on the bioavailability from a 25-mg oral sumatriptan tablet resulted in an approximately 7-fold increase in systemic exposure.

Alcohol: Alcohol consumed 30 minutes prior to sumatriptan ingestion had no effect on the pharmacokinetics of sumatriptan.

CLINICAL STUDIES

The efficacy of IMITREX Tablets in the acute treatment of migraine headaches was demonstrated in 3, randomized, double-blind, placebo-controlled studies. Patients enrolled in these 3 studies were predominately female (87%) and Caucasian (97%), with a mean age of 40 years (range, 18 to 65 years). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed up to 4 hours after dosing. Associated symptoms such as nausea, photophobia, and phonophobia were also assessed. Maintenance of response was assessed for up to 24 hours postdose. A second dose of IMITREX Tablets or other medication was allowed 4 to 24 hours after the initial treatment for recurrent headache. Acetaminophen was offered to patients in Studies 2 and 3 beginning at 2 hours after initial treatment if the migraine pain had not improved or worsened. Additional medications were allowed 4 to 24 hours after the initial treatment for recurrent headache or as rescue in all 3 studies. The frequency and time to use of these additional treatments were also determined. In all studies, doses of 25, 50, and 100 mg were compared to placebo in the treatment of migraine attacks. In 1 study, doses of 25, 50, and 100 mg were also compared to each other.

In all 3 trials, the percentage of patients achieving headache response 2 and 4 hours after treatment was significantly greater among patients receiving IMITREX Tablets at all doses compared to those who received placebo. In 1 of the 3 studies, there was a statistically significant greater percentage of patients with headache response at 2 and 4 hours in the 50-or 100-mg group when compared to the 25-mg dose groups. There were no statistically significant differences between the 50-and 100-mg dose groups in any study. The results from the 3 controlled clinical trials are summarized in Table 1.

Comparisons of drug performance based upon results obtained in different clinical trials are never reliable. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment response and the timing of response may be expected to vary considerably from study to study.

Table 1. Percentage of Patients With Headache Response (No or Mild Pain) 2 and 4 Hours Following Treatment

	Placebo		IMITREX Tablets 25 mg		IMITREX Tablets 50 mg		IMITREX Tablets 100 mg	
	2 hr	4 hr	2 hr	4 hr	2 hr	4 hr	2 hr	4 hr
Study 1	27%	38%	52% *	67% *	61% *[**/*]	78% *[**/*]	62% *[**/*]	79% *[**/*]
	(N = 94)		(N = 298)		(N = 296)		(N = 296)	
Study 2	26%	38%	52% *	70% *	50% *	68% *	56% *	71% *
	(N = 65)		(N = 66)		(N = 62)		(N = 66)	
Study 3	17%	19%	52% *	65% *	54% *	72% *	57% *	78% *
	(N = 47)		(N = 48)		(N = 46)		(N = 46)	

*p <0.05 in comparison with placebo.
[**/*] p<0.05 in comparison with 25 mg.

The estimated probability of achieving an initial headache response over the 4 hours following treatment is depicted in Figure 1.

See Image

For patients with migraine-associated nausea, photophobia, and/or phonophobia at baseline, there was a lower incidence of these symptoms at 2 hours (Study 1) and at 4 hours (Studies 1, 2, and 3) following administration of IMITREX Tablets compared to placebo.

As early as 2 hours in Studies 2 and 3 or 4 hours in Study 1, through 24 hours following the initial dose of study

treatment, patients were allowed to use additional treatment for pain relief in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 2.

See Image

There is evidence that doses above 50 mg do not provide a greater effect than 50 mg. There was no evidence to suggest that treatment with sumatriptan was associated with an increase in the severity of recurrent headaches. The efficacy of IMITREX Tablets was unaffected by presence of aura; duration of headache prior to treatment; gender, age, or weight of the patient; relationship to menses; or concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants). There were insufficient data to assess the impact of race on efficacy.

INDICATIONS AND USAGE

IMITREX Tablets are indicated for the acute treatment of migraine attacks with or without aura in adults.

IMITREX Tablets are not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of IMITREX Tablets have not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS

IMITREX Tablets should not be given to patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes. In addition, patients with other significant underlying cardiovascular diseases should not receive IMITREX Tablets. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks. Peripheral vascular disease includes, but is not limited to, ischemic bowel disease (see WARNINGS).

Because IMITREX Tablets may increase blood pressure, they should not be given to patients with uncontrolled hypertension.

Concurrent administration of MAO-A inhibitors or use within 2 weeks of discontinuation of MAO-A inhibitor therapy is contraindicated (see CLINICAL PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug Interactions).

IMITREX Tablets should not be administered to patients with hemiplegic or basilar migraine.

IMITREX Tablets and any ergotamine-containing or ergot-type medication (like dihydroergotamine or methysergide) should not be used within 24 hours of each other, nor should IMITREX and another 5-HT[1] agonist.

IMITREX Tablets are contraindicated in patients with hypersensitivity to sumatriptan or any of their components.

IMITREX Tablets are contraindicated in patients with severe hepatic impairment.

WARNINGS

IMITREX Tablets should only be used where a clear diagnosis of migraine headache has been established.

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events: Sumatriptan should not be given to patients with documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). It is strongly recommended that sumatriptan not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of

CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, sumatriptan should not be administered (see CONTRAINDICATIONS).

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of sumatriptan tablets take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received sumatriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following IMITREX Tablets, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of sumatriptan and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use sumatriptan.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to sumatriptan.

Drug-Associated Cardiac Events and Fatalities: Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of IMITREX(R) (sumatriptan succinate) Injection or IMITREX Tablets. Considering the extent of use of sumatriptan in patients with migraine, the incidence of these events is extremely low.

The fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of CAD, and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug. In many cases, however, where there has been known underlying coronary artery disease, the relationship is uncertain.

Premarketing Experience With Sumatriptan: Of 6,348 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of oral sumatriptan, 2 experienced clinical adverse events shortly after receiving oral sumatriptan that may have reflected coronary vasospasm. Neither of these adverse events was associated with a serious clinical outcome.

Among the more than 1,900 patients with migraine who participated in premarketing controlled clinical trials of subcutaneous sumatriptan, there were 8 patients who sustained clinical events during or shortly after receiving sumatriptan that may have reflected coronary artery vasospasm. Six of these 8 patients had ECG changes consistent with transient ischemia, but without accompanying clinical symptoms or signs. Of these 8 patients, 4 had either findings suggestive of CAD or risk factors predictive of CAD prior to study enrollment.

Among approximately 4,000 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of sumatriptan nasal spray, 1 patient experienced an asymptomatic subendocardial infarction possibly subsequent to a coronary vasospastic event.

Postmarketing Experience With Sumatriptan: Serious cardiovascular events, some resulting in death, have been reported in association with the use of IMITREX Injection or IMITREX Tablets. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by sumatriptan or to reliably assess causation in individual cases. On clinical grounds, the longer the latency between the administration of IMITREX and the onset of the clinical event, the less likely the association is to be causative. Accordingly, interest has focused on events beginning within 1 hour of the administration of IMITREX.

Cardiac events that have been observed to have onset within 1 hour of sumatriptan administration include: coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia and ventricular fibrillation, cardiac arrest, and death.

Some of these events occurred in patients who had no findings of CAD and appear to represent consequences of coronary artery vasospasm. However, among domestic reports of serious cardiac events within 1 hour of sumatriptan administration, almost all of the patients had risk factors predictive of CAD and the presence of significant underlying CAD was established in most cases (see CONTRAINDICATIONS).

Drug-Associated Cerebrovascular Events and Fatalities: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with oral or subcutaneous sumatriptan, and some have resulted in fatalities. The relationship of sumatriptan to these events is uncertain. In a number of cases, it appears possible that the cerebrovascular events were primary, sumatriptan having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. It should also be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., cerebrovascular accident, transient ischemic attack).

Other Vasospasm-Related Events: Sumatriptan may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported. Very rare reports of transient and permanent blindness and significant partial vision loss have been reported with the use of sumatriptan. Visual disorders may also be part of a migraine attack.

Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients with and without a history of hypertension. Sumatriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS). Sumatriptan should be administered with caution to patients with controlled hypertension as transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients.

Concomitant Drug Use: In patients taking MAO-A inhibitors, sumatriptan plasma levels attained after treatment with recommended doses are 7-fold higher following oral administration than those obtained under other conditions. Accordingly, the coadministration of IMITREX Tablets and an MAO-A inhibitor is contraindicated (see CLINICAL PHARMACOLOGY and CONTRAINDICATIONS).

Hypersensitivity: Hypersensitivity (anaphylaxis/anaphylactoid) reactions have occurred on rare occasions in patients receiving sumatriptan. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens (see CONTRAINDICATIONS).

PRECAUTIONS

General: Chest discomfort and jaw or neck tightness have been reported following use of IMITREX Tablets and have also been reported infrequently following administration of IMITREX Nasal Spray. Chest, jaw, or neck tightness is relatively common after administration of IMITREX Injection. Only rarely have these symptoms been associated with ischemic ECG changes. However, because sumatriptan may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following sumatriptan should be evaluated for the presence of CAD or a predisposition to Prinzmetal variant angina before receiving additional doses of sumatriptan, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud syndrome following sumatriptan should be evaluated for atherosclerosis or predisposition to vasospasm (see WARNINGS).

IMITREX should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as impaired hepatic or renal function.

There have been rare reports of seizure following administration of sumatriptan. Sumatriptan should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold.

Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine headache or who experience a headache that is atypical for them. There have been rare reports where patients received sumatriptan for severe headaches that were subsequently shown to have been secondary to an evolving neurologic lesion (see WARNINGS).

For a given attack, if a patient does not respond to the first dose of sumatriptan, the diagnosis of migraine should be reconsidered before administration of a second dose.

Binding to Melanin-Containing Tissues: In rats treated with a single subcutaneous dose (0.5 mg/kg) or oral dose (2 mg/kg) of radiolabeled sumatriptan, the elimination half-life of radioactivity from the eye was 15 and 23 days, respectively, suggesting that sumatriptan and/or its metabolites bind to the melanin of the eye. Because there could be an accumulation in melanin-rich tissues over time, this raises the possibility that sumatriptan could cause toxicity in these tissues after extended use. However, no effects on the retina related to treatment with sumatriptan were noted in any of the oral or subcutaneous toxicity studies. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Corneal Opacities: Sumatriptan causes corneal opacities and defects in the corneal epithelium in dogs; this raises the possibility that these changes may occur in humans. While patients were not systematically evaluated for these changes in clinical trials, and no specific recommendations for monitoring are being offered, prescribers should be aware of the possibility of these changes (see ANIMAL TOXICOLOGY).

Information for Patients: See PATIENT INFORMATION at the end of this labeling for the text of the separate leaflet provided for patients. (The separate patient leaflet is not included in the hospital unit dose pack.)

Laboratory Tests: No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with sumatriptan.

Drug Interactions: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and sumatriptan within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

MAO-A inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure. Therefore, the use of IMITREX Tablets in patients receiving MAO-A inhibitors is contraindicated (see CLINICAL PHARMACOLOGY and CONTRAINDICATIONS).

Selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with sumatriptan. If concomitant treatment with sumatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.

Drug/Laboratory Test Interactions: IMITREX Tablets are not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: *Carcinogenesis:* In carcinogenicity studies, rats and mice were given sumatriptan by oral gavage (rats, 104 weeks) or drinking water (mice, 78 weeks). Average exposures achieved in mice receiving the highest dose (target dose of 160 mg/kg/day) were approximately 40 times the exposure attained in humans after the maximum recommended single oral dose of 100 mg. The highest dose administered to rats (160 mg/kg/day, reduced from 360 mg/kg/day during week 21) was approximately 15 times the maximum recommended

single human oral dose of 100 mg on a mg/m[2] basis. There was no evidence of an increase in tumors in either species related to sumatriptan administration.

Mutagenesis: Sumatriptan was not mutagenic in the presence or absence of metabolic activation when tested in 2 gene mutation assays (the Ames test and the in vitro mammalian Chinese hamster V79/HGPRT assay). In 2 cytogenetics assays (the in vitro human lymphocyte assay and the in vivo rat micronucleus assay) sumatriptan was not associated with clastogenic activity.

Impairment of Fertility: In a study in which male and female rats were dosed daily with oral sumatriptan prior to and throughout the mating period, there was a treatment-related decrease in fertility secondary to a decrease in mating in animals treated with 50 and 500 mg/kg/day. The highest no-effect dose for this finding was 5 mg/kg/day, or approximately one half of the maximum recommended single human oral dose of 100 mg on a mg/m[2] basis. It is not clear whether the problem is associated with treatment of the males or females or both combined. In a similar study by the subcutaneous route there was no evidence of impaired fertility at 60 mg/kg/day, the maximum dose tested, which is equivalent to approximately 6 times the maximum recommended single human oral dose of 100 mg on a mg/m[2] basis.

Pregnancy: Pregnancy Category C. In reproductive toxicity studies in rats and rabbits, oral treatment with sumatriptan was associated with embryolethality, fetal abnormalities, and pup mortality. When administered by the intravenous route to rabbits, sumatriptan has been shown to be embryolethal. There are no adequate and well-controlled studies in pregnant women. Therefore, IMITREX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In assessing this information, the following findings should be considered.

Embryolethality: When given orally or intravenously to pregnant rabbits daily throughout the period of organogenesis, sumatriptan caused embryolethality at doses at or close to those producing maternal toxicity. In the oral studies this dose was 100 mg/kg/day, and in the intravenous studies this dose was 2.0 mg/kg/day. The mechanism of the embryolethality is not known. The highest no-effect dose for embryolethality by the oral route was 50 mg/kg/day, which is approximately 9 times the maximum single recommended human oral dose of 100 mg on a mg/m[2] basis. By the intravenous route, the highest no-effect dose was 0.75 mg/kg/day, or approximately one tenth of the maximum single recommended human oral dose of 100 mg on a mg/m[2] basis.

The intravenous administration of sumatriptan to pregnant rats throughout organogenesis at 12.5 mg/kg/day, the maximum dose tested, did not cause embryolethality. This dose is equivalent to the maximum single recommended human oral dose of 100 mg on a mg/m[2] basis. Additionally, in a study in rats given subcutaneous sumatriptan daily prior to and throughout pregnancy at 60 mg/kg/day, the maximum dose tested, there was no evidence of increased embryo/fetal lethality. This dose is equivalent to approximately 6 times the maximum recommended single human oral dose of 100 mg on a mg/m[2] basis.

Teratogenicity: Oral treatment of pregnant rats with sumatriptan during the period of organogenesis resulted in an increased incidence of blood vessel abnormalities (cervicothoracic and umbilical) at doses of approximately 250 mg/kg/day or higher. The highest no-effect dose was approximately 60 mg/kg/day, which is approximately 6 times the maximum single recommended human oral dose of 100 mg on a mg/m[2] basis. Oral treatment of pregnant rabbits with sumatriptan during the period of organogenesis resulted in an increased incidence of cervicothoracic vascular and skeletal abnormalities. The highest no-effect dose for these effects was 15 mg/kg/day, or approximately 3 times the maximum single recommended human oral dose of 100 mg on a mg/m[2] basis.

A study in which rats were dosed daily with oral sumatriptan prior to and throughout gestation demonstrated embryo/fetal toxicity (decreased body weight, decreased ossification, increased incidence of rib variations) and an increased incidence of a syndrome of malformations (short tail/short body and vertebral disorganization) at 500 mg/kg/day. The highest no-effect dose was 50 mg/kg/day, or approximately 5 times the maximum single recommended human oral dose of 100 mg on a mg/m[2] basis. In a study in rats dosed daily with subcutaneous sumatriptan prior to and throughout pregnancy, at a dose of 60 mg/kg/day, the maximum dose tested, there was no evidence of teratogenicity. This dose is equivalent to approximately 6 times the maximum recommended single human oral dose of 100 mg on a mg/m[2] basis.

Pup Deaths: Oral treatment of pregnant rats with sumatriptan during the period of organogenesis resulted in a decrease in pup survival between birth and postnatal day 4 at doses of approximately 250 mg/kg/day or higher. The highest no-effect dose for this effect was approximately 60 mg/kg/day, or 6 times the maximum single recommended human oral dose of 100 mg on a mg/m[2] basis.

Oral treatment of pregnant rats with sumatriptan from gestational day 17 through postnatal day 21 demonstrated a decrease in pup survival measured at postnatal days 2, 4, and 20 at the dose of 1,000 mg/kg/day. The highest no-effect dose for this finding was 100 mg/kg/day, approximately 10 times the maximum single recommended human oral dose of 100 mg on a mg/m[2] basis. In a similar study in rats by the subcutaneous route there was no increase in pup death at 81 mg/kg/day, the highest dose tested, which is equivalent to 8 times the maximum single recommended human oral dose of 100 mg on a mg/m[2] basis.

Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to IMITREX, GlaxoSmithKline maintains a Sumatriptan Pregnancy Registry. Physicians are encouraged to register patients by calling (800) 336-2176.

Nursing Mothers: Sumatriptan is excreted in human breast milk. Therefore, caution should be exercised when considering the administration of IMITREX Tablets to a nursing woman.

Pediatric Use: Safety and effectiveness of IMITREX Tablets in pediatric patients under 18 years of age have not been established; therefore, IMITREX Tablets are not recommended for use in patients under 18 years of age.

Two controlled clinical trials evaluating sumatriptan nasal spray (5 to 20 mg) in pediatric patients aged 12 to 17 years enrolled a total of 1,248 adolescent migraineurs who treated a single attack. The studies did not establish the efficacy of sumatriptan nasal spray compared to placebo in the treatment of migraine in adolescents. Adverse events observed in these clinical trials were similar in nature to those reported in clinical trials in adults.

Five controlled clinical trials (2 single attack studies, 3 multiple attack studies) evaluating oral sumatriptan (25 to 100 mg) in pediatric patients aged 12 to 17 years enrolled a total of 701 adolescent migraineurs. These studies did not establish the efficacy of oral sumatriptan compared to placebo in the treatment of migraine in adolescents. Adverse events observed in these clinical trials were similar in nature to those reported in clinical trials in adults. The frequency of all adverse events in these patients appeared to be both dose-and age-dependent, with younger patients reporting events more commonly than older adolescents.

Postmarketing experience documents that serious adverse events have occurred in the pediatric population after use of subcutaneous, oral, and/or intranasal sumatriptan. These reports include events similar in nature to those reported rarely in adults, including stroke, visual loss, and death. A myocardial infarction has been reported in a 14-year-old male following the use of oral sumatriptan; clinical signs occurred within 1 day of drug administration. Since clinical data to determine the frequency of serious adverse events in pediatric patients who might receive injectable, oral, or intranasal sumatriptan are not presently available, the use of sumatriptan in patients aged younger than 18 years is not recommended.

Geriatric Use: The use of sumatriptan in elderly patients is not recommended because elderly patients are more likely to have decreased hepatic function, they are at higher risk for CAD, and blood pressure increases may be more pronounced in the elderly (see WARNINGS).

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following the use of IMITREX Injection or Tablets. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS , WARNINGS, and PRECAUTIONS).

Significant hypertensive episodes, including hypertensive crises, have been reported on rare occasions in patients with or without a history of hypertension (see WARNINGS).

Incidence in Controlled Clinical Trials: Table 2 lists adverse events that occurred in placebo-controlled clinical trials in patients who took at least 1 dose of study drug. Only events that occurred at a frequency of 2% or more in any group treated with IMITREX Tablets and were more frequent in that group than in the placebo group are included in Table 2. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

Table 2. Treatment-Emergent Adverse Events Reported by at Least 2% of Patients in Controlled Migraine Trials *

Adverse Event Type	Percent of Patients Reporting			
	Placebo (N = 309)	IMITREX 25 mg (N = 417)	IMITREX 50 mg (N = 771)	IMITREX 100 mg (N = 437)
Atypical sensations	4%	5%	6%	6%
Paresthesia (all types)	2%	3%	5%	3%
Sensation warm/cold	2%	3%	2%	3%
Pain and other pressure sensations	4%	6%	6%	8%
Chest - pain/tightness / pressure and/or heaviness	1%	1%	2%	2%
Neck/throat /jaw - pain/ tightness /pressure	<1%	<1%	2%	3%
Pain - location specified	1%	2%	1%	1%
Other - pressure/tightness/ heaviness	2%	1%	1%	3%
Neurological				
Vertigo	<1%	<1%	<1%	2%
Other				
Malaise/fatigue	<1%	2%	2%	3%

*Events that occurred at a frequency of 2% or more in the group treated with IMITREX Tablets and that occurred more frequently in that group than the placebo group.

Other events that occurred in more than 1% of patients receiving IMITREX Tablets and at least as often on placebo included nausea and/or vomiting, migraine, headache, hyposalivation, dizziness, and drowsiness/sleepiness.

IMITREX Tablets are generally well tolerated. Across all doses, most adverse reactions were mild and transient and did not lead to long-lasting effects. The incidence of adverse events in controlled clinical trials was not affected by gender or age of the patients. There were insufficient data to assess the impact of race on the incidence of adverse events.

Other Events Observed in Association With the Administration of IMITREX Tablets: In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open and uncontrolled studies, the role of IMITREX Tablets in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used IMITREX Tablets (25, 50, or 100 mg) and reported an event divided by the total number of patients (N = 6,348) exposed to IMITREX Tablets. All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients, infrequent adverse events are those occurring in 1/100 to 1/1,000 patients, and rare adverse events are those occurring in fewer than 1/1,000 patients.

Atypical Sensations: Frequent were burning sensation and numbness. Infrequent was tight feeling in head. Rare were dysesthesia.

Cardiovascular: Frequent were palpitations, syncope, decreased blood pressure, and increased blood pressure. Infrequent were arrhythmia, changes in ECG, hypertension, hypotension, pallor, pulsating sensations, and tachycardia. Rare were angina, atherosclerosis, bradycardia, cerebral ischemia, cerebrovascular lesion, heart block, peripheral cyanosis, thrombosis, transient myocardial ischemia, and vasodilation.

Ear, Nose, and Throat: Frequent were sinusitis, tinnitus; allergic rhinitis; upper respiratory inflammation; ear, nose, and throat hemorrhage; external otitis; hearing loss; nasal inflammation; and sensitivity to noise. Infrequent were hearing disturbances and otalgia. Rare was feeling of fullness in the ear(s).

Endocrine and Metabolic: Infrequent was thirst. Rare were elevated thyrotropin stimulating hormone (TSH) levels; galactorrhea; hyperglycemia; hypoglycemia; hypothyroidism; polydipsia; weight gain; weight loss; endocrine cysts, lumps, and masses; and fluid disturbances.

Eye: Rare were disorders of sclera, mydriasis, blindness and low vision, visual disturbances, eye edema and swelling, eye irritation and itching, accommodation disorders, external ocular muscle disorders, eye hemorrhage, eye pain, and keratitis and conjunctivitis.

Gastrointestinal: Frequent were diarrhea and gastric symptoms. Infrequent were constipation, dysphagia, and gastroesophageal reflux. Rare were gastrointestinal bleeding, hematemesis, melena, peptic ulcer, gastrointestinal pain, dyspeptic symptoms, dental pain, feelings of gastrointestinal pressure, gastroesophageal reflux, gastritis, gastroenteritis, hypersalivation, abdominal distention, oral itching and irritation, salivary gland swelling, and swallowing disorders.

Hematological Disorders: Rare was anemia.

Musculoskeletal: Frequent was myalgia. Infrequent was muscle cramps. Rare were tetany; muscle atrophy, weakness, and tiredness; arthralgia and articular rheumatitis; acquired musculoskeletal deformity; muscle stiffness, tightness, and rigidity; and musculoskeletal inflammation.

Neurological: Frequent were phonophobia and photophobia. Infrequent were confusion, depression, difficulty

concentrating, disturbance of smell, dysarthria, euphoria, facial pain, heat sensitivity, incoordination, lacrimation, monoplegia, sleep disturbance, shivering, syncope, and tremor. Rare were aggressiveness, apathy, bradylogia, cluster headache, convulsions, decreased appetite, drug abuse, dystonic reaction, facial paralysis, hallucinations, hunger, hyperesthesia, hysteria, increased alertness, memory disturbance, neuralgia, paralysis, personality change, phobia, radiculopathy, rigidity, suicide, twitching, agitation, anxiety, depressive disorders, detachment, motor dysfunction, neurotic disorders, psychomotor disorders, taste disturbances, and raised intracranial pressure.

Respiratory: Frequent was dyspnea. Infrequent was asthma. Rare were hiccoughs, breathing disorders, cough, and bronchitis.

Skin: Frequent was sweating. Infrequent were erythema, pruritus, rash, and skin tenderness. Rare were dry/scaly skin, tightness of skin, wrinkling of skin, eczema, seborrheic dermatitis, and skin nodules.

Breasts: Infrequent was tenderness. Rare were nipple discharge; breast swelling; cysts, lumps, and masses of breasts; and primary malignant breast neoplasm.

Urogenital: Infrequent were dysmenorrhea, increased urination, and intermenstrual bleeding. Rare were abortion and hematuria, urinary frequency, bladder inflammation, micturition disorders, urethritis, urinary infections, menstruation symptoms, abnormal menstrual cycle, inflammation of fallopian tubes, and menstrual cycle symptoms.

Miscellaneous: Frequent was hypersensitivity. Infrequent were fever, fluid retention, and overdose. Rare were edema, hematoma, lymphadenopathy, speech disturbance, voice disturbances, contusions.

Other Events Observed in the Clinical Development ofIMITREX: The following adverse events occurred in clinical trials with IMITREX Injection and IMITREX Nasal Spray. Because the reports include events observed in open and uncontrolled studies, the role of IMITREX in their causation cannot be reliably determined. All reported events are included except those already listed, those too general to be informative, and those not reasonably associated with the use of the drug.

Atypical Sensations: Feeling strange, prickling sensation, tingling, and hot sensation.

Cardiovascular: Abdominal aortic aneurysm, abnormal pulse, flushing, phlebitis, Raynaud syndrome, and various transient ECG changes (nonspecific ST or T wave changes, prolongation of PR or QTc intervals, sinus arrhythmia, nonsustained ventricular premature beats, isolated junctional ectopic beats, atrial ectopic beats, delayed activation of the right ventricle).

Chest Symptoms: Chest discomfort.

Endocrine and Metabolic: Dehydration.

Ear, Nose, and Throat: Disorder/discomfort nasal cavity and sinuses, ear infection, Meniere disease, and throat discomfort.

Eye: Vision alterations.

Gastrointestinal: Abdominal discomfort, colitis, disturbance of liver function tests, flatulence/eructation, gallstones, intestinal obstruction, pancreatitis, and retching.

Injection Site Reaction

Miscellaneous: Difficulty in walking, hypersensitivity to various agents, jaw discomfort, miscellaneous laboratory abnormalities, "serotonin agonist effect," swelling of the extremities, and swelling of the face.

Mouth and Teeth: Disorder of mouth and tongue (e.g., burning of tongue, numbness of tongue, dry mouth).

Musculoskeletal: Arthritis, backache, intervertebral disc disorder, neck pain/stiffness, need to flex calf muscles, and various joint disturbances (pain, stiffness, swelling, ache).

Neurological: Bad/unusual taste, chills, diplegia, disturbance of emotions, sedation, globus hystericus, intoxication, myoclonia, neoplasm of pituitary, relaxation, sensation of lightness, simultaneous hot and cold sensations, stinging sensations, stress, tickling sensations, transient hemiplegia, and yawning.

Respiratory: Influenza and diseases of the lower respiratory tract and lower respiratory tract infection.

Skin: Skin eruption, herpes, and peeling of the skin.

Urogenital: Disorder of breasts, endometriosis, and renal calculus.

Postmarketing Experience (Reports for Subcutaneous or Oral Sumatriptan): The following section enumerates potentially important adverse events that have occurred in clinical practice and that have been reported spontaneously to various surveillance systems. The events enumerated represent reports arising from both domestic and nondomestic use of oral or subcutaneous dosage forms of sumatriptan. The events enumerated include all except those already listed in the ADVERSE REACTIONS section above or those too general to be informative. Because the reports cite events reported spontaneously from worldwide postmarketing experience, frequency of events and the role of sumatriptan in their causation cannot be reliably determined. It is assumed, however, that systemic reactions following sumatriptan use are likely to be similar regardless of route of administration.

Blood: Hemolytic anemia, pancytopenia, thrombocytopenia.

Cardiovascular: Atrial fibrillation, cardiomyopathy, colonic ischemia (see WARNINGS), Prinzmetal variant angina, pulmonary embolism, shock, thrombophlebitis.

Ear, Nose, and Throat: Deafness.

Eye: Ischemic optic neuropathy, retinal artery occlusion, retinal vein thrombosis, loss of vision.

Gastrointestinal: Ischemic colitis with rectal bleeding (see WARNINGS), xerostomia.

Hepatic: Elevated liver function tests.

Neurological: Central nervous system vasculitis, cerebrovascular accident, dysphasia, subarachnoid hemorrhage.

Non-Site Specific: Angioneurotic edema, cyanosis, death (see WARNINGS), temporal arteritis.

Psychiatry: Panic disorder.

Respiratory: Bronchospasm in patients with and without a history of asthma.

Skin: Exacerbation of sunburn, hypersensitivity reactions (allergic vasculitis, erythema, pruritus, rash, shortness of breath, urticaria; in addition, severe anaphylaxis/anaphylactoid reactions have been reported see WARNINGS), photosensitivity.

Urogenital: Acute renal failure.

DRUG ABUSE AND DEPENDENCE

One clinical study with IMITREX(R) (sumatriptan succinate) Injection enrolling 12 patients with a history of substance abuse failed to induce subjective behavior and/or physiologic response ordinarily associated with drugs that have an

established potential for abuse.

OVERDOSAGE

Patients (N = 670) have received single oral doses of 140 to 300 mg without significant adverse effects. Volunteers (N = 174) have received single oral doses of 140 to 400 mg without serious adverse events.

Overdose in animals has been fatal and has been heralded by convulsions, tremor, paralysis, inactivity, ptosis, erythema of the extremities, abnormal respiration, cyanosis, ataxia, mydriasis, salivation, and lacrimation. The elimination half-life of sumatriptan is approximately 2.5 hours (see CLINICAL PHARMACOLOGY), and therefore monitoring of patients after overdose with IMITREX Tablets should continue for at least 12 hours or while symptoms or signs persist.

It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of sumatriptan.

DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 25, 50, or 100 mg of IMITREX Tablets were effective for the acute treatment of migraine in adults. There is evidence that doses of 50 and 100 mg may provide a greater effect than 25 mg (see CLINICAL TRIALS). There is also evidence that doses of 100 mg do not provide a greater effect than 50 mg. Individuals may vary in response to doses of IMITREX Tablets. The choice of dose should therefore be made on an individual basis, weighing the possible benefit of a higher dose with the potential for a greater risk of adverse events.

If the headache returns or the patient has a partial response to the initial dose, the dose may be repeated after 2 hours, not to exceed a total daily dose of 200 mg. If a headache returns following an initial treatment with IMITREX Injection, additional single IMITREX Tablets (up to 100 mg/day) may be given with an interval of at least 2 hours between tablet doses. The safety of treating an average of more than 4 headaches in a 30-day period has not been established.

Because of the potential of MAO-A inhibitors to cause unpredictable elevations in the bioavailability of oral sumatriptan, their combined use is contraindicated (see CONTRAINDICATIONS).

Hepatic disease/functional impairment may also cause unpredictable elevations in the bioavailability of orally administered sumatriptan. Consequently, if treatment is deemed advisable in the presence of liver disease, the maximum single dose should in general not exceed 50 mg (see CLINICAL PHARMACOLOGY for the basis of this recommendation).

HOW SUPPLIED

IMITREX Tablets, 25, 50, and 100 mg of sumatriptan (base) as the succinate.

IMITREX Tablets, 25 mg are white, triangular-shaped, film-coated tablets debossed with "I" on one side and "25" on the other in blister packs of 9 tablets (NDC 0173-0735-00).

IMITREX Tablets, 50 mg are white, triangular-shaped, film-coated tablets debossed with "IMITREX 50" on one side and a chevron shape (caret) on the other in blister packs of 9 tablets (NDC 0173-0736-01) and hospital unit dose packs of 18 tablets (NDC 0173-0736-02).

IMITREX Tablets, 100 mg, are pink, triangular-shaped, film-coated tablets debossed with "IMITREX 100" on one side and a chevron shape (caret) on the other in blister packs of 9 tablets (NDC 0173-0737-01) and hospital unit dose packs of 18 tablets (NDC 0173-0737-02).

Store between 36 deg. and 86 deg. F (2 deg. and 30 deg. C).

PRODUCT PHOTO(S): NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

The product samples shown here have been supplied by the manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.
See Image

ANIMAL TOXICOLOGY

Corneal Opacities: Dogs receiving oral sumatriptan developed corneal opacities and defects in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg/day, and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a 60-week study. Earlier examinations for these toxicities were not conducted and no-effect doses were not established; however, the relative exposure at the lowest dose tested was approximately 5 times the human exposure after a 100-mg oral dose. There is evidence of alterations in corneal appearance on the first day of intranasal dosing to dogs. Changes were noted at the lowest dose tested, which was approximately one half the maximum single human oral dose of 100 mg on a mg/m[2] basis.

PATIENT INFORMATION

The following wording is contained in a separate leaflet provided for patients.

Information for the Patient

IMITREX(R) (sumatriptan succinate) Tablets

Please read this leaflet carefully before you take IMITREX Tablets. This provides a summary of the information available on your medicine. Please do not throw away this leaflet until you have finished your medicine. You may need to read this leaflet again. This leaflet does not contain all the information on IMITREX Tablets. For further information or advice, ask your doctor or pharmacist.

Information About Your Medicine:

The name of your medicine is IMITREX (sumatriptan succinate) Tablets. It can be obtained only by prescription from your doctor. The decision to use IMITREX Tablets is one that you and your doctor should make jointly, taking into account your individual preferences and medical circumstances. If you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal or a male over 40 years of age), you should tell your doctor, who should evaluate you for heart disease in order to determine if IMITREX is appropriate for you. Although the vast majority of those who have taken IMITREX have not experienced any significant side effects, some individuals have experienced serious heart problems and, rarely, considering the extensiveness of IMITREX use worldwide, deaths have been reported. In all but a few instances, however, serious problems occurred in people with known heart disease and it was not clear whether IMITREX was a contributory factor in these deaths.

The Purpose of Your Medicine:
IMITREX Tablets are intended to relieve your migraine, but not to prevent or reduce the number of attacks you experience. Use IMITREX Tablets only to treat an actual migraine attack.*Important Questions to Consider Before Taking IMITREX Tablets:*
If the answer to any of the following questions is YES or if you do not know the answer, then please discuss it with your doctor before you use IMITREX Tablets.
Are you pregnant? Do you think you might be pregnant? Are you trying to become pregnant? Are you using inadequate contraception? Are you breastfeeding?Do you have any chest pain, heart disease, shortness of breath, or irregular heartbeats? Have you had a heart attack?Do you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal or a

male over 40 years of age)?Have you had a stroke, transient ischemic attacks (TIAs), or Raynaud syndrome?Do you have high blood pressure?Have you ever had to stop taking this or any other medicine because of an allergy or other problems?Are you taking any other migraine medicines, including other 5-HT[1] agonists or any other medicines containing ergotamine, dihydroergotamine, or methysergide?Are you taking any medicine for depression (monoamine oxidase inhibitors or selective serotonin reuptake inhibitors SSRIs)?Have you had, or do you have, any disease of the liver or kidney?Have you had, or do you have, epilepsy or seizures?Is this headache different from your usual migraine attacks?

Remember, if you answered YES to any of the above questions, then discuss it with your doctor.*The Use of IMITREX Tablets During Pregnancy:*

Do not use IMITREX Tablets if you are pregnant, think you might be pregnant, are trying to become pregnant, or are not using adequate contraception, unless you have discussed this with your doctor.*How to Use IMITREX Tablets:*

For adults, the usual dose is a single tablet swallowed whole with water or other fluids. Do not split tablets.

A second tablet may be taken if your symptoms of migraine come back or if you have a partial response to the initial dose, but not sooner than 2 hours following the first tablet. For a given attack, if you have no response to the first tablet, do not take a second tablet without first consulting with your doctor. Do not take more than a total of 200 mg of IMITREX Tablets in any 24-hour period. The safety of treating an average of more than 4 headaches in a 30-day period has not been established.*Side Effects to Watch for:* Some patients experience pain or tightness in the chest or throat when using IMITREX Tablets. If this happens to you, then discuss it with your doctor before using any more IMITREX Tablets. If the chest pain is severe or does not go away, call your doctor immediately.If you have sudden and/or severe abdominal pain following IMITREX Tablets, call your doctor immediately.Shortness of breath; wheeziness; heart throbbing; swelling of eyelids, face, or lips; or a skin rash, skin lumps, or hives happens rarely. If it happens to you, then tell your doctor immediately. Do not take any more IMITREX Tablets unless your doctor tells you to do so.Some people may have feelings of tingling, heat, flushing (redness of face lasting a short time), heaviness or pressure after treatment with IMITREX Tablets. A few people may feel drowsy, dizzy, tired, or sick. Tell your doctor of these symptoms at your next visit.If you feel unwell in any other way or have any symptoms that you do not understand, you should contact your doctor immediately.*What to Do if an Overdose is Taken:*

If you have taken more medicine than you have been told, contact either your doctor, hospital emergency department, or nearest poison control center immediately.*Storing Your Medicine:*

Keep your medicine in a safe place where children cannot reach it. It may be harmful to children. Do not remove tablets from the packaging until you are ready to use them. Do not store the tablets in any other container.

Store your medicine away from heat and light. Do not store at temperatures above 86 deg. F (30 deg. C), or below 36 deg. F (2 deg. C).

If your medicine has expired (the expiration date is printed on the treatment pack), throw it away as instructed. If your doctor decides to stop your treatment, do not keep any leftover medicine unless your doctor tells you to. Throw away your medicine as instructed.

GlaxoSmithKline, Research Triangle Park, NC 27709

December 2004/RL-2157

LANGUAGE: ENGLISH

LOAD-DATE: March 9, 2006

Thank you for your request. Here are the latest results from the TARR web server.

This page was generated by the TARR system on 2006-06-27 20:20:33 ET

Serial Number: 74184442 Assignment Information

Registration Number: 1821952 Assignment Information

Mark (words only): PAXIL

Standard Character claim: No

Current Status: This registration has been renewed.

Date of Status: 2004-04-10

Filing Date: 1991-07-12

Transformed into a National Application: No

Registration Date: 1994-02-15

Register: Principal

Law Office Assigned: LAW OFFICE 11

If you are the applicant or applicant's attorney and have questions about this file, please contact the Trademark Assistance Center at TrademarkAssistanceCenter@uspto.gov

Current Location: 900 -File Repository (Franconia)

Date In Location: 2004-04-15

LAST APPLICANT(S)/OWNER(S) OF RECORD

1. SMITHKLINE BEECHAM CORPORATION

Address:
SMITHKLINE BEECHAM CORPORATION
(FP2220) One Franklin Plaza, P.O. Box 7929
Philadelphia, PA 19101
United States
Legal Entity Type: Corporation
State or Country of Incorporation: Pennsylvania

GOODS AND/OR SERVICES

International Class: 005
Class Status: Active

pharmaceuticals; namely, antidepressants
Basis: 1(a)
First Use Date: 1993-02-00
First Use in Commerce Date: 1993-02-00

ADDITIONAL INFORMATION

(NOT AVAILABLE)

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2004-04-10 - First renewal 10 year

2004-04-10 - Section 8 (10-year) accepted/ Section 9 granted

2004-02-17 - Combined Section 8 (10-year)/Section 9 filed

2004-02-17 - TEAS Section 8 & 9 Received

2000-05-12 - Section 8 (6-year) accepted & Section 15 acknowledged

2000-02-03 - Section 8 (6-year) and Section 15 Filed

1994-02-15 - Registered - Principal Register

1993-12-09 - Allowed for Registration - Principal Register (SOU accepted)

1993-11-22 - Statement of use processing complete

1993-11-22 - Extension 1 granted

1993-08-24 - Amendment to Use filed

1993-08-24 - Extension 1 filed

1993-04-13 - Notice of allowance - mailed

1992-04-07 - Published for opposition

1992-03-06 - Notice of publication

1991-10-28 - Approved for Pub - Principal Register (Initial exam)

CORRESPONDENCE INFORMATION

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Teresa M. Hechmer (Attorney of record)

TERESA M. HECHMER
SMITHKLINE BEECHAM CORPORATION
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Thank you for your request. Here are the latest results from the TARR web server.

This page was generated by the TARR system on 2006-06-27 20:21:07 ET

Serial Number: 76429099

Registration Number: 2785710

Mark

(words only): PAXILCR

Standard Character claim: No

Current Status: Registered.

Date of Status: 2003-11-25

Filing Date: 2002-07-10

Transformed into a National Application: No

Registration Date: 2003-11-25

Register: Principal

Law Office Assigned: LAW OFFICE 111

If you are the applicant or applicant's attorney and have questions about this file, please contact the Trademark Assistance Center at TrademarkAssistanceCenter@uspto.gov

Current Location: 900 -File Repository (Franconia)

Date In Location: 2004-01-21

LAST APPLICANT(S)/OWNER(S) OF RECORD

1. SmithKline Beecham Corporation

Address:
SmithKline Beecham Corporation
One Franklin Plaza

Philadelphia, PA 19101
United States
Legal Entity Type: Corporation
State or Country of Incorporation: Pennsylvania
Phone Number: 610-270-4479
Fax Number: 610-270-4440

GOODS AND/OR SERVICES

International Class: 016
Class Status: Active
PRINTED MATERIALS, NAMELY, PAMPHLETS AND BOOKLETS RELATING TO THE TREATMENT OF DEPRESSION
Basis: 1(a)
First Use Date: 2002-04-00
First Use in Commerce Date: 2002-04-00

ADDITIONAL INFORMATION

Design Search Code(s):
02.01.33 - Men, grotesque; Monsters (not robots); Snowmen; Stick figures
04.07.03 - Geometric figures or combinations of geometric figures representing a person; Geometric figures representing a person; Geometric shapes forming a person; Person formed by geometric shapes
26.01.02 - Circles, plain single line; Plain single line circles
26.01.21 - Circles that are totally or partially shaded.
26.17.02 - Bands, wavy; Bars, wavy; Lines, wavy; Wavy line(s), band(s) or bar(s)
26.17.05 - Bands, horizontal; Bars, horizontal; Horizontal line(s), band(s) or bar(s); Lines, horizontal
26.17.13 - Letters or words underlined and/or overlined by one or more strokes or lines; Overlined words or letters; Underlined words or letters

Prior Registration Number(s):
1821952
2144154
2166898
2219908
2219909
2220037
2220043
2425515

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2003-11-25 - Registered - Principal Register

2003-09-02 - Published for opposition

2003-08-13 - Notice of publication

2003-07-03 - Approved for Pub - Principal Register (Initial exam)

2003-06-05 - Communication received from applicant

2003-06-05 - TEAS Response to Office Action Received

2002-12-18 - Non-final action mailed

2002-12-17 - Assigned To Examiner

2002-12-10 - Assigned To Examiner

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Fax Number: 610-270-4440

136 of 201 DOCUMENTS

Physician's Desk Reference for Prescription Drugs

Paxil CR Controlled-Release Tablets(GlaxoSmithKline)

BODY:

Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of PAXIL CR or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PAXIL CR is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS — Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION PAXIL CR (paroxetine hydrochloride) is an orally administered psychotropic drug with a chemical structure unrelated to other selective serotonin reuptake inhibitors or to tricyclic, tetracyclic, or other available antidepressant or antipanic agents. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4 *R*-(4'-fluorophenyl)-3 *S* - (3',4'-methylenedioxyphenoxy) methyl piperidine hydrochloride hemihydrate and has the empirical formula of C[19] H[20] FNO[3] *HCl*1/2H[2] O. The molecular weight is 374.8 (329.4 as free base).

Paroxetine hydrochloride is an odorless, off-white powder, having a melting point range of 120 deg. to 138 deg. C and a solubility of 5.4 mg/mL in water. Each enteric, film-coated, controlled-release tablet contains paroxetine hydrochloride equivalent to paroxetine as follows: 12.5 mg-yellow, 25 mg-pink, 37.5 mg-blue. One layer of the tablet consists of a degradable barrier layer and the other contains the active material in a hydrophilic matrix.

Inactive ingredients consist of hypromellose, polyvinylpyrrolidone, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, glyceryl behenate, methacrylic acid copolymer type C, sodium lauryl sulfate, polysorbate 80, talc, triethyl citrate, and 1 or more of the following colorants: Yellow ferric oxide, red ferric oxide, D&C Red No. 30, D&C Yellow No. 6, D&C Yellow No. 10, FD&C Blue No. 2.

CLINICAL PHARMACOLOGY

Pharmacodynamics: The efficacy of paroxetine in the treatment of major depressive disorder, panic disorder, social anxiety disorder, and premenstrual dysphoric disorder (PMDD) is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. In vitro studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. In vitro radioligand binding studies indicate that paroxetine has little affinity for muscarinic, alpha[1]-, alpha[2]-, beta-adrenergic-, dopamine (D[2])-, 5-HT[1]-, 5-HT[2]-, and histamine (H[1])-receptors; antagonism

of muscarinic, histaminergic, and alpha[1]-adrenergic receptors has been associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs.

Because the relative potencies of paroxetine's major metabolites are at most 1/50 of the parent compound, they are essentially inactive.

Pharmacokinetics: Tablets of PAXIL CR contain a degradable polymeric matrix (GEOMATRIX(TM)) designed to control the dissolution rate of paroxetine over a period of approximately 4 to 5 hours. In addition to controlling the rate of drug release in vivo, an enteric coat delays the start of drug release until tablets of PAXIL CR have left the stomach.

Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male and female subjects (n = 23) received single oral doses of PAXIL CR at 4 dosage strengths (12.5 mg, 25 mg, 37.5 mg, and 50 mg), paroxetine C[max] and AUC[0-inf] increased disproportionately with dose (as seen also with immediate-release formulations). Mean C[max] and AUC[0-inf] values at these doses were 2.0, 5.5, 9.0, and 12.5 ng/mL, and 121, 261, 338, and 540 ng*hr./mL, respectively. T[max] was observed typically between 6 and 10 hours post-dose, reflecting a reduction in absorption rate compared with immediate-release formulations. The mean elimination half-life of paroxetine was 15 to 20 hours throughout this range of single doses of PAXIL CR. The bioavailability of 25 mg PAXIL CR is not affected by food.

During repeated administration of PAXIL CR (25 mg once daily), steady state was reached within 2 weeks (i.e., comparable to immediate-release formulations). In a repeat-dose study in which normal male and female subjects (n = 23) received PAXIL CR (25 mg daily), mean steady state C[max] , C[min] , and AUC[0-24] values were 30 ng/mL, 20 ng/mL, and 550 ng*hr./mL, respectively.

Based on studies using immediate-release formulations, steady-state drug exposure based on AUC[0-24] was several-fold greater than would have been predicted from single-dose data. The excess accumulation is a consequence of the fact that 1 of the enzymes that metabolizes paroxetine is readily saturable.

In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of the immediate-release formulation of 20 mg to 40 mg daily for the elderly and 20 mg to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to C[min] values after 20 mg daily, values after 40 mg daily were only about 2 to 3 times greater than doubled.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by cytochrome P[450] IID[6] . Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions (see PRECAUTIONS).

Approximately 64% of a 30-mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period.

Distribution: Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma.

Protein Binding: Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/mL. Paroxetine does not alter the in vitro protein binding of phenytoin or warfarin.

Renal and Liver Disease: Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic impairment. The mean plasma concentrations in patients with creatinine clearance below 30 mL/min. was approximately 4 times greater than seen in normal volunteers. Patients with creatinine clearance of 30 to 60 mL/min. and patients

with hepatic functional impairment had about a 2-fold increase in plasma concentrations (AUC, C[max]).

The initial dosage should therefore be reduced in patients with severe renal or hepatic impairment, and upward titration, if necessary, should be at increased intervals (see DOSAGE AND ADMINISTRATION).

Elderly Patients: In a multiple-dose study in the elderly at daily doses of 20, 30, and 40 mg of the immediate-release formulation, C[min] concentrations were about 70% to 80% greater than the respective C[min] concentrations in non-elderly subjects. Therefore the initial dosage in the elderly should be reduced (see DOSAGE AND ADMINISTRATION).

Clinical Trials

Major Depressive Disorder: The efficacy of PAXIL CR controlled-release tablets as a treatment for major depressive disorder has been established in two 12-week, flexible-dose, placebo-controlled studies of patients with DSM-IV Major Depressive Disorder. One study included patients in the age range 18 to 65 years, and a second study included elderly patients, ranging in age from 60 to 88. In both studies, PAXIL CR was shown to be significantly more effective than placebo in treating major depressive disorder as measured by the following: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI)-Severity of Illness score.

A study of outpatients with major depressive disorder who had responded to immediate-release paroxetine tablets (HDRS total score <8) during an initial 8-week open-treatment phase and were then randomized to continuation on immediate-release paroxetine tablets or placebo for 1 year demonstrated a significantly lower relapse rate for patients taking immediate-release paroxetine tablets (15%) compared to those on placebo (39%). Effectiveness was similar for male and female patients.

Panic Disorder: The effectiveness of PAXIL CR in the treatment of panic disorder was evaluated in three 10-week, multicenter, flexible-dose studies (Studies 1, 2, and 3) comparing paroxetine controlled-release (12.5 to 75 mg daily) to placebo in adult outpatients who had panic disorder (DSM-IV), with or without agoraphobia. These trials were assessed on the basis of their outcomes on 3 variables: (1) the proportions of patients free of full panic attacks at endpoint; (2) change from baseline to endpoint in the median number of full panic attacks; and (3) change from baseline to endpoint in the median Clinical Global Impression Severity score. For Studies 1 and 2, PAXIL CR was consistently superior to placebo on 2 of these 3 variables. Study 3 failed to consistently demonstrate a significant difference between PAXIL CR and placebo on any of these variables.

For all 3 studies, the mean dose of PAXIL CR for completers at endpoint was approximately 50 mg/day. Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

Long-term maintenance effects of the immediate-release formulation of paroxetine in panic disorder were demonstrated in an extension study. Patients who were responders during a 10-week double-blind phase with immediate-release paroxetine and during a 3-month double-blind extension phase were randomized to either immediate-release paroxetine or placebo in a 3-month double-blind relapse prevention phase. Patients randomized to paroxetine were significantly less likely to relapse than comparably treated patients who were randomized to placebo.

Social Anxiety Disorder: The efficacy of PAXIL CR as a treatment for social anxiety disorder has been established, in part, on the basis of extrapolation from the established effectiveness of the immediate-release formulation of paroxetine. In addition, the effectiveness of PAXIL CR in the treatment of social anxiety disorder was demonstrated in a 12-week, multicenter, double-blind, flexible-dose, placebo-controlled study of adult outpatients with a primary diagnosis of social anxiety disorder (DSM-IV). In the study, the effectiveness of PAXIL CR (12.5 to 37.5 mg daily) compared to placebo was evaluated on the basis of (1) change from baseline in the Liebowitz Social Anxiety Scale (LSAS) total score and (2) the proportion of responders who scored 1 or 2 (very much improved or much improved) on the Clinical Global Impression (CGI) Global Improvement score.

PAXIL CR demonstrated statistically significant superiority over placebo on both the LSAS total score and the CGI Improvement responder criterion. For patients who completed the trial, 64% of patients treated with PAXIL CR

compared to 34.7% of patients treated with placebo were CGI Improvement responders.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of gender. Subgroup analyses of studies utilizing the immediate-release formulation of paroxetine generally did not indicate differences in treatment outcomes as a function of age, race, or gender.

Premenstrual Dysphoric Disorder: The effectiveness of PAXIL CR for the treatment of PMDD utilizing a continuous dosing regimen has been established in 2 placebo-controlled trials. Patients in these trials met DSM-IV criteria for PMDD. In a pool of 1,030 patients, treated with daily doses of PAXIL CR 12.5 or 25 mg/day, or placebo the mean duration of the PMDD symptoms was approximately 11 +/-7 years. Patients on systemic hormonal contraceptives were excluded from these trials. Therefore, the efficacy of PAXIL CR in combination with systemic (including oral) hormonal contraceptives for the continuous daily treatment of PMDD is unknown. In both positive studies, patients (N = 672) were treated with 12.5 mg/day or 25 mg/day of PAXIL CR or placebo continuously throughout the menstrual cycle for a period of 3 menstrual cycles. The VAS-Total score is a patient-rated instrument that mirrors the diagnostic criteria of PMDD as identified in the DSM-IV, and includes assessments for mood, physical symptoms, and other symptoms. 12.5 mg/day and 25 mg/day of PAXIL CR were significantly more effective than placebo as measured by change from baseline to the endpoint on the luteal phase VAS-Total score.

In a third study employing intermittent dosing, patients (N = 366) were treated for the 2 weeks prior to the onset of menses (luteal phase dosing, also known as intermittent dosing) with 12.5 mg/day or 25 mg/day of PAXIL CR or placebo for a period of 3 months. 12.5 mg/day and 25 mg/day of PAXIL CR, as luteal phase dosing, was significantly more effective than placebo as measured by change from baseline luteal phase VAS total score.

There is insufficient information to determine the effect of race or age on outcome in these studies.

INDICATIONS AND USAGE

Major Depressive Disorder: PAXIL CR is indicated for the treatment of major depressive disorder.

The efficacy of PAXIL CR in the treatment of a major depressive episode was established in two 12-week controlled trials of outpatients whose diagnoses corresponded to the DSM-IV category of major depressive disorder (see CLINICAL PHARMACOLOGY — Clinical Trials).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed mood or loss of interest or pleasure in nearly all activities, representing a change from previous functioning, and includes the presence of at least 5 of the following 9 symptoms during the same 2-week period: Depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt, or suicidal ideation.

The antidepressant action of paroxetine in hospitalized depressed patients has not been adequately studied.

PAXIL CR has not been systematically evaluated beyond 12 weeks in controlled clinical trials; however, the effectiveness of immediate-release paroxetine hydrochloride in maintaining a response in major depressive disorder for up to 1 year has been demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY— Clinical Trials). The physician who elects to use PAXIL CR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Panic Disorder: PAXIL CR is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of PAXIL CR controlled-release tablets was established in two 10-week trials in panic disorder patients

whose diagnoses corresponded to the DSM-IV category of panic disorder (see CLINICAL PHARMACOLOGY — Clinical Trials).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

Long-term maintenance of efficacy with the immediate-release formulation of paroxetine was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to immediate-release paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY — Clinical Trials). Nevertheless, the physician who prescribes PAXIL CR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Social Anxiety Disorder: PAXIL CR is indicated for the treatment of social anxiety disorder, also known as social phobia, as defined in DSM-IV (300.23). Social anxiety disorder is characterized by a marked and persistent fear of 1 or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational or academic functioning, or social activities or relationships, or there is marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

The efficacy of PAXIL CR as a treatment for social anxiety disorder has been established, in part, on the basis of extrapolation from the established effectiveness of the immediate-release formulation of paroxetine. In addition, the efficacy of PAXIL CR was established in a 12-week trial, in adult outpatients with social anxiety disorder (DSM-IV). PAXIL CR has not been studied in children or adolescents with social phobia (see CLINICAL PHARMACOLOGY — Clinical Trials).

The effectiveness of PAXIL CR in long-term treatment of social anxiety disorder, i.e., for more than 12 weeks, has not been systematically evaluated in adequate and well-controlled trials. Therefore, the physician who elects to prescribe PAXIL CR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Premenstrual Dysphoric Disorder: PAXIL CR is indicated for the treatment of PMDD.

The efficacy of PAXIL CR in the treatment of PMDD has been established in 3 placebo-controlled trials (see CLINICAL PHARMACOLOGY — Clinical Trials).

The essential features of PMDD, according to DSM-IV, include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating, and weight gain. These symptoms occur regularly during the luteal phase and remit within a few days following the onset of menses; the disturbance markedly interferes with work or school or with usual social activities and relationships with others. In making the diagnosis, care should be taken to rule out other cyclical mood disorders that may be exacerbated by treatment with an antidepressant.

The effectiveness of PAXIL CR in long-term use, that is, for more than 3 menstrual cycles, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use PAXIL CR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Concomitant use in patients taking either monoamine oxidase inhibitors (MAOIs) or thioridazine is contraindicated (see WARNINGS and PRECAUTIONS).

Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).

PAXIL CR is contraindicated in patients with a hypersensitivity to paroxetine or to any of the inactive ingredients in PAXIL CR.

WARNINGS

Clinical Worsening and Suicide Risk: Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in any of these trials. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION — Discontinuation of Treatment With PAXIL CR , for a description of the risks of discontinuation of PAXIL CR).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for PAXIL CR should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that PAXIL CR is not approved for use in treating bipolar depression.

Potential for Interaction With Monoamine Oxidase Inhibitors: In patients receiving another serotonin reuptake inhibitor drug in combination with an MAOI, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. While there are no human data showing such an interaction with paroxetine hydrochloride, limited animal data on the effects of combined use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that PAXIL CR not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. At least 2 weeks should be allowed after stopping PAXIL CR before starting an MAOI.

Potential Interaction With Thioridazine: Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias, and sudden death. This effect appears to be dose related.

An in vivo study suggests that drugs which inhibit P[450] IID[6] , such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).

PRECAUTIONS

General: *Activation of Mania/Hypomania:* During premarketing testing of immediate-release paroxetine hydrochloride, hypomania or mania occurred in approximately 1.0% of paroxetine-treated unipolar patients compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for immediate-release paroxetine and 11.6% for the combined active-control groups. Among 1,627 patients with major depressive disorder, panic disorder, social anxiety disorder, or PMDD treated with PAXIL CR in controlled clinical studies, there were no reports of mania or hypomania. As with all drugs effective in the treatment of major depressive disorder, PAXIL CR should be used cautiously in patients with a history of mania.

Seizures: During premarketing testing of immediate-release paroxetine hydrochloride, seizures occurred in 0.1%

of paroxetine-treated patients, a rate similar to that associated with other drugs effective in the treatment of major depressive disorder. Among 1,627 patients who received PAXIL CR in controlled clinical trials in major depressive disorder, panic disorder, social anxiety disorder, or PMDD, 1 patient (0.1%) experienced a seizure. PAXIL CR should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Discontinuation of Treatment With PAXIL CR: Adverse events while discontinuing therapy with PAXIL CR were not systematically evaluated in most clinical trials; however, in recent placebo-controlled clinical trials utilizing daily doses of PAXIL CR up to 37.5 mg/day, spontaneously reported adverse events while discontinuing therapy with PAXIL CR were evaluated. Patients receiving 37.5 mg/day underwent an incremental decrease in the daily dose by 12.5 mg/day to a dose of 25 mg/day for 1 week before treatment was stopped. For patients receiving 25 mg/day or 12.5 mg/day, treatment was stopped without an incremental decrease in dose. With this regimen in those studies, the following adverse events were reported for PAXIL CR, at an incidence of 2% or greater for PAXIL CR and were at least twice that reported for placebo: Dizziness, nausea, nervousness, and additional symptoms described by the investigator as associated with tapering or discontinuing PAXIL CR (e.g., emotional lability, headache, agitation, electric shock sensations, fatigue, and sleep disturbances). These events were reported as serious in 0.3% of patients who discontinued therapy with PAXIL CR.

During marketing of PAXIL CR and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, (particularly when abrupt), including the following: Dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with PAXIL CR. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

See also PRECAUTIONS — Pediatric Use , for adverse events reported upon discontinuation of treatment with paroxetine in pediatric patients.

Akathisia: The use of paroxetine or other SSRIs has been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. This is most likely to occur within the first few weeks of treatment.

Hyponatremia: Several cases of hyponatremia have been reported with immediate-release paroxetine hydrochloride. The hyponatremia appeared to be reversible when paroxetine was discontinued. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

Serotonin Syndrome: The development of a serotonin syndrome may occur in association with treatment with paroxetine, particularly with concomitant use of serotonergic drugs and with drugs which may have impaired metabolism of immediate-release paroxetine hydrochloride. Symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia, and tremor. The concomitant use of PAXIL CR with serotonin precursors (such as tryptophan) is not recommended (see WARNINGS — Potential for Interaction With Monoamine Oxidase Inhibitors and PRECAUTIONS — Drug Interactions).

Abnormal Bleeding: Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In 2 studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see Drug Interactions). Although these

studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of paroxetine with NSAIDs, aspirin, or other drugs that affect coagulation.

Use in Patients With Concomitant Illness: Clinical experience with immediate-release paroxetine hydrochloride in patients with certain concomitant systemic illness is limited. Caution is advisable in using PAXIL CR in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

As with other SSRIs, mydriasis has been infrequently reported in premarketing studies with paroxetine hydrochloride. A few cases of acute angle closure glaucoma associated with therapy with immediate-release paroxetine have been reported in the literature. As mydriasis can cause acute angle closure in patients with narrow angle glaucoma, caution should be used when PAXIL CR is prescribed for patients with narrow angle glaucoma.

PAXIL CR or the immediate-release formulation has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during premarket testing. Evaluation of electrocardiograms of 682 patients who received immediate-release paroxetine hydrochloride in double-blind, placebo-controlled trials, however, did not indicate that paroxe-tine is associated with the development of significant ECG abnormalities. Similarly, paroxetine hydrochloride does not cause any clinically important changes in heart rate or blood pressure.

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance <30 mL/min.) or severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients: Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with PAXIL CR and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for PAXIL CR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking PAXIL CR.

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

PAXIL CR should not be chewed or crushed, and should be swallowed whole.

Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.): Patients should be cautioned about the concomitant use of paroxetine and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

Interference With Cognitive and Motor Performance: Any psychoactive drug may impair judgment, thinking, or motor skills. Although in controlled studies immediate-release paroxetine hydrochloride has not been shown to impair

psychomotor performance, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with PAXIL CR does not affect their ability to engage in such activities.

Completing Course of Therapy: While patients may notice improvement with use of PAXIL CR in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant Medications: Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Although immediate-release paroxetine hydrochloride has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking PAXIL CR.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised to notify their physician if they are breast-feeding an infant (see PRECAUTIONS—Nursing Mothers).

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions: *Tryptophan:* As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are coadministered. Adverse experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been reported when tryptophan was administered to patients taking immediate-release paroxetine. Consequently, concomitant use of PAXIL CR with tryptophan is not recommended (see Serotonin Syndrome).

Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS and WARNINGS .

Pimozide: In a controlled study of healthy volunteers, after PAXIL CR was titrated to 60 mg daily, co-administration of a single dose of 2 mg pimozide was associated with mean increases in pimozide AUC of 151% and C[max] of 62%, compared to pimozide administered alone. Due to the narrow therapeutic index of pimozide and its known ability to prolong the QT interval, concomitant use of pimozide and PAXIL CR is contraindicated (see CONTRAINDICATIONS).

Serotonergic Drugs: Based on the mechanism of action of paroxetine and the potential for serotonin syndrome, caution is advised when PAXIL CR is coadministered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, serotonin reuptake inhibitors, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see Serotonin Syndrome).

Thioridazine: See CONTRAINDICATIONS and WARNINGS .

Warfarin: Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis in the face of unaltered prothrombin time) between paroxetine and warfarin. Since there is little clinical experience, the concomitant administration of PAXIL CR and warfarin should be undertaken with caution (see Drugs That Interfere With Hemostasis).

Triptans: There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with a triptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised (see Serotonin Syndrome).

Drugs Affecting Hepatic Metabolism: The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug-metabolizing enzymes.

Cimetidine: Cimetidine inhibits many cytochrome P[450] (oxidative) enzymes. In a study where immediate-release paroxetine (30 mg once daily) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during coadministration with oral cimetidine (300 mg three times daily) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of PAXIL CR after the starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not studied.

Phenobarbital: Phenobarbital induces many cytochrome P[450] (oxidative) enzymes. When a single oral 30-mg dose of immediate-release paroxetine was administered at phenobarbital steady state (100 mg once daily for 14 days), paroxetine AUC and T[1/2] were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. Since paroxetine exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustment with PAXIL CR is considered necessary when coadministered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

Phenytoin: When a single oral 30-mg dose of immediate-release paroxetine was administered at phenytoin steady state (300 mg once daily for 14 days), paroxetine AUC and T[1/2] were reduced (by an average of 50% and 35%, respectively) compared to immediate-release paroxetine administered alone. In a separate study, when a single oral 300-mg dose of phenytoin was administered at paroxetine steady state (30 mg once daily for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustments are considered necessary when PAXIL CR is coadministered with phenytoin; any subsequent adjustments should be guided by clinical effect (see ADVERSE REACTIONS — Postmarketing Reports).

Drugs Metabolized by Cytochrome P[450] IID[6] : Many drugs, including most drugs effective in the treatment of major depressive disorder (paroxetine, other SSRIs, and many tricyclics), are metabolized by the cytochrome P[450] isozyme P[450] IID[6] . Like other agents that are metabolized by P[450] IID[6] , paroxetine may significantly inhibit the activity of this isozyme. In most patients (>90%), this P[450] IID[6] isozyme is saturated early during paroxetine dosing. In 1 study, daily dosing of immediate-release paroxetine (20 mg once daily) under steady-state conditions increased single-dose desipramine (100 mg) C[max] , AUC, and T[1/2] by an average of approximately 2-, 5-, and 3-fold, respectively. Concomitant use of PAXIL CR with other drugs metabolized by cytochrome P[450] IID[6] has not been formally studied but may require lower doses than usually prescribed for either PAXIL CR or the other drug.

Therefore, coadministration of PAXIL CR with other drugs that are metabolized by this isozyme, including certain drugs effective in the treatment of major depressive disorder (e.g., nortriptyline, amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines, risperidone, and Type 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

However, due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, paroxetine and thioridazine should not be coadministered (see CONTRAINDICATIONS and WARNINGS).

At steady state, when the P[450] IID[6] pathway is essentially saturated, paroxetine clearance is governed by alternative P[450] isozymes that, unlike P[450] IID[6] , show no evidence of saturation (see PRECAUTIONS — Tricyclic Antidepressants).

Drugs Metabolized by Cytochrome P[450] IIIA[4] : An in vivo interaction study involving the coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for P[450] IIIA[4] , revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of P[450] IIIA[4] activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporine. Based on the assumption that the relationship between paroxetine's in vitro K[i] and its lack of effect on terfenadine's in vivo clearance predicts its effect on other IIIA[4] substrates, paroxetine's extent of inhibition of IIIA[4] activity is not likely to be of clinical significance.

Tricyclic Antidepressants (TCAs): Caution is indicated in the coadministration of TCAs with PAXIL CR, because paroxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is coadministered with PAXIL CR (see PRECAUTIONS — Drugs Metabolized by Cytochrome P[450] IID[6]).

Drugs Highly Bound to Plasma Protein: Because paroxetine is highly bound to plasma protein, administration of PAXIL CR to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.

Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.): Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with paroxetine.

Alcohol: Although paroxetine does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking PAXIL CR.

Lithium: A multiple-dose study with immediate-release paroxetine hydrochloride has shown that there is no pharmacokinetic interaction between paroxetine and lithium carbonate. However, due to the potential for serotonin syndrome, caution is advised when immediate-release paroxetine hydrochloride is coadministered with lithium.

Digoxin: The steady-state pharmacokinetics of paroxetine was not altered when administered with digoxin at steady state. Mean digoxin AUC at steady state decreased by 15% in the presence of paroxetine. Since there is little clinical experience, the concurrent administration of PAXIL CR and digoxin should be undertaken with caution.

Diazepam: Under steady-state conditions, diazepam does not appear to affect paroxetine kinetics. The effects of paroxetine on diazepam were not evaluated.

Procyclidine: Daily oral dosing of immediate-release paroxetine (30 mg once daily) increased steady-state AUC[0-24] , C[max] , and C[min] values of procyclidine (5 mg oral once daily) by 35%, 37%, and 67%, respectively, compared to procyclidine alone at steady state. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

Beta-Blockers: In a study where propranolol (80 mg twice daily) was dosed orally for 18 days, the established steady-state plasma concentrations of propranolol were unaltered during coadministration with immediate-release paroxetine (30 mg once daily) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS — Postmarketing Reports).

Theophylline: Reports of elevated theophylline levels associated with immediate-release paroxetine treatment have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

Electroconvulsive Therapy (ECT): There are no clinical studies of the combined use of ECT and PAXIL CR.

Carcinogenesis, Mutagenesis, Impairment of Fertility: *Carcinogenesis:* Two-year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to approximately 2 (mouse) and 3 (rat) times the maximum recommended human dose (MRHD) on a mg/m[2] basis. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis: Paroxetine produced no genotoxic effects in a battery of 5 in vitro and 2 in vivo assays that included the following: Bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations in vivo in mouse bone marrow and in vitro in human lymphocytes and in a dominant lethal test in rats.

Impairment of Fertility: A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day, which is approximately twice the MRHD on a mg/m[2] basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (approximately 8 and 4 times the MRHD on a mg/m[2] basis).

Pregnancy: Pregnancy Category C. Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 8 (rat) and 2 (rabbit) times the MRHD on an mg/m[2] basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or approximately one-sixth of the MRHD on an mg/m[2] basis. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Neonates exposed to PAXIL CR and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS — Potential for Interaction With Monoamine Oxidase Inhibitors).

There have also been postmarketing reports of premature births in pregnant women exposed to paroxetine or other SSRIs.

When treating a pregnant woman with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

Labor and Delivery: The effect of paroxetine on labor and delivery in humans is unknown.

Nursing Mothers: Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when PAXIL CR is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS — Clinical Worsening and Suicide Risk). Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with PAXIL, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of PAXIL CR in a child or adolescent must balance the potential risks with the clinical need.

In placebo-controlled clinical trials conducted with pediatric patients, the following adverse events were reported in at least 2% of pediatric patients treated with immediate-release paroxetine hydrochloride and occurred at a rate at least twice that for pediatric patients receiving placebo: emotional lability (including self-harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia, and agitation.

Events reported upon discontinuation of treatment with immediate-release paroxetine hydrochloride in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2% of patients who received immediate-

release paroxetine hydrochloride and which occurred at a rate at least twice that of placebo, were: emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain (see Discontinuation of Treatment With PAXIL CR).

Geriatric Use: In worldwide premarketing clinical trials with immediate-release paroxetine hydrochloride, 17% of paroxetine-treated patients (approximately 700) were 65 years or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

In a controlled study focusing specifically on elderly patients with major depressive disorder, PAXIL CR was demonstrated to be safe and effective in the treatment of elderly patients (>60 years) with major depressive disorder. (See CLINICAL PHARMACOLOGY — Clinical Trials and ADVERSE REACTIONS—Table 2.)

ADVERSE REACTIONS

The information included under the " Adverse Findings Observed in Short-Term, Placebo-Controlled Trials With PAXIL CR " subsection of ADVERSE REACTIONS is based on data from 11 placebo-controlled clinical trials. Three of these studies were conducted in patients with major depressive disorder, 3 studies were done in patients with panic disorder, 1 study was conducted in patients with social anxiety disorder, and 4 studies were done in female patients with PMDD. Two of the studies in major depressive disorder, which enrolled patients in the age range 18 to 65 years, are pooled. Information from a third study of major depressive disorder, which focused on elderly patients (60 to 88 years), is presented separately as is the information from the panic disorder studies and the information from the PMDD studies. Information on additional adverse events associated with PAXIL CR and the immediate-release formulation of paroxetine hydrochloride is included in a separate subsection (see Other Events).

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials With PAXIL CR:

Adverse Events Associated With Discontinuation of Treatment: *Major Depressive Disorder:* Ten percent (21/212) of patients treated with PAXIL CR discontinued treatment due to an adverse event in a pool of 2 studies of patients with major depressive disorder. The most common events (>/=1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for PAXIL CR compared to placebo) included the following:

	PAXIL CR (n = 212)	Placebo (n = 211)
Nausea	3.7%	0.5%
Asthenia	1.9%	0.5%
Dizziness	1.4%	0.0%
Somnolence	1.4%	0.0%

In a placebo-controlled study of elderly patients with major depressive disorder, 13% (13/104) of patients treated with PAXIL CR discontinued due to an adverse event. Events meeting the above criteria included the following:

	PAXIL CR (n = 104)	Placebo (n = 109)
Nausea	2.9%	0.0%
Headache	1.9%	0.9%
Depression	1.9%	0.0%
LFT's abnormal	1.9%	0.0%

Panic Disorder: Eleven percent (50/444) of patients treated with PAXIL CR in panic disorder studies discontinued treatment due to an adverse event. Events meeting the above criteria included the following:

	PAXIL CR (n = 444)	Placebo (n = 445)
Nausea	2.9%	0.4%
Insomnia	1.8%	0.0%
Headache	1.4%	0.2%
Asthenia	1.1%	0.0%

Social Anxiety Disorder: Three percent (5/186) of patients treated with PAXIL CR in the social anxiety disorder study discontinued treatment due to an adverse event. Events meeting the above criteria included the following:

	PAXIL CR (n = 186)	Placebo (n = 184)
Nausea	2.2%	0.5%
Headache	1.6%	0.5%
Diarrhea	1.1%	0.5%

Premenstrual Dysphoric Disorder: Spontaneously reported adverse events were monitored in studies of both continuous and intermittent dosing of PAXIL CR in the treatment of PMDD. Generally, there were few differences in the adverse event profiles of the 2 dosing regimens. Thirteen percent (88/681) of patients treated with PAXIL CR in PMDD studies of continuous dosing discontinued treatment due to an adverse event.

The most common events (>/=1%) associated with discontinuation in either group treated with PAXIL CR with an incidence rate that is at least twice that of placebo in PMDD trials that employed a continuous dosing regimen are shown in the following table. This table also shows those events that were dose dependent (indicated with an asterisk) as defined as events having an incidence rate with 25 mg of PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR (as well as the placebo group).

	PAXIL CR 25 mg (n = 348)	PAXIL CR 12.5 mg (n = 333)	Placebo (n = 349)
TOTAL	15%	9.9%	6.3%
Nausea *	6.0%	2.4%	0.9%
Asthenia	4.9%	3.0%	1.4%
Somnolence *	4.3%	1.8%	0.3%
Insomnia	2.3%	1.5%	0.0%
Concentration Impaired *	2.0%	0.6%	0.3%
Dry mouth *	2.0%	0.6%	0.3%
Dizziness *	1.7%	0.6%	0.6%
Decreased Appetite *	1.4%	0.6%	0.0%
Sweating *	1.4%	0.0%	0.3%
Tremor *	1.4%	0.3%	0.0%

Yawn *	1.1%	0.0%	0.0%
Diarrhea	0.9%	1.2%	0.0%

*Events considered to be dose dependent are defined as events having an incidence rate with 25 mg of PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR (as well as the placebo group).

Commonly Observed Adverse Events: *Major Depressive Disorder:* The most commonly observed adverse events associated with the use of PAXIL CR in a pool of 2 trials (incidence of 5.0% or greater and incidence for PAXIL CR at least twice that for placebo, derived from Table 1) were: Abnormal ejaculation, abnormal vision, constipation, decreased libido, diarrhea, dizziness, female genital disorders, nausea, somnolence, sweating, trauma, tremor, and yawning.

Using the same criteria, the adverse events associated with the use of PAXIL CR in a study of elderly patients with major depressive disorder were: Abnormal ejaculation, constipation, decreased appetite, dry mouth, impotence, infection, libido decreased, sweating, and tremor.

Panic Disorder: In the pool of panic disorder studies, the adverse events meeting these criteria were: Abnormal ejaculation, somnolence, impotence, libido decreased, tremor, sweating, and female genital disorders (generally anorgasmia or difficulty achieving orgasm).

Social Anxiety Disorder: In the social anxiety disorder study, the adverse events meeting these criteria were: Nausea, asthenia, abnormal ejaculation, sweating, somnolence, impotence, insomnia, and libido decreased.

Premenstrual Dysphoric Disorder: The most commonly observed adverse events associated with the use of PAXIL CR either during continuous dosing or luteal phase dosing (incidence of 5% or greater and incidence for PAXIL CR at least twice that for placebo, derived from Table 5) were: Nausea, asthenia, libido decreased, somnolence, insomnia, female genital disorders, sweating, dizziness, diarrhea, and constipation.

In the luteal phase dosing PMDD trial, which employed dosing of 12.5 mg/day or 25 mg/day of PAXIL CR limited to the 2 weeks prior to the onset of menses over 3 consecutive menstrual cycles, adverse events were evaluated during the first 14 days of each off-drug phase. When the 3 off-drug phases were combined, the following adverse events were reported at an incidence of 2% or greater for PAXIL CR and were at least twice the rate of that reported for placebo: Infection (5.3% versus 2.5%), depression (2.8% versus 0.8%), insomnia (2.4% versus 0.8%), sinusitis (2.4% versus 0%), and asthenia (2.0% versus 0.8%).

Incidence in Controlled Clinical Trials: Table 1 enumerates adverse events that occurred at an incidence of 1% or more among patients treated with PAXIL CR, aged 18 to 65, who participated in 2 short-term (12-week) placebo-controlled trials in major depressive disorder in which patients were dosed in a range of 25 mg to 62.5 mg/day. Table 2 enumerates adverse events reported at an incidence of 5% or greater among elderly patients (ages 60 to 88) treated with PAXIL CR who participated in a short-term (12-week) placebo-controlled trial in major depressive disorder in which patients were dosed in a range of 12.5 mg to 50 mg/day. Table 3 enumerates adverse events reported at an incidence of 1% or greater among patients (19 to 72 years) treated with PAXIL CR who participated in short-term (10-week) placebo-controlled trials in panic disorder in which patients were dosed in a range of 12.5 mg to 75 mg/day. Table 4 enumerates adverse events reported at an incidence of 1% or greater among adult patients treated with PAXIL CR who participated in a short-term (12-week), double-blind, placebo-controlled trial in social anxiety disorder in which patients were dosed in a range of 12.5 to 37.5 mg/day. Table 5 enumerates adverse events that occurred at an incidence of 1% or more among patients treated with PAXIL CR who participated in three, 12-week, placebo-controlled trials in PMDD in which patients were dosed at 12.5 mg/day or 25 mg/day and in one 12-week placebo-controlled trial in which patients were dosed for 2 weeks prior to the onset of menses (luteal phase dosing) at 12.5 mg/day or 25 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations

involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 1. Treatment-Emergent Adverse Events Occurring in >/=1% of Patients Treated With PAXIL CR in a Pool of 2 Studies in Major Depressive Disorder 1, 2

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 212)	Placebo (n = 211)
Body as a Whole		
Headache	27%	20%
Asthenia	14%	9%
Infection[3]	8%	5%
Abdominal Pain	7%	4%
Back Pain	5%	3%
Trauma[4]	5%	1%
Pain[5]	3%	1%
Allergic Reaction[6]	2%	1%
Cardiovascular System		
Tachycardia	1%	0%
Vasodilatation[7]	2%	0%
Digestive System		
Nausea	22%	10%
Diarrhea	18%	7%
Dry Mouth	15%	8%
Constipation	10%	4%
Flatulence	6%	4%
Decreased Appetite	4%	2%
Vomiting	2%	1%
Nervous System		
Somnolence	22%	8%
Insomnia	17%	9%
Dizziness	14%	4%
Libido Decreased	7%	3%
Tremor	7%	1%
Hypertonia	3%	1%
Paresthesia	3%	1%
Agitation	2%	1%
Confusion	1%	0%
Respiratory System		
Yawn	5%	0%
Rhinitis	4%	1%
Cough Increased	2%	1%
Bronchitis	1%	0%
Skin and Appendages		
Sweating	6%	2%
Photosensitivity	2%	0%
Special Senses		
Abnormal Vision[8]	5%	1%
Taste Perversion	2%	0%
Urogenital System		

Table 1. Treatment-Emergent Adverse Events Occurring in >/=1% of Patients Treated With PAXIL CR in a Pool of 2 Studies in Major Depressive Disorder 1, 2

Abnormal Ejaculation 9, 10	26%	1%
Female Genital Disorder 9, 11	10%	<1%
Impotence[9]	5%	3%
Urinary Tract Infection	3%	1%
Menstrual Disorder[9]	2%	<1%
Vaginitis[9]	2%	0%

1. Adverse events for which the PAXIL CR reporting incidence was less than or equal to the placebo incidence are not included. These events are: Abnormal dreams, anxiety, arthralgia, depersonalization, dysmenorrhea, dyspepsia, hyperkinesia, increased appetite, myalgia, nervousness, pharyngitis, purpura, rash, respiratory disorder, sinusitis, urinary frequency, and weight gain.
2. <1% means greater than zero and less than 1%.
3. Mostly flu.
4.A wide variety of injuries with no obvious pattern.
5. Pain in a variety of locations with no obvious pattern.
6. Most frequently seasonal allergic symptoms.
7. Usually flushing.
8. Mostly blurred vision.
9. Based on the number of males or females.
10. Mostly anorgasmia or delayed ejaculation.
11. Mostly anorgasmia or delayed orgasm.

Table 2. Treatment-Emergent Adverse Events Occurring in >/=5% of Patients Treated With PAXIL CR in a Study of Elderly Patients With Major Depressive Disorder[1,] 2

	% Reporting Event	
Body System/Adverse Event	PAXIL CR (n = 104)	Placebo (n = 109)
Body as a Whole		
Headache	17%	13%
Asthenia	15%	14%
Trauma	8%	5%
Infection	6%	2%
Digestive System		
Dry Mouth	18%	7%
Diarrhea	15%	9%
Constipation	13%	5%
Dyspepsia	13%	10%
Decreased Appetite	12%	5%
Flatulence	8%	7%
Nervous System		
Somnolence	21%	12%
Insomnia	10%	8%
Dizziness	9%	5%
Libido Decreased	8%	<1%
Tremor	7%	0%
Skin and Appendages		
Sweating	10%	<1%

Table 2. Treatment-Emergent Adverse Events Occurring in >/=5% of Patients Treated With PAXIL CR in a Study of Elderly Patients With Major Depressive Disorder[1,] 2

Urogenital System		
Abnormal Ejaculation[3,] 4	17%	3%
Impotence[3]	9%	3%

1. Adverse events for which the PAXIL CR reporting incidence was less than or equal to the placebo incidence are not included. These events are nausea and respiratory disorder.
2. <1% means greater than zero and less than 1%.
3. Based on the number of males.
4. Mostly anorgasmia or delayed ejaculation.

Table 3. Treatment-Emergent Adverse Events Occurring in >/=1% of Patients Treated With PAXIL CR in a Pool of 3 Panic Disorder Studies 1, 2

	% Reporting Event	
Body System/Adverse Event	PAXIL CR (n = 444)	Placebo (n = 445)
Body as a Whole		
Asthenia	15%	10%
Abdominal Pain	6%	4%
Trauma[3]	5%	4%
Cardiovascular System		
Vasodilation[4]	3%	2%
Digestive System		
Nausea	23%	17%
Dry Mouth	13%	9%
Diarrhea	12%	9%
Constipation	9%	6%
Decreased Appetite	8%	6%
Metabolic/Nutritional Disorders		
Weight Loss	1%	0%
Musculoskeletal System		
Myalgia	5%	3%
Nervous System		
Insomnia	20%	11%
Somnolence	20%	9%
Libido Decreased	9%	4%
Nervousness	8%	7%
Tremor	8%	2%
Anxiety	5%	4%
Agitation	3%	2%
Hypertonia[5]	2%	<1%
Myoclonus	2%	<1%
Respiratory System		
Sinusitis	8%	5%
Yawn	3%	0%
Skin and Appendages		
Sweating	7%	2%
Special Senses		
Abnormal Vision[6]	3%	<1%

Table 3. Treatment-Emergent Adverse Events Occurring in >/=1% of Patients Treated With PAXIL CR in a Pool of 3 Panic Disorder Studies 1, 2

Urogenital System		
Abnormal Ejaculation 7, 8	27%	3%
Impotence[7]	10%	1%
Female Genital Disorders 9, 10	7%	1%
Urinary Frequency	2%	<1%
Urination Impaired	2%	<1%
Vaginitis[9]	1%	<1%

1. Adverse events for which the reporting rate for PAXIL CR was less than or equal to the placebo rate are not included. These events are: Abnormal dreams, allergic reaction, back pain, bronchitis, chest pain, concentration impaired, confusion, cough increased, depression, dizziness, dysmenorrhea, dyspepsia, fever, flatulence, headache, increased appetite, infection, menstrual disorder, migraine, pain, paresthesia, pharyngitis, respiratory disorder, rhinitis, tachycardia, taste perversion, thinking abnormal, urinary tract infection, and vomiting.
2. <1% means greater than zero and less than 1%.
3. Various physical injuries.
4. Mostly flushing.
5. Mostly muscle tightness or stiffness.
6. Mostly blurred vision.
7. Based on the number of male patients.
8. Mostly anorgasmia or delayed ejaculation.
9. Based on the number of female patients.
10. Mostly anorgasmia or difficulty achieving orgasm.

Table 4. Treatment-Emergent Adverse Effects Occurring in >/=1% of Patients Treated With PAXIL CR in a Social Anxiety Disorder Study 1, 2

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 186)	Placebo (n = 184)
Body as a Whole		
Headache	23%	17%
Asthenia	18%	7%
Abdominal Pain	5%	4%
Back Pain	4%	1%
Trauma[3]	3%	<1%
Allergic Reaction[4]	2%	<1%
Chest Pain	1%	<1%
Cardiovascular System		
Hypertension	2%	0%
Migraine	2%	1%
Tachycardia	2%	1%
Digestive System		
Nausea	22%	6%
Diarrhea	9%	8%
Constipation	5%	2%
Dry Mouth	3%	2%

Table 4. Treatment-Emergent Adverse Effects Occurring in >/=1% of Patients Treated With PAXIL CR in a Social Anxiety Disorder Study 1, 2

Dyspepsia	2%	<1%
Decreased Appetite	1%	<1%
Tooth Disorder	1%	0%
Metabolic/Nutritional Disorders		
Weight Gain	3%	1%
Weight Loss	1%	0%
Nervous System		
Insomnia	9%	4%
Somnolence	9%	4%
Libido Decreased	8%	1%
Dizziness	7%	4%
Tremor	4%	2%
Anxiety	2%	1%
Concentration Impaired	2%	0%
Depression	2%	1%
Myoclonus	1%	<1%
Paresthesia	1%	<1%
Respiratory System		
Yawn	2%	0%
Skin and Appendages		
Sweating	14%	3%
Eczema	1%	0%
Special Senses		
Abnormal Vision[5]	2%	0%
Abnormality of Accommodation	2%	0%
Urogenital System		
Abnormal Ejaculation 6, 7	15%	1%
Impotence[6]	9%	0%
Female Genital Disorders 8, 9	3%	0%

1. Adverse events for which the reporting rate for PAXIL CR was less than or equal to the placebo rate are not included. These events are: Dysmenorrhea, flatulence, gastroenteritis, hypertonia, infection, pain, pharyngitis, rash, respiratory disorder, rhinitis, and vomiting.
2. <1% means greater than zero and less than 1%.
3. Various physical injuries.
4. Most frequently seasonal allergic symptoms.
5. Mostly blurred vision.
6. Based on the number of male patients.
7. Mostly anorgasmia or delayed ejaculation.
8. Based on the number of female patients.
9. Mostly anorgasmia or difficulty achieving orgasm.

Table 5. Treatment-Emergent Adverse Events Occurring in >/=1% of Patients Treated With PAXIL CR in a Pool of 3 Premenstrual Dysphoric Disorder Studies with Continuous Dosing or in 1 Premenstrual Dysphoric Disorder Study with Luteal Phase Dosing 1, 2, 3

Body System/Adverse	% Reporting Event

Table 5. Treatment-Emergent Adverse Events Occurring in >/=1% of Patients Treated With PAXIL CR in a Pool of 3 Premenstrual Dysphoric Disorder Studies with Continuous Dosing or in 1 Premenstrual Dysphoric Disorder Study with Luteal Phase Dosing 1, 2, 3

Event	Continuous Dosing		Luteal Phase Dosing	
	Placebo (n = 349)	PAXIL CR (n = 246)	Placebo (n = 120)	
Body as a Whole				
Asthenia	17%	6%	15%	4%
Headache	15%	12%	—	—
Infection	6%	4%	—	—
Abdominal pain	—	—	3%	0%
Cardiovascular System				
Migraine	1%	<1%	—	—
Digestive System				
Nausea	17%	7%	18%	2%
Diarrhea	6%	2%	6%	0%
Constipation	5%	1%	2%	<1%
Dry Mouth	4%	2%	2%	<1%
Increased Appetite	3%	<1%	—	—
Decreased Appetite	2%	<1%	2%	0%
Dyspepsia	2%	1%	2%	2%
Gingivitis	—	—	1%	0%
Metabolic and Nutritional Disorders				
Generalized Edema	—	—	1%	<1%
Weight Gain	—	—	1%	<1%
Musculoskeletal System				
Arthralgia	2%	1%	—	—
Nervous System				
Libido Decreased	12%	5%	9%	6%
Somnolence	9%	2%	3%	<1%
Insomnia	8%	2%	7%	3%
Dizziness	7%	3%	6%	3%
Tremor	4%	<1%	5%	0%
Concentration Impaired	3%	<1%	1%	0%
Nervousness	2%	<1%	3%	2%
Anxiety	2%	1%	—	—
Lack of Emotion	2%	<1%	—	—
Depression	—	—	2%	<1%
Vertigo	—	—	2%	<1%
Abnormal Dreams	1%	<1%	—	—
Amnesia	—	—	1%	0%
Respiratory System				

Table 5. Treatment-Emergent Adverse Events Occurring in >/=1% of Patients Treated With PAXIL CR in a Pool of 3 Premenstrual Dysphoric Disorder Studies with Continuous Dosing or in 1 Premenstrual Dysphoric Disorder Study with Luteal Phase Dosing 1, 2, 3

Sinusitis	—	—	4%	2%
Yawn	2%	<1%	—	—
Bronchitis	—	—	2%	0%
Cough Increased	1%	<1%	—	—
Skin and Appendages				
Sweating	7%	<1%	6%	<1%
Special Senses				
Abnormal Vision	—	—	1%	0%
Urogenital System				
Female Genital Disorders[4]	8%	1%	2%	0%
Menorrhagia	1%	<1%	—	—
Vaginal Moniliasis	1%	<1%	—	—
Menstrual Disorder	—	—	1%	0%

1. Adverse events for which the reporting rate of PAXIL CR was less than or equal to the placebo rate are not included. These events for continuous dosing are: Abdominal pain, back pain, pain, trauma, weight gain, myalgia, pharyngitis, respiratory disorder, rhinitis, sinusitis, pruritis, dysmenorrhea, menstrual disorder, urinary tract infection, and vomiting. The events for luteal phase dosing are: Allergic reaction, back pain, headache, infection, pain, trauma, myalgia, anxiety, pharyngitis, respiratory disorder, cystitis, and dysmenorrhea.
2. <1% means greater than zero and less than 1%.
3. The luteal phase and continuous dosing PMDD trials were not designed for making direct comparisons between the 2 dosing regimens. Therefore, a comparison between the 2 dosing regimens of the PMDD trials of incidence rates shown in Table 5 should be avoided.
4. Mostly anorgasmia or difficulty achieving orgasm.

Dose Dependency of Adverse Events: The following table shows results in PMDD trials of common adverse events, defined as events with an incidence of >/=1% with 25 mg of PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR and with placebo.

Incidence of Common Adverse Events in Placebo, 12.5 mg and 25 mg of PAXIL CR in a Pool of 3 Fixed-Dose PMDD Trials

	PAXIL CR 25 mg (n = 348)	PAXIL CR 12.5 mg (n = 333)	Placebo (n = 349)
Common Adverse Event			
Sweating	8.9%	4.2%	0.9%
Tremor	6.0%	1.5%	0.3%
Concentration Impaired	4.3%	1.5%	0.6%
Yawn	3.2%	0.9%	0.3%

Incidence of Common Adverse Events in Placebo, 12.5 mg and 25 mg of PAXIL CR in a Pool of 3 Fixed-Dose PMDD Trials

Paresthesia	1.4%	0.3%	0.3%
Hyperkinesia	1.1%	0.3%	0.0%
Vaginitis	1.1%	0.3%	0.3%

A comparison of adverse event rates in a fixed-dose study comparing immediate-release paroxetine with placebo in the treatment of major depressive disorder revealed a clear dose dependency for some of the more common adverse events associated with the use of immediate-release paroxetine.

Male and Female Sexual Dysfunction With SSRIs: Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain; however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

The percentage of patients reporting symptoms of sexual dysfunction in the pool of 2 placebo-controlled trials in nonelderly patients with major depressive disorder, in the pool of 3 placebo-controlled trials in patients with panic disorder, in the placebo-controlled trial in patients with social anxiety disorder, and in the intermittent dosing and the pool of 3 placebo-controlled continuous dosing trials in female patients with PMDD are as follows:

	Major Depressive Disorder		Panic Disorder		Social Anxiety Disorder		PMDD Continuous Dosing		PMDD Luteal Phase Dosing	
	PAXIL CR	Placebo	PAXIL CR	Placebo	PAXIL CR	Placebo	PAXIL CR	Placebo	PAXIL CR	Placebo
n (males)	78	78	162	194	88	97	n/a	n/a	n/a	n/a
Decreased Libido	10%	5%	9%	6%	13%	1%	n/a	n/a	n/a	n/a
Ejaculatory Disturbance	26%	1%	27%	3%	15%	1%	n/a	n/a	n/a	n/a
Impotence	5%	3%	10%	1%	9%	0%	n/a	n/a	n/a	n/a
n (females)	134	133	282	251	98	87	681	349	246	120
Decreased Libido	4%	2%	8%	2%	4%	1%	12%	5%	9%	6%
Orgasm	10%	<1%	7%	1%	3%	0%	8%	1%	2%	0%

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There are no adequate, controlled studies examining sexual dysfunction with paroxetine treatment.

Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Weight and Vital Sign Changes: Significant weight loss may be an undesirable result of treatment with paroxetine for some patients but, on average, patients in controlled trials with PAXIL CR or the immediate-release formulation, had minimal weight loss (about 1 pound). No significant changes in vital signs (systolic and diastolic blood pressure, pulse, and temperature) were observed in patients treated with PAXIL CR, or immediate-release paroxetine hydrochloride, in controlled clinical trials.

ECG Changes: In an analysis of ECGs obtained in 682 patients treated with immediate-release paroxetine and 415 patients treated with placebo in controlled clinical trials, no clinically significant changes were seen in the ECGs of either group.

Liver Function Tests: In a pool of 2 placebo-controlled clinical trials, patients treated with PAXIL CR or placebo exhibited abnormal values on liver function tests at comparable rates. In particular, the controlled-release paroxetine-versus-placebo comparisons for alkaline phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

In a study of elderly patients with major depressive disorder, 3 of 104 patients treated with PAXIL CR and none of 109 placebo patients experienced liver transaminase elevations of potential clinical concern.

Two of the patients treated with PAXIL CR dropped out of the study due to abnormal liver function tests; the third patient experienced normalization of transaminase levels with continued treatment. Also, in the pool of 3 studies of patients with panic disorder, 4 of 444 patients treated with PAXIL CR and none of 445 placebo patients experienced liver transaminase elevations of potential clinical concern. Elevations in all 4 patients decreased substantially after discontinuation of PAXIL CR. The clinical significance of these findings is unknown.

In placebo-controlled clinical trials with the immediate-release formulation of paroxetine, patients exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients.

Other Events Observed During the Clinical Development of Paroxetine: The following adverse events were reported during the clinical development of PAXIL CR and/or the clinical development of the immediate-release formulation of paroxetine.

Adverse events for which frequencies are provided below occurred in clinical trials with the controlled-release formulation of paroxetine. During its premarketing assessment in major depressive disorder, panic disorder, social anxiety disorder, and PMDD multiple doses of PAXIL CR were administered to 1,627 patients in phase 3 double-blind, controlled, outpatient studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a COSTART-based dictionary. The frequencies presented, therefore, represent the proportion of the 1,627 patients exposed to PAXIL CR who experienced an event of the type cited on at least 1 occasion while receiving PAXIL CR. All reported events are included except

those already listed in Tables 1 through 5 and those events where a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was deleted or, when possible, replaced with a more informative term. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: Frequent adverse events are those occurring on 1 or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

Adverse events for which frequencies are not provided occurred during the premarketing assessment of immediate-release paroxetine in phase 2 and 3 studies of major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder. The conditions and duration of exposure to immediate-release paroxetine varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose and titration studies. Only those events not previously listed for controlled-release paroxetine are included. The extent to which these events may be associated with PAXIL CR is unknown.

Events are listed alphabetically within the respective body system. Events of major clinical importance are also described in the PRECAUTIONS section.

Body as a Whole: Infrequent were chills, face edema, fever, flu syndrome, malaise; rare were abscess, anaphylactoid reaction, anticholinergic syndrome, hypothermia; also observed were adrenergic syndrome, neck rigidity, sepsis.

Cardiovascular System: Infrequent were angina pectoris, bradycardia, hematoma, hypertension, hypotension, palpitation, postural hypotension, supraventricular tachycardia, syncope; rare were bundle branch block; also observed were arrhythmia nodal, atrial fibrillation, cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, vascular headache, ventricular extrasystoles.

Digestive System: Infrequent were bruxism, dysphagia, eructation, gastritis, gastroenteritis, gastroesophageal reflux, gingivitis, hemorrhoids, liver function test abnormal, melena, pancreatitis, rectal hemorrhage, toothache, ulcerative stomatitis; rare were colitis, glossitis, gum hyperplasia, hepatosplenomegaly, increased salivation, intestinal obstruction, peptic ulcer, stomach ulcer, throat tightness; also observed were aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, jaundice, mouth ulceration, salivary gland enlargement, sialadenitis, stomatitis, tongue discoloration, tongue edema.

Endocrine System: Infrequent were ovarian cyst, testes pain; rare were diabetes mellitus, hyperthyroidism; also observed were goiter, hypothyroidism, thyroiditis.

Hemic and Lymphatic System: Infrequent were anemia, eosinophilia, hypochromic anemia, leukocytosis, leukopenia, lymphadenopathy, purpura; rare were thrombocytopenia; also observed were anisocytosis, basophilia, bleeding time increased, lymphedema, lymphocytosis, lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

Metabolic and Nutritional Disorders: Infrequent were generalized edema, hyperglycemia, hypokalemia, peripheral edema, SGOT increased, SGPT increased, thirst; rare were bilirubinemia, dehydration, hyperkalemia, obesity; also observed were alkaline phosphatase increased, BUN increased, creatinine phosphokinase increased, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperphosphatemia, hypocalcemia, hypoglycemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased.

Musculoskeletal System: Infrequent were arthritis, bursitis, tendonitis; rare were myasthenia, myopathy, myositis; also observed were generalized spasm, osteoporosis, tenosynovitis, tetany.

Nervous System: Frequent were depression; infrequent were amnesia, convulsion, depersonalization, dystonia, emotional lability, hallucinations, hyperkinesia, hypesthesia, hypokinesia, incoordination, libido increased, neuralgia, neuropathy, nystagmus, paralysis, vertigo; rare were ataxia, coma, diplopia, dyskinesia, hostility, paranoid reaction, torticollis, withdrawal syndrome; also observed were abnormal gait, akathisia, akinesia, aphasia, choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, irritability, manic reaction, manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, trismus.

Respiratory System: Frequent were pharyngitis; infrequent were asthma, dyspnea, epistaxis, laryngitis, pneumonia; rare were stridor; also observed were dysphonia, emphysema, hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum increased.

Skin and Appendages: Frequent were rash; infrequent were acne, alopecia, dry skin, eczema, pruritus, urticaria; rare were exfoliative dermatitis, furunculosis, pustular rash, seborrhea; also observed were angioedema, ecchymosis, erythema multiforme, erythema nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash.

Special Senses: Infrequent were conjunctivitis, earache, keratoconjunctivitis, mydriasis, photophobia, retinal hemorrhage, tinnitus; rare were blepharitis, visual field defect; also observed were amblyopia, anisocoria, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss.

Urogenital System: Frequent were dysmenorrhea* ; infrequent were albuminuria, amenorrhea* , breast pain*, cystitis, dysuria, prostatitis*, urinary retention; rare were breast enlargement*, breast neoplasm*, female lactation, hematuria, kidney calculus, metrorrhagia*, nephritis, nocturia, pregnancy and puerperal disorders*, salpingitis, urinary incontinence, uterine fibroids enlarged*; also observed were breast atrophy, ejaculatory disturbance, endometrial disorder, epididymitis, fibrocystic breast, leukorrhea, mastitis, oliguria, polyuria, pyuria, urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage.

* Based on the number of men and women as appropriate.

Postmarketing Reports: Voluntary reports of adverse events in patients taking immediate-release paroxetine hydrochloride that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barre syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events, serotonin syndrome; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide; tremor and trismus; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-SchOnlein purpura). There has been a case report of an elevated phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin coadministration. There has been a case report of severe hypotension when immediate-release paroxetine was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: PAXIL CR is not a controlled substance.

Physical and Psychologic Dependence: PAXIL CR has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this

limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of PAXIL CR (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience: Since the introduction of immediate-release paroxetine hydrochloride in the United States, 342 spontaneous cases of deliberate or accidental overdosage during paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and of the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases that documented the amount of paroxetine ingested were generally confounded by the ingestion of other drugs or alcohol or the presence of significant comorbid conditions. Of 145 non-fatal cases with known outcome, most recovered without sequelae. The largest known ingestion involved 2,000 mg of paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

Commonly reported adverse events associated with paroxetine overdosage include somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other notable signs and symptoms observed with overdoses involving paroxetine (alone or with other substances) include mydriasis, convulsions (including status epilepticus), ventricular dysrhythmias (including torsade de pointes), hypertension, aggressive reactions, syncope, hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

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

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

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

A specific caution involves patients taking or recently having taken paroxetine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see PRECAUTIONS — Drugs Metabolized by Cytochrome P[450] IID[6]).

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

DOSAGE AND ADMINISTRATION

Major Depressive Disorder: *Usual Initial Dosage:* PAXIL CR should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 25 mg/day. Patients were dosed in a range of 25 mg to 62.5 mg/day in the clinical trials demonstrating the effectiveness of PAXIL CR in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, the full effect may be delayed. Some patients not responding to a 25-mg dose may benefit from dose increases, in 12.5-mg/day increments, up to a maximum of 62.5 mg/day. Dose changes should occur at intervals of at least 1 week.

Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be swallowed whole.

Maintenance Therapy: There is no body of evidence available to answer the question of how long the patient treated with PAXIL CR should remain on it. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of immediate-release paroxetine hydrochloride has shown that efficacy is maintained for periods of up to 1 year with doses that averaged about 30 mg, which corresponds to a 37.5-mg dose of PAXIL CR, based on relative bioavailability considerations (see CLINICAL PHARMACOLOGY -- Pharmacokinetics).

Panic Disorder: *Usual Initial Dosage:* PAXIL CR should be administered as a single daily dose, usually in the morning. Patients should be started on 12.5 mg/day. Dose changes should occur in 12.5-mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 12.5 to 75 mg/day in the clinical trials demonstrating the effectiveness of PAXIL CR. The maximum dosage should not exceed 75 mg/day.

Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be swallowed whole.

Maintenance Therapy: Long-term maintenance of efficacy with the immediate-release formulation of paroxetine was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to immediate-release paroxetine demonstrated a lower relapse rate compared to patients on placebo. Panic disorder is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Social Anxiety Disorder: *Usual Initial Dosage:* PAXIL CR should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 12.5 mg/day. Patients were dosed in a range of 12.5 mg to 37.5 mg/day in the clinical trial demonstrating the effectiveness of PAXIL CR in the treatment of social anxiety disorder. If the dose is increased, this should occur at intervals of at least 1 week, in increments of 12.5 mg/day, up to a maximum of 37.5 mg/day.

Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be swallowed whole.

Maintenance Therapy: There is no body of evidence available to answer the question of how long the patient treated with PAXIL CR should remain on it. Although the efficacy of PAXIL CR beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, social anxiety disorder is recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Premenstrual Dysphoric Disorder: *Usual Initial Dosage:* PAXIL CR should be administered as a single daily dose, usually in the morning, with or without food. PAXIL CR may be administered either daily throughout the menstrual cycle or limited to the luteal phase of the menstrual cycle, depending on physician assessment. The recommended initial dose is 12.5 mg/day. In clinical trials, both 12.5 mg/day and 25 mg/day were shown to be effective. Dose changes should occur at intervals of at least 1 week.

Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be swallowed whole.

Maintenance/Continuation Therapy: The effectiveness of PAXIL CR for a period exceeding 3 menstrual cycles has not been systematically evaluated in controlled trials. However, women commonly report that symptoms worsen with age until relieved by the onset of menopause. Therefore, it is reasonable to consider continuation of a responding patient. Patients should be periodically reassessed to determine the need for continued treatment.

Special Populations: *Treatment of Pregnant Women During the Third Trimester:* Neonates exposed to PAXIL CR and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering paroxetine in the third trimester.

Dosage for Elderly or Debilitated Patients, and Patients With Severe Renal or Hepatic Impairment: The recommended initial dose of PAXIL CR is 12.5 mg/day for elderly patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 50 mg/day.

Switching Patients to or From a Monoamine Oxidase Inhibitor: At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with PAXIL CR. Similarly, at least 14 days should be allowed after stopping PAXIL CR before starting an MAOI.

Discontinuation of Treatment With PAXIL CR: Symptoms associated with discontinuation of immediate-release paroxetine hydrochloride or PAXIL CR have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which PAXIL CR is being prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

HOW SUPPLIED

PAXIL CR is supplied as an enteric film-coated, controlled-release, round tablet, as follows:

12.5-mg yellow tablets, engraved with PAXIL CR and 12.5

NDC 0029-3206-13 Bottles of 30

NDC 0029-3206-20 Bottles of 100

25-mg pink tablets, engraved with PAXIL CR and 25

NDC 0029-3207-13 Bottles of 30

NDC 0029-3207-20 Bottles of 100

NDC 0029-3207-21 SUP 100s (intended for institutional use only)

37.5-mg blue tablets, engraved with PAXIL CR and 37.5

NDC 0029-3208-13 Bottles of 30

Store at or below 25 deg. C (77 deg. F) see USP .

PAXIL CR is a registered trademark of GlaxoSmithKline.

GEOMATRIX is a trademark of Jago Pharma, Muttenz, Switzerland.

PRODUCT PHOTO(S): NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

The product samples shown here have been supplied by the manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember

that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.
See Image

Medication Guide

PAXIL CR(R) (PAX-il) (paroxetine hydrochloride)

Controlled-Release Tablets

About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

There is a risk of suicidal thoughts or actionsHow to try to prevent suicidal thoughts or actions in your childYou should watch for certain signs if your child is taking an antidepressantThere are benefits and risks when using antidepressants

There is a Risk of Suicidal Thoughts or Actions
Children and teenagers sometimes think about suicide, and many report trying to kill themselves.
Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality* or *being suicidal.*
A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. *No one committed suicide in these studies,* but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.
For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with Bipolar illness (sometimes called manic-depressive illness)A family history of bipolar illnessA personal or family history of attempting suicide
If any of these are present, make sure you tell your healthcare provider before your child takes an antidepressant.How to Try to Prevent Suicidal Thoughts and Actions
To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.
Whenever an antidepressant is started or its dose is changed, pay close attention to your child. After starting an antidepressant, your child should generally see his or her healthcare provider:
Once a week for the first 4 weeksEvery 2 weeks for the next 4 weeksAfter taking the antidepressant for 12 weeksAfter 12 weeks, follow your healthcare provider's advice about how often to come backMore often if problems or questions arise (see Section 3)
You should call your child's healthcare provider between visits if needed.You Should Watch for Certain Signs If Your Child is Taking an Antidepressant
Contact your child's healthcare provider *right away* if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:
Thoughts about suicide or dyingAttempts to commit suicideNew or worse depressionNew or worse anxietyFeeling very agitated or restlessPanic attacksDifficulty sleeping (insomnia)New or worse irritabilityActing aggressive, being angry, or violentActing on dangerous impulsesAn extreme increase in activity and talkingOther unusual changes in behavior or mood
Never let your child stop taking an antidepressant without first talking to his or her healthcare provider. Stopping an antidepressant suddenly can cause other symptoms.There are Benefits and Risks When Using Antidepressants
Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In

some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your healthcare provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac(R)) * has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac(R)) * , sertraline (Zoloft(R)) * , fluvoxamine, and clomipramine (Anafranil(R)) * .

Your healthcare provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your healthcare provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your healthcare provider or pharmacist where to find more information.

*The following are registered trademarks of their respective manufacturers: Prozac(R)/Eli Lilly and Company; Zoloft(R)/Pfizer Pharmaceuticals; Anafranil(R)/Mallinckrodt Inc.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

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