PEDIATRICS

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ARTICLES

COMMENTARIES

EXPERIENCE AND REASON

Committee Statements—For Contents See Page A13

PediaCare®

Oral Decongestant Drops

Relief for little noses

- The only OTC pseudoephedrine oral drop formula
  —Relieves infants' nasal congestion with pseudoephedrine, the pediatrician-preferred decongestant[1]
- Easy to administer to encourage excellent compliance
  —Pleasant tasting
  —An alcohol-free liquid with calibrated dropper
  —Dosed just like Children's TYLENOL® (acetaminophen) Infant Drops

Relief just for infants' stuffy noses.

McNEIL McNeil Consumer Products Company
Division of McNeil-PPC, Inc.
Fort Washington, PA 19034 U.S.A.

 Printed in U.S.A. March 1992

REFERENCE: 1. Data on file. McNeil Consumer Products Company.

The right combination for an old problem

ISOMIL® DF

Soy Formula For Diarrhea

The first infant soy formula with added fiber clinically proven to shorten the duration of diarrhea* in infants.†

Pedialyte®

Oral Electrolyte
Maintenance Solution

Quickly restores fluids and electrolytes lost in diarrhea. Designed to promote fluid absorption more effectively than household beverages.

ISOMIL®

Soy Formula With Iron

Post-diarrhea for secondary lactose intolerance or whenever a milk-free feeding is needed.

*Defined as the occurrence of loose, watery stools.

†Brown KH, Perez F, Peerson JM, et al: Effect of dietary fiber (soy polysaccharide) on the severity, duration and nutritional outcome of acute, watery diarrhea in children. *Pediatrics* 1993;92:241-247.

The safe way to manage infant diarrhea

ROSS PRODUCTS DIVISION
ABBOTT LABORATORIES
COLUMBUS, OHIO 43215-1724

LITHO IN USA

Factors that are associated with severe bronchiolitis:[1,2,3]

Age ≤ 3 months

Weight ≤ 20 lbs.

Prematurity < 34 weeks

Neurologic and metabolic diseases

Immunodeficiency

Bronchopulmonary dysplasia

Congenital anomalies

Congenital heart disease

Other chronic lung conditions

Identify Patients with Severe Infections

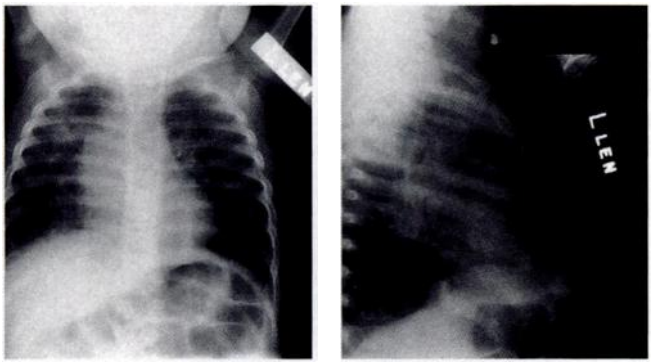
Smaller, Younger Patients–Higher Risk

How can you tell whether a patient with bronchiolitis has a severe infection and is at risk for clinical deterioration?

A recent study[1] was conducted during an RSV epidemic in Philadelphia. Two hundred thirteen infants with bronchiolitis were prospectively followed at the time of initial presentation to identify clues that would help predict disease severity.

The study identified six independent clinical and laboratory findings that were strongly associated with more severe illness: "ill" or "toxic" appearance; oxygen saturation less than 95% as determined by pulse oximetry; gestational age younger the 34 weeks; respiratory rate of 70/minute or greater; atelectasis on chest x-ray; and age younger than 3 months.

Radiographic Images of Severe RSV Infection



RSV-infected infant with bilateral infiltrates (A-P view and lateral view).

RSV–Induced Hypoxia

Hypoxemia resulting from severe bronchiolitis is caused by extensive airway obstruction. There are at least 3 major potential mechanisms for RSV-induced airway obstruction.

First, RSV infections are associated with increased edema of the airway walls causing luminal narrowing.

Second, airway obstruction can result from mucus accumulation and cell debris sloughed into the airways.

Third, irritation of inflamed airways caused by the RSV infections can induce airway smooth muscle contraction.

Treat the Infection–Not Just the Symptoms

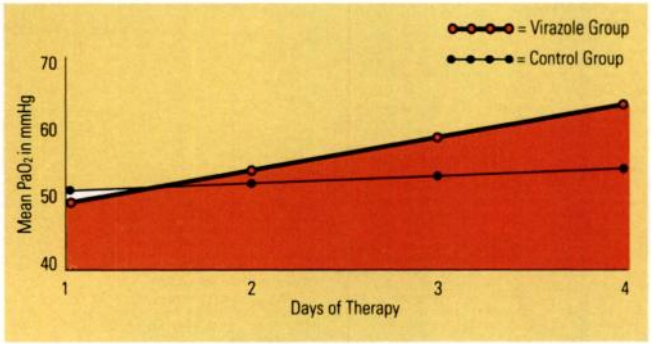
Until recently, physicians could only treat the symptoms of RSV-bronchiolitis. Supplemental oxygen and bronchodilators help control hypoxia, but they do not touch the underlying cause. Neither inhibit viral replication.

Now you can treat the infection–not just the symptoms.

Infants with lower respiratory tract RSV infection, who received Virazole, showed significant improvement in lower respiratory tract signs over untreated controls. Improvement was associated with better levels of arterial oxygen saturation and decreased viral shedding.[4]

"Five placebo-controlled, double-blind studies, each including approximately 30 subjects, have addressed the question of the effect of aerosolized ribavirin [Virazole] on the course of RSV lower respiratory infection. The fact that each was able to establish a beneficial effect despite the small number of subjects is convincing evidence that effect exists."[5]

Resolution of Hypoxia



Virazole significantly raised mean PaO_2.[4]

Accelerate Recovery with Virazole

Since 1986, Virazole has been helping infants with severe bronchiolitis due to RSV breath a little easier.

Studies have shown that Virazole significantly improves oxygen saturation. Early aggressive management of severe infections due to RSV in high-risk children is warranted because of the substantial morbidity in this patient population and the established safety profile of this drug.[4,5]

You can start treatment while awaiting rapid diagnostic test results.[6*]

Severe bronchiolitis can lead to serious complications. Treat severely-ill patients early with Virazole.

Virazole®
(ribavirin)

ICN

ICN Pharmaceuticals Inc.

1. Shaw, KN et al. Outpatient assessment of infants with bronchiolitis. AJDC. February 1991;145:151-154.
2. Lebel, MH et al. Respiratory failure and mechanical ventilation in severe bronchiolitis. Archives of Diseases in Childhood. 1989;64:1431-1437.
3. Report of the Committee on Infectious Diseases, 22nd Ed. American Academy of Pediatrics. 1991;581.
4. Hall C. et al. Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection: A randomized double-blind study. New Eng J Med. 1983;308:1443-1447.
5. McBride, J. Study design considerations for ribavirin: efficacy studies. Ped. Infec. Disease. 1990;Vol. 9. No. 9 Suppl:S74-S78.
6. Virazole prescribing information, ICN Pharmaceuticals.

*Treatment should not be continued without documentation of RSV infection.

Virazole®

(ribavirin for inhalation solution)

PRESCRIBING INFORMATION

WARNINGS:

USE OF AEROSOLIZED VIRAZOLE IN PATIENTS REQUIRING MECHANICAL VENTILATOR ASSISTANCE SHOULD BE UNDERTAKEN ONLY BY PHYSICIANS AND SUPPORT STAFF FAMILIAR WITH THE SPECIFIC VENTILATOR BEING USED AND THIS MODE OF ADMINISTRATION OF THE DRUG. STRICT ATTENTION MUST BE PAID TO PROCEDURES THAT HAVE BEEN SHOWN TO MINIMIZE THE ACCUMULATION OF DRUG PRECIPITATE, WHICH CAN RESULT IN MECHANICAL VENTILATOR DYSFUNCTION AND ASSOCIATED INCREASED PULMONARY PRESSURES (SEE WARNINGS).

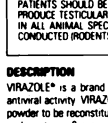
SUDDEN DETERIORATION OF RESPIRATORY FUNCTION HAS BEEN ASSOCIATED WITH INITIATION OF AEROSOLIZED VIRAZOLE USE IN INFANTS. RESPIRATORY FUNCTION SHOULD BE CAREFULLY MONITORED DURING TREATMENT. IF INITIATION OF AEROSOLIZED VIRAZOLE TREATMENT APPEARS TO PRODUCE SUDDEN DETERIORATION OF RESPIRATORY FUNCTION, TREATMENT SHOULD BE STOPPED AND REINSTITUTED ONLY WITH EXTREME CAUTION. CONTINUOUS MONITORING AND CONSIDERATION OF CONCOMITANT ADMINISTRATION OF BRONCHODILATORS (SEE WARNINGS).

VIRAZOLE IS NOT INDICATED FOR USE IN ADULTS. PHYSICIANS AND PATIENTS SHOULD BE AWARE THAT RIBAVIRIN HAS BEEN SHOWN TO PRODUCE TESTICULAR LESIONS IN RODENTS AND TO BE TERATOGENIC IN ALL ANIMAL SPECIES IN WHICH ADEQUATE STUDIES HAVE BEEN CONDUCTED (RODENTS AND RABBITS). (SEE CONTRAINDICATIONS)

DESCRIPTION

VIRAZOLE® is a brand name for ribavirin, a synthetic nucleoside with antiviral activity. VIRAZOLE for inhalation solution is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100 ml glass vial contains 6 grams of ribavirin, and when reconstituted to the recommended volume of 300 ml with sterile water for injection or sterile water for inhalation (no preservatives added), will contain 20 mg of ribavirin per ml, pH approximately 5.5. Aerosolization is to be carried out in a Small Particle Aerosol Generator (SPAG-2) nebulizer only.

Ribavirin is 1-beta-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide, with the following structural formula:



Ribavirin is a stable, white crystalline compound with a maximum solubility in water of 142 mg/ml at 25 °C and with only a slight solubility in ethanol. The empirical formula is $C_8H_{12}N_4O_5$ and the molecular weight is 244.21.

CLINICAL PHARMACOLOGY

Mechanism of Action

In cell cultures the inhibitory activity of ribavirin for respiratory syncytial virus (RSV) is selective. The mechanism of action is unknown. Reversal of the *in vitro* antiviral activity by guanosine or xanthosine suggests ribavirin may act as an analogue of these cellular metabolites.

Microbiology

Ribavirin has demonstrated antiviral activity against RSV *in vitro*[1] and in experimentally infected cotton rats.[2] Several clinical isolates of RSV were evaluated for ribavirin susceptibility by plaque reduction in tissue culture. Plaques were reduced 85-98% by 16 µg/ml, however, results may vary with the test system. The development of resistance has not been evaluated *in vitro* or in clinical trials.

In addition to the above, ribavirin has been shown to have *in vitro* activity against influenza A and B viruses and herpes simplex virus, but the clinical significance of these data is unknown.

Immunologic Effects

Neutralizing antibody responses to RSV were decreased in aerosolized VIRAZOLE treated infants compared to placebo treated infants.[3] One study also showed that RSV-specific IgE antibody in bronchial secretions was decreased in patients treated with aerosolized VIRAZOLE. In rats, ribavirin administration resulted in lymphoid atrophy of the thymus, spleen, and lymph nodes. Humoral immunity was reduced in guinea pigs and ferrets. Cellular immunity was also mildly depressed in animal studies. The clinical significance of these observations is unknown.

Pharmacokinetics

Assay for VIRAZOLE in human materials is by a radioimmunoassay which detects ribavirin and at least one metabolite.

VIRAZOLE brand of ribavirin, when administered by aerosol, is absorbed systemically. Four pediatric patients inhaling VIRAZOLE aerosol administered by face mask for 2.5 hours each day for 3 days had plasma concentrations ranging from 0.44 to 1.55 µM, with a mean concentration of 0.76 µM. The plasma half-life was reported to be 9.5 hours. Three pediatric patients inhaling aerosolized VIRAZOLE administered by face mask or mist tent for 20 hours each day for 5 days had plasma concentrations ranging from 1.5 to 14.3 µM, with a mean concentration of 6.8 µM.

The bioavailability of aerosolized VIRAZOLE is unknown and may depend on the mode of aerosol delivery. After aerosol treatment, peak plasma concentrations of ribavirin are 85% to 98% less than the concentration that reduced RSV plaque formation in tissue culture. After aerosol treatment, respiratory tract secretions are likely to contain ribavirin in concentrations many fold higher than those required to reduce plaque formation. However, RSV is an intracellular virus and it is unknown whether plasma concentrations or respiratory secretion concentrations of the drug better reflect intracellular concentrations in the respiratory tract.

In man, rats, and rhesus monkeys, accumulation of ribavirin and/or metabolites in the red blood cells has been noted, plateauing in red cells in man in about 4 days and gradually declining with an apparent half-life of 40 days (the half-life of erythrocytes). The extent of accumulation of ribavirin following inhalation therapy is not well defined.

Animal Toxicology

Ribavirin, when administered orally or as an aerosol, produced cardiac lesions in mice, rats, and monkeys, when given at doses of 30, 36 and 120 mg/kg or greater for 4 weeks or more (estimated human equivalent doses of 4.8, 12.3 and 111.4 mg/kg for a 5 kg child, or 2.5, 5.1 and 40 mg/kg for a 60 kg adult, based on body surface area adjustment). Aerosolized ribavirin administered to developing ferrets at 60 mg/kg for 10 or 30 days resulted in inflammatory and possibly emphysematous changes in the lungs. Proliferative changes were seen in the lungs following exposure at 131 mg/kg for 30 days. The significance of these findings to human administration is unknown.

INDICATIONS AND USAGE

VIRAZOLE is indicated for the treatment of hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus. Treatment early in the course of severe lower respiratory tract infection may be necessary to achieve efficacy.

Only severe RSV lower respiratory tract infection should be treated with VIRAZOLE. The vast majority of infants and children with RSV infection have disease that is mild, self-limited, and does not require hospitalization or antiviral treatment. Many children with mild lower respiratory tract involvement will require shorter hospitalization than would be required for a full course of VIRAZOLE aerosol (3 to 7 days) and should not be treated with the drug. Thus the decision to treat with VIRAZOLE should be based on the severity of the RSV infection. The presence of an underlying condition such as prematurity, immunosuppression or cardiopulmonary disease may increase the severity of clinical manifestations and complications of RSV infection.

Use of aerosolized VIRAZOLE in patients requiring mechanical ventilator assistance should be undertaken only by physicians and support staff familiar with this mode of administration and the specific ventilator being used (see Warnings, and Dosage and Administration).

Diagnosis

RSV infection should be documented by a rapid diagnostic method such as demonstration of viral antigen in respiratory tract secretions by immunofluorescence[3,4] or ELISA[5] before or during the first 24 hours of treatment. Treatment may be initiated while awaiting rapid diagnostic test results. However, treatment should not be continued without documentation of RSV infection. Non-culture antigen detection techniques may have false positive or false negative results. Assessment of the clinical situation, the time of year and other parameters may warrant reevaluation of the laboratory diagnosis.

Description of Studies

Non-Mechanically-Ventilated Infants: In two placebo controlled trials in infants hospitalized with RSV lower respiratory tract infection, aerosolized VIRAZOLE treatment had a therapeutic effect, as judged by the reduction in severity of clinical manifestations of disease by treatment day 3.[3,4] Treatment was most effective when instituted within the first 3 days of clinical illness. Virus titers in respiratory secretions were also significantly reduced with VIRAZOLE in one of these original studies.[4] Additional controlled studies conducted since these initial trials of aerosolized VIRAZOLE in the treatment of RSV infection have supported these data.

Mechanically-Ventilated Infants: A randomized, double-blind, placebo controlled evaluation of aerosolized VIRAZOLE at the recommended dose was conducted in 28 infants requiring mechanical ventilation for respiratory failure caused by documented RSV infection.[6] Mean age was 14 months (SD, 17 months). Seven patients had underlying diseases predisposing them to severe infection and 21 were previously normal. Aerosolized VIRAZOLE treatment significantly decreased the duration of mechanical ventilation required (4.9 vs. 9.9 days, p=0.01) and duration of required supplemental oxygen (8.7 vs. 13.5 days, p=0.01). Intensive patient management and monitoring techniques were employed in this study. These included endotracheal tube suctioning every 1 to 2 hours, recording of proximal airway pressure, ventilatory rate, and FiO_2 every hour, and arterial blood gas monitoring every 2 to 6 hours. To reduce the risk of VIRAZOLE precipitation and ventilator malfunction, heated wire tubing, two bacterial filters connected in series in the expiratory limb of the ventilator (with filter changes every 4 hours), and water column pressure release valves to monitor internal ventilator pressures were used in connecting ventilator circuits to the SPAG-2.

Employing these techniques, no technical difficulties with VIRAZOLE administration were encountered during the study. Adverse events consisted of bacterial pneumonia in one case, staphylococcus bacteremia in one case and two cases of post-extubation stridor. None were felt to be related to VIRAZOLE administration.

CONTRAINDICATIONS

VIRAZOLE is contraindicated in individuals who have shown hypersensitivity to the drug or its components, and in women who are or may become pregnant during exposure to the drug. Ribavirin has demonstrated significant teratogenic and/or embryocidal potential in all animal species in which adequate studies have been conducted (rodents and rabbits). Therefore, although clinical studies have not been performed, it should be assumed that VIRAZOLE may cause fetal harm in humans. Studies in which the drug has been administered systemically demonstrate that ribavirin is concentrated in the red blood cells and persists for the life of the erythrocyte.

WARNINGS

SUDDEN DETERIORATION OF RESPIRATORY FUNCTION HAS BEEN ASSOCIATED WITH INITIATION OF AEROSOLIZED VIRAZOLE USE IN INFANTS. Respiratory function should be carefully monitored during treatment. If initiation of aerosolized VIRAZOLE treatment appears to produce sudden deterioration of respiratory function, treatment should be stopped and reinstituted only with extreme caution, continuous monitoring, and consideration of concomitant administration of bronchodilators.

Use with Mechanical Ventilators

USE OF AEROSOLIZED VIRAZOLE IN PATIENTS REQUIRING MECHANICAL VENTILATOR ASSISTANCE SHOULD BE UNDERTAKEN ONLY BY PHYSICIANS AND SUPPORT STAFF FAMILIAR WITH THIS MODE OF ADMINISTRATION AND THE SPECIFIC VENTILATOR BEING USED. Strict attention must be paid to procedures that have been shown to minimize the accumulation of drug precipitate, which can result in mechanical ventilator dysfunction and associated increased pulmonary pressures. These procedures include the use of bacteria filters in series in the expiratory limb of the ventilator circuit with frequent changes (every 4 hours), water column pressure release valves to indicate elevated ventilator pressures, frequent monitoring of these devices and verification that ribavirin crystals have not accumulated within the ventilator circuitry, and frequent suctioning and monitoring of the patient (see Clinical Studies).

Those administering aerosolized VIRAZOLE in conjunction with mechanical ventilator use should be thoroughly familiar with detailed descriptions of these procedures as outlined in the SPAG-2 manual.

PRECAUTIONS

General

Patients with severe lower respiratory tract infection due to respiratory syncytial virus require optimum monitoring and attention to respiratory and fluid status (see SPAG-2 manual).

Drug Interactions

Clinical studies of interactions of VIRAZOLE with other drugs commonly used to treat infants with RSV infections, such as digoxin, bronchodilators, other antiviral agents, antibiotics or anti-metabolites, have not been conducted. Interference by VIRAZOLE with laboratory tests has not been evaluated.

Carcinogenesis and Mutagenesis

Ribavirin increased the incidence of cell transformations and mutations in mouse Balb/c 3T3 (fibroblasts) and L5178Y (lymphoma) cells at concentrations of 0.015 and 0.03-5.0 mg/ml, respectively (without metabolic activation). Modest increases in mutation rates (3-4x) were observed at concentrations between 3.75-10.0 mg/ml in L5178Y cells *in vitro* with the addition of a metabolic activation fraction. In the mouse micronucleus assay, ribavirin was clastogenic at intravenous doses of 20-200 mg/kg, (estimated human equivalent of 1.67-16.7 mg/kg, based on body surface area adjustment for a 60 kg adult). Ribavirin was not mutagenic in a dominant lethal assay in rats at intraperitoneal doses between 50-200 mg/kg when administered for 5 days (estimated human equivalent of 7.14-28.6 mg/kg, based on body surface area adjustment, see Pharmacokinetics).

In vivo carcinogenicity studies with ribavirin are incomplete. However, results of a chronic feeding study with ribavirin in rats, at doses of 16-100 mg/kg/day (estimated human equivalent of 2.3-14.3 mg/kg/day, based on body surface area adjustment for the adult), suggest that ribavirin may induce benign mammary, pancreatic, pituitary and adrenal tumors. Preliminary results of 2 oral gavage oncogenicity studies in the mouse and rat (18-24 months, doses of 20-75 and 10-40 mg/kg/day, respectively [estimated human equivalent of 1.67-6.25 and 1.43-5.71 mg/kg/day, respectively, based on body surface area adjustment for the adult]) are inconclusive as to the carcinogenic potential of ribavirin (see Pharmacokinetics). However, these studies have demonstrated a relationship between chronic ribavirin exposure and increased incidences of vascular lesions (microscopic hemorrhages in mice) and retinal degeneration (in rats).

Impairment of Fertility

The fertility of ribavirin-treated animals (male or female) has not been fully investigated. However, in the mouse, administration of ribavirin at doses between 35-150 mg/kg/day (estimated human equivalent of 2.92-12.5 mg/kg/day, based on body surface area adjustment for the adult) resulted in significant seminiferous tubule atrophy, decreased sperm concentrations, and increased numbers of sperm with abnormal morphology. Partial recovery of sperm production was apparent 3-6 months following dose cessation. In several additional toxicology studies, ribavirin has been shown to cause testicular lesions (tubular atrophy) in adult rats at oral dose levels as low as 16 mg/kg/day (estimated human equivalent of 2.29 mg/kg/day, based on body surface area adjustment; see Pharmacokinetics). Lower doses were not tested. The reproductive capacity of treated male animals has not been studied.

Pregnancy: Category X

Ribavirin has demonstrated significant teratogenic and/or embryocidal potential in all animal species in which adequate studies have been conducted. Teratogenic effects were evident after single oral doses of 2.5 mg/kg or greater in the hamster, and after daily oral doses of 0.3 and 1.0 mg/kg in the rabbit and rat, respectively (estimated human equivalent doses of 0.12 and 0.14 mg/kg, based on body surface area adjustment for the adult). Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. Survival of fetuses and offspring was reduced. Ribavirin caused embryolethality in the rabbit at daily oral dose levels as low as 1 mg/kg. No teratogenic effects were evident in the rabbit and rat administered daily oral doses of 0.1 and 0.3 mg/kg, respectively with estimated human equivalent doses of 0.01 and 0.04 mg/kg, based on body surface area adjustment (see Pharmacokinetics). These doses are considered to define the "No Observable Teratogenic Effects Level" (NOTEL) for ribavirin in the rabbit and rat.

Following oral administration of ribavirin in the pregnant rat (1.0 mg/kg) and rabbit (0.3 mg/kg), mean plasma levels of drug ranged from 0.10-0.20 µM [0.024-0.049 µg/ml] at 1 hour after dosing, to undetectable levels at 24 hours. At 1 hour following the administration of 0.3 or 0.1 mg/kg in the rat and rabbit (NOTEL), respectively, mean plasma levels of drug in both species were near or below the limit of detection (0.05 µM; see Pharmacokinetics).

Although clinical studies have not been performed, VIRAZOLE may cause fetal harm in humans. As noted previously, ribavirin is concentrated in red blood cells and persists for the life of the cell. Thus the terminal half-life for the systemic elimination of ribavirin is essentially that of the half-life of circulating erythrocytes. The minimum interval following exposure to VIRAZOLE before pregnancy may be safely initiated is unknown (see Contraindications, Warnings, and Information for Health Care Personnel).

Nursing Mothers

VIRAZOLE has been shown to be toxic to lactating animals and their offspring. It is not known if VIRAZOLE is excreted in human milk.

Information for Health Care Personnel

Health care workers directly providing care to patients receiving aerosolized VIRAZOLE should be aware that ribavirin has been shown to be teratogenic in all animal species in which adequate studies have been conducted (rodents and rabbits). Although no reports of teratogenesis in offspring of mothers who were exposed to aerosolized VIRAZOLE during pregnancy have been confirmed, no controlled studies have been conducted in pregnant women. Studies of environmental exposure in treatment settings have shown that the drug can disperse into the immediate bedside area during routine patient care activities with highest ambient levels closest to the patient and extremely low levels outside of the immediate bedside area. Adverse reactions resulting from actual occupational exposure in adults are described below (see Adverse Events in Health Care Workers). Some studies have documented ambient drug concentrations at the bedside that could potentially lead to systemic exposures above those considered safe for exposure during pregnancy (1/1000 of the NOTEL dose in the most sensitive animal species).[7,8]

A 1992 study conducted by the National Institute of Occupational Safety and Health (NIOSH) demonstrated measurable urine levels of ribavirin in health care workers exposed to aerosol in the course of direct patient care.[7] Levels were lowest in workers caring for infants receiving aerosolized VIRAZOLE with mechanical ventilation and highest in those caring for patients being administered the drug via an oxygen tent or hood. This study employed a more sensitive assay to evaluate ribavirin levels in urine than was available for several previous studies of environmental exposure that failed to detect measurable ribavirin levels in exposed workers. Creatinine adjusted urine levels in the NIOSH study ranged from less than 0.001 to 0.140 µM of ribavirin per gram of creatinine in exposed workers. However, the relationship between urinary ribavirin levels in exposed workers, plasma levels in animal studies, and the specific risk of teratogenesis in exposed pregnant women is unknown.

It is good practice to avoid unnecessary occupational exposure to chemicals wherever possible. Hospitals are encouraged to conduct training programs to minimize potential occupational exposure to VIRAZOLE. Health care workers who are pregnant should consider avoiding direct care of patients receiving aerosolized VIRAZOLE. If close patient contact cannot be avoided, precautions to limit exposure should be taken. These include administration of VIRAZOLE in negative pressure rooms; adequate room ventilation (at least six air exchanges per hour); the use of VIRAZOLE aerosol scavenging devices, turning off the SPAG-2 device for 5 to 10 minutes prior to prolonged patient contact; and wearing appropriately fitted respirator masks. Surgical masks do not provide adequate filtration of VIRAZOLE particles. Further information is available from NIOSH's Hazard Evaluation and Technical Assistance Branch and additional recommendations have been published in an Aerosol Consensus Statement by the American Respiratory Care Foundation and the American Association for Respiratory Care.[9]

ADVERSE REACTIONS

The description of adverse reactions is based on events from clinical studies (approximately 200 patients) conducted prior to 1986, and the controlled trial of aerosolized VIRAZOLE conducted in 1989-1990. Additional data from spontaneous post-marketing reports of adverse events in individual patients have been available since 1986.

Deaths

Deaths during or shortly after treatment with aerosolized VIRAZOLE have been reported in 20 cases of patients treated with VIRAZOLE (12 of these patients were being treated for RSV infections). Several cases have been characterized as "possibly related" to VIRAZOLE by the treating physician; these were in infants who experienced worsening respiratory status related to bronchospasm while being treated with the drug. Several other cases have been attributed to mechanical ventilator malfunction in which VIRAZOLE precipitation within the ventilator apparatus led to excessively high pulmonary pressures and diminished oxygenation. In these cases the monitoring procedures described in the current package insert were not employed (see Description of Studies, Warnings, and Dosage and Administration).

Pulmonary and Cardiovascular

Pulmonary function significantly deteriorated during aerosolized VIRAZOLE treatment in six of six adults with chronic obstructive lung disease and in four of six asthmatic adults. Dyspnea and chest soreness were also reported in the latter group. Minor abnormalities in pulmonary function were also seen in healthy adult volunteers.

In the original study population of approximately 200 infants who received aerosolized VIRAZOLE, several serious adverse events occurred in severely ill infants with life-threatening underlying diseases, many of whom required assisted ventilation. The role of VIRAZOLE in these events is indeterminate. Since the drug's approval in 1986, additional reports of similar serious, though non-fatal, events have been filed infrequently. Events associated with aerosolized VIRAZOLE use have included the following:

Pulmonary: Worsening of respiratory status, bronchospasm, pulmonary edema, hypoventilation, cyanosis, dyspnea, bacterial pneumonia, pneumothorax, apnea, atelectasis and ventilator dependence.

Cardiovascular: Cardiac arrest, hypotension, bradycardia and digitalis toxicity. Bigeminy, bradycardia and tachycardia have been described in patients with underlying congenital heart disease.

Some subjects requiring assisted ventilation experienced serious difficulties, due to inadequate ventilation and gas exchange. Precipitation of drug within the ventilatory apparatus, including the endotracheal tube, has resulted in increased positive end expiratory pressure and increased positive inspiratory pressure. Accumulation of fluid in tubing ("rain out") has also been noted. Measures to avoid these complications should be followed carefully (see Dosage and Administration).

Hematologic

Although anemia was not reported with use of aerosolized VIRAZOLE in controlled clinical trials, most infants treated with the aerosol have not been evaluated 1 to 2 weeks post-treatment when anemia is likely to occur. Anemia has been shown to occur frequently with experimental oral and intravenous VIRAZOLE in humans. Also, cases of anemia (type unspecified), reticulocytosis and hemolytic anemia associated with aerosolized VIRAZOLE use have been reported through post-marketing reporting systems. All have been reversible with discontinuation of the drug.

Other

Rash and conjunctivitis have been associated with the use of aerosolized VIRAZOLE. These usually resolve within hours of discontinuing therapy. Seizures and asthenia associated with experimental intravenous VIRAZOLE therapy have also been reported.

Adverse Events in Health Care Workers

Studies of environmental exposure to aerosolized VIRAZOLE in health care workers administering care to patients receiving the drug have not detected adverse signs or symptoms related to exposure. However, 152 health care workers have reported experiencing adverse events through post-marketing surveillance. Nearly all were in individuals providing direct care to infants receiving aerosolized VIRAZOLE. Of 358 events from these 152 individual health care worker reports, the most common signs and symptoms were headache (51% of reports), conjunctivitis (32%), and rhinitis, nausea, rash, dizziness, pharyngitis, or lacrimation (10-20% each). Several cases of bronchospasm and/or chest pain were also reported, usually in individuals with known underlying reactive airway disease. Several case reports of damage to contact lenses after prolonged close exposure to aerosolized VIRAZOLE have also been reported. Most signs and symptoms reported as having occurred in exposed health care workers resolved within minutes to hours of discontinuing close exposure to aerosolized VIRAZOLE (also see Information for Health Care Personnel).

The symptoms of RSV in adults can include headache, conjunctivitis, sore throat and/or cough, fever, hoarseness, nasal congestion and wheezing, although RSV infections in adults are typically mild and transient. Such infections represent a potential hazard to uninfected hospital patients. It is unknown whether certain symptoms cited in reports from health care workers were due to exposure to the drug or infection with RSV. Hospitals should implement appropriate infection control procedures.

Overdosage

No overdosage with VIRAZOLE by aerosol administration has been reported in humans. The LD_{50} in mice is 2 gm orally and is associated with hypoactivity and gastrointestinal symptoms (estimated human equivalent dose of 0.17gm/kg, based on body surface area conversion). The mean plasma half-life after administration of aerosolized ViRAZOLE for pediatric patients is 9.5 hours. VIRAZOLE is concentrated and persists in red blood cells for the life of the erythrocyte (see Pharmacokinetics).

DOSAGE AND ADMINISTRATION

BEFORE USE, READ THOROUGHLY THE VIRATEK SMALL PARTICLE AEROSOL GENERATOR (SPAG) MODEL SPAG-2 OPERATOR'S MANUAL FOR SMALL PARTICLE AEROSOL GENERATOR OPERATING INSTRUCTIONS. AEROSOLIZED VIRAZOLE SHOULD NOT BE ADMINISTERED WITH ANY OTHER AEROSOL GENERATING DEVICE.

The recommended treatment regimen is 20 mg/ml VIRAZOLE as the starting solution in the drug reservoir of the SPAG-2 unit, with continuous aerosol administration for 12-18 hours per day for 3 to 7 days. Using the recommended drug concentration of 20 mg/ml the average aerosol concentration for a 12 hour delivery period would be 190 micrograms/liter of air. Aerosolized VIRAZOLE should not be administered in a mixture for combined aerosolization or simultaneously with other aerosolized medications.

Non-mechanically ventilated infants

VIRAZOLE should be delivered to an infant oxygen hood from the SPAG-2 aerosol generator. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed (see SPAG-2 manual). However, the volume and condensation area are larger in a tent and this may alter delivery dynamics of the drug.

Mechanically ventilated infants

The recommended dose and administration schedule for infants who require mechanical ventilation is the same as for those who do not. Either a pressure or volume cycle ventilator may be used in conjunction with the SPAG-2. In either case, patients should have their endotracheal tubes suctioned every 1-2 hours, and their pulmonary pressures monitored frequently (every 2-4 hours). For both pressure and volume ventilators, heated wire connective tubing and bacteria filters in series in the expiratory limb of the system (which must be changed frequently, i.e., every 4 hours) must be used to minimize the risk of VIRAZOLE precipitation in the system and the subsequent risk of ventilator dysfunction. Water column pressure release valves should be used in the ventilator circuit for pressure cycled ventilators, and may be utilized with volume cycled ventilators (SEE SPAG-2 MANUAL FOR DETAILED INSTRUCTIONS).

Method of Preparation

VIRAZOLE brand of ribavirin is supplied as 6 grams of lyophilized powder per 100 ml vial for aerosol administration only. By sterile technique, solubilize drug with Sterile Water for Injection, USP, or Inhalation in the 100 ml vial. Transfer to the clean, sterilized 500 ml SPAG-2 reservoir and further dilute to a final volume of 300 ml with Sterile Water for Injection, USP, or Inhalation. The final concentration should be 20 mg/ml. **Important:** This water should NOT have had any antimicrobial agent or other substance added. The solution should be inspected visually for particulate matter and discoloration prior to administration. Solutions that have been placed in the SPAG-2 unit should be discarded at least every 24 hours and when the liquid level is low before adding newly reconstituted solution.

HOW SUPPLIED:

VIRAZOLE (ribavirin for inhalation solution) is supplied in 100 ml glass vials with 6 grams of sterile, lyophilized drug which is to be reconstituted with 300 ml Sterile Water for Injection or Sterile Water for Inhalation (no preservatives added) and administered only by a small particle aerosol generator (SPAG-2). Vials containing the lyophilized drug powder should be stored in a dry place at 15-25° C (59-78° F). Reconstituted solutions may be stored, under sterile conditions, at room temperature (20-30° C; 68-86° F) for 24 hours. Solutions which have been placed in the SPAG-2 unit should be discarded at least every 24 hours.

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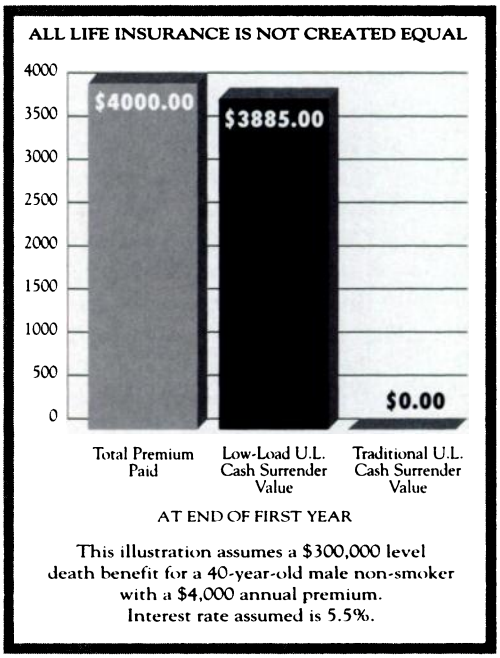

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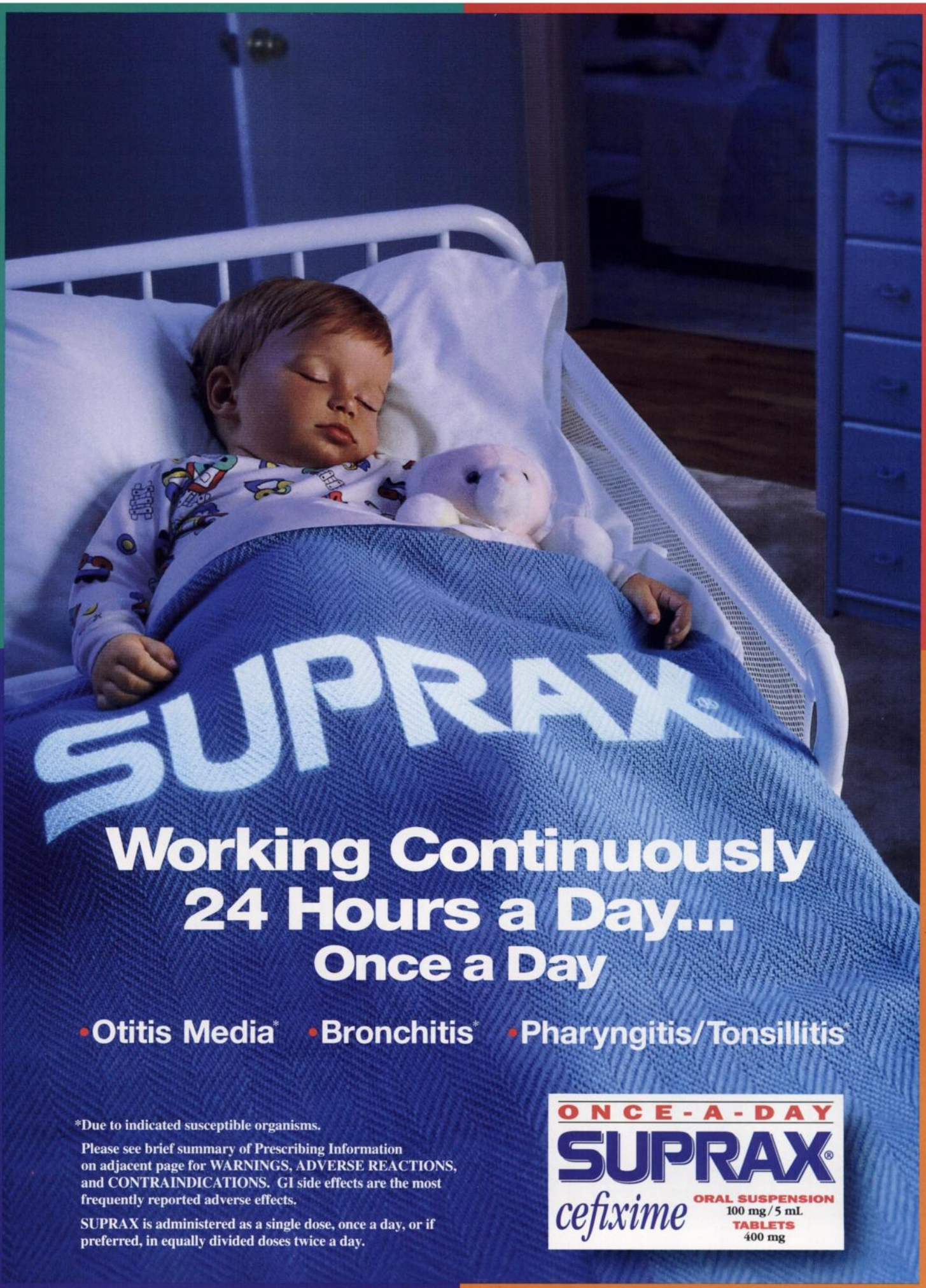

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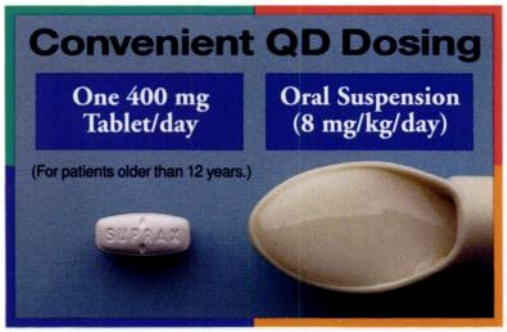
In clinical trials of otitis media in nearly 400 children between the ages of 6 months to 10 years, *S pneumoniae* was isolated from 47% of the patients, *H influenzae* from 34%, *M (B) catarrhalis* from 15%, and *S pyogenes* from 4%.

The overall response rate of *S pneumoniae* to cefixime was approximately 10% lower and that of *H influenzae* or *M (B) catarrhalis* approximately 7% higher (12% when beta-lactamase positive strains of *H influenzae* are included) than the response rates of these organisms to the active control drugs.

In these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg BID or 8 mg/kg QD, or with a standard antibiotic regimen. Sixty-nine percent to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated 2 to 4 weeks posttreatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had *H influenzae* resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the 2- to 4-week follow-up, a total of 30% to 31% of patients had evidence of either treatment failure or recurrent disease.



Bacteriological Outcome of Otitis Media at 2 to 4 Weeks Posttherapy
Based on Repeat Middle Ear Fluid Culture or
Extrapolation from Clinical Outcome

Organism	Cefixime[a] 4 mg/kg BID	Cefixime[a] 8 mg/kg QD	Control[a] drugs
Streptococcus pneumoniae	48/70 (69%)	18/22 (82%)	82/100 (82%)
Haemophilus influenzae beta-lactamase negative	24/34 (71%)	13/17 (76%)	23/34 (68%)
Haemophilus influenzae beta-lactamase positive	17/22 (77%)	9/12 (75%)	1/1[b]
Moraxella (Branhamella) catarrhalis	26/31 (84%)	5/5	18/24 (75%)
S pyogenes	5/5	3/3	6/7
All Isolates	120/162 (74%)	48/59 (81%)	130/166 (78%)

[a] Number eradicated/number isolated.

[b] An additional 20 beta-lactamase positive strains of *H influenzae* were isolated, but were excluded from this analysis because they were resistant to the control antibiotic. In 19 of these, the clinical course could be assessed, and a favorable outcome occurred in 10. When these cases are included in the overall bacteriological evaluation of therapy with the control drugs, 140/185 (76%) of pathogens were considered to be eradicated.

Tablets should not be substituted for suspension when treating otitis media.

CONTRAINDICATIONS

SUPRAX is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

BEFORE THERAPY WITH SUPRAX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO SUPRAX OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY

REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Administer cautiously to allergic patients.

Treatment with broad-spectrum antibiotics, including SUPRAX, alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of severe antibiotic-associated diarrhea including pseudomembranous colitis.

Pseudomembranous colitis has been reported with the use of SUPRAX and other broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider this diagnosis in patients who develop diarrhea in association with the use of antibiotics. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment and may range in severity from mild to life-threatening. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, management should include fluids, electrolytes, and protein supplementation. If the colitis does not improve after the drug has been discontinued, or if the symptoms are severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes of colitis should be excluded.

PRECAUTIONS

General: Use, especially when prolonged, may result in overgrowth of resistant organisms. If superinfection occurs during therapy, take appropriate measures.

Carefully monitor patients on dialysis. Adjust dosage of SUPRAX in patients with renal impairment and those undergoing continuous ambulatory peritoneal dialysis and hemodialysis. (See **DOSAGE AND ADMINISTRATION** in package insert.)

Prescribe cautiously in patients with a history of gastrointestinal disease, particularly colitis.

Drug Interactions: No significant drug interactions have been reported to date.

Drug/Laboratory Test Interactions: A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.

SUPRAX administration may result in a false-positive reaction for glucose in the urine using Clinitest®,** Benedict's solution, or Fehling's solution. Use glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®** or Tes-Tape®**).

A false-positive direct Coombs test has been reported during treatment with other cephalosporin antibiotics; therefore, it should be recognized that a positive Coombs test may be due to the drug.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no lifetime animal studies have been conducted to evaluate carcinogenic potential, no mutagenic potential of SUPRAX was found in standard laboratory tests. In rats, reproductive studies revealed no fertility impairment at doses up to 125 times the adult therapeutic dose.

Usage in Pregnancy: *Pregnancy Category B:* Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of harm to the fetus due to SUPRAX. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: SUPRAX has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers: It is not known whether SUPRAX is excreted in human milk. Consider discontinuing nursing temporarily during treatment with this drug.

Pediatric Use: Safety and effectiveness of SUPRAX in children aged less than 6 months have not been established.

The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to that seen in adult patients receiving tablets.

ADVERSE REACTIONS

Most adverse reactions observed in clinical trials were of a mild and transient nature. Five percent (5%) of patients in the US trials discontinued therapy because of drug-related adverse reactions. The most commonly seen adverse reactions in US trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the BID or the QD regimen. Clinically mild gastrointestinal side effects occurred in 20% of all patients, moderate events occurred in 9% of all patients, and severe adverse reactions occurred in 2% of all patients. Individual event rates included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 4%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to that seen in adult patients receiving tablets.

These symptoms usually responded to symptomatic therapy or ceased when SUPRAX was discontinued.

Several patients developed severe diarrhea and/or documented pseudomembranous colitis, and a few required hospitalization.

The following adverse reactions have been reported following the use of SUPRAX. Incidence rates were less than 1 in 50 (less than 2%), except as noted above for gastrointestinal events.

Gastrointestinal: Diarrhea, loose stools, abdominal pain, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous colitis were identified during the studies. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

Hypersensitivity Reactions: Skin rashes, urticaria, drug fever, and pruritus. Erythema multiforme, Stevens-Johnson syndrome, and serum sickness-like reactions have been reported.

Hepatic: Transient elevations in SGPT, SGOT, and alkaline phosphatase.

Renal: Transient elevations in BUN or creatinine.

Central Nervous System: Headaches or dizziness.

Hemic and Lymphatic Systems: Transient thrombocytopenia, leukopenia, and eosinophilia. Prolongation in prothrombin time was seen rarely.

Other: Genital pruritus, vaginitis, candidiasis.

The following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Allergic reactions including anaphylaxis, toxic epidermal necrolysis, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, and colitis.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**). If seizures associated with drug therapy occur, discontinue drug. Administer anticonvulsant therapy if clinically indicated.

Abnormal Laboratory Tests: Positive direct Coombs test, elevated bilirubin, elevated LDH, pancytopenia, neutropenia, agranulocytosis.

OVERDOSAGE

Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of SUPRAX did not differ from the profile seen in patients treated at the recommended doses.

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Theoretical Cost Effectiveness of Management Options for Children With Persisting Middle Ear Effusions

Stephen Berman, MD*; Robert Roark, MS, PA-C*; and Dennis Luckey, PhD‡

ABSTRACT. *Objective.* The purpose of this theoretical study is to assess the cost effectiveness of options involving observation, antibiotics alone, corticosteroids alone, corticosteroids plus antibiotics, and surgery to clear persisting middle ear effusions during three visits.

Methodology. In a hypothetical case the expected average per patient expenditures are calculated using the efficacy rates determined by the meta-analysis of randomized controlled clinical trials involving corticosteroids plus an antibiotic (six trials), corticosteroids alone (three trials), and antibiotic alone (four trials). In this analysis, all children whose bilateral middle ear effusions persist for 12 weeks despite medical management are referred for ventilating tubes.

Results. The most cost-effective intervention combination is corticosteroid plus an antibiotic at visit 1 (6 weeks after diagnosis of acute otitis media) followed by a second antibiotic in nonresponders at visit 2 (9 weeks after diagnosis of acute otitis media) and referral for ventilating tubes in nonresponders at visit 3 (12 weeks after diagnosis of acute otitis media). The expected average expenditures per case to clear the bilateral middle ear effusions is $600.91 based on reimbursement of private practice charges and $350.27 based on Medicaid reimbursement (all payments to providers are based on 1992 data from Colorado). The difference in the expected average total expenditures per case between this most cost-effective approach versus the use of sequential courses of antibiotics followed by surgery is $372.81 ($973.72 – $600.91) with full reimbursement of private practice charges and $202.57 ($552.84 – $350.27) with Medicaid reimbursement. In clearing the middle ear effusion, the average estimated travel expenses per case is $21.46, and lost parental wages per case are $45.12. When the expenditures associated with an additional 6-month follow-up period are included, the expected average per case expenditures is $1088.54 with reimbursement of private practice charges and $659.00 with Medicaid reimbursement. The difference in the expected average per case expenditures to clear the effusions and follow-up for 6 months between the most cost-effective approach using corticosteroids plus antibiotics at the 6- and 9-week visits followed by surgery in nonresponders at 12 weeks versus sequential courses of antibiotics is $405.30 ($1493.84 – $1088.54) with reimbursement of private practice charges and $217.32 ($876.32 – $659.00) with Medicaid reimbursement.

Recommendations. Although the analysis does not consider risks, side effects, and parental or provider preferences, the findings suggest that the implementation of cost-effective clinical guidelines can potentially reduce national expenditures for managing persistent middle ear effusions. *Pediatrics* 1994;93:353–363; *middle ear effusion, antibiotic, corticosteroid, otitis media with effusion, ventilating tubes, cost effectiveness.*

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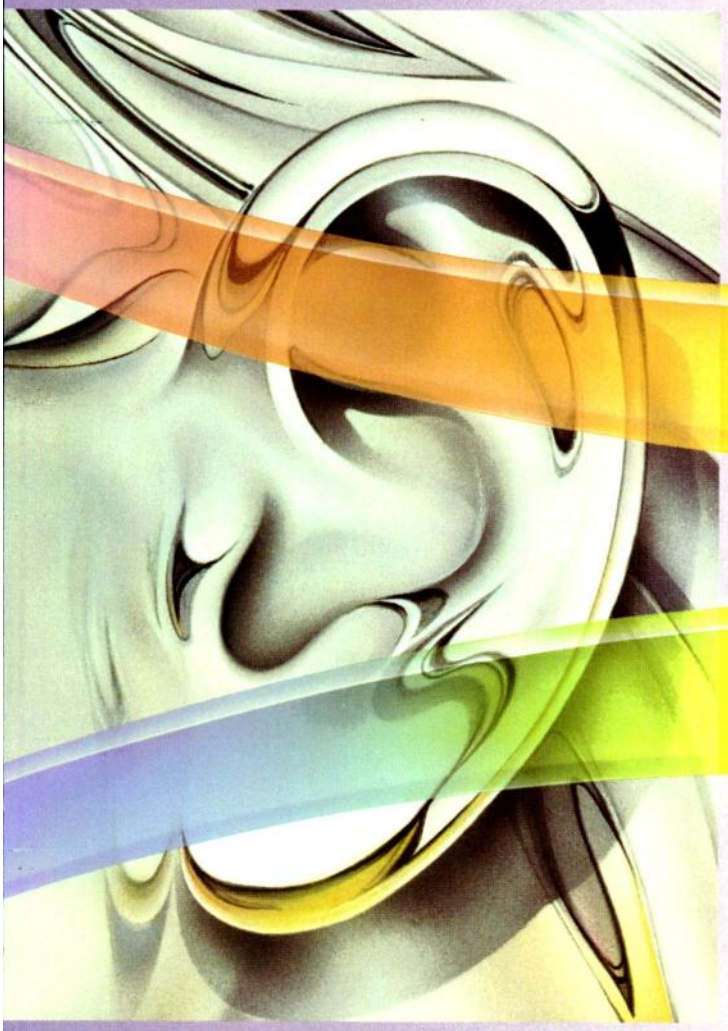
There are three important reasons to analyze the cost effectiveness of options to manage middle ear effusions that persist for 6 weeks despite antibiotic therapy. First, this condition is very common. There are 4.1 million births each year in the United States,[1,2] and during the first 2 years of life the reported annual incidence rate for acute otitis media is 1.14 episodes per year.[3] Thus, 9.3 million cases of acute otitis media are experienced by children <2 years of age each year. In addition, a middle ear effusion persists for 6 weeks after treating acute otitis media in about 20% of cases,[4–8] resulting in 1.9 million cases of persistent middle ear effusion each year in children <2 years of age. Second, the national annual expenditures associated with this condition are very high. Depending on the number of these children receiving care, between 2 and 4 billion dollars may be spent each year on the medical and surgical management of this condition. This is consistent with another estimate that 2 billion dollars are spent each year for ventilating tube placement for children of all ages.[9] Third, the conductive loss associated with persistent middle ear effusions may have a major long-term impact on the quality of life. The benefit of rapid restoration of hearing is a critical issue. The spontaneous resolution rates for effusions present longer than 6 weeks despite previous antimicrobial therapy vary from 6% to 57% during the subsequent 1 to 3 months.[10–20] Risk factors associated with persistence include atopic history,

In Acute Otitis Media*



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Diarrhea, the most frequent drug-related adverse reaction during clinical trials, was reported in 7% of patients following multiple doses of oral suspension. Other common adverse reactions were diaper rash (3.5%), other skin rashes (1.8%), and vomiting (1.7%).

Simple BID dosing schedule

Vantin is available in a lemon creme-flavored oral suspension, which may be administered without regard to food.

Reference

1. Data on file, The Upjohn Company, Kalamazoo, Mich.

Upjohn USJ 1156.00 December 1993

Vantin® Tablets and Oral Suspension
brand of cefpodoxime proxetil tablets and cefpodoxime proxetil for oral suspension

CONTRAINDICATIONS. Known allergy to cefpodoxime or to cephalosporins.

WARNINGS. BEFORE STARTING THERAPY WITH *VANTIN*, CAREFULLY INQUIRE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFPODOXIME, OTHER CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. CROSS-HYPERSENSITIVITY AMONG β-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO *VANTIN* OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, IF INDICATED.

PSEUDOMEMBRANOUS COLITIS HAS BEEN REPORTED WITH NEARLY ALL ANTIBIOTICS, INCLUDING CEFPODOXIME, AND MAY RANGE FROM MILD TO LIFE THREATENING. THIS DIAGNOSIS MUST BE CONSIDERED IN PATIENTS WHO PRESENT WITH DIARRHEA SUBSEQUENT TO USE OF ANTIBACTERIAL AGENTS.

Observe extreme caution when using this product in patients at increased risk for antibiotic-induced pseudomembranous colitis because of exposure to institutional settings, such as nursing homes or hospitals with endemic *Clostridium difficile*.

VANTIN can alter normal colonic flora and may permit overgrowth of clostridia; a toxin produced by *C difficile* is the primary cause of "antibiotic-associated colitis." Initiate therapeutic measures once the diagnosis of pseudomembranous colitis has been established. Mild cases usually respond to drug discontinuation alone. Moderate to severe cases may require management with fluids and electrolytes, protein supplementation, and treatment with an oral antibiotic effective against *C difficile*.

C difficile organisms or toxin was reported in **10%** of adult patients treated with VANTIN who had diarrhea; however, no specific diagnosis of pseudomembranous colitis was made. Postmarketing experience outside the United States includes reports of pseudomembranous colitis associated with use of VANTIN.

PRECAUTIONS. General. Reduce total daily doses of VANTIN in patients with transient or persistent reduction in urinary output due to renal insufficiency because high and prolonged serum levels can occur following usual doses. Administer with caution to patients taking potent diuretics. Prolonged use may cause overgrowth of nonsusceptible organisms. Take appropriate measures if superinfection occurs during therapy.

Drug Interactions. High doses of antacids or H$_2$ blockers reduce peak blood levels and extent of cefpodoxime absorption; rate of absorption is not altered. Oral anticholinergics delay peak blood levels but do not affect extent of absorption. Probenecid inhibits renal excretion of cefpodoxime, resulting in increased absorption and peak plasma levels of cefpodoxime. Closely monitor renal function when VANTIN is administered concomitantly with known nephrotoxic compounds.

Drug/Laboratory Test Interactions. A positive direct Coombs' test may be induced.

Carcinogenesis, Mutagenesis, Fertility Impairment. Long-term carcinogenesis studies have not been done. Mutagenesis studies were negative. No untoward effects on fertility or reproduction in rats.

Pregnancy - Teratogenic Effects: Pregnancy Category B/**Labor and Delivery.** Has not been studied; use only if clearly needed.

Nursing Mothers. Cefpodoxime is excreted in human milk. Because of the potential for serious reactions in nursing infants, decide whether to discontinue nursing or discontinue drug, taking into account the importance of the drug to the mother.

Pediatric Use. Safety and efficacy in infants less than 6 months old have not been established.

Geriatric Use. There were no overall differences in effectiveness or safety between the elderly and younger patients. Plasma half-life was prolonged and urinary recovery reduced in healthy geriatric volunteers with normal renal function when compared with healthy young adults; other pharmacokinetic parameters were unchanged. Dosage adjustment in elderly patients with normal renal function is not necessary.

ADVERSE REACTIONS. Clinical Trials: The following adverse reactions were considered possibly or probably related to VANTIN:

Film-coated tablets (multiple dose): 3,338 patients. Incidence >1%: Diarrhea, 7.2% (diarrhea or loose stools were dose related, decreasing from 10.6% of patients who received 800 mg per day to 5.9% of those who received 200 mg per day; of patients with diarrhea, 10% had *C difficile* organism or toxin in the stool–see WARNINGS); nausea, 3.8%; vaginal fungal infections, 3.1%; abdominal pain, 1.6%; rash, 1.4%; headache, 1.1%; and vomiting, 1.1%. Incidence <1%: *Cardiovascular:* Chest pain, hypotension; *Dermatologic:* Fungal skin infection, skin scaling/peeling; *Endocrine:* Menstrual irregularity; *Genital:* Pruritus; *GI:* Flatulence, decreased salivation, candidiasis, pseudomembranous colitis; *Hypersensitivity:* Anaphylactic shock; *Metabolic:* Decreased appetite; *Miscellaneous:* Malaise, fever; *CNS:* Dizziness, fatigue, anxiety, insomnia, flushing, nightmares, weakness; *Respiratory:* Cough, epistaxis; and *Special senses:* Taste alteration, eye itching, tinnitus. Eighty-one patients (2.4%) discontinued medication due to adverse events thought possibly or probably related to drug toxicity. Sixty-six (66%) of the 100 patients who discontinued therapy (regardless of relationship to therapy) did so because of GI disturbances, usually diarrhea. Significantly more patients discontinued drug because of adverse events at a dose of 800 mg daily than at a dose of 400 mg daily or at a dose of 200 mg daily.

Oral suspension (multiple dose): 758 patients (90% were less than 12 years old). Incidence >1%: Diarrhea, 7.0% (incidence ranged from 17.8% in infants and toddlers to 4.1% in 2- to 12-year-olds to 6.0% in adolescents); diaper rash, 3.5%; other skin rashes, 1.8%; and vomiting, 1.7%. Incidence <1%: *CNS:* Headache; *Dermatologic:* Exacerbation of acne; *Genital:* Pruritus or vaginitis; *GI:* Nausea, abdominal pain, candidiasis; *Metabolic:* Decreased appetite; and *Miscellaneous:* Fever. Seven patients (<1%) discontinued medication because of adverse events thought possibly or probably related to drug toxicity, primarily for GI disturbances, usually diarrhea or diaper rashes.

Film-coated tablets (single dose): 509 patients. Incidence >1%: Nausea, 1.4%, and diarrhea, 1.2%. Incidence <1%: *CNS:* Dizziness, headache, syncope; *Dermatologic:* Rash; *Genital:* Vaginitis; *GI:* Abdominal pain; and *Psychiatric:* Anxiety.

Laboratory Changes. The following significant laboratory changes were reported, without regard to drug relationship. Most were transient and not clinically significant.

Adults: *Hepatic:* Transient increases in AST (SGOT), ALT (SGPT), GGT, alkaline phosphatase, bilirubin, and LDH. *Hematologic:* Eosinophilia, leukocytosis, lymphocytosis, granulocytosis, basophilia, monocytosis, thrombocytosis, decreased hemoglobin, leukopenia, neutropenia, lymphocytopenia, thrombocytopenia, positive Coombs' test, and prolonged PT and PTT. *Serum Chemistry:* Increases in glucose; decreases in glucose, serum albumin, and serum total protein. *Renal:* Increases in BUN and creatinine.

Children: *Hematologic:* Eosinophilia, decreased hemoglobin, and decreased hematocrit. *Hepatic:* Transient increases in ALT (SGPT).

Postmarketing Experience. Serious adverse events outside the United States were pseudomembranous colitis, bloody diarrhea with abdominal pain, ulcerative colitis, rectorrhagia with hypotension, anaphylactic shock, acute liver injury, in utero exposure with miscarriage, purpuric nephritis, pulmonary infiltrate with eosinophilia, and eyelid dermatitis. One death was attributed to pseudomembranous colitis and disseminated intravascular coagulation.

Cephalosporin Class Labeling. Other adverse reactions and altered laboratory tests reported for cephalosporin class antibiotics are allergic reactions including Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage; agranulocytosis; and pancytopenia. Several cephalosporins have triggered seizures, particularly in patients with renal impairment when dosage was not reduced (see DOSAGE AND ADMINISTRATION and OVERDOSAGE). If seizures associated with drug therapy occur, discontinue the drug; anticonvulsants may be indicated.

OVERDOSAGE. Cefpodoxime proxetil produced no adverse effects in acute rodent toxicity studies. Information on overdosage in humans is not available. If a serious toxic reaction from overdosage occurs, hemodialysis or peritoneal dialysis may aid in removing cefpodoxime from the body, particularly if renal function is compromised. Toxic symptoms following overdosage of β-lactam antibiotics may include nausea, vomiting, epigastric distress, and diarrhea.

DOSAGE AND ADMINISTRATION. VANTIN Tablets should be given with food to enhance absorption; VANTIN Oral Suspension may be given without regard to food. Acute otitis media (children 6 months through 12 years): 5 mg/kg q12h (maximum 400 mg/day) for 10 days. **Patients with renal dysfunction.** See full prescribing information for dosing adjustments recommended for patients with severe renal impairment (<30 mL/min creatinine clearance) or maintained on hemodialysis. **Patients with cirrhosis.** Dosage adjustment is not necessary in cirrhotic patients, with or without ascites.

Caution: Federal law prohibits dispensing without a prescription.

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References:

1. Data on file, McNeil Consumer Products Company. **2.** Cooper SA. *Arch Intern Med.* 1981;141:282-285. **3.** Aspirin or paracetamol? *Lancet.* 1981; 11:287-289. **4.** Bertin L et al. Randomized, double-blind, multicenter, controlled trial of ibuprofen versus acetaminophen (paracetamol) and placebo for treatment of symptoms of tonsillitis and pharyngitis in children. *J Pediatr.* 1991;119(5):811-814. **5.** Hopkinson J et al. *Curr Ther Res.* 1974; 16(3):194-200. **6.** Reuter SH et al. *Arch Otolaryngol.* 1964;80:214. **7.** Skelbred P et al. *Eur J Clin Pharmacol.* 1977;12:257. **8.** Mehlisch DR, Frakes LA. *Clin Ther.* 1985;7(1):89-97. **9.** Barabas G. *Pediatr Ann.* 1983;12:806. **10.** Pediatric Update: New Developments in Fever Management. Proceedings of a satellite teleconference, November 2, 1989; Philadelphia, Pa. *Pediatric Update.* McNeil Consumer Products Company. **11.** Amadio P Jr. *Am J Med.* September 1984;17-26.

McNEIL McNeil Consumer Products Company
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I Will Sing Life: Voices from the Hole in the Wall Gang Camp. L. Berger, D. Lithwick, and seven campers. Boston: Little, Brown and Company; 1992, $22.95 (hardcover), 207 pp.

The Pediatric Patient: An Approach to History and Physical Examination. P. S. Algranati. Baltimore: Williams & Wilkins; 1992, $30.00 (paperback), 217 pp.

Pediatric Dosage Handbook—1992. C. K. Taketomo, J. H. Hodding, and D. M. Kraus. Hudson, OH: Lexi-Comp Inc.; 1992, $29.50 (paperback), 594 pp.

Adoption and the Family System: Strategies for Treatment. M. Reitz and K. Watson. New York, NY: The Guilford Press; 1992, $30.00 (hardcover), 340 pp.

Advances in Body Composition Assessment. T. Lohman. Champaign, IL: Human Kinetics Publishers; 1992, $18.00 (paperback), 150 pp.

Brain Mechanisms, Attention-Deficit, and Related Mental Disorders: A Clinical and Theoretical Assessment of Attention-Deficit. J. Joseph. Springfield, IL: Charles C. Thomas, Publisher; 1992, $89.75 (hardcover), 592 pp.

Comprehensive Adolescent Health Care. S. Friedman, M. Fisher, and S. Schonberg, eds. St. Louis, MO: Quality Medical Publishing, Inc.; 1992, $85.00 (hardcover), 1231 pp.

The Golden Wand of Medicine—A History of the Caduceus Symbol in Medicine. W. Friedlander. Westport, CT: Greenwood Press; 1992, $45.00 (hardcover), 181 pp.

How to Read Pediatric ECGs. 3rd Ed. M. Park and W. Guntheroth. St. Louis, MO: Mosby Year Book; 1992 (paperback), 248 pp.

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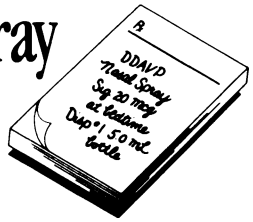
(desmopressin acetate) 5mL

Dry Nights For Good Mornings



Brief Summary
CONTRAINDICATION: Known hypersensitivity to DDAVP Nasal Spray
WARNINGS:
1. For intranasal use only.
2. In very young and elderly patients in particular, fluid intake should be adjusted in order to decrease the potential occurrence of water intoxication and hyponatremia. Particular attention should be paid to the possibility of the rare occurrence of an extreme decrease in plasma osmolality and resulting seizures.
PRECAUTIONS:
General: DDAVP Nasal Spray at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.
DDAVP Nasal Spray should be used with caution in patients with conditions associated with fluid and electrolyte imbalance, such as cystic fibrosis, because these patients are prone to hyponatremia.
Central Cranial Diabetes Insipidus: Since DDAVP Nasal Spray is used intranasally, changes in the nasal mucosa such as scarring, edema, or other disease may cause erratic, unreliable absorption in which case DDAVP Nasal Spray should not be used. For such situations, DDAVP injection should be considered.
Primary Nocturnal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. DDAVP Nasal Spray should be discontinued until the nasal problems resolve.
Information for Patients: Patients should be informed that the bottle accurately delivers 50 doses of 10 mcg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.
Laboratory Tests: Laboratory tests for following the patient with central cranial diabetes insipidus or post-surgical or head trauma-related polyuria and polydipsia include urine volume and osmolality. In some cases plasma osmolality may be required. For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days.
Drug Interactions: Although the pressor activity of DDAVP Nasal Spray is very low compared to the antidiuretic activity, use of large doses of DDAVP Nasal Spray with other pressor agents should only be done with careful patient monitoring.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Teratology studies in rats have shown no abnormalities. No further information is available.
Pregnancy-Category B: Reproduction studies performed in rats and rabbits with doses up to 12.5 times the human intranasal dose (i.e. about 125 times the total adult human dose given systemically) have revealed no evidence of harm to the fetus due to desmopressin acetate. There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported; however, no controlled studies in pregnant women have been carried out. Published reports stress that, as opposed to preparations containing the natural hormones, DDAVP Nasal Spray (desmopressin acetate) in antidiuretic doses has no uterotonic action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case.
Nursing Mothers: There have been no controlled studies in nursing mothers. A single study in a post-partum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP Nasal Spray in breast milk following an intranasal dose of 10 mcg.
Pediatric Use: Primary Nocturnal Enuresis: DDAVP Nasal Spray has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) DDAVP Nasal Spray administration has been shown to be safe and modestly effective in children aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with DDAVP Nasal Spray in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.
Central Cranial Diabetes Insipidus: DDAVP Nasal Spray has been used in children with diabetes insipidus. Use in infants and children will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication. The dose must be individually adjusted to the patient with attention in the very young to the danger of an extreme decrease in plasma osmolality with resulting convulsions. Dose should start at 0.05 mL or less.
Since the spray cannot deliver less than 0.1 mL (10 mcg), smaller doses should be administered using the rhinal tube delivery system. Do not use the nasal spray in pediatric patients requiring less than 0.1 mL (10 mcg) per dose.
There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.
ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nose-bleed, sore throat, cough and upper respiratory infections have also been reported.
The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

ADVERSE REACTION	PLACEBO (N=58) %	DDAVP 20 mcg (N=60) %	DDAVP 40 mcg (N=61) %
BODY AS A WHOLE			
Abdominal Pain	0	2	2
Asthenia	0	0	2
Chills	0	0	2
Headache	0	2	5
Throat Pain	2	0	0
NERVOUS SYSTEM			
Depression	2	0	0
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	2	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2	0	0
Rash	2	0	0
SPECIAL SENSES			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

OVERDOSAGE: See adverse reactions above. In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for DDAVP Nasal Spray. An oral LD_{50} has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.
HOW SUPPLIED: A 5-mL bottle with spray pump delivering 50 doses of 10 mcg (NDC 0075-2450-02). Also available as 2.5 mL per vial, packaged with two rhinal tube applicators per carton (NDC 0075-2450-01). Keep refrigerated at 2°-8°C (36°-46°F). When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 22°C (72°F).
CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.
Please see full prescribing information in product circular.

References:

1. **Aladjem M,** Wohl R, Boichis H, et al: Desmopressin in nocturnal enuresis. *Arch Dis Child* 1982;57:137-140.
2. **Bloom DA:** The American experience with desmopressin. *Clin Pediatr* 1993(July, special edition):28-31.

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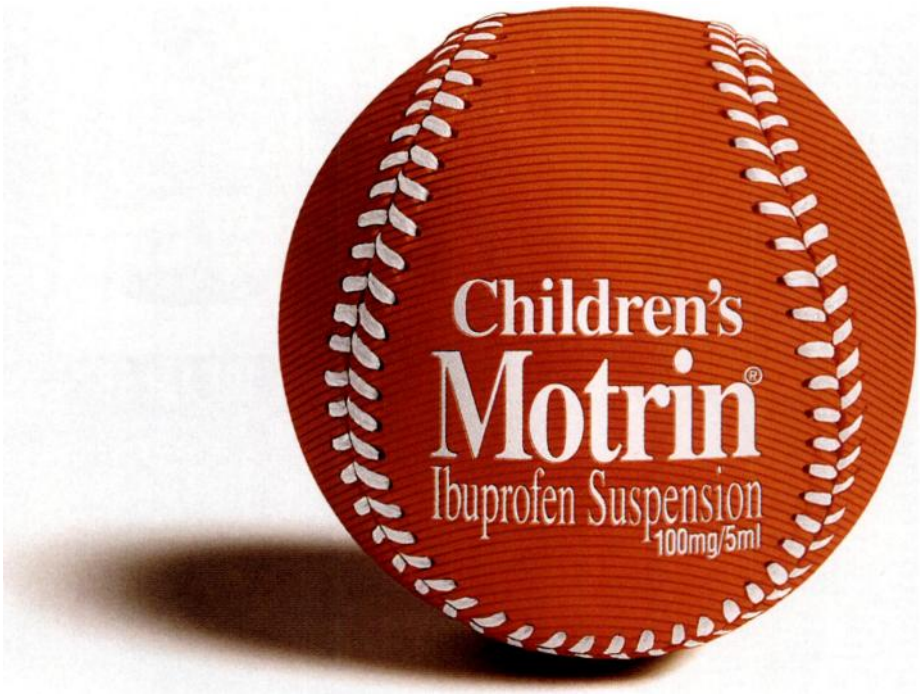

When you need to replace your starter it's time for Children's Motrin. Its proven efficacy[1] and demonstrated safety[1,2] profile help ensure your confidence. You can count on Children's Motrin for up to 6-to-8-hour fever relief. And Children's Motrin encourages patient compliance with its pleasant-tasting flavor and easy-to-pour liquid.

The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal.
Children's Motrin is contraindicated in patients hypersensitive to aspirin, ibuprofen, or other NSAIDs.

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References: 1. Walson PD et al. Ibuprofen, acetaminophen and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17. 2. Walson PD et al. Comparison of multidose ibuprofen and acetaminophen therapy in febrile children. *AJDC.* 1992;146:626-632.

Please see brief summary of Prescribing Information on the next page.

suffering and the duration of hypoxemia associated with routine treatment procedures. Stabilization of oxygenation and hemodynamics is assumed to be very important in efforts to prevent brain injury in premature and critically ill neonates, and thus adequate analgesia with opioids may improve the results of medical treatment and is at least indicated for humanitarian reasons, to alleviate suffering.

ACKNOWLEDGMENTS

This work was supported by the Foundation for Paediatric Research in Finland, Helsinki and the Alma och K. A. Snellman Foundation, Oulu, Finland.

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Abstract Deadline for 1994 Annual Perinatal Section Meeting

The Section on Perinatal Pediatrics, American Academy of Pediatrics, announces that the abstract deadline for the 1994 Annual Perinatal Section Meeting (October 22–24, 1994, Dallas, Texas) has been set as April 1, 1994. For further information, contact AAP Headquarters, 141 Northwest Point Blvd, PO Box 927, Elk Grove Village, IL 60009–0927, or telephone 708/981–7879.

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DESCRIPTION: TOBREX® (TOBRAMYCIN 0.3%) is a sterile topical ophthalmic antibiotic formulation prepared specifically for topical therapy of external ophthalmic infections.

INDICATIONS AND USAGE: TOBREX is a topical antibiotic indicated in the treatment of external infections of the eye and its adnexa caused by susceptible bacteria. Appropriate monitoring of bacterial response to topical antibiotic therapy should accompany the use of TOBREX. Clinical studies have shown tobramycin to be safe and effective for use in children.

CONTRAINDICATIONS: TOBREX Ophthalmic Solution and Ointment are contraindicated in patients with known hypersensitivity to any of their components.

WARNINGS: NOT FOR INJECTION INTO THE EYE. Sensitivity to topically applied aminoglycosides may occur in some patients. If a sensitivity reaction to TOBREX occurs, discontinue use.

PRECAUTIONS: General. As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. Ophthalmic ointments may retard corneal wound healing. Information for Patients: Do not touch dropper or tube tip to any surface, as this may contaminate the contents.

Pregnancy Category B. Reproduction studies in three types of animals at doses up to thirty-three times the normal human systemic dose have revealed no evidence of impaired fertility or harm to the fetus due to tobramycin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive in human response, this drug should be used during pregnancy only if clearly needed. Nursing Mothers. Because of the potential for adverse reactions in nursing infants from TOBREX®, a decision should be made whether to discontinue nursing the infant or discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS: The most frequent adverse reactions to TOBREX Ophthalmic Solution and Ointment are hypersensitivity and localized ocular toxicity, including lid itching and swelling, and conjunctival erythema. These reactions occur in less than three of 100 patients treated with TOBREX. Similar reactions may occur with the topical use of other aminoglycoside antibiotics. Other adverse reactions have not been reported from TOBREX therapy; however, if topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration. In clinical trials, TOBREX Ophthalmic Ointment produced significantly fewer adverse reactions (3.7%) than did GARAMYCIN® Ophthalmic Ointment (10.6%).

OVERDOSAGE: Clinically apparent signs and symptoms of an overdose of TOBREX Ophthalmic Solution or Ointment (punctate keratitis, erythema, increased lacrimation, edema and lid itching) may be similar to adverse reaction effects seen in some patients.

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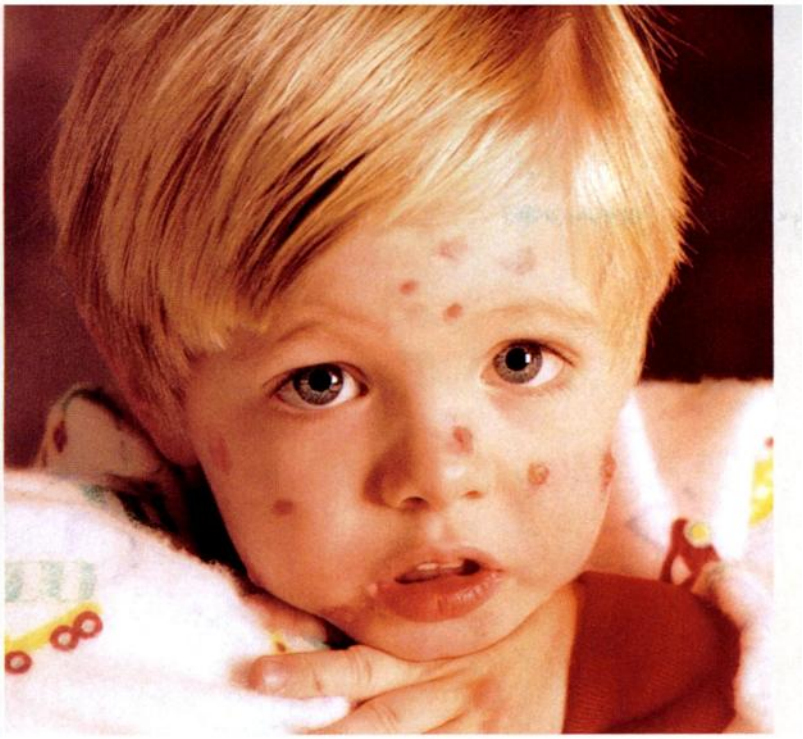

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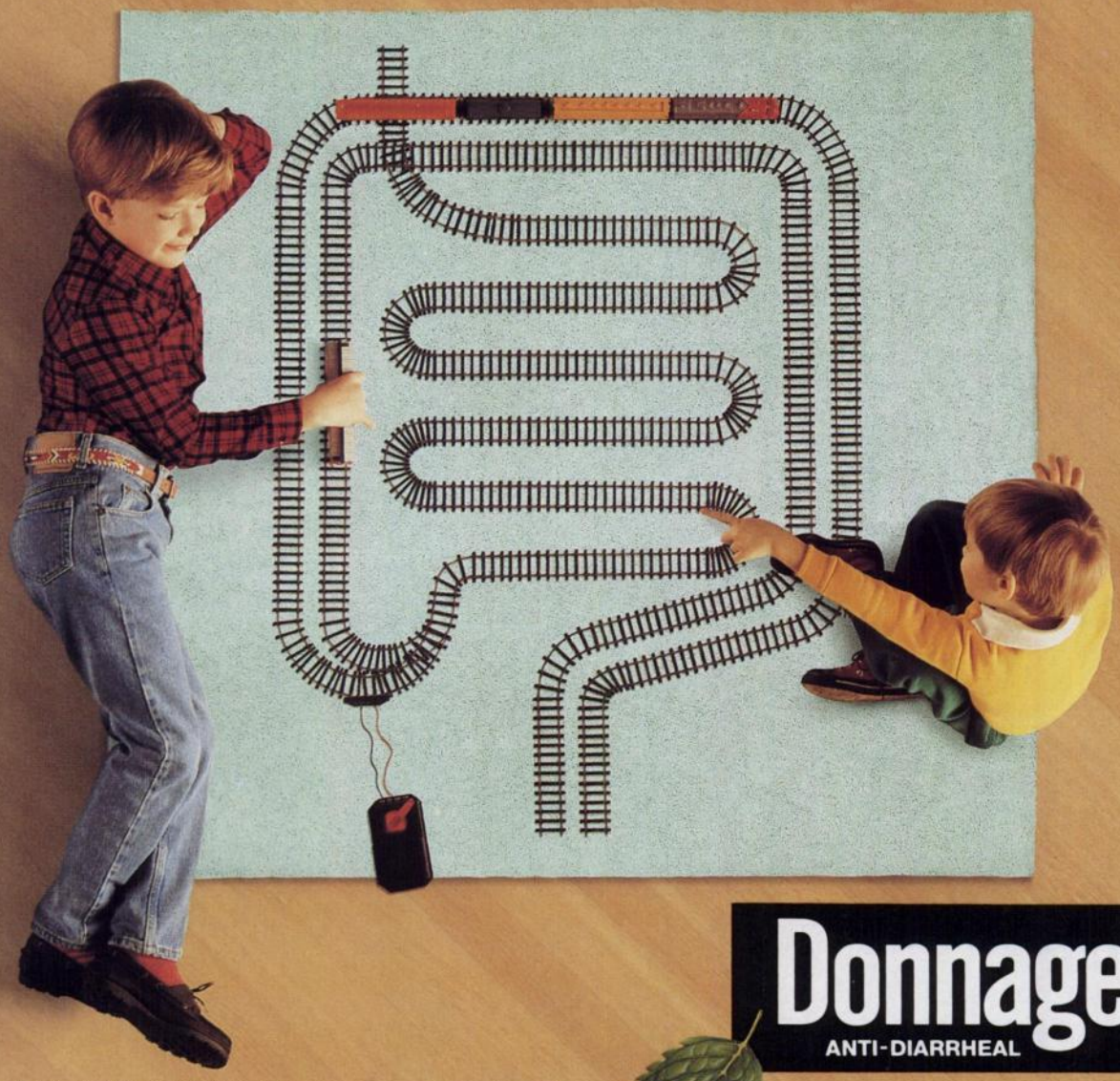

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References: 1. de Sola Pool N, Loehle K, Radzik AJ, et al. A comparison of nonsystemic and systemic antidiarrheal agents in the treatment of acute nonspecific diarrhea in adults. *Today's Therapeutic Trends.* 1987;5:31-38. 2. Pondaven JY. Comparison between attapulgite and an intestinal transit inhibitor in the treatment of acute diarrhea in adults. *Rev Fr Gastroenterol.* 1990; 26:30-33. 3. Dukes GE. Over-the-counter antidiarrheal medications used for the self-treatment of acute nonspecific diarrhea. *Am J Med.* 1990;88(suppl 6A):24S-26S.

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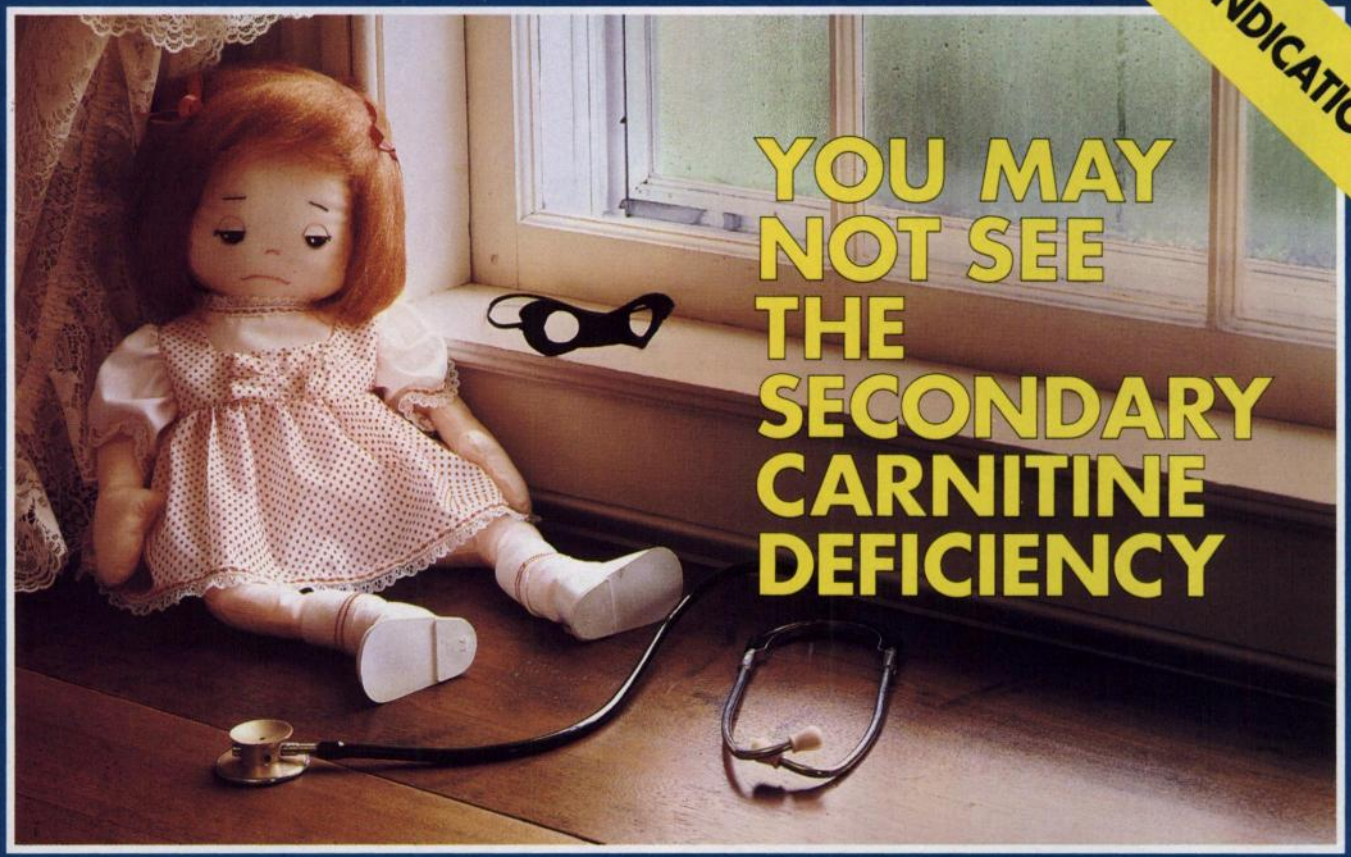

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Side effects with CARNITOR® Injection are mild and transient; nausea and vomiting have been reported infrequently. Side effects with oral CARNITOR® are also mild and transient and include nausea, vomiting, body odor, and gastritis.

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CARNITOR® (Levocarnitine)
Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE:
CARNITOR® (Levocarnitine) Tablets and Oral Solution are indicated in the treatment of primary systemic carnitine deficiency.
Tablets and Oral Solution are also indicated for the acute and chronic treatment of patients with an inborn error of metabolism which results in a secondary carnitine deficiency.

CONTRAINDICATIONS None known.

WARNINGS None.

PRECAUTIONS

General CARNITOR® Oral Solution is for oral/internal use only. **Not for parenteral use**. Gastrointestinal reactions may result from too rapid consumption. CARNITOR® Oral Solution may be consumed alone, or dissolved in drinks or other liquid foods to reduce taste fatigue. It should be consumed slowly and doses should be spaced evenly throughout the day (every 3-4 hours, preferably during or following meals) to maximize tolerance.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Mutagenicity tests have been performed in *Salmonella typhimurium, Saccharomyces cerevisiae,* and *Schizosaccharomyces pombe* that do not indicate that CARNITOR® is mutagenic. Long-term animal studies have not been conducted to evaluate the carcinogenicity of the compound.

Pregnancy
Pregnancy Category B
Reproductive studies have been performed in rats and rabbits at doses up to 3.8 times the human dose on the basis of surface area and have revealed no evidence of impaired fertility or harm to the fetus due to CARNITOR®. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing mothers It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, a decision should be made whether to discontinue nursing or whether to discontinue the drug, taking into account the importance of the drug to the mother.

Metabolism and excretion

Reference: Rebouce CJ, et al: Carnitine metabolism and deficiency syndromes. Mayo Clin Proc 58:533-540, 1983.

Pediatric use See **Dosage and Administration.**

ADVERSE REACTIONS Various mild gastrointestinal complaints have been reported during the long-term administration of oral L- or D, L-carnitine; these include transient nausea and vomiting, abdominal cramps, and diarrhea. Mild myasthenia has been described only in uremic patients receiving D, L-carnitine. Gastrointestinal adverse reactions with CARNITOR® (Levocarnitine) Oral Solution dissolved in liquids might be avoided by a slow consumption of the solution or by greater dilution. Decreasing the dosage often diminishes or eliminates drug-related patient body odor or gastrointestinal symptoms when present. Tolerance should be monitored very closely during the first week of administration, and after any dosage increases.

OVERDOSAGE There have been no reports of toxicity from carnitine overdosage. The oral LD_{50} of levocarnitine in mice is 19.2 g/kg. Carnitine may cause diarrhea. Overdosage should be treated with supportive care.

DOSAGE AND ADMINISTRATION
CARNITOR® Tablets: Recommended adult dosage is 990 mg two or three times a day using the 330 mg tablets, depending on clinical response. Oral Solution: the recommended dosage of levocarnitine is 1 to 3 g/day for a 50 kg subject which is equivalent to 10 to 30 mL/day of CARNITOR® (Levocarnitine) Oral Solution.
Recommended dosage for infants and children is 50-100 mg/kg/day in divided doses, with a maximum of 3 g/day. Dosage should start at 50 mg/kg/day and be increased slowly to a maximum of 3 g/day (30 mL/day) while assessing tolerance and therapeutic response. Monitoring should include periodic blood chemistries, vital signs, plasma carnitine concentrations, and overall clinical condition.

HOW SUPPLIED CARNITOR® Tablets are supplied as 330 mg, individually foil-wrapped tablets in boxes of 90. Store at room temperature (25°C/77°F). CARNITOR® Oral Solution is supplied in 118 ml (4 fl oz) multiple-unit plastic containers packaged 24 per case. Store at room temperature (25°C/77°F).

CARNITOR® (LEVOCARNITINE) Injection
For Intravenous Use Only

CARNITOR® (Levocarnitine) Injection 1 g per 5 mL
CARNITOR® (Levocarnitine)
Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE:
For the acute and chronic treatment of patients with an inborn error of metabolism that results in secondary carnitine deficiency.

CONTRAINDICATIONS None known.

WARNINGS None.

PRECAUTIONS
Carcinogenesis, Mutagenesis, Impairment of Fertility
Mutagenicity tests performed in *Salmonella typhimurium. Saccharomyces cerevisiae,* and *Schizosaccharomyces pombe* indicate that levocarnitine is not mutagenic. No long-term animal studies have been performed to evaluate the carcinogenic potential of levocarnitine.

Pregnancy
Pregnancy Category B
Reproductive studies have been performed in rats and rabbits at doses up to 3.8 times the human dose on the basis of surface area and have revealed no evidence of impaired fertility or harm to the fetus due to CARNITOR®. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing mothers It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Metabolism and excretion
Reference: Rebouche CJ, et al: Carnitine metabolism and deficiency syndromes. Mayo Clin Proc 58:533-540, 1983.

Pediatric use See **Dosage and Administration.**

ADVERSE REACTIONS Transient nausea and vomiting have been observed. Less frequent adverse reactions are body odor, nausea, and gastritis. An incidence for these reactions is difficult to estimate due to the confounding effects of the underlying pathology.

OVERDOSAGE There have been no reports of toxicity from levocarnitine overdosage. The oral LD_{50} of levocarnitine in mice is 19.2 g/kg. Large doses of levocarnitine may cause diarrhea.

DOSAGE AND ADMINISTRATION
CARNITOR® Injection is administered intravenously.
The recommended dose is 50 mg/kg given as a slow 2-3 minute bolus injection or by infusion. Often a loading dose is given in patients with severe metabolic crisis followed by an equivalent dose over the following 24 hours. It should be administered q3h or q4h, and never less than q6h either by infusion or by intravenous injection. All subsequent daily doses are recommended to be in the range of 50 mg/kg or as therapy may require. The highest dose administered has been 300 mg/kg.

It is recommended that a plasma carnitine level be obtained prior to beginning this parenteral therapy. Weekly and monthly monitoring is recommended as well. This monitoring should include blood chemistries, vital signs, plasma carnitine concentrations (the plasma free carnitine level should be between 35 and 60 micromoles/liter), and overall clinical condition.

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

HOW SUPPLIED CARNITOR® (Levocarnitine) Injection, 1 gram per 5 mL, is available in 5 mL single dose ampoules packaged 5 ampoules per carton.

Store ampoules at room temperature (25°C/77°F) in carton until their use to protect from light. Discard unused portion of an opened ampoule, as they contain no preservative.

sigma-tau Pharmaceuticals, Inc.
Gaithersburg, MD
A leader in metabolic research

For moderate to severe asthma

UNFOLD THE MANY BENEFITS OF BECLOVENT

Compatible with a variety of spacer devices

See your Allen & Hanburys representative for details on a complimentary spacer offer.*

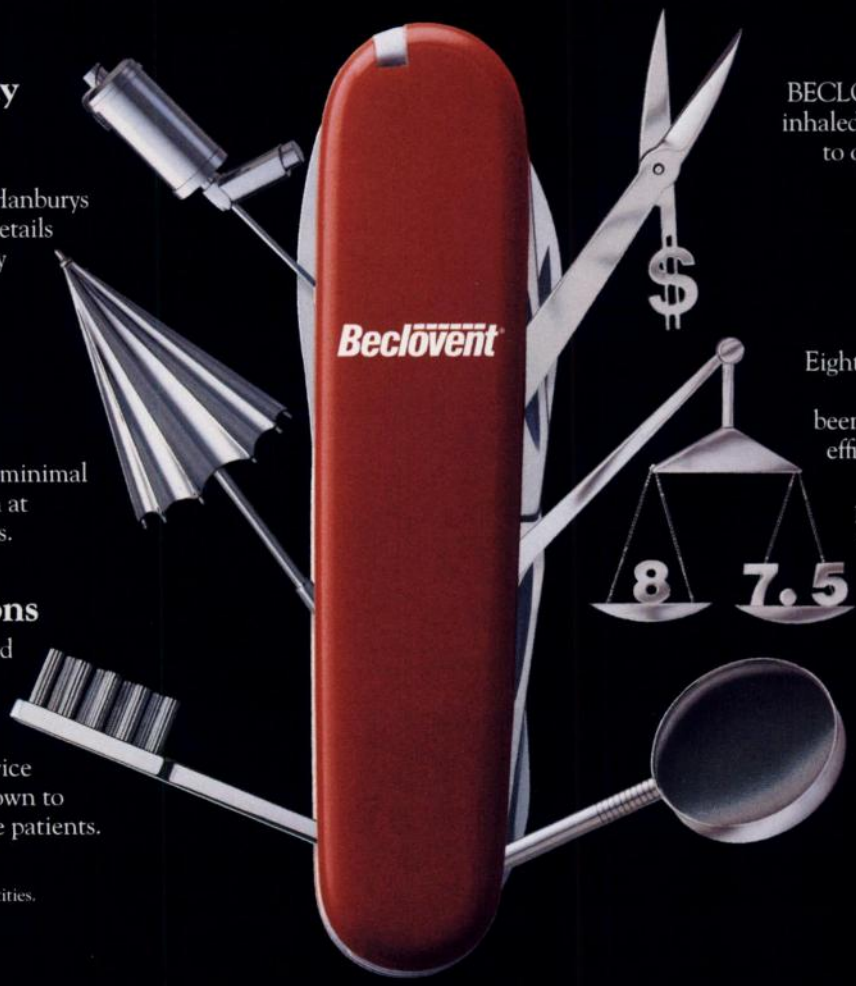
Minimal systemic absorption

BECLOVENT has minimal systemic absorption at recommended doses.

Dosing options

Usual recommended dosage is two inhalations three to four times daily. Four inhalations twice daily have been shown to be effective in some patients.

*Available in limited quantities.



Cut costs

BECLOVENT is the only inhaled anti-inflammatory to offer an economical refill canister.[1]

Weigh the potency

Eight puffs (336 mcg) of BECLOVENT has been shown to provide efficacy similar to that of 7.5 mg of oral prednisone without the systemic effects of prednisone.[2,3]

Examine the record

Established safety and efficacy for more than 20 years.[4]

Beclovent®
(BECLOMETHASONE DIPROPIONATE, USP)
INHALATION AEROSOL AND REFILL

The safety you look for... the control you expect.

CAUTION: Adrenal insufficiency may occur when transferring steroid-dependent patients from systemic steroids to BECLOVENT due to the minimal systemic effects at recommended doses (see **WARNINGS**).

Allen & Hanburys
DIVISION OF GLAXO INC.
a world leader in respiratory care
Research Triangle Park, NC 27709

Please consult Brief Summary of Prescribing Information on adjacent page.

No. 2 in a series

Breathing Easier

Please copy and share with your asthma patients. Offered as a service of Allen & Hanburys.

The asthma trigger control plan

What are asthma triggers?

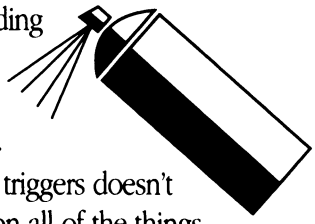
Asthma triggers stimulate asthma episodes. Because the airways in people who have asthma are very sensitive, exposure to these triggers can often irritate the lungs. Not only can triggers initiate asthma episodes, they may also make episodes more severe, and may even prevent you from feeling better. Below is a list of some common asthma triggers.

- Dust and dust mites
- Pollen from trees, grasses, and weeds
- Mold
- Animal dander (cats and dogs)
- Smoke
- Perfume
- Foods to which you are allergic
- Some chemicals found in household cleaners and hair spray

How do I know what *my* asthma triggers are?

Think of the things that make you cough and wheeze. Make a list and share it with your physician (especially if you're a new asthma patient).

What can I do about my asthma triggers?



Try your best to avoid your triggers. Knowing what your triggers are and avoiding them are two important keys to a successful asthma management program. Remember, avoiding your triggers doesn't mean having to miss out on all of the things you like to do. Just exercise caution if you think you'll be exposed to your triggers. Taking simple, preventive steps can help you feel better.

What else can I do to help manage my asthma?

Your physician can give you medications that can help you feel better by relieving your symptoms. Some of these treatments work quickly to open blocked airways in your lungs. Others prevent inflammation and help keep airways from becoming blocked. Your physician will tell you which treatment is right for you.

A good asthma management program includes carefully following your physician's instructions and avoiding your asthma triggers.

Ask your physician if you have any questions about your asthma triggers or your asthma treatment program.

Physician's name and phone number

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Please consult Brief Summary of Prescribing Information on adjacent page.

BEV331R0 Printed in USA November 1993

Beclovent®
(beclomethasone dipropionate, USP)
Inhalation Aerosol
For Oral Inhalation Only

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Beclovent® Inhalation Aerosol product labeling.

CONTRAINDICATIONS: Beclovent® 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 this preparation contraindicates its use.

WARNINGS:

Particular care is needed in patients who are transferred from systemically active corticosteroids to Beclovent® Inhalation Aerosol because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosol beclomethasone dipropionate. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infections, particularly gastroenteritis. Although Beclovent Inhalation Aerosol may provide control of asthmatic symptoms during these episodes, it does NOT provide the systemic steroid that is necessary for coping with these emergencies.

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning resting cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal only if it falls at or near the normal mean level.

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 nonimmune 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.

Localized infections with *Candida albicans* or *Aspergillus niger* have occurred frequently in the mouth and pharynx and occasionally in the larynx. Positive cultures for oral *Candida* may be present in up to 75% of patients. Although the frequency of clinically apparent infection is considerably lower, these infections may require treatment with appropriate antifungal therapy or discontinuation of treatment with Beclovent Inhalation Aerosol.

Beclovent Inhalation Aerosol is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

Patients should be instructed to contact their physician immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment with Beclovent Inhalation Aerosol. During such episodes, patients may require therapy with systemic corticosteroids.

There is no evidence that control of asthma can be achieved by the administration of Beclovent Inhalation Aerosol in amounts greater than the recommended doses.

Transfer of patients from systemic steroid therapy to Beclovent Inhalation Aerosol may unmask allergic conditions previously suppressed by the systemic steroid therapy, e.g., rhinitis, conjunctivitis, and eczema.

PRECAUTIONS: During withdrawal from oral steroids, some patients may experience symptoms of systemically active steroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function (see DOSAGE AND ADMINISTRATION).

In responsive patients, beclomethasone dipropionate may permit control of asthmatic symptoms without suppression of HPA function, as discussed below (see CLINICAL STUDIES). Since beclomethasone dipropionate is absorbed into the circulation and can be systemically active, the beneficial effects of Beclovent® Inhalation Aerosol in minimizing or preventing HPA dysfunction may be expected only when recommended dosages are not exceeded.

Because of the possibility of systemic absorption of orally inhaled corticosteroids, including beclomethasone, patients should be monitored for symptoms of systemic effects such as mental disturbances, increased bruising, weight gain, cushingoid features, and cataracts. Therefore, if such changes occur, Beclovent Inhalation Aerosol should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroids.

In addition, children should be monitored for a reduction in growth velocity, although the relationship between growth velocity and final adult height is not known.

The long-term effects of beclomethasone dipropionate in human subjects are still unknown. In particular, the local effects of the agent on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. There is also no information about the possible long-term systemic effects of the agent.

The potential effects of Beclovent Inhalation Aerosol on acute, recurrent, or chronic pulmonary infections, including active or quiescent tuberculosis, are not known. Similarly, the potential effects of long-term administration of the drug on lung or other tissues are unknown.

Pulmonary infiltrates with eosinophilia may occur in patients on Beclovent Inhalation Aerosol therapy. Although it is possible that in some patients this state may become manifest because of systemic steroid withdrawal when inhalational steroids are administered, a causative role for beclomethasone dipropionate and/or its vehicle cannot be ruled out.

Information for Patients: Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Pregnancy: *Teratogenic Effects:* Glucocorticoids are known teratogens in rodent species and beclomethasone dipropionate is no exception.

Teratology studies were done in rats, mice, and rabbits treated with subcutaneous beclomethasone dipropionate. Beclomethasone dipropionate was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and partial agenesis of the thymus. Well-controlled trials relating to fetal risk in humans are not available. Glucocorticoids are secreted in human milk. It is not known whether beclomethasone dipropionate would be secreted in human milk, but it is safe to assume that it is likely. The use of beclomethasone dipropionate in pregnant women, nursing mothers, or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother, embryo, or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for hypoadrenalism.

ADVERSE REACTIONS: Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosol beclomethasone dipropionate (see WARNINGS).

Suppression of HPA function (reduction of early morning plasma cortisol levels) has been reported in adult patients who received 1,600-mcg daily doses of Beclovent® Inhalation Aerosol for 1 month. A few patients on Beclovent Inhalation Aerosol have complained of hoarseness or dry mouth.

Rare cases of immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm, have been reported after the use of beclomethasone oral or intranasal inhalers.

DOSAGE AND ADMINISTRATION: Patients experiencing symptoms of systemically active steroid withdrawal should be encouraged to continue with the inhaler but should be watched carefully for objective signs of adrenal insufficiency such as hypotension and weight loss. If evidence of adrenal insufficiency occurs, the systemic steroid dose should be boosted temporarily and thereafter further withdrawal should continue more slowly.

WARNING: Contains trichloromonofluoromethane and dichlorodifluoromethane, substances which harm public health and environment by destroying ozone in the upper atmosphere.

Allen & Hanburys
DIVISION OF GLAXO INC.
Research Triangle Park, NC 27709

November 1993
RL-090

References:

1. *Medi-Span®*, December 1993.
2. Lal S, Harris DM, Bhalla KK, Singhal SN, Butler AG. Comparison of beclomethasone dipropionate aerosol and prednisolone in reversible airways obstruction. *Br Med J.* August 5, 1972;3:314-317.
3. British Thoracic and Tuberculosis Association. A controlled trial of inhaled corticosteroids in patients receiving prednisone tablets for asthma. *Br J Dis Chest.* 1976;70:95-103.
4. Data on file, Glaxo Inc.

BEV365R1 Printed in USA January 1994

THE AAP PERINATAL SECTION
SPRING WORKSHOP

Marriott's Mountain Shadows Resort—Scottsdale, Arizona

April 8–10, 1994

TOPICS AND FACULTY

The perinatal piece of health care reform
Richard Ehrenkranz
Shoo K. Lee

Health care reform—the role of the state
Jane Pearson

Health care reform—the office practice
Marilyn Laughead
Lou Pollack

Perinatal training programs
Robert Cotton
Richard Molteni
David Stevenson

Health Policy—"The NICU Arms Race"
Douglas Richardson

How to survive managed health care
Herb Koffler

"A Look at the Future through the Rear View Mirror"
Fred Battaglia

Organizational Political Strategies
George Comerci
Patricia Johnson
Richard Johnston
George Little
Tom Purdon
Steve Saunders

Neonatal CPT Coding Update
Bernard Feldman

Health Policy—What is the evidence that regional perinatal care is cost and quality effective?
Ciaran Phibbs
David Wirtschafter

There will also be a poster session and small group sessions. To register or to receive more information on the 1994 Section on Perinatal Pediatrics Spring Workshop, please call Nicole Blankenship in the Division of Sections at 800/433-9016 ext. 7658, or 708/981-7658.

Overstuffed noses, rhinorrhea, sneezing, coughing, and watery eyes. That's what colds and flu are made of. But the Bromfed® family of products is made of something even stronger — an effective nasal decongestant, a well-tolerated antihistamine, and the added benefit of a safe antitussive agent in Bromfed-DM® Cough Syrup. Three ingredients that can knock the stuffing and other miseries out of any cold or flu.

Choose from Bromfed® Syrup, Bromfed-DM® Cough Syrup, or Bromfed-PD® Timed-Release Capsules when cold or flu symptoms show their face in your practice.

BROMFED-DM®
Each 5 mL contains brompheniramine maleate 2 mg, pseudoephedrine hydrochloride 30 mg, and dextromethorphan hydrobromide 10 mg
COUGH SYRUP Rx ONLY

BROMFED-PD®
(brompheniramine maleate 6 mg and pseudoephedrine hydrochloride 60 mg)
TIMED-RELEASE CAPSULES

BROMFED®
Each 5 mL contains brompheniramine maleate 2 mg, pseudoephedrine hydrochloride 30 mg
SYRUP

Please see adjacent page for summary of prescribing information.

Muro

BROMFED-DM®
Cough Syrup
BRIEF SUMMARY
CONTRAINDICATIONS
Hypersensitivity to any of the ingredients. Do not use in the newborn, in premature infants, in nursing mothers, in patients with severe hypertension or severe coronary artery disease, or in those receiving monoamine oxidase (MAO) inhibitors.

Antihistamines should not be used to treat lower respiratory tract conditions including asthma.

WARNINGS
Especially in infants and small children, antihistamines in overdosage may cause hallucinations, convulsions, and death.

Antihistamines may diminish mental alertness. In the young child, they may produce excitation.

PRECAUTIONS
General: Because of its antihistamine component, **BROMFED-DM® Cough Syrup** should be used with caution in patients with a history of bronchial asthma, narrow angle glaucoma, gastrointestinal obstruction, or urinary bladder neck obstruction. Because of its sympathomimetic component, **BROMFED-DM® Cough Syrup** should be used with caution in patients with diabetes, hypertension, heart disease, or thyroid disease.

Information for Patients: Patients should be warned about engaging in activities requiring mental alertness, such as driving a car or operating dangerous machinery.

Drug Interactions: Antihistamines have additive effects with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, antianxiety agents, etc.) MAO inhibitors prolong and intensify the anticholinergic (drying) effects of antihistamines. MAO inhibitors may enhance the effect of pseudoephedrine. Sympathomimetics may reduce the effects of antihypertensive drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Animal studies of **BROMFED-DM® Cough Syrup** to assess the carcinogenic and mutagenic potential of the effect on fertility have not been performed.

Pregnancy
Teratogenic Effects — Pregnancy Category C
Animal reproduction studies have not been conducted with **BROMFED-DM® Cough Syrup**. It is also not known whether **BROMFED-DM® Cough Syrup** can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. **BROMFED-DM® Cough Syrup** should be given to a pregnant woman only if clearly needed.

Reproduction studies of brompheniramine maleate (a component of **BROMFED-DM® Cough Syrup**) in rats and mice at doses up to 16 times the maximum human dose have revealed no evidence of impaired fertility or harm to the fetus.

Nursing Mothers: Because of the higher risk of intolerance of antihistamines in small infants generally, and in newborns and prematures in particular, **BROMFED-DM® Cough Syrup** is contraindicated in nursing mothers.

ADVERSE REACTIONS
The most frequent adverse reaction to **BROMFED-DM® Cough Syrup** are: sedation, dryness of mouth, nose and throat; thickening of bronchial secretions; dizziness. Other adverse reactions may include:

Dermatologic: Urticaria, drug rash, photosensitivity, pruritus.

Cardiovascular System: Hypotension, hypertension, cardiac arrhythmias, palpitation.

CNS: Disturbed coordination, tremor, irritability, insomnia, visual disturbances, weakness, nervousness, convulsions, headache, euphoria, and dysphoria.

G.U. System: Urinary frequency, difficult urination.

G.I. System: Epigastric discomfort, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Tightness of chest and wheezing, shortness of breath.

Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis.

OVERDOSAGE:
Signs and Symptoms: Central nervous system effects from overdosage of brompheniramine may vary from depression to stimulation, especially in children. Anticholinergic effects may be noted. Toxic doses of pseudoephedrine may result in CNS stimulation, tachycardia, hypertension, and cardiac arrhythmias; signs of CNS depression may occasionally be seen. Dextromethorphan in toxic doses will cause drowsiness, ataxia, nystagmus, opisthotonos, and convulsive seizures.

Toxic Doses: Data suggest that individuals may respond in an unexpected manner to apparently small amounts of a particular drug. A 2½-year-old child survived the ingestion of 21 mg/kg of dextromethorphan exhibiting only ataxia, drowsiness, and fever, but seizures have been reported in 2 children following the ingestion of 13-17 mg/kg. Another 2½-year-old child survived a dose of 300-900 mg of brompheniramine. The toxic dose of pseudoephedrine should be less than that of ephedrine, which is estimated to be 50 mg/kg.

Treatment: Induce emesis if patient is alert and is seen prior to 6 hours following ingestion. Precautions against aspiration must be taken, especially in infants and small children. Gastric lavage may be carried out, although in some instances tracheostomy may be necessary prior to lavage. Naloxone hydrochloride 0.005 mg/kg intravenously may be of value in reversing the CNS depression that may occur from an overdose of dextromethorphan. CNS stimulants may counter CNS depression. Should CNS hyperactivity or convulsive seizures occur, intravenous short-acting barbiturates may be indicated. Hypertensive responses and/or tachycardia should be treated appropriately. Oxygen, intravenous fluids, and other supportive measures should be employed as indicated.

CAUTION: Federal law prohibits dispensing without prescription.

BRD-1S

BROMFED® CAPSULES A light green and clear capsule containing white beads. Timed-Release. Each capsule contains:
Brompheniramine maleate ..... 12 mg
Pseudoephedrine hydrochloride ..... 120 mg
in a specially prepared base to provide prolonged action.

BROMFED-PD® CAPSULES A dark green and clear capsule containing white beads. Timed-Release. Each capsule contains:
Brompheniramine maleate ..... 6 mg
Pseudoephedrine hydrochloride ..... 60 mg
in a specially prepared base to provide prolonged action.

BROMFED® and **BROMFED-PD® CAPSULES** also contain as inactive ingredients: benzyl alcohol, butyl paraben, carboxymethylcellulose sodium, D&C yellow #10, edetate calcium disodium, FD&C blue #1, FD&C yellow #6, gelatin, methyl paraben, pharmaceutical glaze, propyl paraben, sodium lauryl sulfate, sodium propionate, starch, sucrose and other ingredients.

KNOCK THE STUFFING OUT OF ANY SIZE COLD OR FLU.

BROMFED-DM®
Each 5 mL contains brompheniramine maleate 2 mg,
pseudoephedrine hydrochloride 30 mg,
and dextromethorphan hydrobromide 10 mg
COUGH SYRUP Rx ONLY

BROMFED-PD®
(brompheniramine maleate 6 mg and
pseudoephedrine hydrochloride 60 mg)
TIMED-RELEASE CAPSULES

BROMFED®
Each 5 mL contains brompheniramine maleate 2 mg,
pseudoephedrine hydrochloride 30 mg
SYRUP

BROMFED® TABLETS A white scored tablet. Each tablet contains:
Brompheniramine maleate 4 mg
Pseudoephedrine hydrochloride 60 mg
Also contains as inactive ingredients colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

BRIEF SUMMARY
CONTRAINDICATIONS
Hypersensitivity to any of the ingredients. Also contraindicated in patients with severe hypertension, severe coronary artery disease, patients on MAO inhibitor therapy, patients with narrow-angle glaucoma, urinary retention, peptic ulcer and during an asthmatic attack.

WARNINGS Considerable caution should be exercised in patients with hypertension, diabetes mellitus, ischemic heart disease, hyperthyroidism, increased intraocular pressure and prostatic hypertrophy. The elderly (60 years or older) are more likely to exhibit adverse reactions.

Antihistamines may cause excitability, especially in children. At dosages higher than the recommended dose, nervousness, dizziness or sleeplessness may occur.

PRECAUTIONS General: Caution should be exercised in patients with high blood pressure, heart disease, diabetes or thyroid disease. The antihistamine in this product may exhibit additive effects with other CNS depressants, including alcohol.

Information for Patients: Antihistamines may cause drowsiness and ambulatory patients who operate machinery or motor vehicles should be cautioned accordingly.

Drug Interactions: MAO inhibitors and beta adrenergic blockers increase the effects of sympathomimetics. Sympathomimetics may reduce the antihypertensive effects of methyldopa, mecamylamine, reserpine and veratrum alkaloids. Concomitant use of antihistamines with alcohol and other CNS depressants may have an additive effect.

Pregnancy: The safety of use of this product in pregnancy has not been established.

ADVERSE REACTIONS Adverse reactions include drowsiness, lassitude, nausea, giddiness, dryness of the mouth, blurred vision, cardiac palpitations, flushing, increased irritability or excitement (especially in children).

CAUTION: FEDERAL (U.S.A.) LAW PROHIBITS DISPENSING WITHOUT A PRESCRIPTION.

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BRP-1S

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No antipyretic/analgesic is safer.
Children's TYLENOL® has a better safety profile than ibuprofen.[1-3] And in a recent clinical study, for even high fevers, 15 mg/kg acetaminophen was as effective as 10 mg/kg ibuprofen.[4]
The recommended dosage range for acetaminophen is 10 mg/kg to 15 mg/kg. Doses should be administered 4 or 5 times daily. Do not exceed five doses in 24 hours.
References: 1. Amadio P Jr. Am J Med. 1984;77 (3A):17-26. 2. Aspirin or paracetamol? Lancet. 1981; 2:287-289. 3. Settipane GA. Am J Med. 1983;74(6A): 102-109. 4. Walson PD et al. AJDC. 1992;146:626-632.
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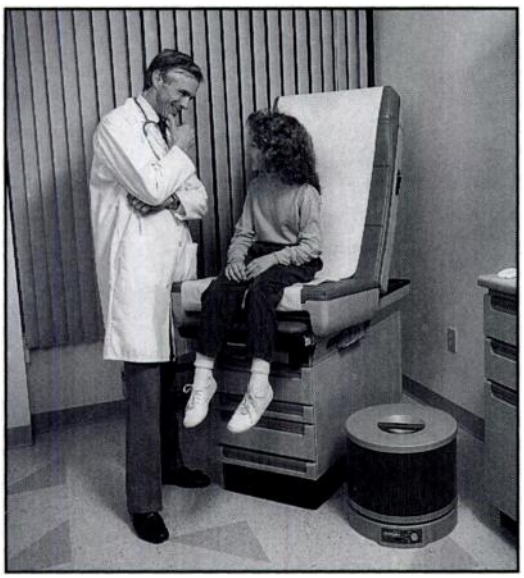

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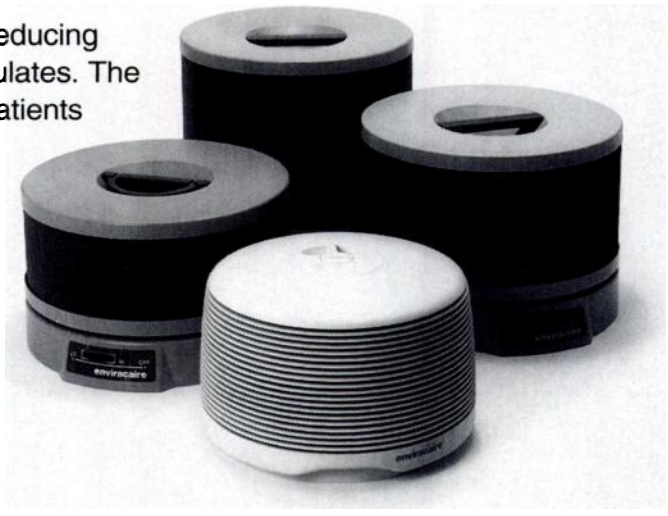

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Cefzil® (CEFPROZIL) means successful.

97%
clinical success in otitis media

due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*[1*†]

In the treatment of otitis media due to beta-lactamase producing organisms, cefprozil had bacteriologic eradication rates somewhat lower than those observed with a product containing a specific beta-lactamase inhibitor. In considering the use of cefprozil, lower overall eradication rates should be balanced against the susceptibility patterns of the common microbes in a given geographic area and the increased potential for toxicity with products containing beta-lactamase inhibitors.

Excellent gram-positive and gram-negative *in vitro*[‡] activity[2,3]

Significantly fewer reports of diarrhea/loose stools[§] compared to amoxicillin/clavulanate[1] and cefixime[4||]

* Randomized, open-label, multicenter study of 122 children (ages 6 months to 13 years) with acute otitis media.
† Improvement or resolution of all signs and symptomatology of the original infection with no new signs or symptoms.
‡ Although a useful guide, *in vitro* activity does not necessarily correlate with clinical response.
§ Probably related to treatment per investigator's opinion.
‖ The most common adverse events for CEFZIL are diarrhea (2.9%) and nausea (3.5%).

Please see brief summary of Prescribing Information on the following page.

Tablets and Oral Suspension

CEFZIL®

(CEFPROZIL)

Tablets and Oral Suspension

CEFZIL®

(CEFPROZIL)

means successful

REFERENCES:

1. Arguedas AG, Zaleska M, Stutman HR, et al. Comparative trial of cefprozil *vs.* amoxicillin clavulanate potassium in the treatment of children with acute otitis media with effusion. *Pediatr Infect Dis J.* 1991;10:375-380. 2. Thornsberry C. Review of the in vitro antibacterial activity of cefprozil, a new oral cephalosporin. *Clin Infect Dis.* 1992;14(suppl 2):189-194. 3. Kessler RE, Fung-Tomc JC. In vitro activity of cefprozil compared with other cephalosporins. *Infect Med.* 1992;9(suppl C):10-18. 4. Poole JM, Rosenberg R, Aronovitz GH, et al. Cefprozil vs. cefixime and cefaclor in otitis media in children. *Infect Med.* 1992;9(suppl E):21-32.

CEFZIL™

(CEFPROZIL)

Tablets–250 mg and 500 mg
Oral Suspension–125 mg and 250 mg/5 mL

BRIEF SUMMARY

The following is a brief summary. Please consult complete Prescribing Information.

INDICATIONS AND USAGE: CEFZIL is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

UPPER RESPIRATORY TRACT: **Pharyngitis/Tonsillitis** caused by *Streptococcus pyogenes.*

NOTE: The usual drug choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever, is penicillin given by the intramuscular route. Cefprozil is generally effective in the eradication of *Streptococcus pyogenes* from the nasopharynx; however, substantial data establishing the efficacy of cefprozil in the subsequent prevention of rheumatic fever are not available at present.

Otitis Media caused by *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella (Branhamella) catarrhalis.* (See CLINICAL STUDIES section.)

NOTE: In the treatment of otitis media due to beta-lactamase producing organisms, cefprozil had bacteriologic eradication rates somewhat lower than those observed with a product containing a specific beta-lactamase inhibitor. In considering the use of cefprozil, lower overall eradication rates should be balanced against the susceptibility patterns of the common microbes in a given geographic area and the increased potential for toxicity with products containing beta-lactamase inhibitors.

LOWER RESPIRATORY TRACT: **Secondary Bacterial Infection of Acute Bronchitis and Acute Bacterial Exacerbation of Chronic Bronchitis** caused by *Streptococcus pneumoniae, Haemophilus influenzae* (beta-lactamase positive and negative strains), and *Moraxella (Branhamella) catarrhalis.*

SKIN AND SKIN STRUCTURE: **Uncomplicated Skin and Skin-Structure Infections** caused by *Staphylococcus aureus* (including penicillinase-producing strains) and *Streptococcus pyogenes.* Abscesses usually require surgical drainage. Culture and susceptibility testing should be performed when appropriate to determine susceptibility of the causative organism to cefprozil.

CONTRAINDICATIONS: CEFZIL is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

WARNINGS: BEFORE THERAPY WITH CEFZIL IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFZIL, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-SENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFZIL OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, and may range 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 a 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 discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug effective against *Clostridium difficile.*

PRECAUTIONS: General: Evaluation of renal status before and during therapy is recommended, especially in seriously ill patients. In patients with known or suspected renal impairment (see DOSAGE AND ADMINISTRATION), careful clinical observation and appropriate laboratory studies should be done prior to and during therapy. The total daily dose of CEFZIL should be reduced in these patients because high and/or prolonged plasma antibiotic concentrations can occur in such individuals from usual doses. Cephalosporins, including CEFZIL, should be given with caution to patients receiving concurrent treatment with potent diuretics since these agents are suspected of adversely affecting renal function.

Prolonged use of CEFZIL may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Cefprozil should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Positive direct Coombs' tests have been reported during treatment with cephalosporin antibiotics.

Information for Patients: Phenylketonurics: CEFZIL for oral suspension contains phenylalanine 28 mg per 5 mL (1 teaspoon) constituted suspension for both the 125 mg/5 mL and 250 mg/5 mL dosage forms.

Drug Interactions: Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporin antibiotics. Concomitant administration of probenecid doubled the AUC for cefprozil.

Drug/Laboratory Test Interactions: Cephalosporin antibiotics may produce a false-positive reaction for glucose in the urine with copper reduction tests (Benedict's or Fehling's solution or with Clinitest®[1] tablets), but not with enzyme-based tests for glycosuria (eg, Tes-Tape®[2]). A false-negative reaction may occur in the ferricyanide test for blood glucose. The presence of cefprozil in the blood does not interfere with the assay of plasma or urine creatinine by the alkaline picrate method.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No mutagenic potential of cefprozil was found in appropriate prokaryotic or eukaryotic cells *in vitro* or *in vivo.* No *in vivo* long-term studies have been performed to evaluate carcinogenic potential.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy: Teratogenic Effects. Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits at doses 14, 7, and 0.7 times the maximum daily human dose (1000 mg) based upon mg/m², and have revealed no evidence of harm to the fetus due to cefprozil. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Cefprozil has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers: It is not known whether cefprozil is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CEFZIL is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children below the age of 6 months have not been established. However, accumulation of other cephalosporin antibiotics in newborn infants (resulting from prolonged drug half-life in this age group) has been reported.

Geriatric Use: Healthy geriatric volunteers (≥65 years old) who received a single 1 g dose of cefprozil had 35%-60% higher AUC and 40% lower renal clearance values when compared to healthy adult volunteers 20-40 years of age. In clinical studies, when geriatric patients received the usual recommended adult doses, clinical efficacy and safety were acceptable and comparable to results in nongeriatric adult patients.

ADVERSE REACTIONS: The adverse reactions to cefprozil are similar to those observed with other orally administered cephalosporins. Cefprozil was usually well tolerated in controlled clinical trials. Approximately 2% of patients discontinued cefprozil therapy due to adverse events.

The most common adverse effects observed in patients treated with cefprozil are:

Gastrointestinal—Diarrhea (2.9%), nausea (3.5%), vomiting (1%), and abdominal pain (1%).

Hepatobiliary—Elevations of AST (SGOT) (2%), ALT (SGPT) (2%), alkaline phosphatase (0.2%), and bilirubin values (<0.1%). As with some penicillins and some other cephalosporin antibiotics, cholestatic jaundice has been reported rarely.

Hypersensitivity—Rash (0.9%), urticaria (0.1%). Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy.

CNS—Dizziness (1%). Hyperactivity, headache, nervousness, insomnia, confusion, and somnolence have been reported rarely (<1%). All were reversible.

Hematopoietic—Decreased leukocyte count (0.2%), eosinophilia (2.3%).

Renal—Elevated BUN (0.1%), serum creatinine (0.1%).

Other—Diaper rash and superinfection (1.5%), genital pruritus and vaginitis (1.6%).

Cephalosporin class paragraph: In addition to the adverse reactions listed above which have been observed in patients treated with cefprozil, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Anaphylaxis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, serum-sickness like reaction, fever, renal dysfunction, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, prolonged prothrombin time, positive Coombs' test, elevated LDH, pancytopenia, neutropenia, agranulocytosis, thrombocytopenia.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment, when the dosage was not reduced. (See DOSAGE AND ADMINISTRATION and OVERDOSAGE.) If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

OVERDOSAGE: Cefprozil is eliminated primarily by the kidneys. In case of severe overdosage, especially in patients with compromised renal function, hemodialysis will aid in the removal of cefprozil from the body.

CLINICAL STUDIES: STUDY ONE: In a controlled clinical study of acute otitis media performed in the United States where significant rates of beta-lactamase producing organisms were found, cefprozil was compared to an oral antimicrobial agent that contained a specific beta-lactamase inhibitor. In this study, using very strict evaluability criteria and microbiologic and clinical response criteria at the 10-16 days post-therapy follow-up, the following presumptive bacterial eradication/clinical cure outcomes (*i.e.* clinical success) and safety results were obtained:

U.S. Acute Otitis Media Study
Cefprozil vs beta-lactamase inhibitor-containing control drug

Efficacy: Pathogen	% of Cases with Pathogen (n = 155)	Outcome
S. pneumoniae	48.4%	cefprozil success rate 5% better than control
H. influenzae	35.5%	cefprozil success rate 17% less than control
M. catarrhalis	13.5%	cefprozil success rate 12% less than control
S. pyogenes	2.6%	cefprozil equivalent to control
Overall	100.0%	cefprozil success 5% less than control

SAFETY: The incidence of adverse events, primarily diarrhea and rash,* were clinically and statistically significantly higher in the control arm versus the cefprozil arm.

Age Group	Cefprozil	Control
6 months - 2 years	21%	41%
3 - 12 years	10%	19%

*The majority of these involved the diaper area in young children.

STUDY TWO: In a controlled clinical study of acute otitis media performed in Europe, cefprozil was compared to an oral antimicrobial agent that contained a specific beta-lactamase inhibitor. As expected in a European population, this study had a lower incidence of beta-lactamase-producing organisms than usually seen in U.S. trials. In this study, using very strict evaluability criteria and microbiologic and clinical response criteria at the 10-16 days post-therapy follow-up, the following presumptive bacterial eradication/clinical cure outcomes (*i.e.* clinical success) were obtained:

European Acute Otitis Media Study
Cefprozil vs beta-lactamase inhibitor-containing control drug

Efficacy: Pathogen	% of Cases with Pathogen (n = 47)	Outcome
S. pneumoniae	51.0%	cefprozil equivalent to control
H. influenzae	29.8%	cefprozil equivalent to control
M. catarrhalis	6.4%	cefprozil equivalent to control
S. pyogenes	12.8%	cefprozil equivalent to control
Overall	100.0%	cefprozil equivalent to control

SAFETY: The incidence of adverse events in the cefprozil arm was comparable to the incidence of adverse events in the control arm (agent that contained a specific beta-lactamase inhibitor).

REFERENCES:

1. Clinitest® is a registered trademark of Miles Laboratories, Inc.
2. Tes-Tape® is a registered trademark of Eli Lilly and Company.

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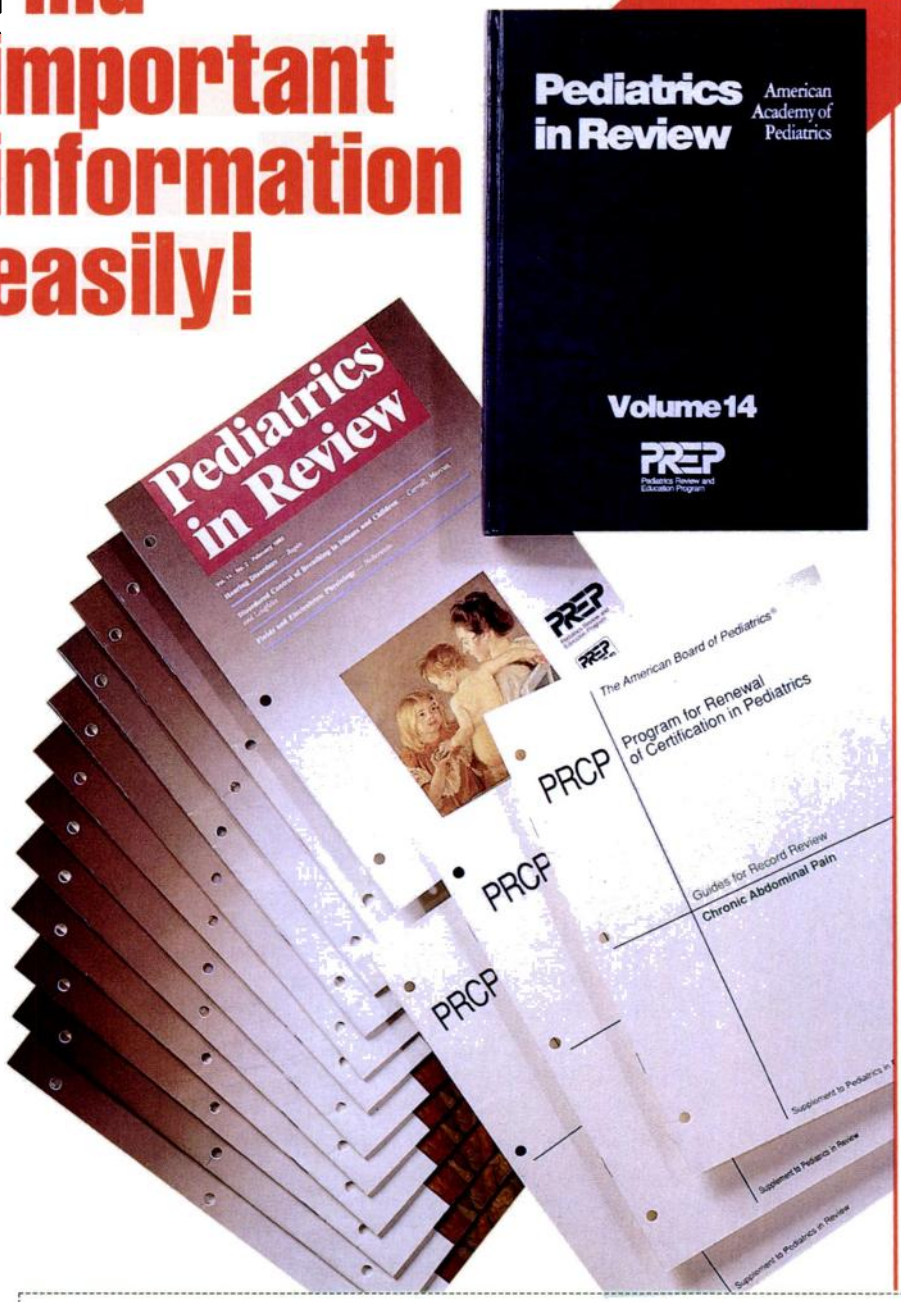

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Two Guides for Record Review, published by the American Board of Pediatrics, serve as supplements to Pediatrics in Review and are included in this bound edition. These two guidebooks are Chronic Abdominal Pain and Closed Head Injury.

Pediatrics in Review bound volume 14 is available for $55. If you purchase three or more copies of volume 14 or any combination of volumes 1-14 the cost for each volume is $40. Limited quantities of volumes 1-13 are available.

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PRACTITIONER RESEARCH AWARD

Dr Wessel

Morris A. Wessel, MD, has been awarded the AAP 1993 Practitioner Research Award. Dr Wessel has been a full-time practicing pediatrician in New Haven, CT since 1951. A clinician for almost 50 years, he has made astute observations in his practice, and then has studied and interpreted issues related to those observations. With more than two hundred publications and presentations, Dr Wessel has written about such diverse topics as colic, feeding techniques, thyroid dysfunction in pregnancy, adoption, corporal punishment, and death and dying. His sensitive observational research in 1954 on colic provides a definition of colic that is still the standard today. His 1963 article on the prenatal pediatric visit stimulated other colleagues to see parents before their infants were born. More recently, he has provided much insight and understanding to the process and impact of death and dying in children and their families.

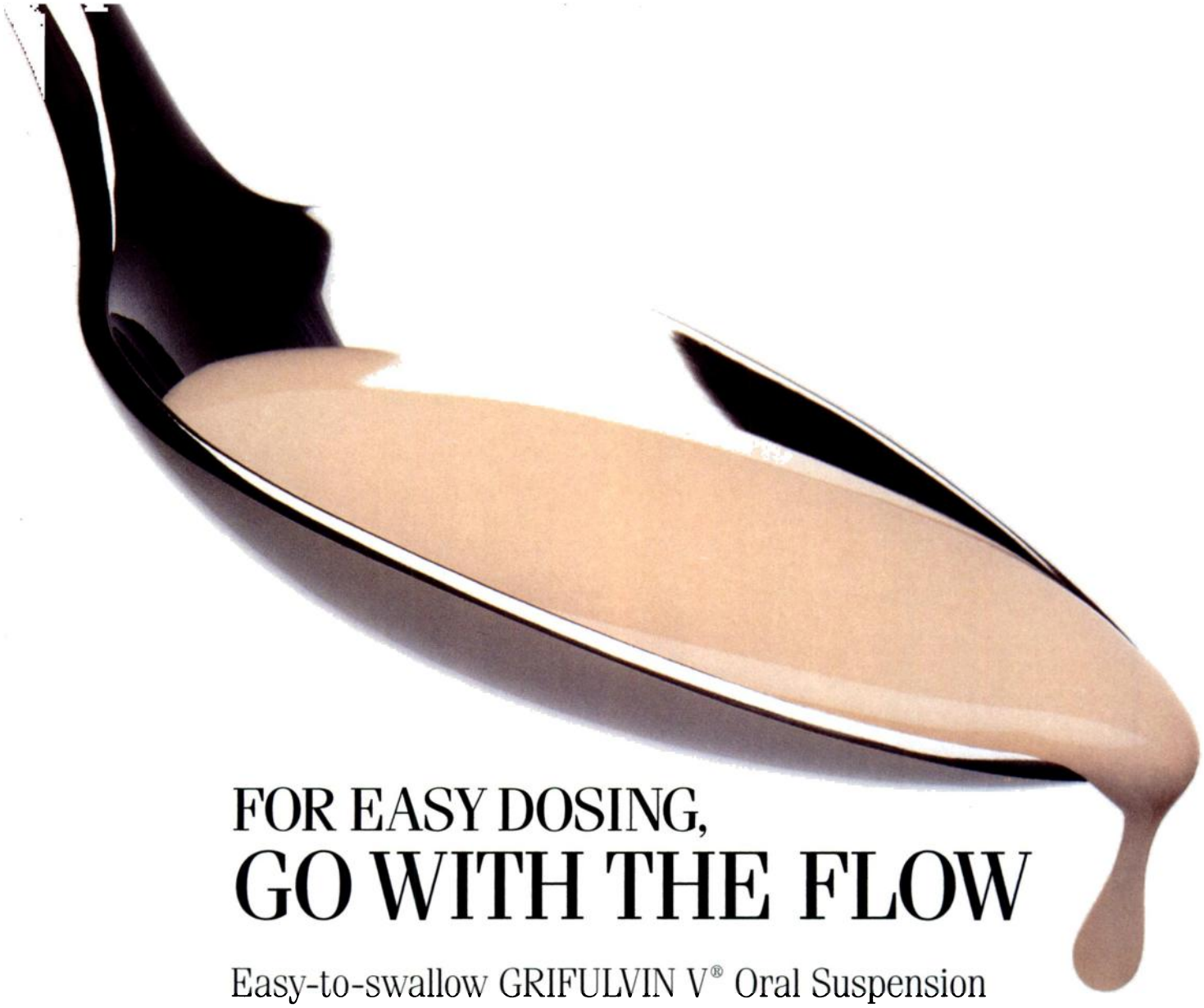
Through his office research, Dr Wessel has influenced a generation of pediatricians, family practitioners, and child psychiatrists. One of his nominators noted that "clinical observation of pediatric practice and issues, carefully and wisely interpreted, and then convincingly transmitted, represents scholarship in its highest form." As "renaissance physician" and scholar, Dr Wessel has been a master of the office-based observational study. In his life-long pursuit of new knowledge about common issues in pediatrics, he serves as an outstanding model of a practitioner researcher.

PEDIATRIC RESIDENT RESEARCH AWARD

Dr Bonthius

Daniel J. Bonthius, MD, PhD, of Charlottesville, VA has been awarded the AAP Pediatric Resident Research Award for 1993. Dr Bonthius received his MD and PhD degrees from the University of Iowa. Subsequently, he was a Fulbright Scholar at the University of Otago Medical School in Dunedin, New Zealand. He is currently a resident in the Department of Pediatrics at the University of Virginia Health Sciences Center. In July 1994, he will begin a fellowship in pediatric neurology at the University of Iowa. During his PL-1 and PL-2 years, Dr Bonthius studied the genetic response to brain injury in rats. Dr Bonthius' senior investigator is Dr Oswald Steward. Their manuscript entitled, "Induction of Cortical Spreading Depression with Potassium Chloride Upregulates Levels of Messenger RNA for Glial Fibrillary Acidic Protein in Cortex and Hippocampus: Inhibition by MK-801" has been accepted for publication in *Brain Research.*

In Dr Bonthius' studies, cortical spreading depression was induced by direct application of potassium chloride on the cerebral cortex. In response to this phenomenon, a dramatic increase in activation of astrocytes occurred as demonstrated by production of glial fibrillary acidic protein. Dr Bonthius demonstrated increased levels of messenger RNA for this acidic protein (GFAP) and further found that the time course of the increase in the glial fibrillary acidic protein differed in the cortex and hippocampus. Finally, Dr Bonthius demonstrated that the increase in GFAP could be prevented by inhibition of the spreading depression by the *N*-methyl-D-aspartate (NMDA) antagonist, MK-801. These data are believed to hold potential for increased understanding of the tissue response to brain injury and for the development of novel therapies for cerebral injury.



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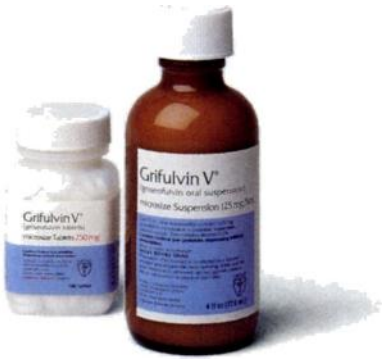

The most commonly reported adverse reactions are of the hypersensitivity type such as skin rashes, urticaria and, rarely angioneurotic edema.

Please see next page for a brief summary of Prescribing Information.

 DD-2232

GRIFULVIN V®

[gri'fulven]
(griseofulvin oral suspension)
microsize Suspension 125mg/5mL
(griseofulvin tablets)
microsize Tablets 250mg or 500mg

Indications and Usage

Major indications for GRIFULVIN V (griseofulvin microsize) are:

- Tinea capitis (ringworm of the scalp)
- Tinea corporis (ringworm of the body)
- Tinea pedis (athlete's foot)
- Tinea unguium (onychomycosis: ringworm of the nails)
- Tinea cruris (ringworm of the thigh)
- Tinea barbae (barber's itch)

GRIFULVIN V (griseofulvin microsize) inhibits the growth of those genera of fungi that commonly cause ringworm infections of the hair, skin, and nails, such as:

Trichophyton rubrum	*Microsporum audouini*
Trichophyton tonsurans	*Microsporum canis*
Trichophyton mentagrophytes	*Microsporum gypseum*
Trichophyton interdigitalis	*Epidermophyton floccosum*
Trichophyton verrucosum	*Trichophyton megnini*
Trichophyton sulphureum	*Trichophyton gallinae*
Trichophyton schoenleini	*Trichophyton crateriform*

Note: Prior to therapy, the type of fungi responsible for the infection should be identified. The use of the drug is not justified in minor or trivial infections which will respond to topical antifungal agents alone.

It is *not* effective in:

- Bacterial infections
- Candidiasis (Moniliasis)
- Histoplasmosis
- Actinomycosis
- Sporotrichosis
- Chromoblastomycosis
- Coccidioidomycosis
- North American Blastomycosis
- Cryptococcosis (Torulosis)
- Tinea versicolor
- Nocardiosis

Contraindications

This drug is contraindicated in patients with porphyria, hepatocellular failure, and in individuals with a history of hypersensitivity to griseofulvin.

Two cases of conjoined twins have been reported in patients taking griseofulvin during the first trimester of pregnancy. Griseofulvin should not be prescribed to pregnant patients.

Warnings

Prophylactic Usage: Safety and efficacy of prophylactic use of this drug has not been established.

Chronic feeding of griseofulvin, at levels ranging from 0.5-2.5% of the diet, resulted in the development of liver tumors in several strains of mice, particularly in males. Smaller particle sizes result in an enhanced effect. Lower oral dosage levels have not been tested. Subcutaneous administration of relatively small doses of griseofulvin once a week during the first three weeks of life has also been reported to induce hepatomata in mice. Although studies in other animal species have not yielded evidence of tumorigenicity, these studies were not of adequate design to form a basis for conclusions in this regard.

In subacute toxicity studies, orally administered griseofulvin produced hepatocellular necrosis in mice, but this has not been seen in other species. Disturbances in porphyrin metabolism have been reported in griseofulvin-treated laboratory animals. Griseofulvin has been reported to have a colchicine-like effect on mitosis and cocarcinogenicity with methylcholanthrene in cutaneous tumor induction in laboratory animals.

Reports of animal studies in the Soviet literature state that a griseofulvin preparation was found to be embryotoxic and teratogenic on oral administration to pregnant Wistar rats. Rat reproduction studies done thus far in the United States and Great Britain have been inconclusive in this regard, and additional animal reproduction studies are underway. Pups with abnormalities have been reported in the litters of a few bitches treated with griseofulvin.

Suppression of spermatogenesis has been reported to occur in rats but investigation in man failed to confirm this.

Precautions

Patients on prolonged therapy with any potent medication should be under close observation. Periodic monitoring of organ system function, including renal, hepatic and hemopoietic, should be done.

Since griseofulvin is derived from species of penicillin, the possibility of cross sensitivity with penicillin exists; however, known penicillin-sensitive patients have been treated without difficulty.

Since a photosensitivity reaction is occasionally associated with griseofulvin therapy, patients should be warned to avoid exposure to intense natural or artificial sunlight. Should a photosensitivity reaction occur, lupus erythematosus may be aggravated.

Drug Interactions: Patients on warfarin-type anticoagulant therapy may require dosage adjustment of the anticoagulant during and after griseofulvin therapy. Concomitant use of barbiturates usually depresses griseofulvin activity and may necessitate raising the dosage.

The concomitant administration of griseofulvin has been reported to reduce the efficacy of oral contraceptives and to increase the incidence of breakthrough bleeding.

Adverse Reactions

When adverse reactions occur, they are most commonly of the hypersensitivity type such as skin rashes, urticaria and rarely, angioneurotic edema, and may necessitate withdrawal of therapy and appropriate countermeasures. Paresthesias of the hands and feet have been reported rarely after extended therapy. Other side effects reported occasionally are oral thrush, nausea, vomiting, epigastric distress, diarrhea, headache, fatigue, dizziness, insomnia, mental confusion and impairment of performance of routine activities.

Proteinuria and leukopenia have been reported rarely. Administration of the drug should be discontinued if granulocytopenia occurs.

When rare, serious reactions occur with griseofulvin, they are usually associated with high dosages and/or long periods of therapy.

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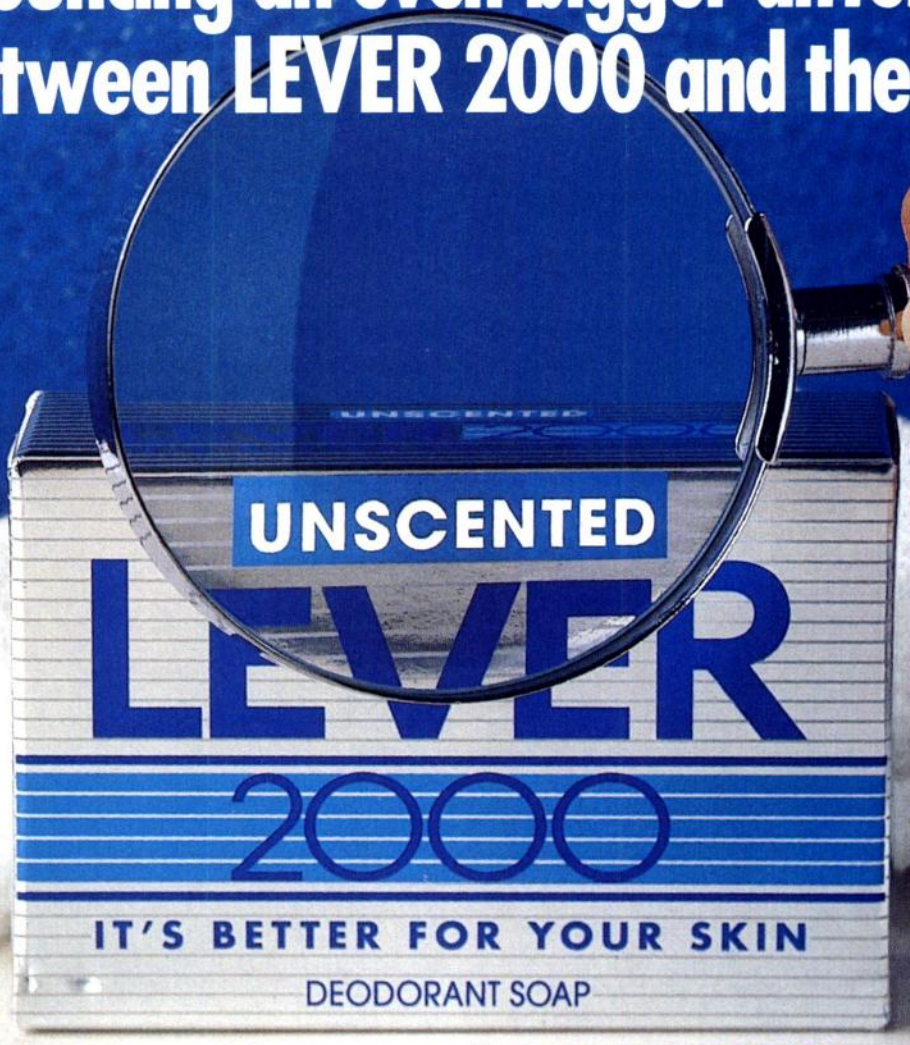

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October 1993

HMOS—ANOTHER ROADBLOCK FOR ALZHEIMER'S DRUG

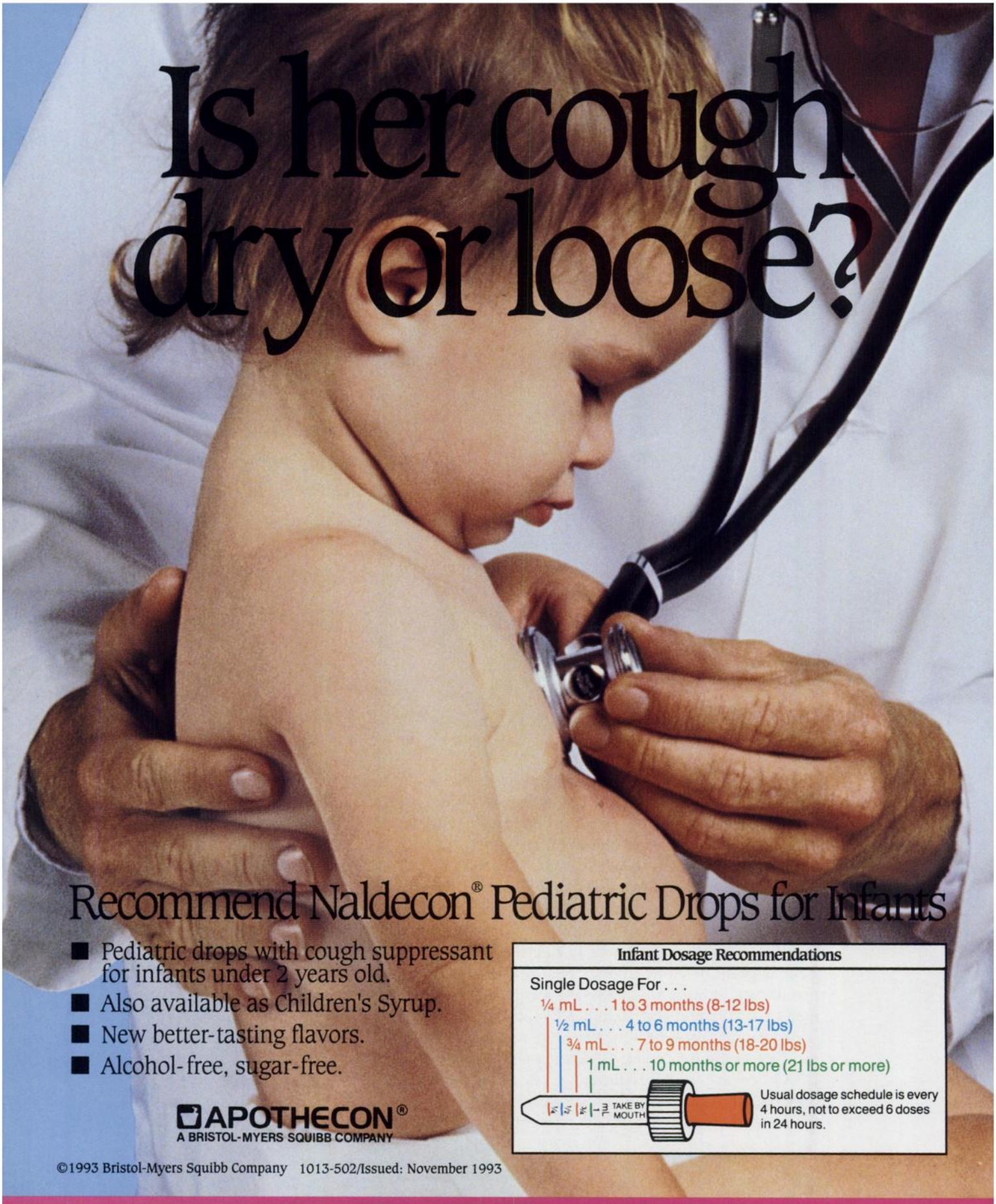
The first Cognex auguries are not promising. These signs of resistance come from two of the nation's largest HMOs, Northern California Kaiser Permanente and the Group Health Cooperative of Puget Sound. Northern California Kaiser has already decided to ban Cognex from its formulary . . .

Cognex is expected to cost about $1,300 to $1,500 annually per patient, and this does not include the costs of blood tests and physician visits required to guard against side effects. Against this Kaiser argues that Cognex helps only some victims of Alzheimer's Disease; the gain is not very great in many patients; and some who take Cognex suffer liver toxicity that the HMOs would have to treat. So from an HMO's point of view, Cognex is not "cost-effective," the magic mantra of HMO health care. But for anyone who's aware of the living hell in which many Alzheimer's patients and their families live, this argument does not wash . . .

Americans still expect their doctors to put patients' interests first. As the Cognex incident at the two major HMOs shows, that expectation need not be satisfied in HMO health care. Mr. Clinton, his health reform, and the American people can only benefit if the president takes specific measures to ensure that patients' expectations and HMO reality are congruent.

Schwartz H. *The Wall Street Journal*. 1993.

Noted by J.F.L., MD



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¾ mL . . . 7 to 9 months (18-20 lbs)

1 mL . . . 10 months or more (21 lbs or more)

Usual dosage schedule is every 4 hours, not to exceed 6 doses in 24 hours.

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important sources of environmental lead. Screening is critical only in the high-risk areas, but is very inefficient in communities without lead exposure. Instead of testing all the children and declaring many of them poisoned, it would be more logical today to test all the houses in which children live that were built before lead-based paint was eliminated. Several communities have laws mandating window guards in all apartments where young children live or are moving in. It would be more effective if state legislatures, instead of decreeing mandatory screening of all children <6 years, voted instead to establish mandatory inspection of all dwellings built before 1950 in which those children may live. State and federal funds would be better spent to help home owners and landlords remedy the residual lead risk, rather than undertaking the expensive and useless screening of children who are not at risk.

The situation has been well synthesized recently by Oski, "It would be prudent to spend the money on prevention rather than detection."[12]

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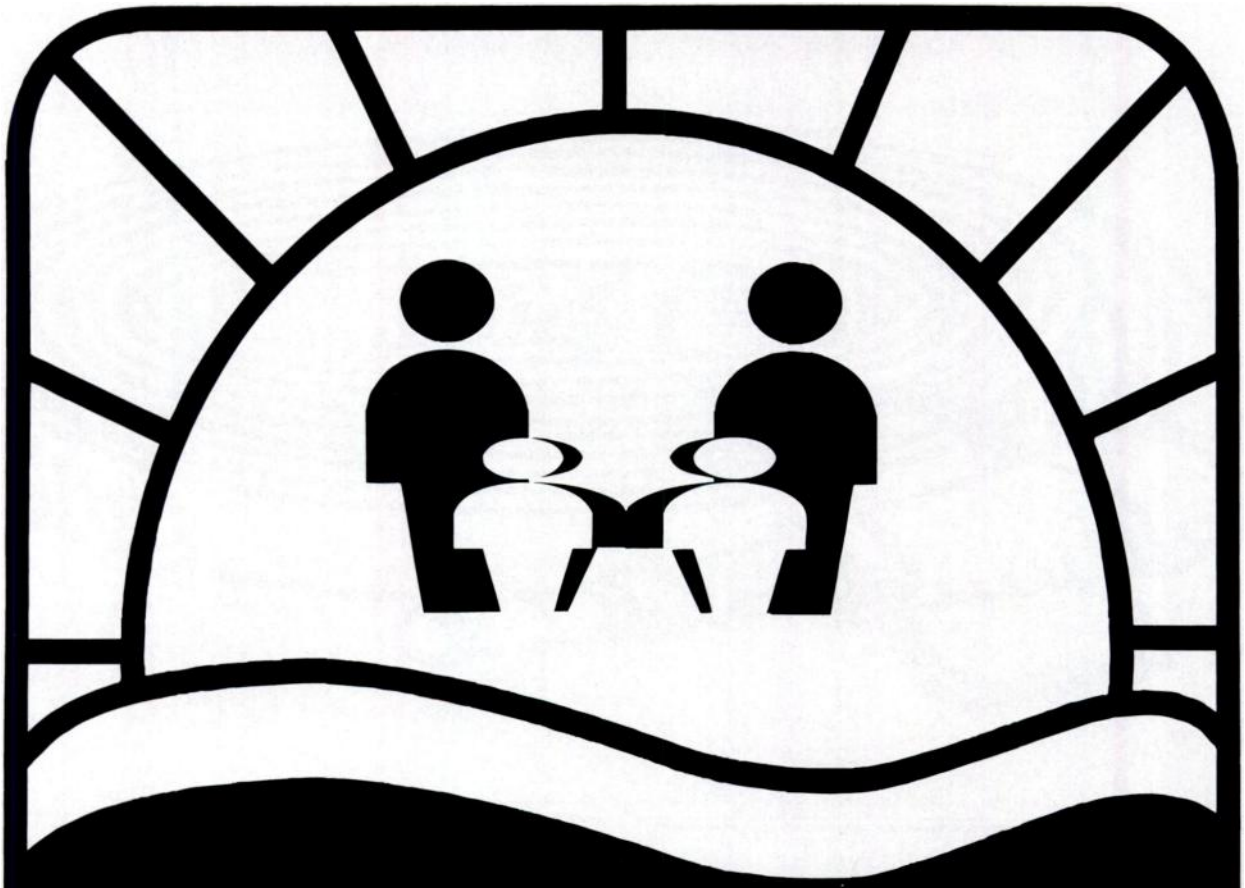

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WHERE HAVE ALL THE PRIMARY CARE APPLICANTS GONE?

Jack M. Colwill, M.D.

TABLE 1. U.S. Medical School Graduates Matched with Positions by the National Residency Matching Program in 1986 and 1991, According to Primary Care Specialty.*

Specialty	No. of Graduates		Percent Decline
	1986	1991	
Internal medicine†	4,069	3,058	25
Family practice	1,680	1,374	18
Pediatrics‡	1,366	1,316	4
Total primary care	7,115	5,748	19
Total matched	13,756	12,985	6

* Data are from the National Residency Matching Program.
† Includes categorical, medicine/pediatrics, and primary care (preliminary programs have been excluded because most graduates in them enter other specialties).
‡ Includes categorical and primary care.

TABLE 2. Interest in Primary Care Among U.S. Medical School Graduates in 1982 and 1989.*

Specialty	Percent of Graduates		Percent Decline
	1982	1989	
Family practice	15.5	11.7	24.5
General internal medicine	14.3	6.0	58.0
General pediatrics	6.2	4.8	22.6
Total primary care	36.0	22.5	37.5

* Data are from the AAMC and include specialties that were selected and the first choices of those who were undecided.

Colwill JM. Where have all the primary care applicants gone? *N Engl J Med.* 1992;326:388–393.

Noted by J.F.L., MD