For patients with persistent asthma

Introducing the first multiple-strength inhaled corticosteroid with high topical anti-inflammatory activity

- B.i.d. convenience
- Multiple strengths to minimize the number of puffs per dose
- Relatively rapid onset of action
- Rare reports (<1%) of unpleasant taste[1]

Maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment. Onset of action and degree of symptom relief may vary.

FLOVENT is indicated for the maintenance treatment of asthma as prophylactic therapy for patients ≥12 years of age and for patients requiring oral corticosteroid therapy for asthma, many of whom may be able to reduce or eliminate their requirement for oral corticosteroids over time.

FLOVENT is NOT indicated for the relief of acute bronchospasm.

CAUTION: Adrenal insufficiency may occur when transferring patients from systemic steroids (see WARNINGS).

NEW

Control made convenient

FloVent™ 44 mcg 110 mcg 220 mcg

(fluticasone propionate) Inhalation Aerosol

Custom-tailored treatment for *starting, switching, and sparing*

Reference: 1. Data on file, Glaxo Wellcome Inc.

Please consult Brief Summary of Prescribing Information on adjacent page.

GlaxoWellcome

FloVent™ 44 mcg 110 mcg 220 mcg
(fluticasone propionate) Inhalation Aerosol

For Oral Inhalation Only **BRIEF SUMMARY**

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

CONTRAINDICATIONS: FLOVENT Inhalation Aerosol is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of these preparations contraindicates their use.

WARNINGS:

Particular care is needed for patients who are transferred from systemically active corticosteroids to FLOVENT Inhalation Aerosol because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although fluticasone propionate inhalation aerosol may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to fluticasone propionate inhalation aerosol. In a trial of 96 patients, prednisone reduction was successfully accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during transfer to inhaled fluticasone propionate. Successive reduction of prednisone dose was allowed only when lung function, symptoms, and as-needed beta-agonist use were better than or comparable to that seen before initiation of prednisone dose reduction. Lung function (forced expiratory volume in 1 second [FEV$_1$] or morning peak expiratory flow rate [AM PEFR]), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to fluticasone propionate inhalation aerosol may unmask conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, and arthritis.

Persons who are on drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Fluticasone propionate inhalation aerosol is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

As with other inhaled asthma medications, bronchospasm may occur with an immediate increase in wheezing after dosing. If bronchospasm occurs following dosing with FLOVENT Inhalation Aerosol, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with FLOVENT Inhalation Aerosol should be discontinued and alternative therapy instituted.

Patients should be instructed to contact their physicians immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment with fluticasone propionate inhalation aerosol. During such episodes, patients may require therapy with oral corticosteroids.

PRECAUTIONS:

General: During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

Fluticasone propionate will often permit control of asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of fluticasone propionate inhalation aerosol in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing fluticasone propionate inhalation aerosol.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear in a small number of patients, particularly at higher doses. If such changes occur, fluticasone propionate inhalation aerosol should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

A reduction of growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should closely follow the growth of adolescents taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression if an adolescent's growth appears slowed.

The long-term effects of fluticasone propionate in human subjects are not fully known. In particular, the effects resulting from chronic use of fluticasone propionate on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients have received fluticasone propionate inhalation aerosol on a continuous basis for periods of 3 years or longer. In clinical studies with patients treated for nearly 2 years with inhaled fluticasone propionate, no apparent differences in the type or severity of adverse reactions were observed after long- versus short-term treatment.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids.

In clinical studies with inhaled fluticasone propionate, the development of localized infections of the pharynx with *Candida albicans* has occurred. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while remaining on treatment with fluticasone propionate inhalation aerosol, but at times therapy with fluticasone propionate may need to be interrupted.

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

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

Patients should use FLOVENT Inhalation Aerosol at regular intervals as directed. Results of clinical trials indicated significant improvement may occur within the first day or two of treatment; however, the full benefit may not be achieved until treatment has been administered for 1 to 2 weeks or longer. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.

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

For the proper use of FLOVENT Inhalation Aerosol and to attain maximum improvement, the patient should read and follow carefully the Patient's Instructions for Use accompanying the product.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone propionate demonstrated no tumorigenic potential in studies of oral doses up to 1,000 mcg/kg (approximately two times the maximum human daily inhalation dose based on mcg/m^2) for 78 weeks in the mouse or inhalation of up to 57 mcg/kg (approximately 1/4 the maximum human daily inhalation dose based on mcg/m^2) for 104 weeks in the rat.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells *in vitro*. No significant clastogenic effect was seen in cultured human peripheral lymphocytes *in vitro* or in the mouse micronucleus test when administered at high doses by the oral or subcutaneous routes. Furthermore, the compound did not delay erythroblast division in bone marrow.

No evidence of impairment of fertility was observed in reproductive studies conducted in rats dosed subcutaneously with doses up to 50 mcg/kg (approximately 1/4 the maximum human daily inhalation dose based on mcg/m^2) in males and females. However, prostate weight was significantly reduced in rats.

Pregnancy: *Teratogenic Effects: Pregnancy Category C:* Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg, respectively (approximately 1/10 and 1/2 the maximum human daily inhalation dose based on mcg/m^2, respectively), revealed fetal toxicity characteristic of potent glucocorticoid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed following subcutaneous doses of 4 mcg/kg (approximately 1/25 the maximum human daily inhalation dose based on mcg/m^2). However, following oral administration of up to 300 mcg/kg (approximately 3 times the maximum human daily inhalation dose based on mcg/m^2) of fluticasone propionate to the rabbit, there were no maternal effects nor increased incidence of external, visceral, or skeletal fetal defects. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY section of full prescribing information).

Less than 0.008% of the administered dose crossed the placenta following oral administration of 100 mcg/kg to rats or 300 mcg/kg to rabbits (approximately 1/2 and 3 times the maximum human daily inhalation dose based on mcg/m^2, respectively).

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

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

Nursing Mothers: It is not known whether fluticasone propionate is excreted in human breast milk. Subcutaneous administration of 10 mcg/kg titrated drug to lactating rats (approximately 1/20 the maximum human daily inhalation dose based on mcg/m^2) resulted in measurable radioactivity in both plasma and milk. Because glucocorticoids are excreted in human milk, caution should be exercised when fluticasone propionate inhalation aerosol is administered to a nursing woman.

Pediatric Use: One hundred thirty-seven (137) patients between the ages of 12 and 16 years were treated with fluticasone propionate inhalation aerosol in the US pivotal clinical trials. The safety and effectiveness of FLOVENT Inhalation Aerosol in children below 12 years of age have not been established. Oral corticosteroids have been shown to cause a reduction in growth velocity in children and teenagers with extended use. If a child or teenager on any corticosteroid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of corticosteroids should be considered (see PRECAUTIONS).

Geriatric Use: Five hundred seventy-four (574) patients 65 years of age or older have been treated with fluticasone propionate inhalation aerosol in US and non-US clinical trials. There were no differences in adverse reactions compared to those reported by younger patients.

ADVERSE REACTIONS: The following incidence of common adverse experiences is based upon seven placebo-controlled US clinical trials in which 1,243 patients (509 female and 734 male adolescents and adults previously treated with as-needed bronchodilators and/or inhaled corticosteroids) were treated with fluticasone propionate inhalation aerosol (doses of 88 to 440 mcg twice daily for up to 12 weeks) or placebo.

Overall Adverse Experiences With >3% Incidence on Fluticasone Propionate in US Controlled Clinical Trials With MDI in Patients Previously Receiving Bronchodilators and/or Inhaled Corticosteroids

Adverse Event	Placebo (n = 475) %	FLOVENT 88 mcg twice daily (n = 488) %	FLOVENT 220 mcg twice daily (n = 95) %	FLOVENT 440 mcg twice daily (n = 185) %
Ear, nose, and throat				
Pharyngitis	7	10	14	14
Nasal congestion	8	8	16	10
Sinusitis	4	3	6	5
Nasal discharge	3	5	4	4
Dysphonia	1	4	3	8
Allergic rhinitis	4	5	3	3
Oral candidiasis	1	2	3	5
Respiratory				
Upper respiratory infection	12	15	22	16
Influenza	2	3	8	5
Neurological				
Headache	14	17	22	17
Average duration of exposure (days)	44	66	64	59

The table above includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of over 3% in the combined fluticasone propionate inhalation aerosol groups and were more common than in the placebo group. In considering these data, differences in average duration of exposure should be taken into account.

These adverse reactions were mostly mild to moderate in severity, with ≤2% of patients discontinuing the studies because of adverse events. Rare cases of immediate and delayed hypersensitivity reactions, including urticaria and rash and other rare events of angioedema and bronchospasm, have been reported.

Systemic glucocorticoid side effects were not reported during controlled clinical trials with fluticasone propionate inhalation aerosol. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, e.g., Cushing's syndrome, could occur.

Other adverse events that occurred in these clinical trials using fluticasone propionate inhalation aerosol with an incidence of 1% to 3% and which occurred at a greater incidence than with placebo were:

Ear, Nose, and Throat: Pain in nasal sinus(es), rhinitis.
Eye: Irritation of the eye(s).
Gastrointestinal: Nausea and vomiting, diarrhea, dyspepsia and stomach disorder.
Miscellaneous: Fever.
Mouth and Teeth: Dental problem.
Musculoskeletal: Pain in joint, sprain/strain, aches and pains, pain in limb.
Neurological: Dizziness/giddiness.
Respiratory: Bronchitis, chest congestion.
Skin: Dermatitis, rash/skin eruption.
Urogenital: Dysmenorrhea.

In a 16-week study in asthmatics requiring oral corticosteroids, the effects of fluticasone propionate inhalation aerosol, 660 mcg twice daily (n = 32) and 880 mcg twice daily (n = 32), were compared with placebo. Adverse events (whether considered drug-related or nondrug-related by the investigator) reported by more than three patients in either fluticasone propionate group and which were more common with fluticasone propionate than placebo are shown below:

Ear, Nose, and Throat: Pharyngitis (9% and 25%); nasal congestion (19% and 22%); sinusitis (19% and 22%); nasal discharge (16% and 16%); dysphonia (19% and 9%); pain in nasal sinus(es) (13% and 0%); Candida-like oral lesions (16% and 9%); oropharyngeal candidiasis (25% and 19%).
Respiratory: Upper respiratory infection (31% and 19%); influenza (0% and 13%).
Other: Headache (28% and 34%); pain in joint (19% and 13%); nausea and vomiting (22% and 16%); muscular soreness (22% and 13%); malaise/fatigue (22% and 28%); insomnia (3% and 13%).

OVERDOSAGE: There are no data available on the effects of acute or chronic overdosage with FLOVENT Inhalation Aerosol. Inhalation by healthy volunteers of a single dose of 1,760 or 3,520 mcg of fluticasone propionate inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at doses of 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups. Chronic overdosage may result in signs/symptoms of hypercorticism (see PRECAUTIONS). The oral and subcutaneous median lethal doses in rats and mice were >1,000 mg/kg (>2,000 times the maximum human daily inhalation dose based on mg/m^2).

Made in England June 1996 RL-323

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Research Triangle Park, NC 27709

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Announcing

The American Medical Association

Morris Fishbein Fellowship

July 1, 1997, through June 30, 1998

Applications are now being taken for the Morris Fishbein Fellowship in Medical Editing sponsored by the American Medical Association. Physicians interested in making a substantial commitment to medical editing are invited to apply for this full-time 1-year fellowship program.

Work With JAMA The successful candidate will work with the editorial and production staff of The Journal of the American Medical Association in all facets of editing and publishing a major weekly journal. At the completion of the program, it is expected that the candidate will be proficient in manuscript review and selection, issue makeup, copy editing and styling, art and layout of articles, issue planning and managing, in addition to the many other elements of journal publication. He/she will also be conversant with marketing and advertising procedures.

Publishing The candidate must have proven writing ability at the time of application, since he/she will be required during the course of the year to prepare articles for publication. Although the fellow will work under the supervision of a physician-editor, ability to work independently is a must.

Stipend A stipend of $40,000 will be provided to the successful candidate to cover the 1-year period.

Application Forms For an application blank, please write to Richard M. Glass, MD, Deputy Editor, The Journal of the American Medical Association, 515 N State St, Chicago, IL 60610.

Deadline for Applying Completed applications should be forwarded as soon as possible and must be received no later than December 20, 1996.

American Medical Association

Physicians dedicated to the health of America

ARCHIVES OF FAMILY MEDICINE

VOL 5 NO. 9, OCTOBER 1996

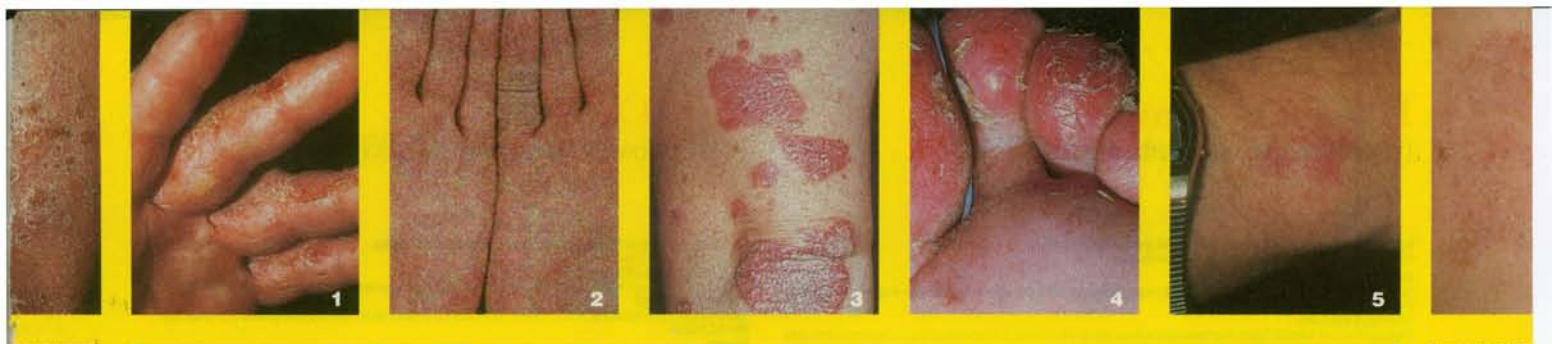
SPECIAL SELECTION

LETTERS TO THE EDITOR

SPECIAL ARTICLE

ORIGINAL CONTRIBUTIONS

American Medical Association
Physicians dedicated to the health of America



PSORCON® Cream

(diflorasone diacetate 0.05%)

- **Highly Potent for Rapid Relief.[1]**
- **Fewer Dosing Restrictions[2] for Prescribing Confidence & Convenience.**
  - **No 2 week Restriction[2]**
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  - **Approved for use under Occlusion[2]**
- **Also available in Ointment for Severe or Resistant Rashes**

Available in 15g, 30g, and economical 60g tubes.

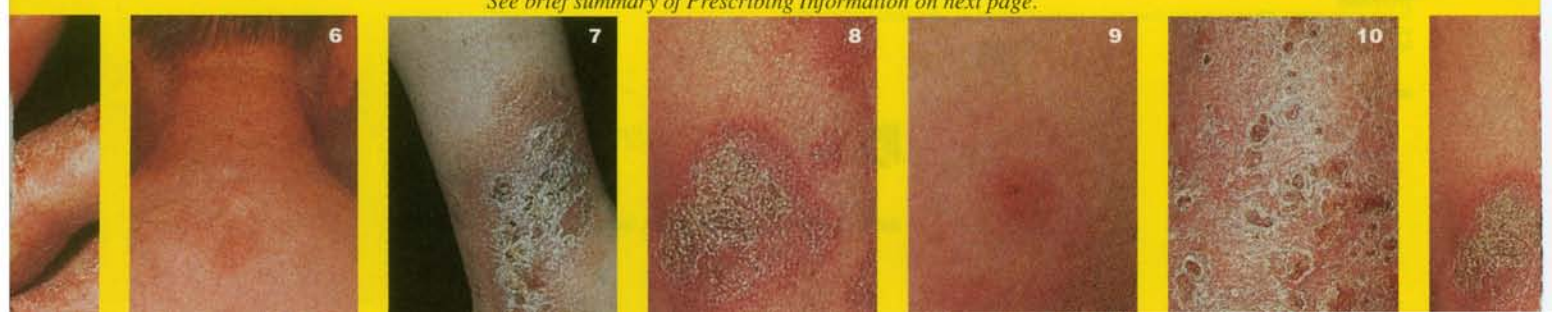
Rash Decisions Diagnosis Code: **1**. Atopic Dermatitis; **2**. Dyshidrotic Eczema; **3**. Psoriasis; **4**. Irritant Contact Dermatitis; **5**. Allergic Contact Dermatitis; **6**. Seborrheic Dermatitis; **7**. Stasis Dermatitis; **8**. Nummular Eczema; **9**. Insect Bites; **10**. Lichen Simplex Chronicus

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).

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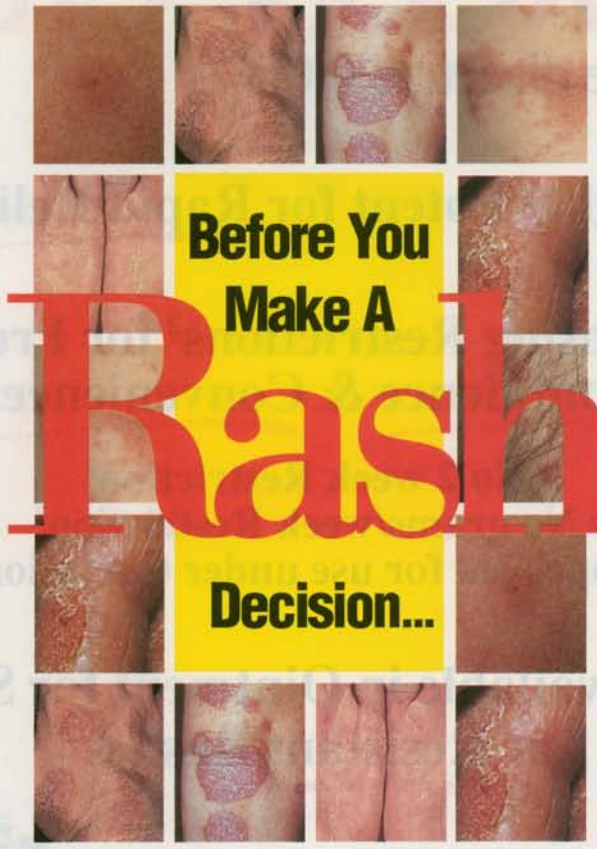

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Not For Ophthalmic Use.

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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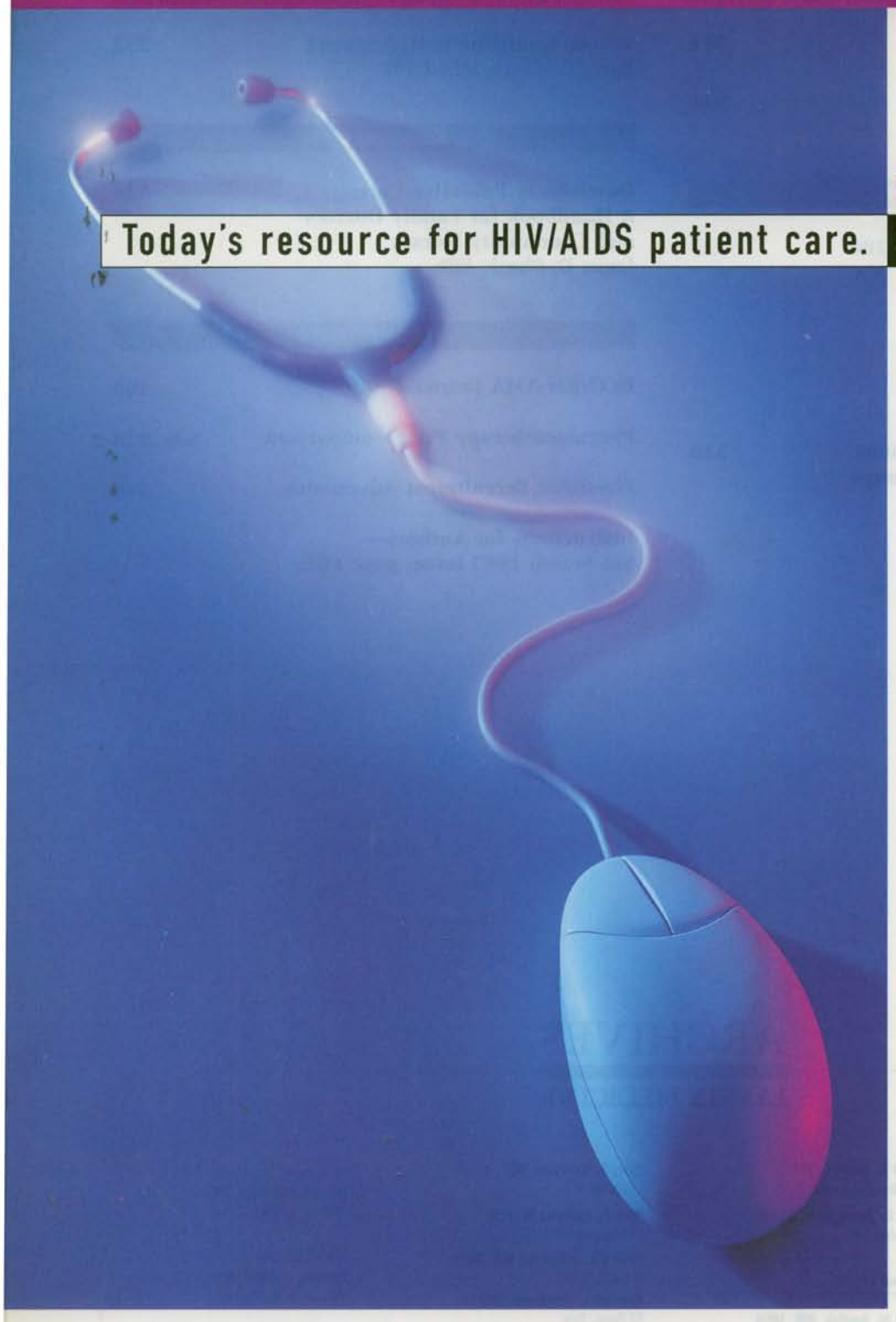

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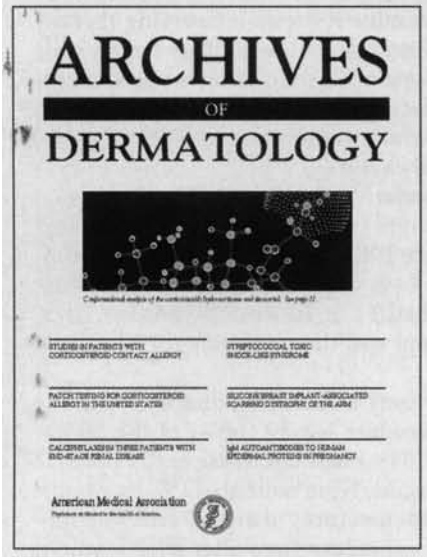

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Editor: Kenneth A. Arndt, MD

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It certainly is true that many of us who practiced medicine in the 1970s and 1980s have a sense of loss with the remarkable recent changes in the American health care system. The feelings engendered by these perceived losses of control, stature, choice, and autonomy are reflected in the discussions in the doctors' lounges of our hospitals, the letters columns of our journals, and the conversations we have with our children about their career plans.

Is the grieving model from the literature of thanatology a useful model to characterize these losses? There is much that is attractive in the model, for it is tempting to want a system to understand our feelings, and many of us have been angry and confused at times. But the model implies a finality—for death is certainly immutable—and a true (rather than perceived) loss of having any control over our destiny. This may not truly represent our situation with health care and insurance reform.

The grieving model is too passive, with *acceptance* rather than *adaptation* as the final stage. The dynamic notions of *learning* and *restructuring* from the modern model of Continuous Quality Improvement fit doctors' take-charge personalities better and are perhaps more appropriate than grieving's *denial* and *bargaining*. I believe that most physicians are being energetically creative to be effective and satisfied in a practice world where change has truly been the norm rather than the exception for many decades. Health Care Reform is a challenge rather than a fatality, and I think that most of us are up to it.

Donald Kollisch, MD
Community and Family Medicine
Dartmouth Medical School
Hanover, NH 03755

Examining Errors In Health Care:

Developing a Prevention, Education and Research Agenda

October 13-15, 1996

at Annenberg Center for Health Sciences at Eisenhower
Rancho Mirage, California

Despite remarkable advances in almost every field of medicine, an age-old problem continues to haunt medical care – the occurrence of errors. Although the error rate in health care is unknown, and may be unknowable, any error is a cause for concern. Errors can result in tragedy for patients and their families, add cost to an already overburdened health care system, and can lead to wasteful litigation. Errors in health care can also affect health care professionals who are dedicated to helping their patients.

The American Association for the Advancement of Science, the American Medical Association, the Annenberg Center for Health Sciences, and the Joint Commission on Accreditation of Healthcare Organizations are convening a multidisciplinary conference to examine errors in health care – how to define error, how to measure error, what factors contribute to error, and how error can be reduced or prevented.

Speakers will represent a broad spectrum of perspectives and disciplines, including experts from industries outside of health care, who have lessons to teach in error detection and reduction. The conference will include plenary sessions, as well as breakout sessions that will allow interaction with the speakers. Attendees will help develop an agenda for organizations and individuals oriented toward improving the quality of care and reducing the potential for human and organizational error.

Primary Objectives

- To develop an agenda for further research into errors, identify educational or other approaches to their prevention, and target next steps for stakeholders.
- To promote greater understanding of the occurrence of errors and strategies for preventing them.
- To generate candid discussion of accountability in health care and explore alternate ways of responding to errors.
- To provide an opportunity for networking in a multidisciplinary setting.

Registration and Cancellation

The registration fee is $295. Registrations postmarked after September 19 will be $350. The fee includes all course materials, continental breakfast, breaks, lunch and dinner served at the Annenberg Center, and transportation between the conference hotels and the Annenberg Center for conference sessions. Space is limited, so please register early.

All requests for cancellation must be received in writing by October 3. There will be a $25 administrative fee. No refunds will be issued after October 3.

A Multidisciplinary Leadership Conference Convened by: American Association for the Advancement of Science, American Medical Association, Annenberg Center for Health Sciences at Eisenhower, and Joint Commission on Accreditation of Healthcare Organizations

Co-Sponsors: Aetna, Agency for Health Care Policy and Research, American Hospital Association, American Society of Health-System Pharmacists Research and Education Foundation, CNA HealthPro, Glaxo Wellcome Inc., Institute for Healthcare Improvement, MMI Companies, Inc., Pfizer, Inc., Physician Insurers Association of America, and Robert Wood Johnson Foundation.

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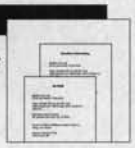

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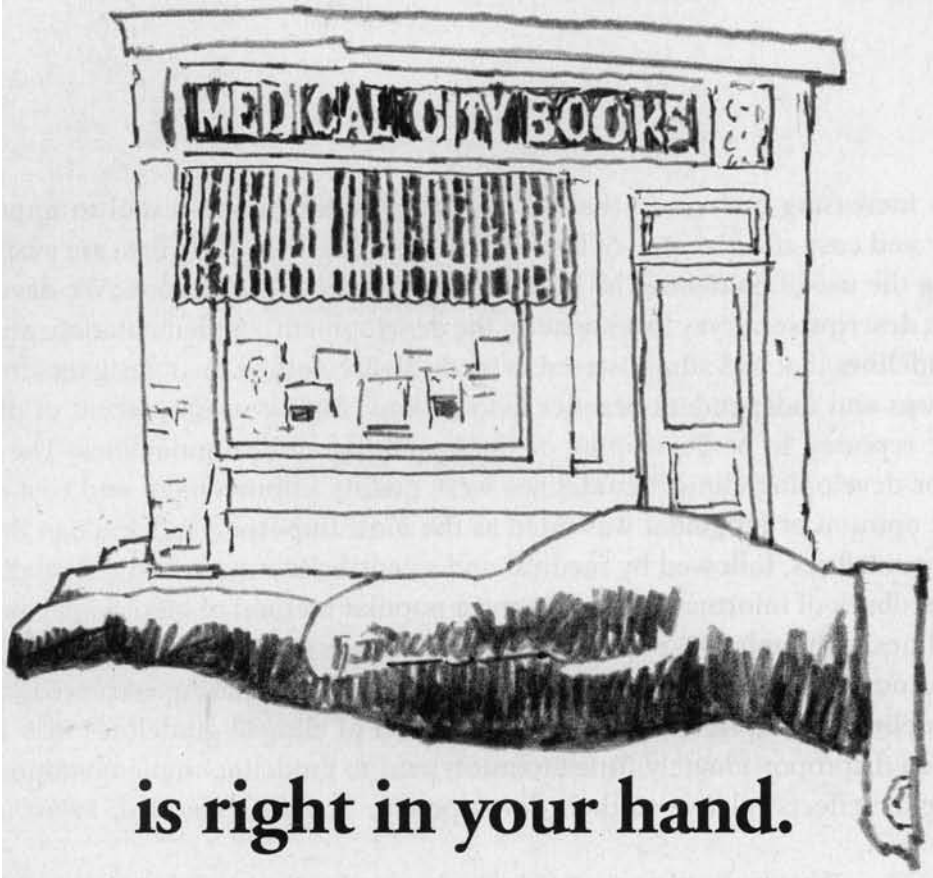

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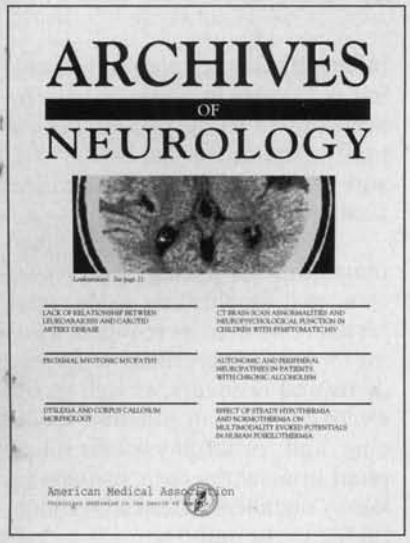

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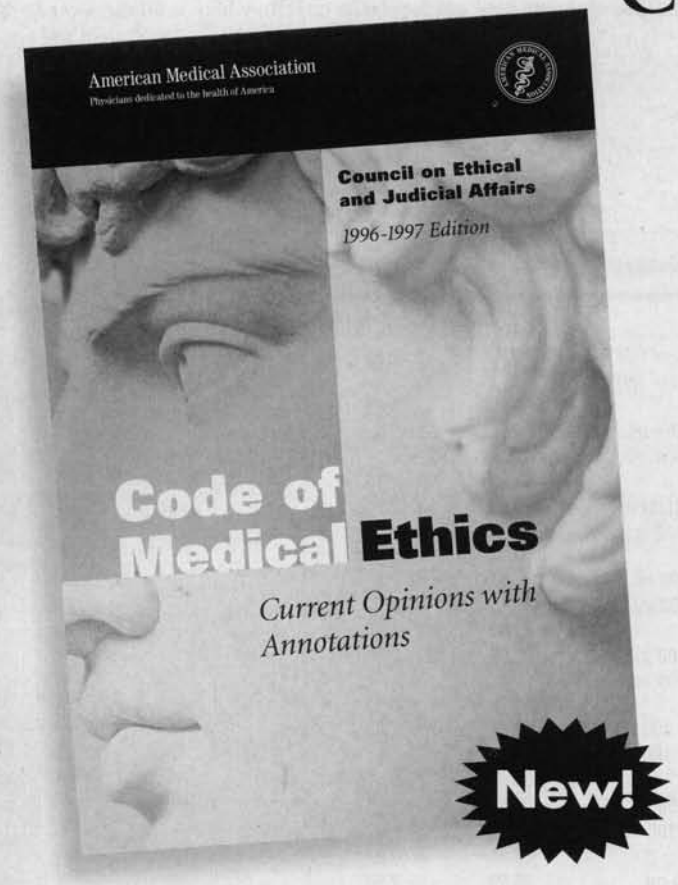

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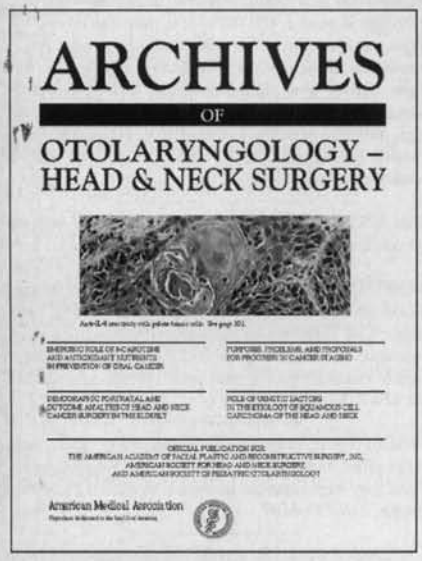

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Lower Respiratory Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae,* or *Streptococcus pneumoniae.*

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *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* (methicillin susceptible), *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, Staphylococcus saprophyticus,* or *Enterococcus faecalis.*

Acute Uncomplicated Cystitis in females caused by *Escherichia coli* or *Staphylococcus saprophyticus.* (See DOSAGE AND ADMINISTRATION.)

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 effects 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.

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.

Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with ciprofloxacin and other quinolones. Ciprofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon.

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.

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 as 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.

Patients should be advised to discontinue treatment; rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon.

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.

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.)

Altered serum levels of phenytoin (increased and decreased) have been reported in patients receiving concomitant ciprofloxacin.

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

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 was 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 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: arthralgia 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 expenences 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:

BODY AS A WHOLE: change in serum phenytoin

CARDIOVASCULAR: postural hypotension, vasculitis

CENTRAL NERVOUS SYSTEM: agitation, confusion, delirium, dysphasia, myoclonus, nystagmus, toxic psychosis

GASTROINTESTINAL: constipation, dyspepsia, flatulence, hepatic necrosis, jaundice, pancreatitis, pseudomembranous colitis (The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.)

HEMIC/LYMPHATIC: agranulocytosis, hemolytic anemia, methemoglobinemia, prolongation of prothrombin time

METABOLIC/NUTRITIONAL: elevation of serum triglycerides, cholesterol, blood glucose, serum potassium

MUSCULOSKELETAL: myalgia, possible exacerbation of myasthenia gravis, tendinitis/tendon rupture

RENAL/UROGENITAL: albuminuria, candiduria, renal calculi, vaginal candidiasis

SKIN/HYPERSENSITIVITY: anaphylactic reactions, erythema multiforme/Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis

SPECIAL SENSES: anosmia

(See PRECAUTIONS.)

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

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 courses 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.

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Highly effective second-line therapy for acute exacerbations of chronic bronchitis.

Cipro Tablets are indicated for mild/moderate/severe/complicated lower respiratory infections caused by *E coli, K pneumoniae, E cloacae, P mirabilis, P aeruginosa, H influenzae, H parainfluenzae, S pneumoniae.*

NOTE: SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF CIPROFLOXACIN AND THEOPHYLLINE. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN CHILDREN, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED.

All quinolones should be used with caution in patients predisposed to seizures. Ciprofloxacin should be discontinued at the first sign of an allergic reaction. Patients should be advised: 1. not to take antacids containing magnesium, aluminum or calcium; 2. of a possible decrease in mental alertness and coordination.

Most frequently reported adverse events (>1%) without regard to drug relationship: nausea; diarrhea; vomiting; abdominal pain/discomfort; headache; rash; restlessness.

Please see brief summary of prescribing information on adjacent page.

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