VALTREX®
valacyclovir HCl
500 mg CAPLETS

References: 1. Complete prescribing information for VALTREX® (valacyclovir HCl) Caplets, December 1995. **2.** Data on file, Glaxo Wellcome Inc.

BRIEF SUMMARY

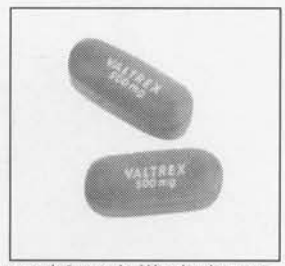
VALTREX®
(valacyclovir hydrochloride)
Caplets

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

FOR EPISODIC TREATMENT OF RECURRENT GENITAL HERPES
IN IMMUNOCOMPETENT ADULTS

VALTREX®

valacyclovir HCl
500 mg CAPLETS

TM

TM

NEW INDICATION:

Proven Effective for Recurrent Genital Herpes[1,2]

- **Shortens duration of recurrent episodes**
- **One 500-mg caplet BID x 5 days**
- **The most common adverse events with VALTREX versus placebo are mild and include headache (17% vs 14%), nausea (6% vs 8%), diarrhea (4% vs 6%), and dizziness (3% vs 3%)**

WARNING: 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.

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

Please see references and brief summary of prescribing information on reverse side.

Printed in U.S.A. VAL111RO February 1996

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Research Triangle Park, NC 27709

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ARCHIVES OF FAMILY MEDICINE

VOL 5 NO. 5, MAY 1996

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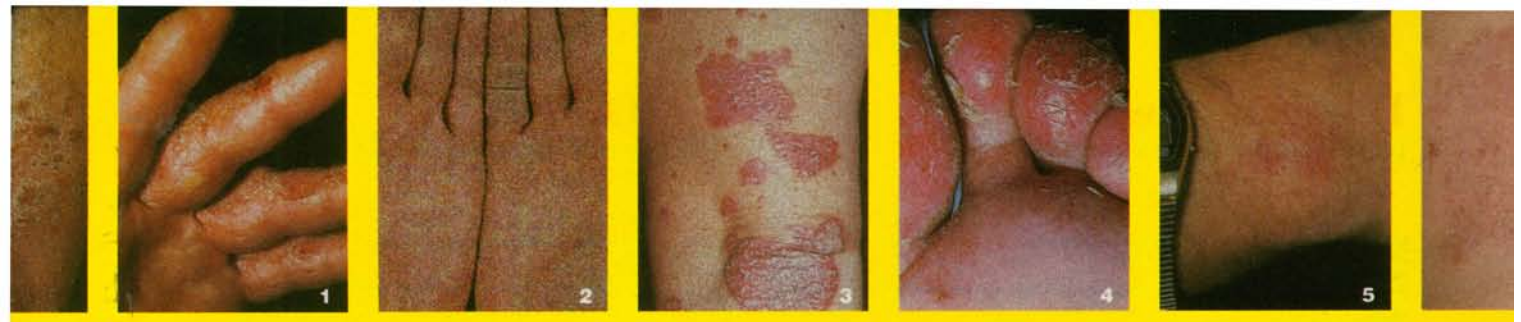

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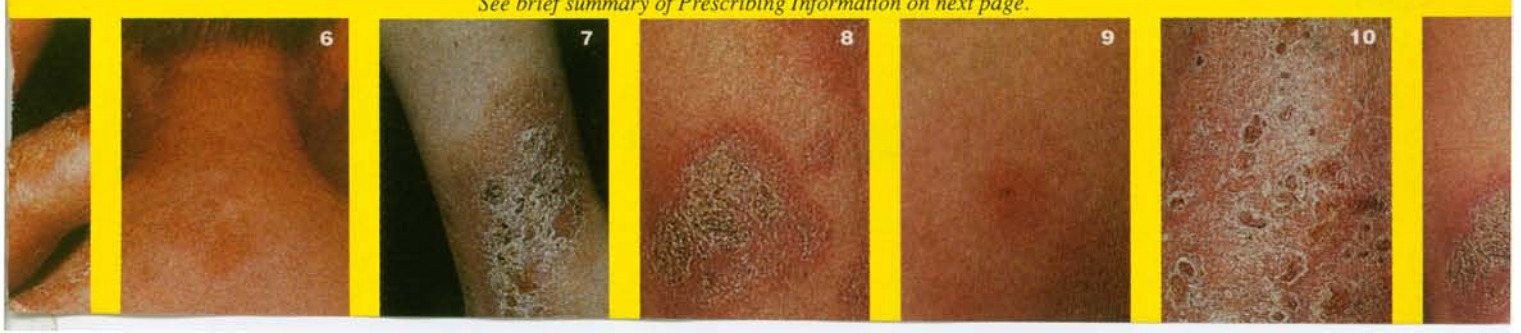
1. Data on file, Dermik Laboratories, Inc.
2. Manufacturer's Prescribing Information

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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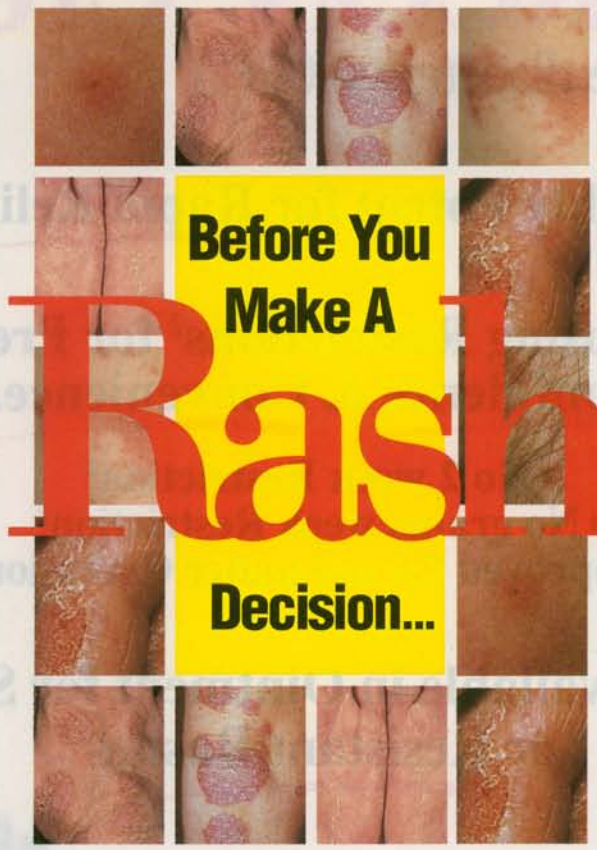

PSORCON® Ointment
(diflorasone diacetate 0.05%)

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.)

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1. A. Morales et al., New England Journal of Medicine: 1221 November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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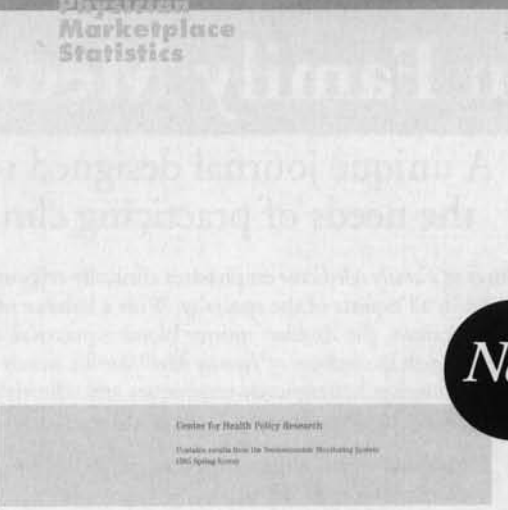

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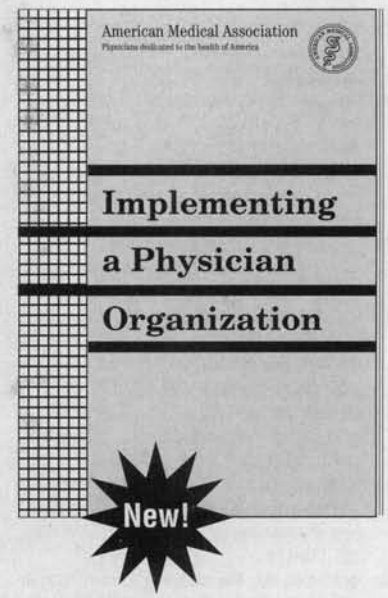

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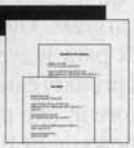

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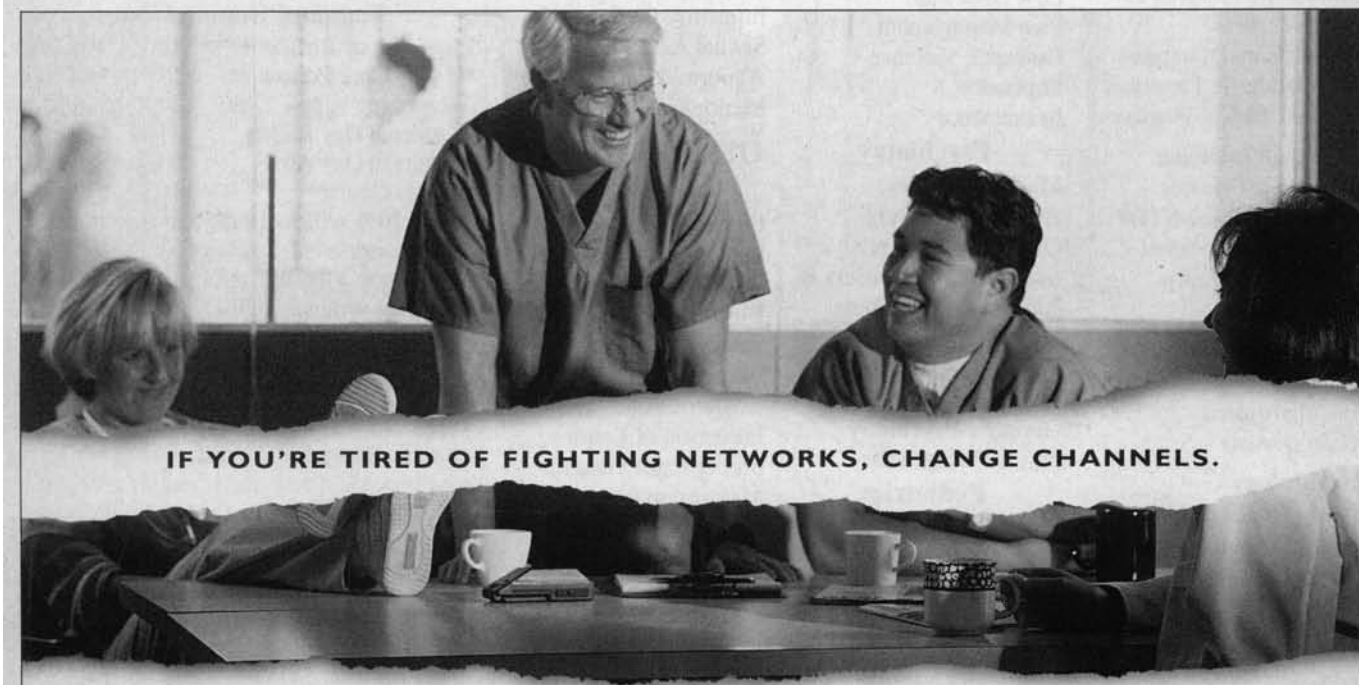

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2. **Congestive Heart Failure**. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
3. **Hypotension**. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury**. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS
General
CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.
Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions
Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with other agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)
As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Especially in patients with renal and/or hepatic impairment, dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, may require adjustment when starting or stopping concomitantly administered diltiazem to maintain optimum therapeutic blood levels.
Beta-blockers. Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.
Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)
Cimetidine. A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.
Digitalis. Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)
Anesthetics. The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.
Cyclosporine. A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15% to 48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted, or discontinued.
The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.
Carbamazepine. Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40% to 72% increase), resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility
A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy
Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.
There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

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

ADVERSE REACTIONS
Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.
The following table presents the most common adverse reactions reported in placebo-controlled angina and hypertension trials in patients receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

CARDIZEM CD Capsule Placebo-Controlled Angina and Hypertension Trials Combined

Adverse Reactions	Cardizem CD (n=607)	Placebo (n=301)
Headache	5.4%	5.0%
Dizziness	3.0%	3.0%
Bradycardia	3.3%	1.3%
AV Block First Degree	3.3%	0.0%
Edema	2.6%	1.3%
ECG Abnormality	1.6%	2.3%
Asthenia	1.8%	1.7%

In clinical trials of CARDIZEM CD capsules, CARDIZEM tablets, and CARDIZEM SR capsules involving over 3200 patients, the most common events (ie, greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.2%).
In addition, the following events were reported infrequently (less than 1%) in angina or hypertension trials:
Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles
Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor
Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, dyspepsia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase
Dermatological: Petechiae, photosensitivity, pruritus, urticaria
Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties
The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

Prescribing Information as of April 1995

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Kansas City, MO 64137 USA

ccdb0495a

References: **1.** Cardizem CD prescribing information. **2.** Felicetta JV, Serfer HM, Cutler NR, et al. *Am Heart J.* 1992;123:1022-1026. **3.** Thadani U, Glasser S, Bittar N, Beach CL, Diltiazem CD Study Group. *Am J Cardiol.* 1994;74:9-17. **4.** Food and Drug Administration. *Approved Drug Products With Therapeutic Equivalence Evaluations* (Orange Book), US Dept of Health and Human Services. 15th ed. Washington, DC;1995.

Benefits of a nondihydropyridine CCB*

A UNIQUE HEMODYNAMIC AND SAFETY PROFILE DIFFERENT FROM DIHYDROPYRIDINES

Effective 24-hour control of hypertension or angina

- Reduces blood pressure with no reflex tachycardia[1]
- Increases exercise tolerance, reduces vasospasm, and decreases heart rate in angina[1]

Well tolerated control regardless of age or gender†

- A side-effect discontinuation rate comparable to placebo[2,3]
- Most commonly reported side effects are headache (5.4%), bradycardia (3.3%), first-degree AV block (3.3%), dizziness (3.0%), edema (2.6%), ECG abnormality (1.6%), and asthenia (1.8%)[1]

True 24-hour control from a unique patented delivery system

- No other diltiazem is therapeutically equivalent to Cardizem CD[4‡]

*Cardizem CD is a benzothiazepine calcium channel blocker.

† In clinical trials with Cardizem CD.
‡ FDA does not, at this time, consider other diltiazems to be therapeutically equivalent because bioequivalence has not been demonstrated through appropriate studies.

Please see brief summary of prescribing information on adjacent page.

FOR HYPERTENSION OR ANGINA

ONCE-A-DAY

CARDIZEM® CD

(diltiazem HCl) 120-, 180-, 240-, 300-mg Capsules

No other diltiazem is therapeutically equivalent[4‡]