Safety profile proven comparable to acyclovir in clinical trials

In recurrent genital herpes, the most common adverse events with VALTREX versus placebo are mild and include headache (17% vs 14%) and nausea (6% vs 8%). For herpes zoster, the most common adverse events with VALTREX versus acyclovir are mild and include nausea (16% vs 19%) and headache (13% vs 13%).

Reference:

1. de Miranda P, Burnette TC, Smith C, Harrington J, Reardon J. Mechanisms of the enhanced oral bioavailability of acyclovir with the prodrug valacyclovir HCl (VALTREX™). Presented at the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy. October 4-7, 1994; Orlando, Fla. Abstract A70.

BRIEF SUMMARY

VALTREX®

(valacyclovir hydrochloride)
Caplets

CONTRAINDICATIONS: VALTREX is contraindicated in patients with a known hypersensitivity or intolerance to valacyclovir, acyclovir, or any component of the formulation.

WARNINGS: THROMBOTIC THROMBOCYTOPENIC PURPURA/HEMOLYTIC UREMIC SYNDROME (TTP/HUS), IN SOME CASES RESULTING IN DEATH, HAS BEEN REPORTED IN PATIENTS WITH ADVANCED HIV DISEASE AND ALSO IN BONE MARROW TRANSPLANT AND RENAL TRANSPLANT RECIPIENTS PARTICIPATING IN CLINICAL TRIALS OF VALTREX. VALTREX IS NOT INDICATED FOR THE TREATMENT OF IMMUNOCOMPROMISED PATIENTS. THIS SYNDROME HAS NOT BEEN OBSERVED IN IMMUNOCOMPETENT PATIENTS TREATED WITH VALTREX IN CLINICAL TRIALS.

PRECAUTIONS: The efficacy of VALTREX has not been established in immunocompromised patients or for the treatment of initial genital herpes infection, disseminated herpes zoster, or suppression of recurrent genital herpes.

Dosage adjustment is recommended when administering VALTREX to patients with renal impairment (see DOSAGE AND ADMINISTRATION). Caution should also be exercised when administering VALTREX to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction and/or the risk of reversible central nervous system symptoms such as those that have been reported in patients treated with intravenous acyclovir.

Information for Patients: ***Herpes Zoster:*** There are no data on treatment initiated more than 72 hours after onset of the zoster rash. Patients should be advised to initiate treatment as soon as possible after a diagnosis of herpes zoster.

Recurrent Genital Herpes: Patients should be informed that VALTREX is not a cure for genital herpes. There are no data evaluating whether VALTREX will prevent transmission of infection to others. Because genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. If medical management of a genital herpes recurrence is indicated, patients should be advised to initiate therapy at the first sign or symptom of an episode. There are no data on the effectiveness of treatment with VALTREX when initiated more than 24 hours after the onset of signs or symptoms.

Drug Interactions: An additive increase in acyclovir AUC and C_{max} was observed when VALTREX was administered to healthy volunteers who were taking cimetidine, probenecid, or a combination of both cimetidine and probenecid (see CLINICAL PHARMACOLOGY: Pharmacokinetics section of full prescribing information).

Carcinogenesis, Mutagenesis, Impairment of Fertility: The data presented below include references to the steady-state acyclovir AUC observed in humans treated with 1 g VALTREX given orally three times a day to treat herpes zoster. Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir (see CLINICAL PHARMACOLOGY: Pharmacokinetics section of full prescribing information).

Valacyclovir was noncarcinogenic in lifetime carcinogenicity bioassays at single daily doses (gavage) of up to 120 mg/kg/day for mice and 100 mg/kg/day for rats. There was no significant difference in the incidence of tumors between treated and control animals, nor did valacyclovir shorten the latency of tumors. Plasma concentrations of acyclovir were equivalent to human levels in the mouse bioassay and 1.4 to 2.3 times human levels in the rat bioassay.

Valacyclovir was tested in five genetic toxicity assays. An Ames assay was negative in the absence or presence of metabolic activation. Also negative were an in vitro cytogenetic study with human lymphocytes and a rat cytogenetic study at a single oral dose of 3000 mg/kg (8 to 9 times human plasma levels).

In the mouse lymphoma assay, valacyclovir was negative in the absence of metabolic activation. In the presence of metabolic activation (76% to 88% conversion to acyclovir), valacyclovir was weakly mutagenic.

A mouse micronucleus assay was negative at 250 mg/kg but weakly positive at 500 mg/kg (acyclovir concentrations 26 to 51 times human plasma levels).

Valacyclovir did not impair fertility or reproduction in rats at 200 mg/kg/day (6 times human plasma levels).

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B. Valacyclovir was not teratogenic in rats or rabbits given 400 mg/kg (which results in exposures of 10 and 7 times human plasma levels, respectively) during the period of major organogenesis. There are no adequate and well-controlled studies of VALTREX or ZOVIRAX® (acyclovir) in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy has been ongoing since 1984. As of December 1994, outcomes of live births have been documented in 380 women exposed to systemic acyclovir during the first trimester of pregnancy. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. VALTREX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy Exposure Registry: To monitor maternal-fetal outcomes of pregnant women exposed to VALTREX, Glaxo Wellcome Inc. maintains a Valacyclovir in Pregnancy Registry. Physicians are encouraged to register their patients by calling (800) 722-9292, ext. 58465.

Nursing Mothers: There is no experience with VALTREX. However, acyclovir concentrations have been documented in breast milk in two women following oral administration of ZOVIRAX and ranged from 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir as high as 0.3 mg/kg/day. VALTREX should be administered to a nursing mother with caution and only when indicated. Consideration should be given to temporary discontinuation of nursing, as the safety of VALTREX has not been established in infants.

Pediatric Use: Safety and effectiveness of VALTREX in pediatric patients have not been established.

Geriatric Use: Of the total number of patients included in clinical studies of VALTREX, 810 were age 65 or older, and 339 were age 75 or older. A total of 34 volunteers age 65 or older completed a pharmacokinetic trial of VALTREX. The pharmacokinetics of acyclovir following single- and multiple-dose oral administration of VALTREX in geriatric volunteers varied with renal function. Dosage reduction may be required in geriatric patients, depending on the underlying renal status of the patient (see CLINICAL PHARMACOLOGY section of full prescribing information and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: The adverse events reported by greater than 2% of a given treatment group in clinical trials of VALTREX are listed in Table 1.

Table 1
Incidence (%) of Adverse Events in Herpes Zoster and Genital Herpes Study Populations

	Herpes Zoster				Genital Herpes	
	>50 years Median age = 69		18-50 years Median age = 36		18-79 years Median age = 34	
Adverse Event	**VALTREX** (n=765) 1 g tid x 14 days: n=381; 7 days: n=384	**ZOVIRAX** (n=376) 800 mg 5x daily x 7 days	**VALTREX** (n=202) 1 g tid x 7 days	**Placebo** (n=195)	**VALTREX** (n=1235) 1 g bid x 5 days: n=876 500 mg bid x 5 days: n=359	**Placebo** (n=439)
Nausea	16	19	10	8	6	8
Headache	13	13	17	12	17	14
Vomiting	7	8	4	3	<1	<1
Diarrhea	5	7	4	6	4	6
Constipation	5	5	1	3	<1	<1
Asthenia	4	5	3	4	2	4
Dizziness	4	6	2	2	3	3
Abdominal Pain	3	3	2	2	2	3
Anorexia	3	3	<1	2	<1	<1

OVERDOSAGE: There have been no reports of overdosage from the administration of VALTREX. However, it is known that precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION: (For complete dosage and administration information, see full product labeling for VALTREX.)

Patients with Acute or Chronic Renal Impairment: In patients with reduced renal function, reduction in dosage is recommended (see Table 2).

Table 2
Dosages for Patients with Renal Impairment

Creatinine Clearance (mL/min)	Dosage for Herpes Zoster	Dosage for Genital Herpes
≥50	1 g every 8 hours	500 mg every 12 hours
30 - 49	1 g every 12 hours	500 mg every 12 hours
10 - 29	1 g every 24 hours	500 mg every 24 hours
<10	500 mg every 24 hours	500 mg every 24 hours

U.S. Patent No. 4957924

December 1995

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

Take Your Antiherpetic Experience Beyond Acyclovir...

VALTREX— Write Now

From Glaxo Wellcome Inc.—the creators of acyclovir

VALTREX is indicated for herpes zoster and episodic treatment of recurrent genital herpes in otherwise healthy adults*

Better acyclovir absorption[1]

Greater convenience than acyclovir
One caplet BID x 5 days for recurrent genital herpes†
Two caplets TID x 7 days for herpes zoster‡

Proven effective to reduce the pain and discomfort of recurrent genital herpes

May shorten the duration of postherpetic neuralgia vs acyclovir§

WARNING: Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), in some cases resulting in death, has been reported in some severely immunocompromised patients receiving VALTREX in clinical trials. This syndrome has not been observed in otherwise healthy patients receiving VALTREX.

* VALTREX is not indicated for use in immunocompromised patients.

† No data are available on efficacy of treatment started greater than 24 hours after onset of signs and symptoms.

‡ Most effective when therapy is initiated within 48 hours of rash onset. No data are available on efficacy of treatment started greater than 72 hours after rash onset.

§ In patients ≥ 50 years of age. No effect on the incidence of PHN.

Please see brief summary of Prescribing Information on adjacent pages.

VALTREX®
valacyclovir HCl
500 mg CAPLETS

GlaxoWellcome

BRIEF SUMMARY

ZOVIRAX® Capsules
ZOVIRAX® Tablets
ZOVIRAX® Suspension
(acyclovir)

The following is a brief summary only; see full prescribing information for complete product information, including references.

CONTRAINDICATIONS: ZOVIRAX Capsules, Tablets, and Suspension are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulations.

WARNINGS: ZOVIRAX Capsules, Tablets, and Suspension are intended for oral ingestion only.

PRECAUTIONS:

General: ZOVIRAX has caused decreased spermatogenesis at high parenteral doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility). The recommended dosage should not be exceeded (see DOSAGE AND ADMINISTRATION section of full prescribing information).

Exposure of herpes simplex and varicella-zoster isolates to acyclovir in vitro can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in humans must be borne in mind when treating patients. The relationship between the in vitro sensitivity of herpes simplex or varicella-zoster virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY: Microbiology section of full prescribing information).

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Caution should be exercised when administering ZOVIRAX to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction.

Information for Patients: Patients are instructed to consult with their physician if they experience severe or troublesome adverse reactions, they become pregnant or intend to become pregnant, they intend to breastfeed while taking orally administered ZOVIRAX, or they have any other questions.

Genital Herpes Infections: Genital herpes is a sexually transmitted disease and patients should avoid intercourse when visible lesions are present because of the risk of infecting intimate partners. ZOVIRAX Capsules, Tablets, and Suspension are for oral ingestion only. Medication should not be shared with others. The prescribed dosage should not be exceeded. ZOVIRAX does not eliminate latent viruses. Patients are instructed to consult with their physician if they do not receive sufficient relief in the frequency and severity of their genital herpes recurrences.

There are still unanswered questions concerning reproductive/gonadal toxicity and mutagenesis; long-term studies are continuing. Decreased sperm production has been seen at high doses in some animals; a placebo-controlled clinical study using 400 mg or 1000 mg of ZOVIRAX per day for 6 months in humans did not show similar findings. Chromosomal breaks were seen in vitro after brief exposure to high concentrations. Some other currently marketed medications also cause chromosomal breaks, and the significance of this finding is unknown. A placebo-controlled clinical study using 800 mg of ZOVIRAX per day for 1 year in humans did not show any abnormalities in structure or number of chromosomes.

Herpes Zoster Infections: Adults age 50 or older tend to have more severe shingles, and treatment with ZOVIRAX showed more significant benefit for older patients. Treatment was begun within 72 hours of rash onset in these studies, and was more useful if started within the first 48 hours.

Chickenpox: Although chickenpox in otherwise healthy children is usually a self-limited disease of mild to moderate severity, adolescents and adults tend to have more severe disease. Treatment was initiated within 24 hours of the typical chickenpox rash in the controlled studies, and there is no information regarding the effects of treatment begun later in the disease course. It is unknown whether the treatment of chickenpox in childhood has any effect on long-term immunity. However, there is no evidence to indicate that treatment of chickenpox with ZOVIRAX would have any effect on either decreasing or increasing the incidence or severity of subsequent recurrences of herpes zoster (shingles) later in life. Intravenous ZOVIRAX is indicated for the treatment of varicella-zoster infections in immunocompromised patients.

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced. The clinical effects of this combination have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 6 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 6 times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see CLINICAL PHARMACOLOGY: Pharmacokinetics section of full prescribing information).

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. At 450 mg/kg/day, plasma concentrations were 3 to 6 times human levels in the mouse bioassay and 1 to 2 times human levels in the rat bioassay.

Acyclovir was tested in two in vitro cell transformation assays. Positive results were observed at the highest concentration tested (31 to 63 times human levels) in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative (40 to 80 times human levels) in the other, possibly less sensitive, transformation assay.

In acute cytogenetic studies, there was an increase, though not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of acyclovir (100 mg/kg) in rats (62 to 125 times human levels) but not in Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters (380 to 760 times human levels). In addition, no activity was found after 5 days dosing in a dominant lethal study in mice (36 to 73 times human levels). In all 4 microbial assays, no evidence of mutagenicity was observed. Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells in vitro. In human lymphocytes, a positive response for chromosomal damage was seen at concentrations 150 to 300 times the acyclovir plasma levels achieved in humans. At one locus in mouse lymphoma cells, mutagenicity was observed at concentrations 250 to 500 times human plasma levels. Results in the other five mammalian cell loci follow: at 3 loci in a Chinese hamster ovary cell line, the results were inconclusive at concentrations at least 1850 times human levels; at 2 other loci in mouse lymphoma cells, no evidence of mutagenicity was observed at concentrations at least 1500 times human levels.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). In the mouse study, plasma levels were 9 to 18 times human levels, while in the rat study they were 8 to 15 times human levels. At a higher dose in the rat (50 mg/kg/day, s.c.), there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day (16 to 31 times human levels). No effect upon implantation efficiency was observed when the same dose was administered intravenously (53 to 106 times human levels). In a rat peri- and postnatal study at 50 mg/kg/day s.c. (11 to 22 times human levels), there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites, and live fetuses in the F_1 generation. Although not statistically significant, there was also a dose-related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size (plasma levels were not measured). However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (53 to 106 times human levels), no drug-related reproductive effects were observed.

Intraperitoneal doses of 80 or 320 mg/kg/day acyclovir given to rats for 6 and 1 months, respectively, caused testicular atrophy. Plasma levels were not measured in the 1-month study and were 24 to 48 times human levels in the 6-month study. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. At 100 mg/kg/day plasma levels were 47 to 94 times human levels, while at 200 mg/kg/day they were 159 to 317 times human levels. No testicular abnormalities were seen in dogs given 50 mg/kg/day i.v. for 1 month (21 to 41 times human levels) and in dogs given 60 mg/kg/day orally for 1 year (6 to 12 times human levels).

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.), or in standard tests in the rat (50 mg/kg/day, s.c.). These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels. In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity. In this test, rats were given 3 s.c. doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Pregnancy Exposure Registry: To monitor maternal-fetal outcomes of pregnant women exposed to systemic acyclovir, Glaxo Wellcome Inc. maintains an Acyclovir in Pregnancy Registry. Physicians are encouraged to register patients by calling (800) 722-9292, ext. 58465.

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of ZOVIRAX and ranged from 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Caution should be exercised when ZOVIRAX is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children less than 2 years of age have not been adequately studied.

ADVERSE REACTIONS:

Herpes Simplex: ***Short-Term Administration:*** The most frequent adverse events reported during clinical trials of treatment of genital herpes with orally administered ZOVIRAX were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

Less frequent adverse events, each of which occurred in 1 of 298 patient treatments with orally administered ZOVIRAX (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste, and sore throat.

Long-Term Administration: The most frequent adverse events reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 patients treated with ZOVIRAX were: nausea (4.8%), diarrhea (2.4%), headache (1.9%), and rash (1.7%). The 589 control patients receiving intermittent treatment of recurrences with ZOVIRAX for 1 year reported diarrhea (2.7%), nausea (2.4%), headache (2.2%), and rash (1.5%).

The most frequent adverse events reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1.5%), rash (1.3%), and paresthesia (0.8%). Adverse events reported by 329 patients during the third year included asthenia (1.2%), paresthesia (1.2%), and headache (0.9%).

Herpes Zoster: The most frequent adverse events reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral ZOVIRAX 5 times daily for 7 to 10 days in 323 patients were: malaise (11.5%), nausea (8.0%), headache (5.9%), vomiting (2.5%), diarrhea (1.5%), and constipation (0.9%). The 323 placebo recipients reported malaise (11.1%), nausea (11.5%), headache (11.1%), vomiting (2.5%), diarrhea (0.3%), and constipation (2.4%).

Chickenpox: The most frequent adverse events reported during three clinical trials of treatment of chickenpox with oral ZOVIRAX in 495 patients were: diarrhea (3.2%), abdominal pain (0.6%), rash (0.6%), vomiting (0.6%), and flatulence (0.4%). The 498 patients receiving placebo reported: diarrhea (2.2%), flatulence (0.8%), and insomnia (0.4%).

Observed During Clinical Practice: Based on clinical practice experience in patients treated with oral ZOVIRAX in the U.S., spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate of their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events which have been received since market introduction include:

General: fever, headache, pain, peripheral edema, and rarely, anaphylaxis
Nervous: confusion, dizziness, hallucinations, paresthesia, somnolence (These symptoms may be marked, particularly in older adults.)
Digestive: diarrhea, elevated liver function tests, gastrointestinal distress, nausea
Hemic and Lymphatic: leukopenia, lymphadenopathy
Musculoskeletal: myalgia
Skin: alopecia, pruritus, rash, urticaria
Special Senses: visual abnormalities
Urogenital: elevated creatinine

OVERDOSAGE: Patients have ingested intentional overdoses of up to 100 capsules (20 g) of ZOVIRAX, with no unexpected adverse effects.

Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) in the intratubular fluid is exceeded. Renal lesions considered to be related to obstruction of renal tubules by precipitated drug crystals occurred in the following species: rats treated with i.v. and i.p. doses of 20 mg/kg/day for 21 and 31 days, respectively, and at s.c. doses of 100 mg/kg/day for 10 days; rabbits at s.c. and i.v. doses of 50 mg/kg/day for 13 days; and dogs at i.v. doses of 100 mg/kg/day for 31 days. A 6-hour hemodialysis results in a 60% decrease in plasma acyclovir concentration. Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION section of full prescribing information).

U.S. Patent No. 4199574

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Research Triangle Park, NC 27709

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VOL 5 NO. 7, JULY/AUGUST 1996

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LETTERS TO THE EDITOR

ORIGINAL CONTRIBUTIONS

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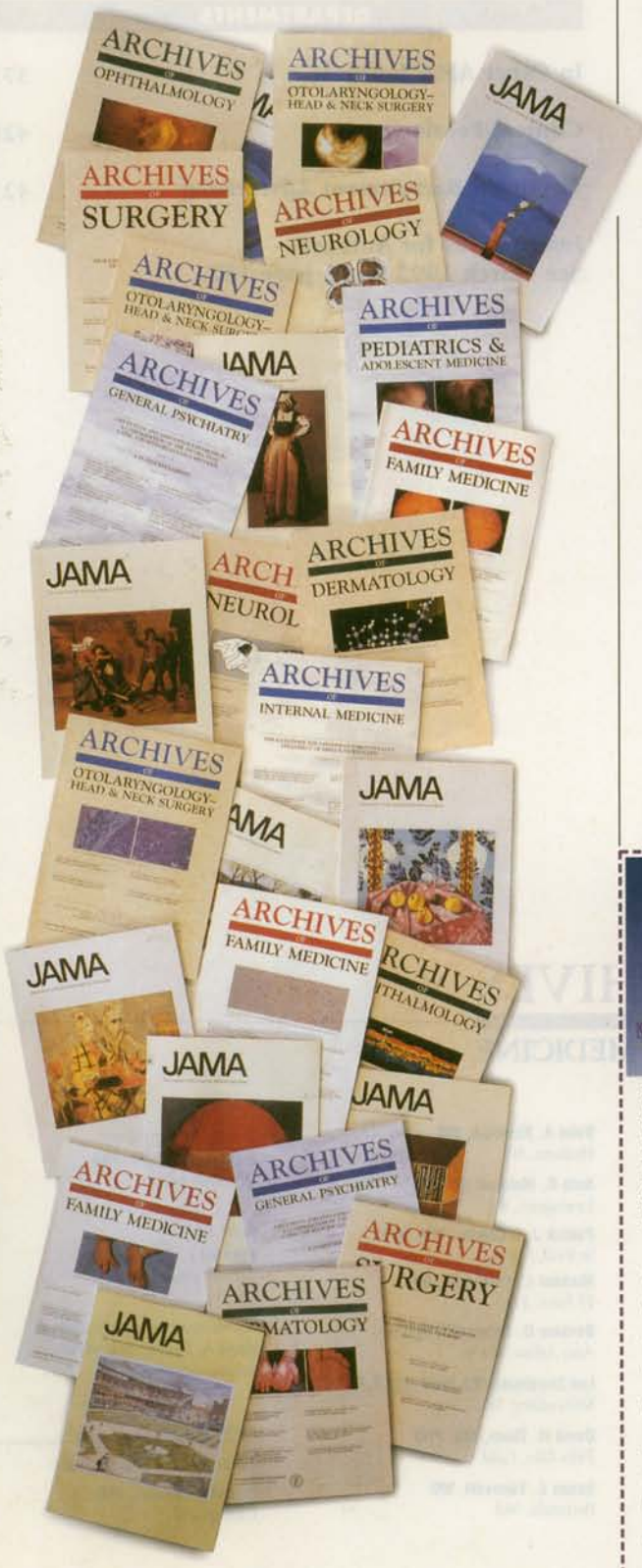

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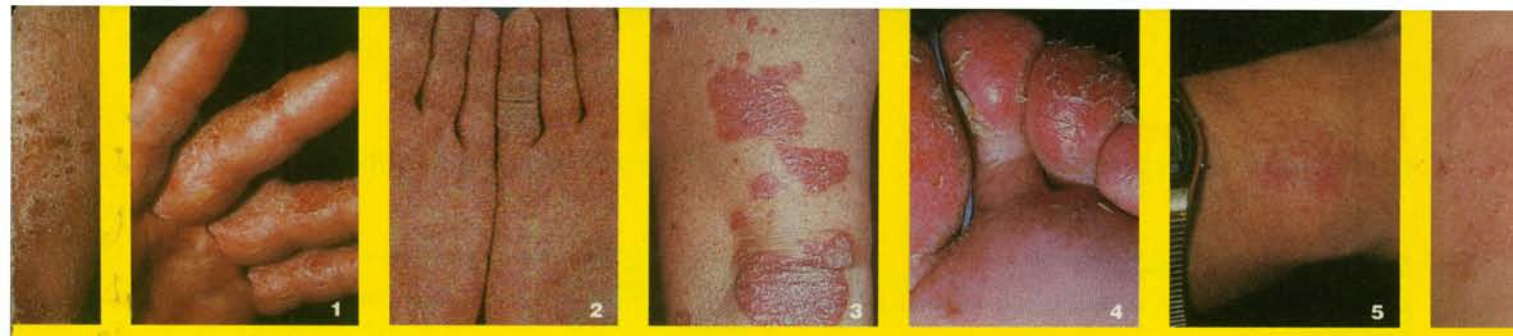

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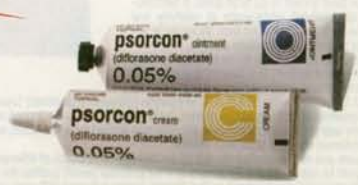

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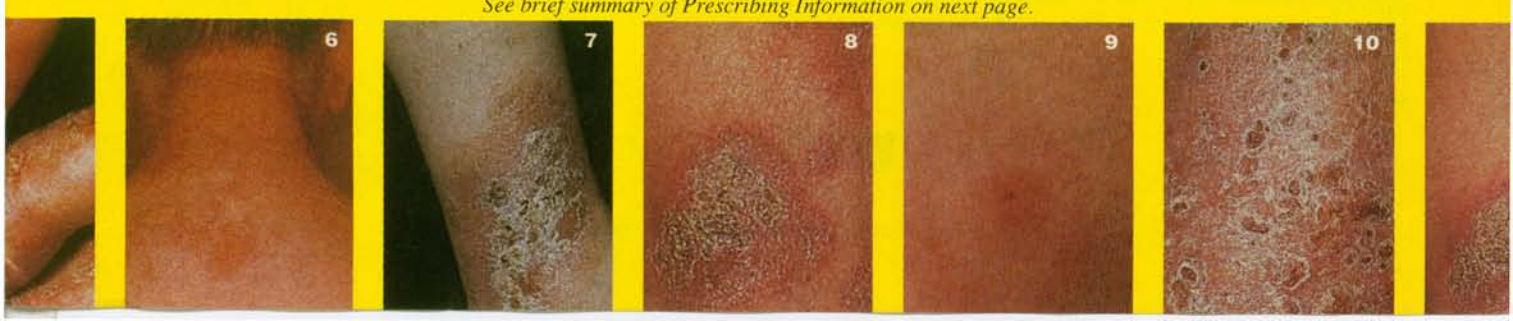
1. Data on file, Dermik Laboratories, Inc.
2. Manufacturer's Prescribing Information

For Your RASH Decisions

Topical corticosteroids may cause local adverse reactions including burning, itching, irritation and dryness. Prolonged use on large body surface areas can produce reversible HPA axis suppression.

See brief summary of Prescribing Information on next page.



PSORCON® Cream
(diflorasone diacetate 0.05%)

Brief Summary — Consult package insert for full prescribing information.
For Dermatological Use Only — Not for Ophthalmic Use.

INDICATION AND USAGE
psorcon (diflorasone diacetate) Cream, 0.05% is a high potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS
psorcon (diflorasone diacetate) Cream is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS
General: Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical cortico-steroids while on treatment.
Patients receiving a large dose of a higher potency topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH-stimulation, A.M. plasma cortisol, and urinary-free cortisol tests.
This product has a greater ability to produce adrenal suppression than does **psorcon** (diflorasone diacetate) Ointment, 0.05%. At 30 g per day (applied as 15 g twice daily) **psorcon** Cream, 0.05% was shown to cause inhibition of the HPA axis in one of two patients following application for one week to psoriatic skin. At 15 g per day (applied as 7.5 g twice daily) **psorcon** Cream was shown to cause mild inhibition of the HPA axis in one of five patients following application for one week to diseased skin (psoriasis or atopic dermatitis). These effects were reversible upon discontinuation of treatment. By comparison, **psorcon** (diflorasone diacetate) Ointment, 0.05% did not produce significant HPA axis suppression when used in divided doses at 30 g per day for one week in patients with psoriasis or atopic dermatitis.
If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur, requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.
Children may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios (see PRECAUTIONS: Pediatric Use).
If irritation develops, **psorcon** (diflorasone diacetate) Cream should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.
If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of **psorcon** (diflorasone diacetate) Cream should be discontinued until the infection has been adequately controlled.
psorcon (diflorasone diacetate) Cream should not be used in the treatment of rosacea or perioral dermatitis, and it should not be used on the face, groin, or axillae.
Information for Patients: Patients using topical corticosteroids should receive the following information and instructions:
1. The medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. The medication should not be used for any disorder other than that for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician.
4. Patients should report to their physician any signs of local adverse reactions.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential of diflorasone diacetate.
Diflorasone diacetate was not found to be mutagenic in a micronucleus test in rats at dosages of 2400 mg/kg.
Studies in the rat following topical administration at doses up to 0.5 mg/kg revealed no effects on fertility.
Pregnancy: Teratogenic effects. Pregnancy Category C. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.
Diflorasone diacetate has been shown to be teratogenic (cleft palate) in rats when applied topically at a dose of approximately 0.001 mg/kg/day to the shaven thorax of pregnant animals. This is approximately 0.3 times the human topical dose of **psorcon** (diflorasone diacetate) Cream. When pregnant rats were treated topically with approximately 0.5 mg/kg/day, uterine deaths were higher in the treated animals than in control animals.
In rabbits, cleft palate was seen when diflorasone diacetate was applied in topical doses as low as 20 mg/kg/day. In addition, fetal weight was depressed and litter sizes were smaller.
There are no adequate and well-controlled studies of the teratogenic potential of diflorasone diacetate in pregnant women. **psorcon** Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when **psorcon** (diflorasone diacetate) Cream is administered to a nursing woman.
Pediatric Use: Safety and effectiveness of **psorcon** (diflorasone diacetate) Cream in children have not been established. Because of a higher ratio of skin surface area to body mass, children are at a greater risk than adults of HPA-axis suppression when they are treated with topical corticosteroids. They are, therefore, also at greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing's syndrome while on treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.
HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

ADVERSE REACTIONS
The following local adverse reactions have been reported infrequently with other topical corticosteroids, and they may occur more frequently with the use of occlusive dressings, especially with higher potency corticosteroids. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infections, skin atrophy, striae, and miliaria.

OVERDOSAGE
Topically applied **psorcon** (diflorasone diacetate) Cream can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).

Rev. September 1992

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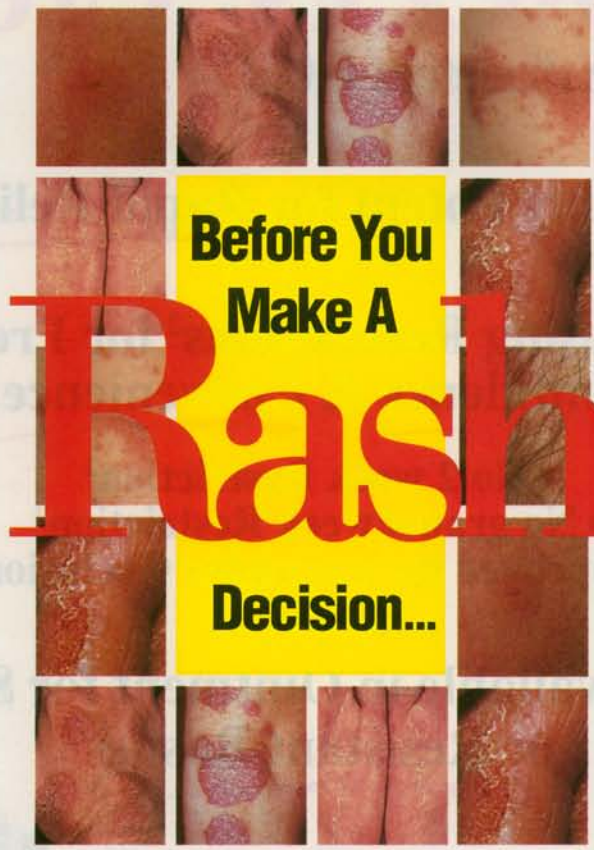

PSORCON® Ointment
(diflorasone diacetate 0.05%)

Brief Summary—Consult package insert for full prescribing information.
Not For Ophthalmic Use.

INDICATIONS AND USAGE
Topical corticosteroids are indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS
Topical steroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS
General
Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.
Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.
Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.
Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.
Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See PRECAUTIONS—Pediatric Use.)
If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.
In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.
Information for the Patient
Patients using topical corticosteroids should receive the following information and instructions:
1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
4. Patients should report any signs of local reactions especially under occlusive dressing.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.
Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.
Pregnancy Category C
Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.
Nursing Mothers
It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities **not** likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.
Pediatric Use
Pediatric patients may demonstrate greater susceptibility to topical corticosteroid- induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.
Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.
Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS
The following local adverse reactions have been reported with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, miliaria.

OVERDOSAGE
Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects. (See PRECAUTIONS.)

Revised June 1990
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anatomic site, oral stimulation, and body position on estimates of body temperature.

Results: Mean rectal temperatures exceeded concurrent oral readings by 0.4°C ± 0.4°C (0.8°F ± 0.7°F), which, in turn, exceeded concurrent tympanic membrane readings (obtained with a digital thermometer [IVAC Corp, San Diego, Calif]) by 0.4°C ± 1.1°C (0.7°F ± 2.0°F). Tympanic membrane readings were significantly more variable (both intrasubject and intersubject) than rectal or oral readings, especially when cerumen was present in the external ear canal being examined ($P<.05$). Mastication and smoking both caused significant increases in oral temperature that persisted for greater than 20 minutes. Drinking ice water caused a significant but more transient decrease in oral temperature. Of these activities, only mastication appeared to influence tympanic membrane readings. Body position exerted a modest effect on rectal temperature readings, but did not significantly affect oral or tympanic membrane readings.

Conclusions: These findings indicate that, in addition to diurnal fluctuations in body temperature, the effects of anatomic site, oral stimulation, and body position should be considered in establishing criteria for the febrile state.

(1996;156:777-780) Ronald P. Rabinowitz, MD, et al, University of Maryland Medical System, R. Adams Crowley Shock Trauma Center, 22 S Greene St, T3R68, Baltimore, MD 21201.

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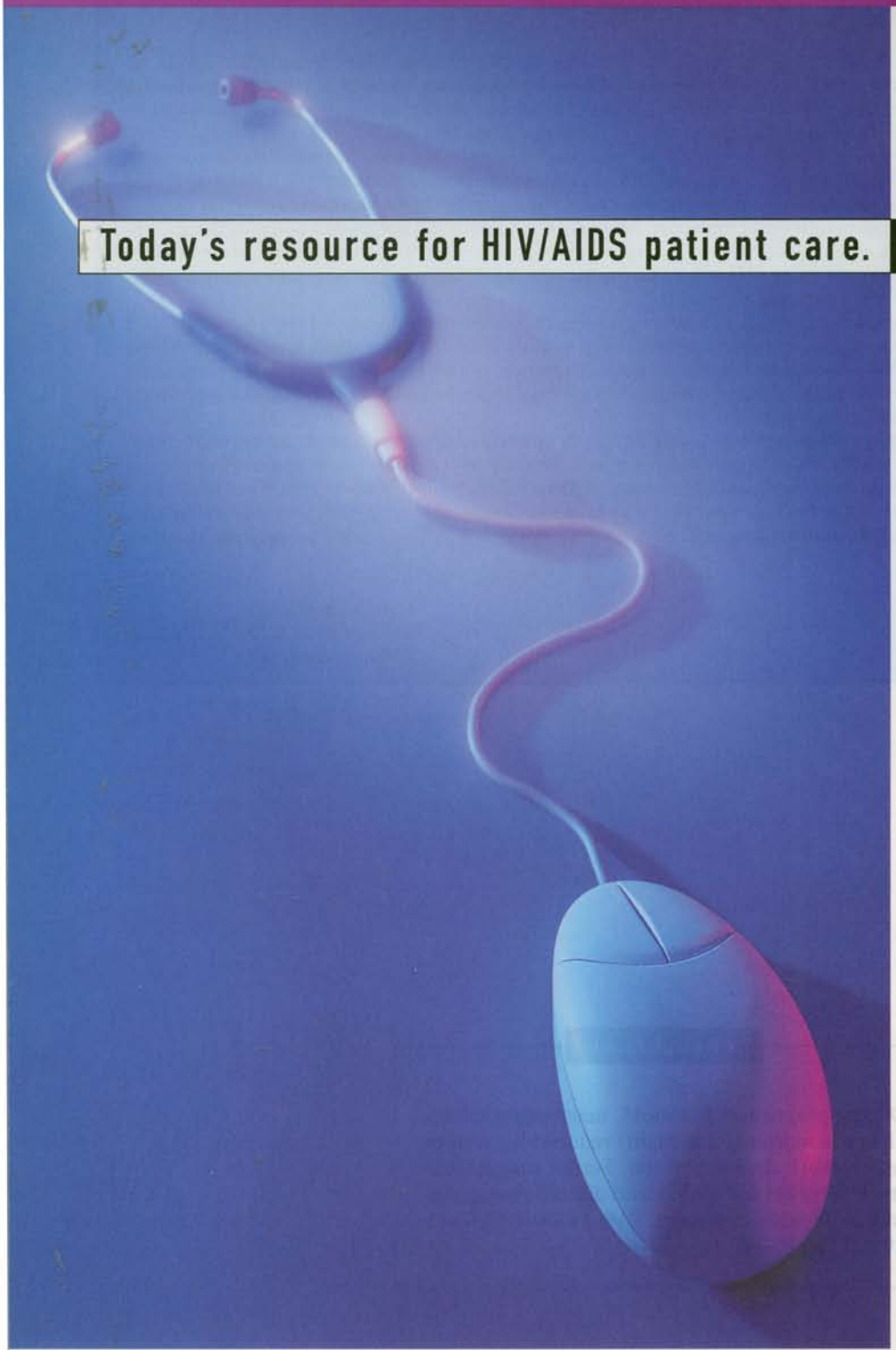

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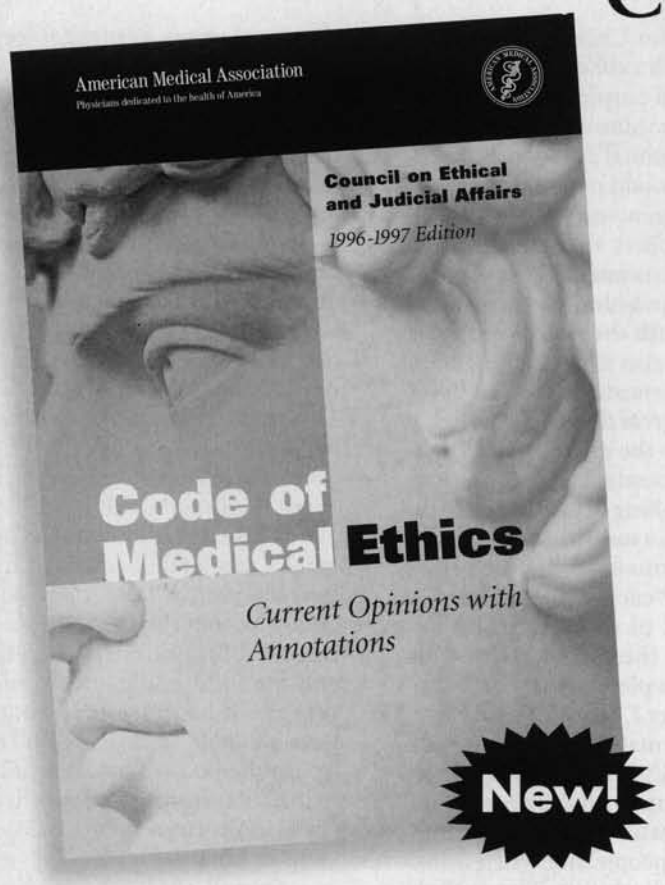

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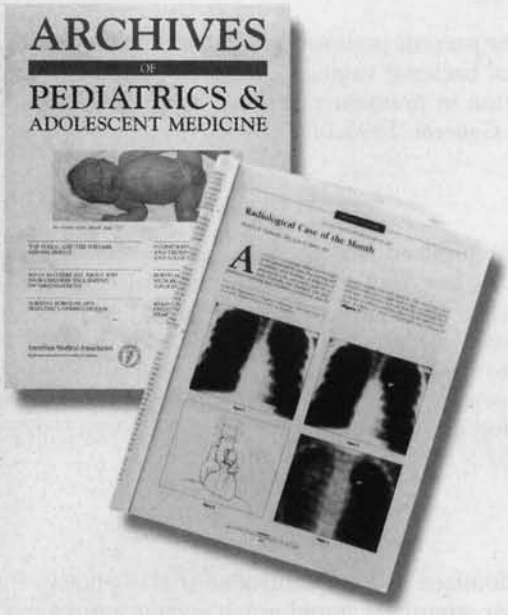

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(ciprofloxacin hydrochloride) TABLETS

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INDICATIONS AND USAGE

Cipro® is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below. Please see DOSAGE AND ADMINISTRATION for specific recommendations.

Lower Respiratory Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae,* or *Streptococcus pneumoniae.*

Skin and Skin Structure Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis,* or *Streptococcus pyogenes.*

Bone and Joint Infections caused by *Enterobacter cloacae, Serratia marcescens,* or *Pseudomonas aeruginosa.*

Urinary Tract Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter diversus, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus epidermidis,* or *Enterococcus faecalis.*

Typhoid Fever (Enteric Fever) caused by *Salmonella typhi.*

NOTE: The efficacy of ciprofloxacin in the eradication of the chronic typhoid carrier state has not been demonstrated.

Sexually Transmitted Diseases (See WARNINGS.)

Uncomplicated cervical and urethral gonorrhea due to *Neisseria gonorrhoeae.*

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni, Shigella flexneri** or *Shigella sonnei** when antibacterial therapy is indicated.

*Although treatment of infections due to this organism in this organ system demonstrated a clinically significant outcome, efficacy was studied in fewer than 10 patients.

If anaerobic organisms are suspected of contributing to the infection, appropriate therapy should be administered.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with Cipro® may be initiated before results of these tests are known; once results become available appropriate therapy should be continued. As with other drugs, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ciprofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

CONTRAINDICATIONS

Cipro® (ciprofloxacin hydrochloride) is contraindicated in persons with a history of hypersensitivity to ciprofloxacin or any member of the quinolone class of antimicrobial agents.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN CHILDREN, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (SEE PRECAUTIONS-PEDIATRIC USE, PREGNANCY AND NURSING MOTHERS SUBSECTIONS.) The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. (See ANIMAL PHARMACOLOGY.)

Convulsions have been reported in patients receiving ciprofloxacin. Convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving drugs in this class. Quinolones may also cause central nervous system (CNS) stimulation which may lead to tremors, restlessness, lightheadedness, confusion and hallucinations. If these reactions occur in patients receiving ciprofloxacin, the drug should be discontinued and appropriate measures instituted. As with all quinolones, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis, epilepsy, and other factors that predispose to seizures. (See ADVERSE REACTIONS.)

SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF CIPROFLOXACIN AND THEOPHYLLINE. These reactions have included cardiac arrest, seizure, status epilepticus and respiratory failure. Although similar serious adverse events have been reported in patients receiving theophylline alone, the possibility that these reactions may be potentiated by ciprofloxacin cannot be eliminated. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Ciprofloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high dose for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with ciprofloxacin should have a follow-up serologic test for syphilis after three months.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should be administered as indicated.

Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have also been rarely reported in patients receiving ciprofloxacin along with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ciprofloxacin, and may range 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, 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.

PRECAUTIONS

General: Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals, which is usually alkaline. (See ANIMAL PHARMACOLOGY.) Crystalluria related to ciprofloxacin has been reported only rarely in humans because human urine is usually acidic. Alkalinity of the urine should be avoided in patients receiving ciprofloxacin. Patients should be well hydrated to prevent the formation of highly concentrated urine.

Alteration of the dosage regimen is necessary for patients with impairment of renal function. (See DOSAGE AND ADMINISTRATION.)

Moderate to severe phototoxicity manifested by an exaggerated sunburn reaction has been observed in patients who are exposed to direct sunlight while receiving some members of the quinolone class of drugs. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity occurs.

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

Information for Patients: Patients should be advised that ciprofloxacin may be taken with or without meals. The preferred time of dosing is two hours after a meal. Patients should also be advised to drink fluids liberally and not take antacids containing magnesium, aluminum, or calcium, products containing iron, or multivitamins containing zinc. However, usual dietary intake of calcium has not been shown to alter the absorption of ciprofloxacin.

Patients should be advised that ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.

Patients should be advised to avoid excessive sunlight or artificial ultraviolet light while receiving ciprofloxacin and to discontinue therapy if phototoxicity occurs.

Ciprofloxacin may cause dizziness and lightheadedness; therefore patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

Patients should be advised that ciprofloxacin may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed while taking quinolones.

Drug Interactions: As with some other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated serum concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. (See WARNINGS.) If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

In rare instances, some quinolones, including ciprofloxacin, have been reported to interact with phenytoin leading to altered levels of serum phenytoin concentrations.

The concomitant administration of some quinolones, including ciprofloxacin, with the sulfonylurea glyburide has on rare occasions resulted in severe hypoglycemia.

Some quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its serum half-life.

Concurrent administration of ciprofloxacin with antacids containing magnesium, aluminum, or calcium; with sucralfate or divalent and trivalent cations such as iron may substantially interfere with the absorption of ciprofloxacin, resulting in serum and urine levels considerably lower than desired. To a lesser extent this effect is demonstrated with zinc-containing multivitamins. (See DOSAGE AND ADMINISTRATION for concurrent administration of these agents with ciprofloxacin.)

Some quinolones, including ciprofloxacin, have been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Quinolones have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

Probenecid interferes with renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

As with other broad spectrum antimicrobial agents, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition and microbial susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below:

- Salmonella/Microsome Test (Negative)
- *E. coli* DNA Repair Assay (Negative)
- Mouse Lymphoma Cell Forward Mutation Assay (Positive)
- Chinese Hamster V_{79} Cell HGPRT Test (Negative)
- Syrian Hamster Embryo Cell Transformation Assay (Negative)
- *Saccharomyces cerevisiae* Point Mutation Assay (Negative)
- *Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion Assay (Negative)
- Rat Hepatocyte DNA Repair Assay (Positive)

Thus 2 of the 8 tests were positive but results of the following 3 *in vivo* test systems gave negative results:

- Rat Hepatocyte DNA Repair Assay
- Micronucleus Test (Mice)
- Dominant Lethal Test (Mice)

Long term carcinogenicity studies in mice and rats have been completed. After daily oral dosing for up to 2 years, there is no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Pregnancy: Teratogenic Effects. Pregnancy Category C: Reproduction studies have been performed in rats and mice at doses up to 6 times the usual daily human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. Ciprofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See WARNINGS.)

Nursing Mothers: Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking ciprofloxacin, a decision should be made either to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children and adolescents less than 18 years of age have not been established. Ciprofloxacin causes arthropathy in juvenile animals. (See WARNINGS.)

ADVERSE REACTIONS

During clinical investigation, 2,799 patients received 2,868 courses of the drug. Adverse events that were considered likely to be drug related occurred in 7.3% of patients treated, possibly related in 9.2% (total of 16.5% thought to be possibly or probably related to drug therapy), and remotely related in 3.0%. Ciprofloxacin was discontinued because of an adverse event in 3.5% of patients treated, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and central nervous system (0.4%).

The most frequently reported events, drug related or not, were nausea (5.2%), diarrhea (2.3%), vomiting (2.0%), abdominal pain/discomfort (1.7%), headache (1.2%), restlessness (1.1%), and rash (1.1%).

Additional events that occurred in less than 1% of ciprofloxacin treated patients are listed below.

CARDIOVASCULAR: palpitation, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis

CENTRAL NERVOUS SYSTEM: dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia (See above.) (See PRECAUTIONS.)

GASTROINTESTINAL: painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding (See above.) Cholestatic jaundice has been reported.

MUSCULOSKELETAL: joint or back pain, joint stiffness, achiness, neck or chest pain, flare up of gout

RENAL/UROGENITAL: interstitial nephritis, nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis

RESPIRATORY: dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, bronchospasm, pulmonary embolism

SKIN/HYPERSENSITIVITY: pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum (See above.)

Allergic reactions ranging from urticaria to anaphylactic reactions have been reported. (See WARNINGS.)

SPECIAL SENSES: blurred vision, disturbed vision (change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste

Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

In several instances nausea, vomiting, tremor, irritability or palpitation were judged by investigators to be related to elevated serum levels of theophylline possibly as a result of drug interaction with ciprofloxacin.

In domestic clinical trials involving 214 patients receiving a single 250 mg oral dose, approximately 5% of patients reported adverse experiences without reference to drug relationship. The most common adverse experiences were vaginitis (2%), headache (1%), and vaginal pruritus (1%). Additional reactions, occurring in 0.3%-1% of patients, were abdominal discomfort, lymphadenopathy, foot pain, dizziness, and breast pain. Less than 20% of these patients had laboratory values obtained, and these results were generally consistent with the pattern noted for multi-dose therapy.

Post-Marketing Adverse Events: Additional adverse events, regardless of relationship to drug, reported from worldwide marketing experience with quinolones, including ciprofloxacin, are anaphylactic reactions, erythema multiforme/Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, vasculitis, jaundice, hepatic necrosis, toxic psychosis, postural hypotension, possible exacerbation of myasthenia gravis, anosmia, confusion, dysphasia, nystagmus, pancreatitis, dyspepsia, flatulence, constipation, myalgia, tendinitis/rupture and pseudomembranous colitis. The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment. Also reported were hemolytic anemia; agranulocytosis; elevation of serum triglycerides, serum cholesterol, blood glucose, serum potassium; prolongation of prothrombin time; albuminuria; candiduria, vaginal candidiasis; renal calculi; and change in serum phenytoin. (See PRECAUTIONS.)

Adverse Laboratory Changes: Changes in laboratory parameters listed as adverse events without regard to drug relationship:

Hepatic	—	Elevations of: ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).
Hematologic	—	Eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).
Renal	—	Elevations of: Serum creatinine (1.1%), BUN (0.9%). CRYSTALLURIA, CYLINDRURIA AND HEMATURIA HAVE BEEN REPORTED.

Other changes occurring in less than 0.1% of patients treated were: Elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, leukocytosis.

For further information, contact the Bayer Information Service: 1-800-642-4776. In VA, call collect: 703-391-7888.

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