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ARTICLES

PEDIATRIC HISTORY

EXPERIENCE AND REASON

EDITORIALS

COMMENTARY

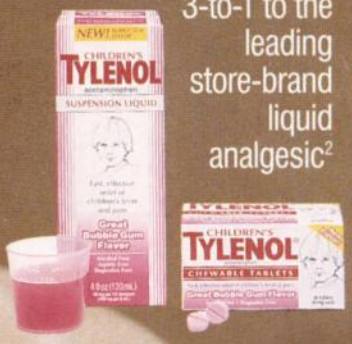
AMERICAN ACADEMY OF PEDIATRICS

Surprise!

New Bubble Gum Flavor

Great Taste Encourages Compliance

- Rated highly by moms for being "easier to give my child without a fuss"[1]
- In a taste test with kids, Children's TYLENOL® Bubble Gum Flavor Suspension Liquid was preferred more than 3-to-1 to the leading store-brand liquid analgesic[2]



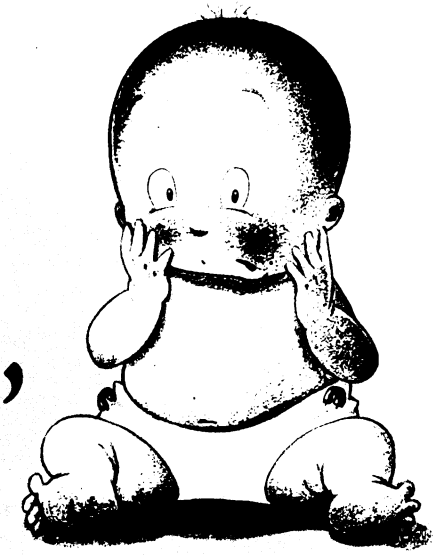
CHILDREN'S
TYLENOL®
acetaminophen
First

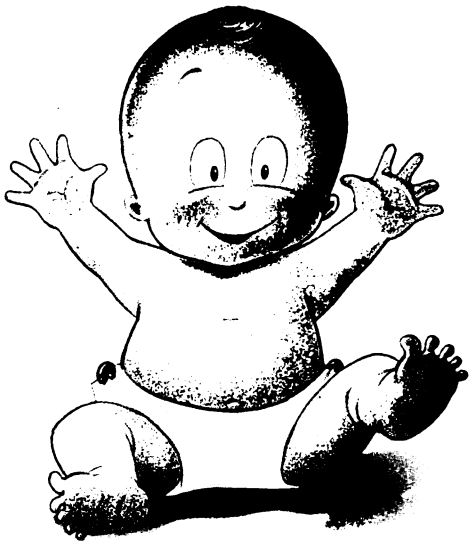
McNEIL

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

References: 1. BASES Study, 1994. **2.** Taste tests performed by Bruno Ridgeway Associates, July 1994.

When it comes to diarrhea,





ISOMIL® DF

Soy Formula For Diarrhea

means less mess!

- Shortens the duration of diarrhea*— mild to severe.[1,2]
- Firms loose stools,† making diapers less messy.
- Is milk free and lactose free.
- Provides complete nutrition that can be fed full strength during diarrhea to help your patients recover and grow.[4,5]

When diarrhea strikes, recommend PEDIALYTE® Oral Electrolyte Maintenance Solution to restore fluids and minerals, and full-strength ISOMIL® DF for up to 7 to 10 days. Recommend ISOMIL® Soy Formula With Iron if lactose intolerance continues.

Clinically proven to shorten the duration of diarrhea and firm loose stools.

From the makers of ISOMIL®, the 1st choice soy formula of more physicians†

References: 1. 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. 2. Ross Study CP-AC96, November 1992. Data available on request. Pediatric Nutrition Research & Development, Ross Laboratories, Columbus, Ohio. 3. Ross Study CP-AC88, July 1990. Data available on request. Pediatric Nutrition Research & Development, Ross Laboratories, Columbus, Ohio. 4. Ross Study CP-AD26, January 1993. Data available on request. Pediatric Nutrition Research & Development, Ross Products Division, Abbott Laboratories, Columbus, Ohio. 5. Treem WR, Hyams JS, Blankschen E, et al: Evaluation of the effect of a fiber-enriched formula on infant colic. *J Pediatr* 1991;119:695-701.

*Loose, watery stools.

†Soy fiber has not been shown to improve constipation in young infants.[3] Do not feed ISOMIL DF to infants or toddlers with constipation.

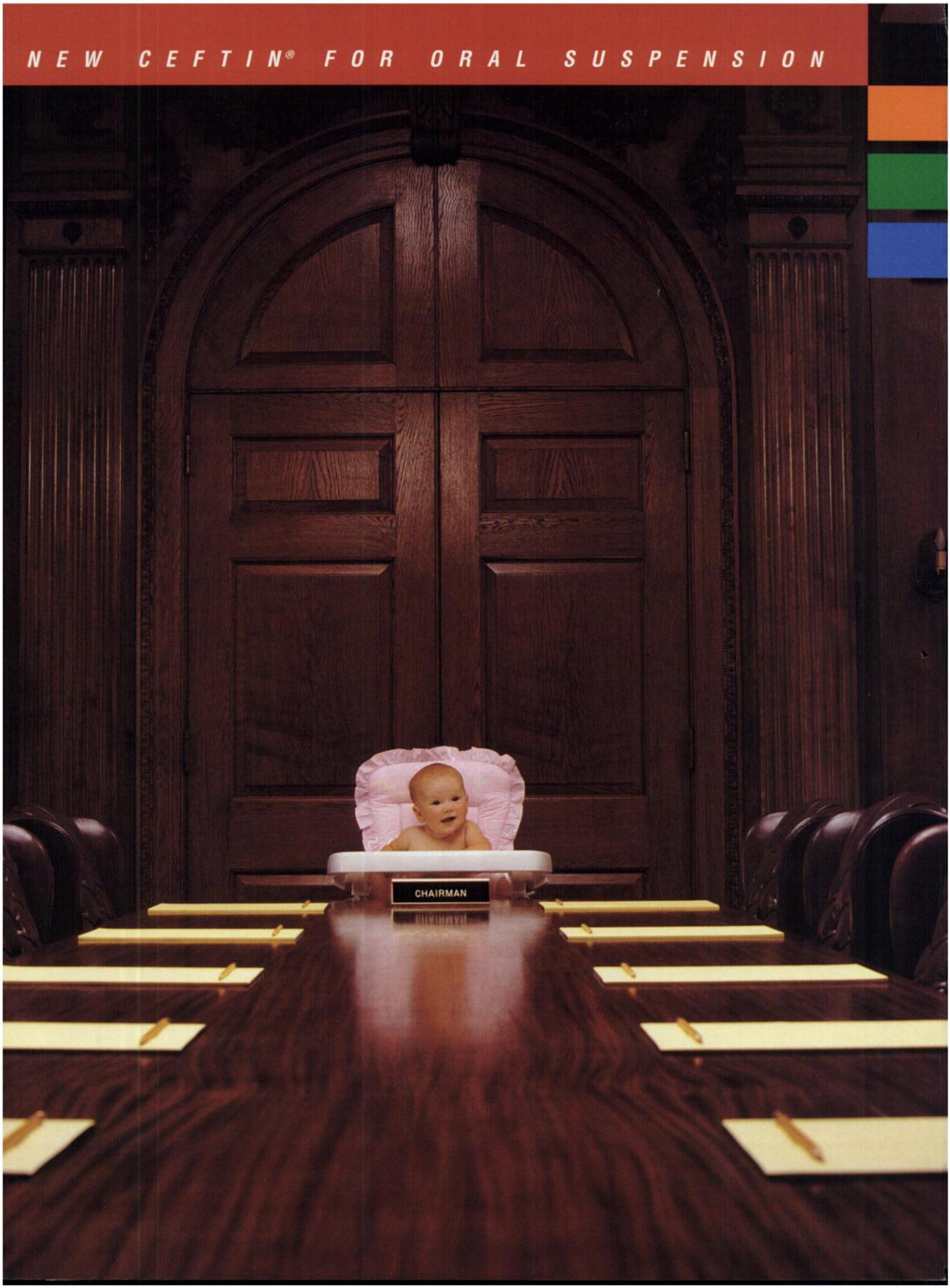
†Chosen more often by national survey

ROSS PRODUCTS DIVISION
ABBOTT LABORATORIES
COLUMBUS, OHIO 43215-1724

B453/4901

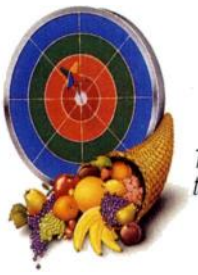
8U82-NHH-JDW2

NEW CEFTIN® FOR ORAL SUSPENSION



Experience the power of CEFTIN for Oral Suspension*

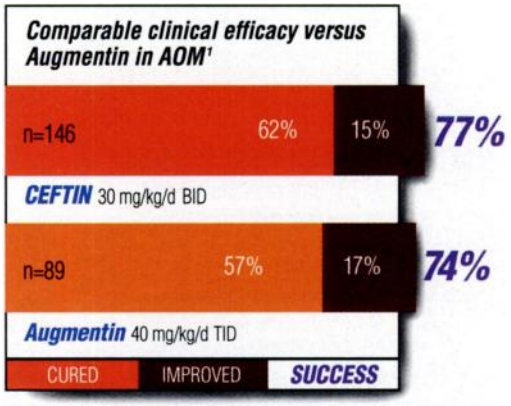
The power of CEFTIN, now in a tutti-frutti—flavored suspension. So it's tough on ear infections but easy on kids.



Tutti-frutti taste

Demonstrated as effective as Augmentin®† in acute otitis media[1,2]

In two multicenter clinical trials involving over 430 evaluable children, CEFTIN for Oral Suspension (30 mg/kg/d BID) was as effective as Augmentin suspension (40 mg/kg/d TID) after 10 days of therapy.



Clinical results of a multicenter trial of 235 evaluable children 3 months to 11 years of age treated for 10 days. Cured: resolution of signs and symptoms lasting through 2-week posttreatment period, with resolution of effusion by at least the 2-week posttreatment visit. Improved: cure but without resolution of effusion at the 2-week posttreatment visit. Success: "cured" and "improved" patients combined.

In US controlled clinical trials with CEFTIN for Oral Suspension, the most commonly reported adverse event was diarrhea/loose stools at 8.6%. In these trials, 5% of patients disliked the taste; however, only 1.4% dropped out because of the taste and/or problems with drug administration.

And a convenient BID dosing schedule

Administered with food just once in the morning, once at night.

CEFTIN®
FOR ORAL SUSPENSION
(cefuroxime axetil powder for oral suspension)

The power of CEFTIN– now in suspension*

*CEFTIN for Oral Suspension is indicated for the treatment of children 3 months to 12 years of age with acute bacterial otitis media, pharyngitis/tonsillitis, and impetigo caused by susceptible strains of designated organisms. CEFTIN for Oral Suspension and CEFTIN® (cefuroxime axetil) Tablets are not bioequivalent and are not substitutable on a mg/mg basis.

† Augmentin® (amoxicillin/clavulanate potassium) is a registered trademark of SmithKline Beecham Pharmaceuticals.

Please consult Brief Summary of Prescribing Information adjacent to this advertisement.

The following is a brief summary only. Before prescribing, see complete prescribing information in Ceftin® Tablets and Ceftin® for Oral Suspension product labeling.

CONTRAINDICATIONS: Ceftin® products are contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS: CEFTIN® TABLETS AND CEFTIN® FOR ORAL SUSPENSION ARE NOT BIOEQUIVALENT AND ARE THEREFORE NOT SUBSTITUTABLE ON A MG/MG BASIS.

BEFORE THERAPY WITH CEFTIN PRODUCTS IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFTIN PRODUCTS, OTHER 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 A CLINICALLY SIGNIFICANT ALLERGIC REACTION TO CEFTIN PRODUCTS OCCURS, DISCONTINUE THE DRUG AND INSTITUTE APPROPRIATE THERAPY. 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, including cefuroxime, 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 normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

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

PRECAUTIONS:

General: As with other broad-spectrum antibiotics, prolonged administration of cefuroxime axetil may result in overgrowth of non-susceptible microorganisms. If superinfection occurs during therapy, appropriate measures should be taken.

Cephalosporins, including cefuroxime axetil, should be given with caution to patients receiving concurrent treatment with potent diuretics because these diuretics are suspected of adversely affecting renal function.

Cefuroxime axetil, as with other broad-spectrum antibiotics, should be prescribed with caution in individuals with a history of colitis. The safety and effectiveness of cefuroxime axetil have not been established in patients with gastrointestinal malabsorption. Patients with gastrointestinal malabsorption were excluded from participating in clinical trials of cefuroxime axetil.

Information for Patients/Caregivers (Pediatric): 1. During clinical trials, the tablet was tolerated by children old enough to swallow the cefuroxime axetil tablet whole. The crushed tablet has a strong, persistent, bitter taste and should not be administered to children in this manner. Children who cannot swallow the tablet whole should receive the oral suspension.

2. Discontinuation of therapy due to taste and/or problems of administering this drug occurred in 1.4% of children given the oral suspension. Complaints about taste (which may impair compliance) occurred in 5% of children.

Drug/Laboratory Test Interactions: A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with Clinitest® tablets), but not with enzyme-based tests for glycosuria (e.g., Clinistix®, Tes-Tape®). As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood/plasma glucose levels in patients receiving cefuroxime axetil. The presence of cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

Drug/Drug Interactions: Concomitant administration of probenecid with cefuroxime axetil tablets increases the area under the serum concentration versus time curve by 50%. The peak serum cefuroxime concentration after a 1.5-g single dose is greater when taken with 1 g of probenecid (mean=14.8 mcg/mL) than without probenecid (mean=12.2 mcg/mL).

Drugs that reduce gastric acidity may result in a lower bioavailability of Ceftin® compared with that of fasting state and tend to cancel the effect of postprandial absorption.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although lifetime studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential was found for cefuroxime axetil in the micronucleus test and a battery of bacterial mutation tests. Reproduction studies in rats at doses up to 1,000 mg/kg per day (nine times the recommended maximum human dose based on mg/m^2) have revealed no evidence of impaired fertility.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and mice at doses up to 3,200 mg/kg per day (23 times the recommended maximum human dose based on mg/m^2) and have revealed no evidence of harm to the fetus due to cefuroxime axetil. 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: Cefuroxime axetil has not been studied for use during labor and delivery.

Nursing Mothers: Because cefuroxime is excreted in human milk, consideration should be given to discontinuing nursing temporarily during treatment with cefuroxime axetil.

Pediatric Use: In controlled clinical trials, cefuroxime axetil has been administered to pediatric patients ranging in age from 3 months to 12 years (see DOSAGE AND ADMINISTRATION section).

Geriatric Use: In clinical trials when 12- to 64-year-old patients and geriatric patients (65 years of age or older) were treated with usual recommended dosages (i.e., 125 to 500 mg b.i.d., depending on type of infections), no overall differences in effectiveness were observed between the two age-groups. The geriatric patients reported somewhat fewer gastrointestinal events and less frequent vaginal candidiasis compared with patients aged 12 to 64 years old; however, no clinically significant differences were reported between the two age-groups. Therefore, no adjustment of the usual adult dose is necessary based on age alone.

ADVERSE REACTIONS:

CEFTIN® TABLETS (MULTIPLE-DOSE DOSING REGIMENS): ***In Clinical Trials:*** In clinical trials using multiple doses of cefuroxime axetil tablets, 912 patients were treated with the recommended dosages of cefuroxime axetil (125 to 500 mg twice a day). There were no deaths or permanent disabilities thought related to drug toxicity. Twenty (2.2%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. Seventeen (85%) of the 20 patients who discontinued therapy did so because of gastrointestinal disturbances, including diarrhea, nausea, vomiting, and abdominal pain. The percentage of cefuroxime axetil tablet-treated patients who discontinued study drug because of adverse events was very similar at daily doses of 1,000, 500, and 250 mg (2.3%, 2.1%, and 2.2%, respectively). However, the incidence of gastrointestinal adverse events increased with the higher recommended doses.

The following adverse events were thought by the investigators to be possibly, probably, or almost certainly related to cefuroxime axetil tablets in multiple-dose clinical trials (n=912 cefuroxime axetil-treated patients).

Adverse Reactions
Ceftin Tablets
Multiple-Dose Dosing Regimens–Clinical Trials

Incidence ≥1%	Diarrhea/loose stools		3.7%
	Nausea/vomiting		3.0%
	Transient elevation in AST		2.0%
	Transient elevation in ALT		1.6%
	Eosinophilia		1.1%
	Transient elevation in LDH		1.0%
Incidence <1% but >0.1%	Abdominal pain	Rash	Mouth ulcers
	Abdominal cramps	Hives	Swollen tongue
	Flatulence	Itch	Sleepiness
	Indigestion	Dysuria	Thirst
	Headache	Chills	Anorexia
	Vaginitis	Chest Pain	Positive Coombs test
	Vulvar itch	Shortness of breath	

In Postmarketing Experience: In addition to the events reported during clinical trials with Ceftin Tablets, the following adverse experiences have been reported from domestic and foreign sources during worldwide postmarketing surveillance: hypersensitivity reactions, including Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, serum sickness–like reactions, anaphylaxis, and angioedema. Jaundice has been reported very rarely. Onset of pseudomembranous colitis symptoms may occur during or after treatment (see WARNINGS).

CEFTIN TABLETS (SINGLE-DOSE REGIMEN FOR UNCOMPLICATED GONORRHEA): ***In Clinical Trials:*** In clinical trials using a single dose of cefuroxime axetil tablets, 644 patients were treated with the recommended dosage of cefuroxime axetil (1,000 mg) for the treatment of uncomplicated gonorrhea. There were no deaths or permanent disabilities thought related to drug toxicity in these studies.

The following adverse events were thought by the investigators to be possibly, probably, or almost certainly related to cefuroxime axetil in 1,000-mg single-dose clinical trials of cefuroxime axetil tablets in the treatment of uncomplicated gonorrhea conducted in the US.

Adverse Reactions
Ceftin Tablets
1-g Single-Dose Regimen for Uncomplicated Gonorrhea–Clinical Trials

Incidence ≥1%	Nausea/vomiting		6.7%
	Diarrhea		4.7%
Incidence <1% but >0.1%	Abdominal pain	Vaginal discharge	Tightness/pain in chest
	Dyspepsia	Headache	Bleeding/pain in urethra
	Erythema	Dizziness	Kidney pain
	Rash	Somnolence	Tachycardia
	Pruritus	Muscle cramps	Lockjaw-type reaction
	Vaginal candidiasis	Muscle stiffness	
	Vaginal itch	Muscle spasm of neck	

CEFTIN® FOR ORAL SUSPENSION (MULTIPLE-DOSE DOSING REGIMENS): ***In Clinical Trials:*** In clinical trials using multiple doses of cefuroxime axetil powder for oral suspension, pediatric patients (96.7% of whom were younger than 12 years of age) were treated with the recommended dosages of cefuroxime axetil (20 to 30 mg/kg per day divided twice a day up to a maximum dose of 500 or 1,000 mg per day, respectively). There were no deaths or permanent disabilities in any of the patients in these studies. Eleven US patients (1.2%) discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. The discontinuations were primarily for gastrointestinal disturbances, usually diarrhea or vomiting. During clinical trials, discontinuation of therapy due to the taste and/or problems with administering this drug occurred in 13 (1.4%) children enrolled at centers in the US.

The following adverse events were thought by the investigators to be possibly, probably, or almost certainly related to cefuroxime axetil for oral suspension in multiple-dose clinical trials (n=931 cefuroxime axetil-treated US patients).

Adverse Reactions
Ceftin for Oral Suspension
Multiple-Dose Dosing Regimens–Clinical Trials

Incidence ≥1%	Diarrhea/loose stools		8.6%
	Dislike of taste		5.0%
	Diaper rash		3.4%
	Nausea/vomiting		2.6%
Incidence <1% but >0.1%	Abdominal pain	Irritable behavior	Cough
	Flatulence	Eosinophilia	Urinary tract infection
	Gastrointestinal infection	Positive direct Coombs test	Joint swelling
	Candidiasis	Elevated liver enzymes	Arthralgia
	Vaginal irritation	Viral illness	Fever
	Rash	Upper respiratory infection	Ptyalism
	Hyperactivity	Sinusitis	

In Postmarketing Experience: In addition to the events reported during clinical trials with Ceftin for Oral Suspension, the following adverse experiences have been reported in postmarketing surveillance: hypersensitivity reactions (including rash, pruritus, urticaria, and anaphylaxis).

CEPHALOSPORIN-CLASS ADVERSE REACTIONS: In addition to the adverse reactions listed above that have been observed in patients treated with cefuroxime axetil, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics: renal dysfunction, toxic nephropathy, hepatic cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, increased prothrombin time, increased BUN, increased creatinine, false-positive test for urinary glucose, increased alkaline phosphatase, neutropenia, thrombocytopenia, leukopenia, elevated bilirubin, pancytopenia, and agranulocytosis.

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: Overdosage of cephalosporins can cause cerebral irritation leading to convulsions. Serum levels of cefuroxime can be reduced by hemodialysis and peritoneal dialysis.

DOSAGE AND ADMINISTRATION:

NOTE: CEFTIN® TABLETS AND CEFTIN® FOR ORAL SUSPENSION ARE NOT BIOEQUIVALENT AND ARE NOT SUBSTITUTABLE ON A MG/MG BASIS.

Ceftin Tablets
(May be administered without regard to meals.)

Population/Infection	Dosage	Duration (days)
Adults (13 years and older)		
Pharyngitis/tonsillitis	250 mg b.i.d.	10
Acute bacterial exacerbations of chronic bronchitis and secondary bacterial infections of acute bronchitis	250 or 500 mg b.i.d.	10
Uncomplicated skin and skin-structure infections	250 or 500 mg b.i.d.	10
Uncomplicated urinary tract infections	125 or 250 mg b.i.d.	7-10
Uncomplicated gonorrhea	1,000 mg once	single dose
Children (who can swallow tablets whole)		
Pharyngitis/tonsillitis	125 mg b.i.d.	10
Acute otitis media	250 mg b.i.d.	10

Ceftin for Oral Suspension: Ceftin for Oral Suspension may be administered to children ranging in age from 3 months to 12 years, according to dosages in the following table:

Ceftin for Oral Suspension
(Must be administered with food. Shake well each time before using.)

Population/Infection	Dosage	Daily Maximum Dose	Duration (days)
Infants and children (3 months to 12 years)			
Pharyngitis/tonsillitis	20 mg/kg/day divided b.i.d.	500 mg	10
Acute otitis media	30 mg/kg/day divided b.i.d.	1,000 mg	10
Impetigo	30 mg/kg/day divided b.i.d.	1,000 mg	10

Patients with Renal Failure: The safety and efficacy of cefuroxime axetil in patients with renal failure have not been established. Since cefuroxime is renally eliminated, its half-life will be prolonged in patients with renal failure.

Directions for Mixing Ceftin for Oral Suspension: Prepare a suspension at the time of dispensing as follows:

1. Shake the bottle to loosen the powder.
2. Remove the cap.
3. Add the total amount of water for reconstitution (see table below) and replace the cap.
4. Invert the bottle and vigorously rock the bottle from side to side so that water rises through the powder.
5. Once the sound of the powder against the bottle disappears, turn the bottle upright and vigorously shake it in a diagonal direction.

Bottle Size	Amount of Water Required for Reconstitution
50 mL	18 mL
100 mL	33 mL
200 mL	66 mL

Each teaspoonful (5 mL) will contain the equivalent of 125 mg of cefuroxime as cefuroxime axetil.

NOTE: SHAKE THE ORAL SUSPENSION WELL BEFORE EACH USE. Replace cap securely after each opening. Reconstituted suspension should be stored between 2° and 25°C (36° and 77°F) (either in the refrigerator or at room temperature). DISCARD AFTER 10 DAYS.

Glaxo Pharmaceuticals
DIVISION OF GLAXO INC.
Research Triangle Park, NC 27709

July 1994
RL-128

References:

1. McLinn SE, Moskal M, Goldfarb J, et al. Comparison of cefuroxime axetil and amoxicillin-clavulanate suspensions in treatment of acute otitis media with effusion in children. *Antimicrob Agents Chemother.* February 1994;38:315-318.

2. Pichichero M, Aronovitz GH, Gooch WM, et al. Comparison of cefuroxime axetil, cefaclor, and amoxicillin-clavulanate potassium suspensions in acute otitis media in infants and children. *South Med J.* October 1990;83:1174-1177.

MANUSCRIPT PREPARATION: INSTRUCTIONS FOR AUTHORS

Send all manuscripts to:
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Manuscripts should be accompanied by a *submission letter*, signed by all authors, stating:

- That the manuscript is being submitted only to *Pediatrics*, that it will not be submitted elsewhere while under consideration, that it has not been published elsewhere, and, should it be published in *Pediatrics*, that it will not be published elsewhere—either in similar form or verbatim—without permission of the editors. These restrictions do not apply to abstracts or to press reports of presentations at scientific meetings.
- That they are responsible for reported research.
- That they have participated in the concept and design; analysis and interpretation of data; drafting or revising of the manuscript, and that they have approved the manuscript as submitted.
- That they are disclosing any affiliation, financial agreement, or other involvement of any author with any company whose product figures prominently in the submitted manuscript so that the editors can discuss with the affected authors whether to print this information and in what manner.

Manuscript Preparation and Processing

Manuscripts—including tables, illustrations, and references—should be prepared according to "Uniform requirements for manuscripts submitted to biomedical journals."[1,2] Only information not included in the uniform requirements will be included in the instructions that follow.

Abstracts should be prepared with a structured format. Four elements should be addressed: why did you start, what did you do, what did you find, and what does it mean. Why did you start is the *objective*. What did you do constitutes the methodology and could include *design, setting, patients or other participants, interventions, and outcome measures*. What did you find is the *results*, and what does it mean would constitute your *conclusions*.[3] Please label each section clearly with the appropriate subheading. Experience and Reason and Commentaries do not require abstracts.

Grammar, punctuation, and scientific writing style should follow the *American Medical Association Manual of Style*, 8th edition.[4] Please use conventional system measurements followed in parentheses by equivalent Système International (SI)[5,6] values.

Generally, abbreviations should be limited to those listed in Chapter 11 of the *AMA Manual of Style*, 8th edition.[4] Any uncommon abbreviations should be listed at the beginning of the article.

Research or project support should be acknowledged as a footnote to the title page; technical and other assistance may be identified in an appendix to the text.

It is expected that all cited references will have been read by the authors. Citing of review articles should be appropriately noted. Otherwise, secondary sources should not be cited.

Authors should submit four (4) complete copies of a manuscript, including tables (in type no smaller than that of the article's text) and glossy prints of any illustrations. Do not send original artwork or printed forms. A reasonable number of black and white illustrations will be printed without charge. Payment for color illustrations and other special processing is the responsibility of the authors and should be arranged before manuscripts are processed.

Receipt of manuscripts will be acknowledged promptly. Generally, all papers will be reviewed by at least two outside consultants.

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Acceptance Criteria

Relevance to readers is of major importance in manuscript selection. *Pediatrics* generally accepts manuscripts in the following categories: reports of original research, particularly clinical research; special articles; and experience and reason.

Reports of original research will be judged on the importance and originality of the research, its scientific strength, its clinical relevance, the clarity with which it is presented, and the number of submissions on the same topic. The decision to publish is not based on the direction of results.

Unsolicited commentaries or editorials will be considered, although most are solicited by the Editors. Review articles generally are not appropriate for publication in *Pediatrics*. Case reports are of interest only when they present a new entity or illustrate a major new aspect of a previously reported entity.

References

1. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J.* 1991; 302:338–341
2. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *N Engl J Med.* 1991;324:424–428
3. Ad Hoc Working Group for Critical Appraisal of the Medical Literature. A proposal for more informative abstracts of clinical articles. *Ann Intern Med.* 1987;106:598–604
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5. Lundberg GD. SI unit implementation: the next step. *JAMA.* 1988;260: 73–76
6. Système International conversion factors for frequently used laboratory components. *JAMA.* 1991;266:45–47

Manuscript Checklist (Please send with manuscript)

____ Four copies, ***entirely*** double-spaced

____ Corresponding author's address on cover page

____ Degrees and affiliations of each author

____ Four sets of photographs of any illustrations, appropriately labeled

____ Submission letter and statement described above

____ Structured abstracts and keywords for articles.

____ References double-spaced and numbered consecutively according to their citation in the text. (Please style according to AMA *Manual of Style*, 8th ed.[4]) List all authors unless more than six (6), in which case, list first three (3) and then "et al."

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ARTICLES

PEDIATRIC HISTORY

Schedule of Meetings

American Academy of Pediatrics

141 Northwest Point Blvd.
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Annual Meetings

1995

San Francisco, California
October 14–18

1996

Boston, Massachusetts
October 26–30

Spring Sessions

1995

Philadelphia, Pennsylvania
April 8–12

1996

Chicago, Illinois
April 13–17

1997

San Diego, California
May 10–14

Experience and Reason

Editorials

Commentary

American Academy of Pediatrics

Letters to the Editor

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ANNUAL MEETINGS

1995

San Francisco, California
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Boston, Massachusetts
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SPRING SESSIONS

1995

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1996

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April 13–17

1997

San Diego, California
May 10–14

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References: 1. Data on file. Johnson & Johnson 2. Shelov SP, Hannemann RE, eds. *The American Academy of Pediatrics: Caring for Your Baby and Young Child: Birth to Age 5.* New York, NY: Bantam Books; 1991:103.

Schedule of Continuing Education Courses

American Academy of Pediatrics

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1994

Pediatric Update
San Antonio, Texas
December 16–18

1995

Current Concepts in Pediatrics
Vail, Colorado
January 12–15

Pediatrics 1995
Maui, Hawaii
March 10–12

State-of-the-Art Pediatrics
New York, New York
April 28–30

Pediatric Advances
Hilton Head Island, South Carolina
May 26–28

Clinical Pediatrics
Washington, DC
June 23–25

Pediatric Trends
Seattle, Washington
September 1–3

New Directions in Pediatrics
New Orleans, Louisiana
November 3–5

Pediatric Update
Williamsburg, Virginia
December 8–10

AUGMENTIN® amoxicillin/clavulanate potassium

BRIEF SUMMARY. FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT.

Indications and Usage: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower Respiratory Tract Infections caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Otitis Media* caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Sinusitis* caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Skin and Skin Structure Infections* caused by β-lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp. *Urinary Tract Infections* caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp. While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic.

Bacteriological studies to determine the causative organisms and their susceptibility to *Augmentin* should be performed together with any indicated surgical procedures. Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once results are known, adjust therapy, if appropriate.

Contraindications: Patients with a history of allergic reactions to any penicillin; or patients with a history of *Augmentin*-associated cholestatic jaundice/hepatic dysfunction.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH *AUGMENTIN*, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.** Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic associated colitis." After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. Use *Augmentin* cautiously in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with *Augmentin* use is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications (see CONTRAINDICATIONS and ADVERSE REACTIONS–*Liver*).

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

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomo-*

Augmentin®: Now, 9 years of undiminished efficacy[1,2]

▲

Excellent clinical response rates in otitis media and sinusitis[2]

▲

Latest† *in vitro* susceptibility‡: still impressive – *H. influenzae*: 100% and *M. catarrhalis*: 99.8%[3]

▲

Actively destroys ß-lactamase[4]

* For susceptible strains of indicated organisms. *Augmentin* is appropriate initial therapy when you suspect ß-lactamase-producing organisms.

† Latest available annual data: January to December 1991.

‡ *In vitro* susceptibility does not necessarily imply *in vivo* efficacy.

Please see brief summary of prescribing information for contraindications, warnings, precautions and adverse reactions.

References: 1. Neu HC, Wilson APR, Grüneberg RN: Amoxicillin/clavulanic acid — a review of its efficacy in over 38,500 patients from 1979 to 1992. *J Chemother* 1993;5(2):67-93. **2.** Data on file, SmithKline Beecham Pharmaceuticals. **3.** Data from the Institutes for Microbiology Research, Franklin, Tenn. **4.** Neu HC: Contribution of beta-lactamases to bacterial resistance and mechanisms to inhibit beta-lactamases. *Am J Med* 1985;79(suppl 5B):2-12.

SB
SmithKline Beecham
Pharmaceuticals
Philadelphia, PA 19101

nas or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.
Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.
Augmentin should not be co-administered with Antabuse® (disulfiram).
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.
Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.
Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.
Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.
Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were mild and transient; <3% of patients discontinued therapy because of them. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.
The following adverse reactions have been reported for ampicillin class antibiotics:
Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis, mucocutaneous candidiasis and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS). Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis). These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (see WARNINGS). A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. Interstitial nephritis and hematuria have been reported rarely. Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*. Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.
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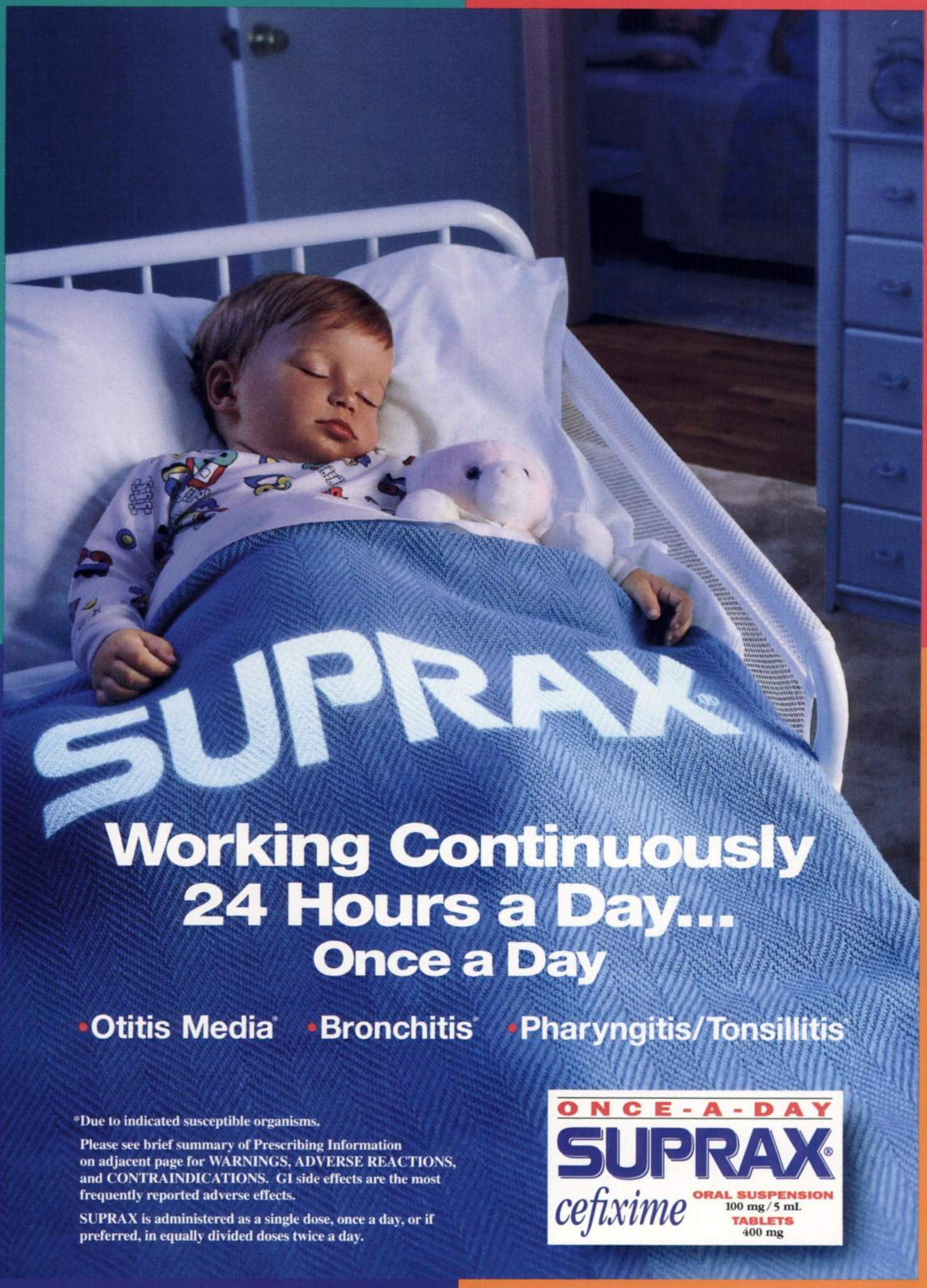


Working Continuously 24 Hours a Day... Once a Day

- Otitis Media*
- Bronchitis*
- Pharyngitis/Tonsillitis*

*Due to indicated susceptible organisms.

Please see brief summary of Prescribing Information on adjacent page for WARNINGS, ADVERSE REACTIONS, and CONTRAINDICATIONS. GI side effects are the most frequently reported adverse effects.

SUPRAX is administered as a single dose, once a day, or if preferred, in equally divided doses twice a day.

ONCE-A-DAY

SUPRAX®

cefixime

ORAL SUSPENSION
100 mg / 5 mL

TABLETS
400 mg

ONCE-A-DAY

SUPRAX®

cefixime

ORAL SUSPENSION
100 mg/5 mL
TABLETS
400 mg

Working 24 hours a day

Brief Summary

SUPRAX®
Cefixime
Oral

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

SUPRAX is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Uncomplicated Urinary Tract Infections caused by *Escherichia coli* and *Proteus mirabilis*.

Otitis Media caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Moraxella (Branhamella) catarrhalis*, (most of which are beta-lactamase positive), and *Streptococcus pyogenes*.*

Note: For information on otitis media caused by *Streptococcus pneumoniae*, see **CLINICAL STUDIES** section.

Pharyngitis and Tonsillitis, caused by *S pyogenes*.

Note: Penicillin is the usual drug of choice in the treatment of *S pyogenes* infections, including the prophylaxis of rheumatic fever. SUPRAX is generally effective in the eradication of *S pyogenes* from the nasopharynx; however, data establishing the efficacy of SUPRAX in the subsequent prevention of rheumatic fever are not available.

Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis, caused by *S pneumoniae* and *H influenzae* (beta-lactamase positive and negative strains).

Uncomplicated Gonorrhea (Cervical/Urethral), caused by *Neisseria gonorrhoeae* (penicillinase- and nonpenicillinase-producing strains).

Appropriate cultures and susceptibility studies should be performed to determine the causative organism and its susceptibility to SUPRAX; however, therapy may be started while awaiting the results of these studies. Therapy should be adjusted, if necessary, once these results are known.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

CLINICAL STUDIES

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][b] 4 mg/kg BID	Cefixime[a][b] 8 mg/kg QD	Control[a][b] 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[c]
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.

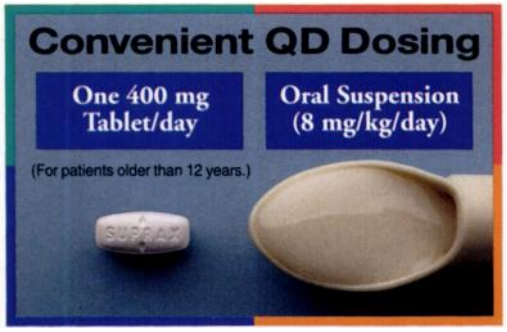
[c] Tablets should not be substituted for suspension when treating otitis media.

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



SUPRAX® cefixime

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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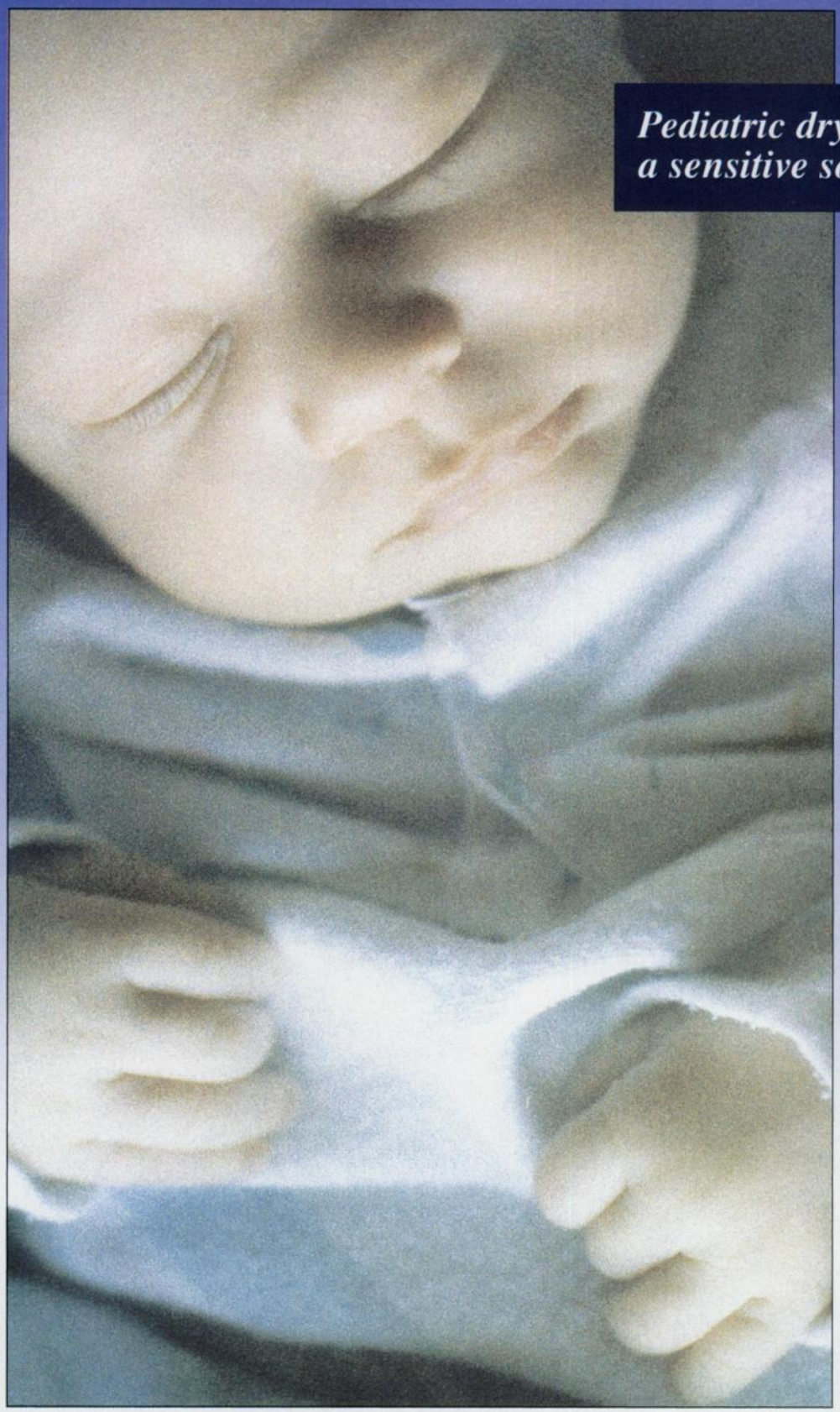

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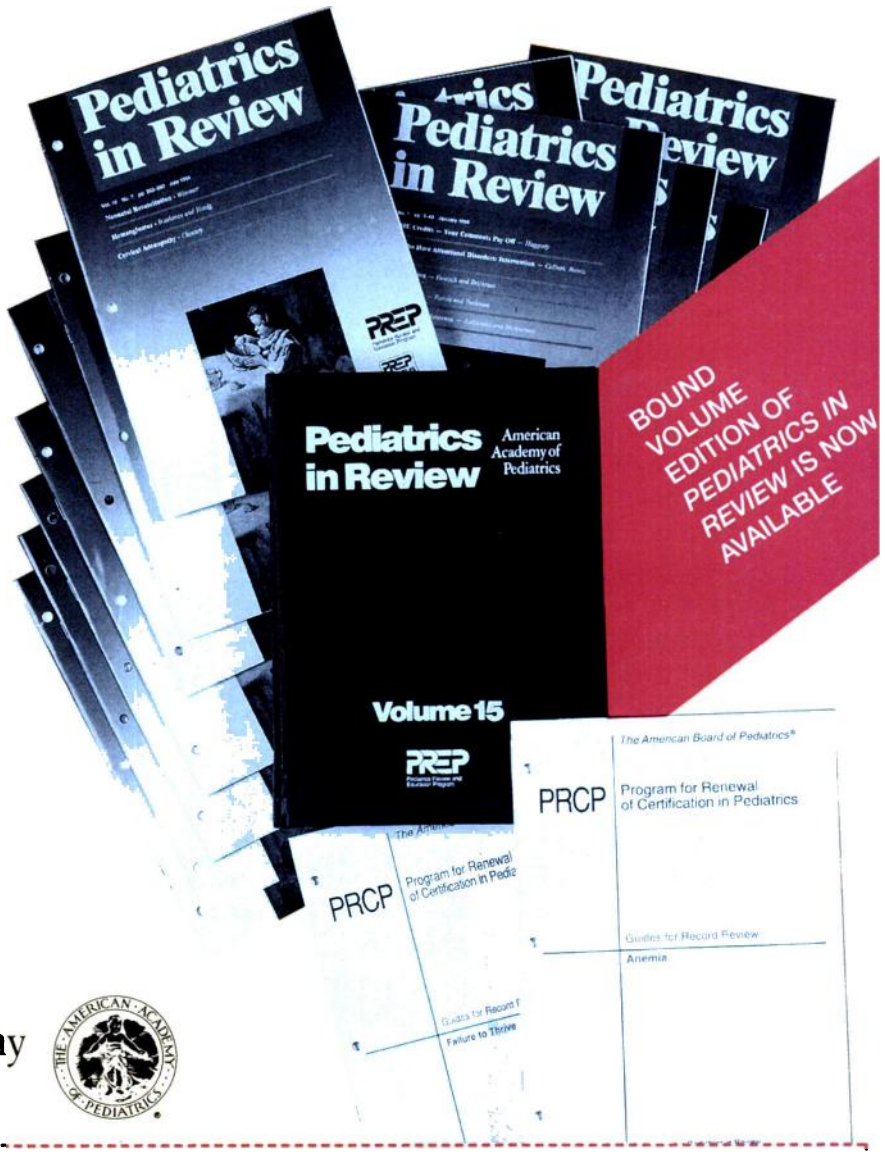

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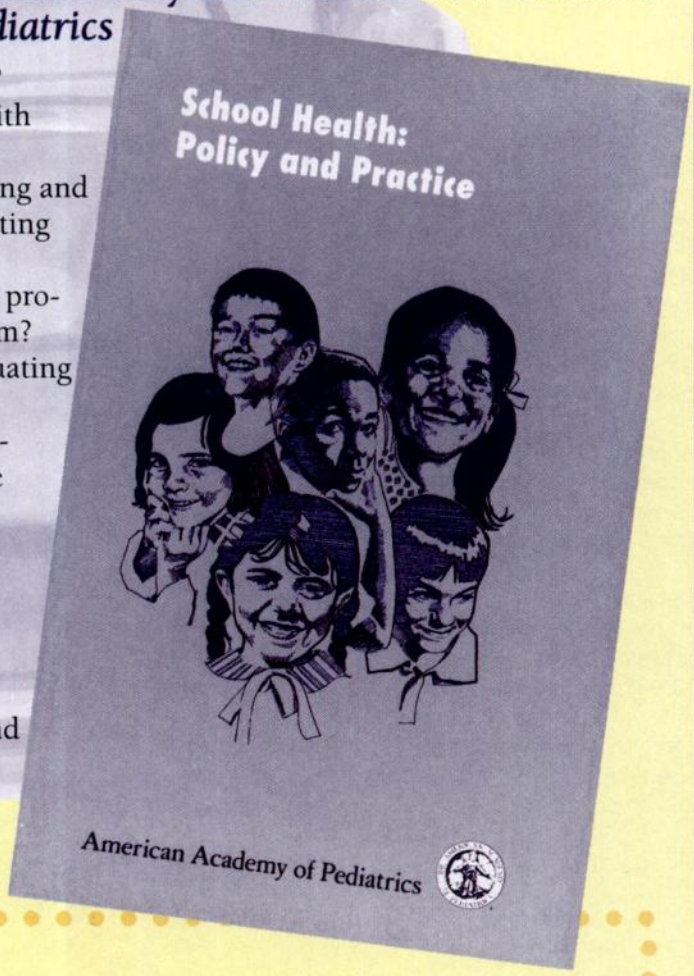

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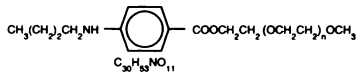

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OVERDOSAGE: Overdose may result in death. The drug is chemically related to tetracaine and other topical anesthetics and shares various aspects of their pharmacology and toxicology. Drugs of this type are generally well absorbed after ingestion. **Signs and Symptoms:** If perles are chewed or dissolved in the mouth, oropharyngeal anesthesia will develop rapidly. CNS stimulation may cause restlessness and tremors which may proceed to clonic convulsions followed by profound CNS depression. **Treatment:** Evacuate gastric contents and administer copious amounts of activated charcoal slurry. Even in the conscious patient, cough and gag reflexes may be so depressed as to necessitate special attention to protection against aspiration of gastric contents and orally administered materials. Convulsions should be treated with a short-acting barbiturate given intravenously and carefully titrated for the smallest effective dosage. Intensive support of respiration and cardiovascular-renal function is an essential feature of the treatment of severe intoxication from overdosage. Do not use CNS stimulants.

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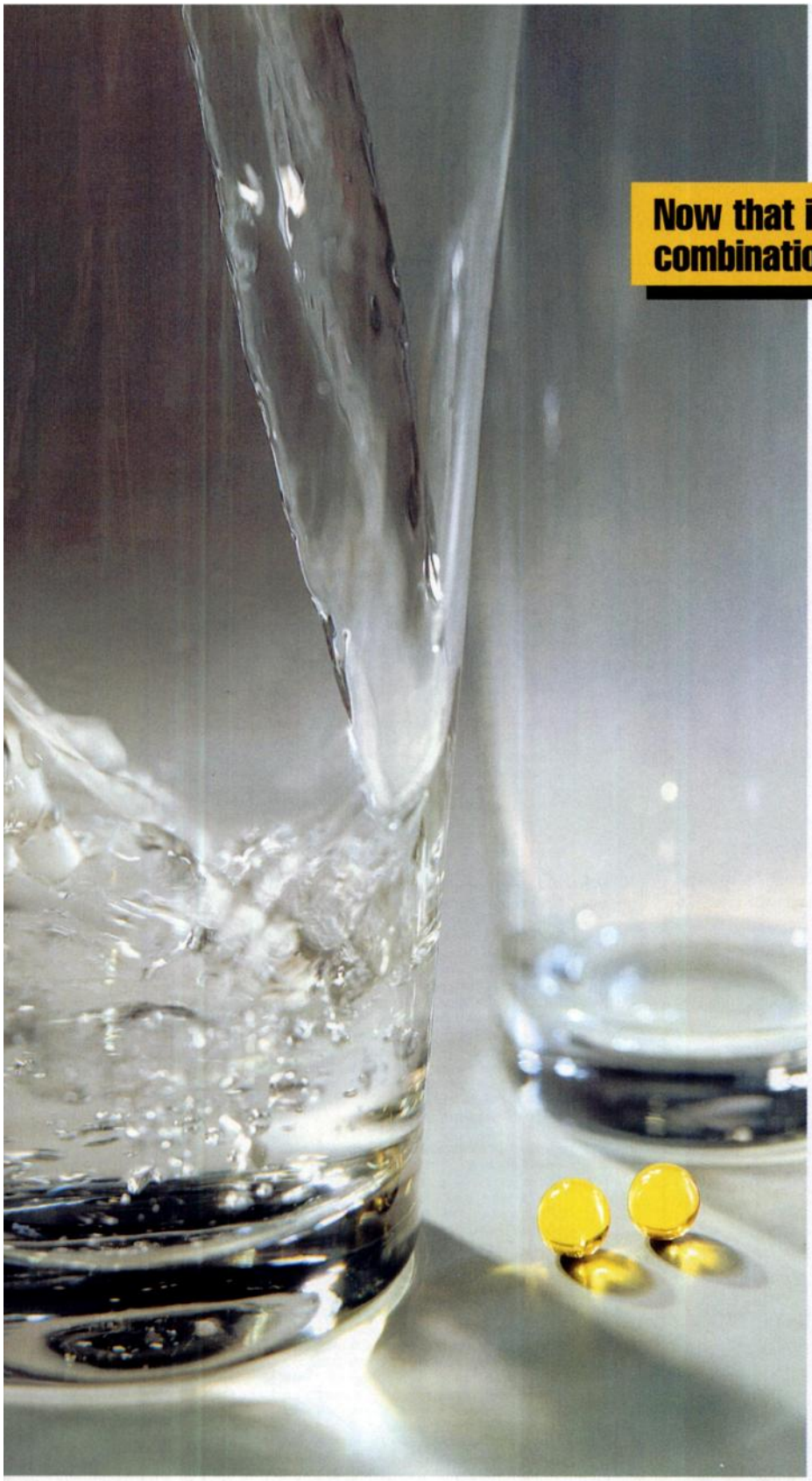

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PEDIATRICS

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Parents' and Children's Adiposity and Eating Style

Susan L. Johnson, PhD and Leann L. Birch, PhD

ABSTRACT. *Objective.* **To investigate children's ability to self-regulate energy intake and to determine whether individual differences in the precision of food intake regulation are related to children's anthropometric measures. We collected information pertaining to parental adiposity and dieting practices, as well as mothers' child-feeding practices. Of special interest was the degree of control imposed by mothers over their children's food intake. Our intent was to explore whether these variables might influence children's regulation of energy intake.**

Subjects and setting. **Seventy-seven 3–5-year-old children who attended a university preschool setting and their parents participated in this experiment.**

Measurements and main results. **Children completed controlled, two-part meals used to estimate their ability to adjust food intake in response to changes in caloric density of the diet. An eating index, reflecting children's precision in the ability to regulate energy intake, was correlated to children's anthropometric measures. These correlations provided evidence for a relation between children's body fat stores and their responsiveness to caloric density cues: Pearson correlation coefficients revealed that children with greater body fat stores were less able to regulate energy intake accurately. The best predictor of children's ability to regulate energy intake was parental control in the feeding situation: mothers who were more controlling of their children's food intake had children who showed less ability to self-regulate energy intake ($r = -.67$, $P < .0001$).**

Conclusions. **These findings suggest that the optimal environment for children's development of self-control of energy intake is that in which parents provide healthy food choices but allow children to assume control of how much they consume.** *Pediatrics* **1994;94:653–661;** ***familial adiposity, energy regulation, parental control, child-feeding practices, compensation, eating index.***

From the Child Development Laboratory and Division of Nutritional Sciences, University of Illinois at Urbana-Champaign, Urbana IL.
Received for publication Dec 7, 1993; accepted Feb 9, 1994.
Reprint requests to (S.L.J.) University of Colorado Health Sciences Ctr, Center for Human Nutrition, Campus Box C225, 4200 E Ninth Ave, Denver, CO 80262.

ABBREVIATIONS. BMI, body mass index; COMPX, compensation index.

It has been estimated that one of every four children in the United States is obese[1] and that prevalence rates have increased as much as 54% in the last 2 decades.[2] Increases in the prevalence of obesity have been attributed to declines in physical activity,[3] improper food habits,[4] and genetic predisposition.[5] Once obesity is in place, it is refractory to change; overweight children tend to become overweight adults[6] and overweight adults continue to struggle with their weight status. Thus, prevention of obesity will be its best cure. The first steps toward the prevention of obesity can be undertaken only when we have an understanding of its etiology.

Familial patterns of adiposity support the hypothesis that variation in body fatness is explained in part by a genetic or heritable component.[5,7,8] Recent evidence suggests that intergenerational transfer of eating styles also contributes to these familial patterns; obese parents may use child-feeding practices that foster the development of obesity.[9] Genetic predisposition may interact synergistically with the physical and social environment to produce inherited patterns of obesity within families.[10] However, at present, scant information exists concerning how the family environment shapes the development of children's eating and exercise behaviors and how parents influence their children's eating and activity patterns.

Experiments from our laboratory that have examined children's eating behaviors have revealed that children can adjust their energy intake in response to changes in the caloric density of the diet.[11,12] We have demonstrated, both in short-term and over longer 24-hour periods,[13] that children decrease food intake ad libitum in response to increasing energy density and consume more in response to caloric dilution of the diet. This adjustment in energy intake has been termed caloric compensation. When the data from these experiments are examined for individual differences among children, it becomes apparent that

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Pediatric Nephrology Subspecialty Examination: Will be held in five cities throughout the United States, August 8, 1995.

First Time Applicants: New Regular Registration: (Fee $1320): November 1, 1994, through December 31, 1994 (postmarked).

Late New Registration: (Fee $1545): January 1, 1995, through January 31, 1995 (postmarked); a late fee is required. No new applications accepted after January 31, 1995 (postmarked).

Re-Registration: Regular Registration: (Fee $1220): January 16, 1995, through March 15, 1995 (postmarked).

Late Re-Registration: (Fee $1445): March 16, 1995, through April 14, 1995 (postmarked); a late fee is required.

Neonatal-Perinatal Medicine Subspecialty Examination: Will be held in three cities throughout the United States, November 14, 1995.

First Time Applications: New Regular Registration: (Fee $1320): February 1, 1995, through March 31, 1995 (postmarked).

Late New Registration: (Fee $1545): April 1, 1995, through April 29, 1995 (postmarked); a late fee is required. No new applications accepted after April 29, 1995 (postmarked).

Re-Registration: Regular Registration: (Fee $1220): April 3, 1995, through May 31, 1995 (postmarked).

Late Re-Registration: (Fee $1445): June 1, 1995, through June 30, 1995 (postmarked); a late fee is required.


When effective fever and pain relief is the first priority.
Children's and Junior Strength
TYLENOL®
acetaminophen
First
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. Walson PD et al. AJDC. 1992;146:626-632. 2. Schachtel BP et al. Clin Pharmacol Ther. 1993;53(5):593-601. 3. Aspirin or paracetamol? Lancet. 1981;2:287-289. 4. Settipane GA. Am J Med. 1983;74(6A):102-109. 5. Risser WL. Pediatr Ann. 1992;21(3):170-173.
*Ibuprofen is not indicated for treatment of pain in children under 12 years of age.
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No pediatric antipyretic/analgesic is more effective.
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THESE KIDS ALL HAD SOMETHING IN COMMON AS INFANTS...

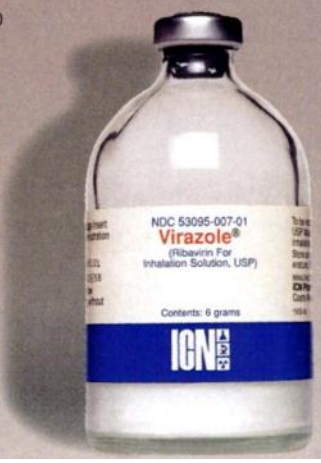
RSV AND WERE TREATED WITH VIRAZOLE®

Respiratory Syncytial Virus is the most important cause of lower respiratory tract disease in infants and young children. All children become infected during their first three years of life. For most infants and young children a trip to the hospital is not necessary. But for those hospitalized with severe lower respiratory tract infections due to RSV, Virazole® may be recommended.

- Since 1986 more than 100,000 patients have been treated successfully with Virazole®.
- Clinical experience indicates Virazole® therapy is both safe and effective.[2]
- Recommended by American Academy of Pediatrics in high risk and severely ill patients.[2]
- May reduce hospital stay and costs in mechanically ventilated infants and young children.[3]
- Treatment early in course of severe illness may achieve best efficacy.[1,2]

VIRAZOLE®
(ribavirin)

THE ONLY ANTIVIRAL THERAPY FOR RSV



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 Prescribing Information and SPAG Operating Manual).[1]

1. *Virazole prescribing information, ICN Pharmaceuticals, Inc.*
2. *Report of the Committee on Infectious Diseases, Pediatrics 1993; Vol. 92, No.3, September: 501-504.*
3. *Smith D et al. A controlled trial of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection. New England Journal of Medicine (July, 4), 1991: 325:24-29*

See full prescribing information on reverse page.

ICN®

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).

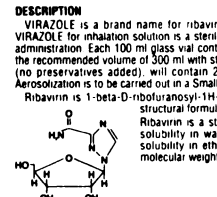
SUDDEN DETERIORATION OF RESPIRATORY FUNCTION HAS BEEN ASSOCIATED WITH INITIATION OF AEROSOLIZED VIRAZOLE USE IN INFANTS. RESPIRATORY FUNCTION SHOULD BE CAREFULLY MONITORED DURING TREATMENT. IF INITIATION OF AEROSOLIZED VIRAZOLE TREATMENT APPEARS TO PRODUCE SUDDEN DETERIORATION OF RESPIRATORY FUNCTION, 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 1.4 months (SD, 1.7 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 F_iO_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 isoproterenol, 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).[7,8,9]

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.[10]

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. Hosprtals 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 0.17 gm/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, reconstitute drug with a minimum of 75 ml of **sterile USP water for injection or inhalation** in the original 100 ml glass vial. Shake well. 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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*Copies of the Report may be purchased from National Technical Information Service, 5285 Port Royal Road, Springfield, VA 22161, Ask for Publication PB 93119-345.

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New research shows learning to like vegetables is a teachable proposition.

In a recent study conducted at the University of Illinois,* babies were given their first vegetables in the form of baby food. After ten exposures, all of them significantly increased their acceptance of green beans or peas. Repeated exposure helped babies overcome initial rejection.

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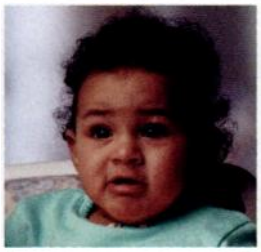
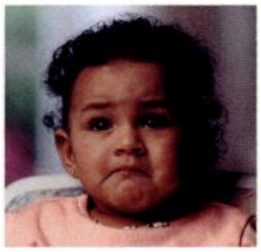


"I don't like green beans."



"I don't want green beans."

"I don't hate green beans."

"OK, I'll have some green beans."

"I finished my green beans."

"I want some more green beans."

"I like green beans."

"HEY, WHERE'S MY GREEN BEANS!!!"

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*The Sullivan and Birch study was conducted at the University of Illinois and published in the February 1994 issue of *Pediatrics*. For a reprint of the article entitled *Infant Dietary Experience and Acceptance of Solid Foods* contact Department of Research, American Academy of Pediatrics, 141 Northwest Point Blvd., PO Box 927, Elk Grove Village, IL 60009-0927

THE VIABILITY LIMIT OF GESTATION FOR THE FETUS AND PREMATURE NEONATES—THE EFFECT OF THE RECENT AMENDMENT OF EUGENIC PROTECTION ACT IN JAPAN

Hiroshi Nishida

Abstract. The Eugenic Protection Act in Japan was amended in respect of the viability limit of gestation from 24 weeks to 22 weeks in 1991, because of the rapid progress of survival rate of extremely low birth weight infants in recent years. At Tokyo Women's Medical College, 112 out of 134 (84%) infants whose birth weight were less than 1,000 grams survived in the past 6 years. The effect of this amendment on perinatal and neonatal health care is discussed from medical, ethical and socioeconomic aspects. Viability is defined as not only "the ability to live" but also "the ability to grow and develop normally." The fundamental thought underlying ethics on viability of extremely premature infants are "recognition of continuity and discontinuity" and "human principle and life principle." *Asian Med J* 1992;35: 9487–494.

Noted by J.F.L., MD

FAXING—150 YEARS OLD!

Although the office fax machine has only become popular in the past decade, this year sees its 150th anniversary. It was patented on 27 May 1843, 30 years even before the telephone. But whereas the telephone quickly established itself as an essential tool for business, commercial success has been much longer coming for a machine that could transmit pictures and documents, within seconds, from one office to another.

The inventor of the idea was Alexander Bain, who was born in 1810. Bain, a Scotsman from a remote croft in Caithness, is reputed to have performed his early experiments using cattle jawbones for hinges, heather for springs and metal plates buried in the earth for batteries. He was apprenticed to a clockmaker in Wick and invented the first electric clock, which used electromagnetism to pull a pendulum from side to side. He then moved to London and patented his fax machine.

Hunkin T. Just give me the fax. *New Scientist*. February 13, 1993, pp. 33–37.

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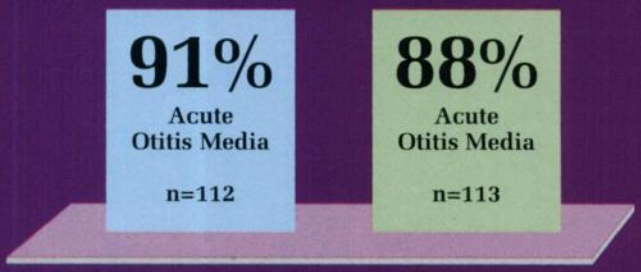

- ✓ **Clinically indicated** for acute otitis media in children due to *H influenzae*, *M catarrhalis*, and *S pneumoniae*[1]
- ✓ **Unaffected by beta-lactamases**[1]
- ✓ **Achieves** high concentration in middle ear fluid[1,3]

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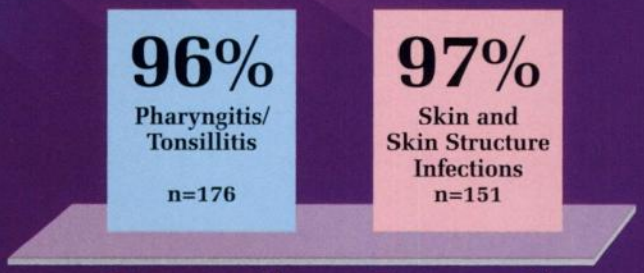

✓ **Also indicated for acute maxillary sinusitis** due to *H influenzae*, *M catarrhalis*, and *S pneumoniae*[1]

Very Well Tolerated in Children

✓ **Low incidence of adverse events**, including diarrhea 6%, vomiting 6%, abdominal pain 3%, rash 3%, headache 2%[1]

✓ **Significantly lower incidence of diarrhea vs Augmentin®** (amoxicillin/clavulanate)† in two well-controlled studies ($P<0.001$)[1]

✓ **Comparable GI tolerability** to Ceclor® (cefaclor)‡[1,5] and amoxicillin[6,7]

* Clinical success = clinical cure or improvement
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- ✓ **Pleasant tasting suspensions** in 100mL bottles:
  — 125mg per/5mL (vanilla)
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— Per 10-day course of therapy for acute otitis media at recommended doses vs. other advanced generation oral antibiotics*[8]

* Based on AWP comparison which is a published list price and may not represent actual price paid by pharmacies and consumers. Dose based on patient weight per course of therapy. Comparison is between BIAXIN; Augmentin; Ceclor; Cefzil® (cefprozil), a registered trademark of Bristol Laboratories; Lorabid™ (loracarbef), a trademark of Eli Lilly and Company; Suprax® (cefixime), a registered trademark of Lederle Laboratories; and Vantin® (cefpodoxime proxetil), a registered trademark of The Upjohn Company.

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306-023-2295A August 1994 PRINTED IN U.S.A.

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BIAXIN® Filmtab® (clarithromycin)

BIAXIN® Granules (clarithromycin for oral suspension)

CONTRAINDICATIONS:
Clarithromycin is contraindicated in patients with a known hypersensitivity to clarithromycin, erythromycin, or any of the macrolide antibiotics.

Clarithromycin is contraindicated in patients receiving terfenadine therapy who have preexisting cardiac abnormalities (arrhythmia, bradycardia, QT interval prolongation, ischemic heart disease, congestive heart failure, etc.) or electrolyte disturbances. (See **PRECAUTIONS** - *Drug Interactions.*)

WARNINGS: CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING THIS DRUG, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. CLARITHROMYCIN HAS DEMONSTRATED ADVERSE EFFECTS OF PREGNANCY OUTCOME AND/OR EMBRYO-FETAL DEVELOPMENT IN MONKEYS, RATS, MICE, AND RABBITS AT DOSES THAT PRODUCED PLASMA LEVELS 2 TO 17 TIMES THE SERUM LEVELS ACHIEVED IN HUMANS TREATED AT THE MAXIMUM RECOMMENDED HUMAN DOSES. (SEE PREGNANCY.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is 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 clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS
General: Clarithromycin is principally excreted via the liver and kidney. Clarithromycin may be administered without dosage adjustment to patients with hepatic impairment and normal renal function. However, in the presence of severe renal impairment with or without coexisting hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate.

Information to Patients: BIAXIN tablets and oral suspension can be taken with or without food and can be taken with milk. Do **NOT** refrigerate the suspension.

Drug Interactions: Clarithromycin use in patients who are receiving theophylline may be associated with an increase of serum theophylline concentrations. Monitoring of serum theophylline concentrations should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range. In two studies in which theophylline was administered with clarithromycin (a theophylline sustained-release formulation was dosed at either 6.5 mg/kg or 12 mg/kg together with 250 or 500 mg q12h clarithromycin), the steady-state levels of C_{max}, C_{min}, and the area under the serum concentration time curve (AUC) of theophylline increased about 20%.

Concomitant administration of single doses of clarithromycin and carbamazepine has been shown to result in increased plasma concentrations of carbamazepine. Blood level monitoring of carbamazepine may be considered.

When clarithromycin and terfenadine were coadministered, plasma concentrations of the active acid metabolite of terfenadine were threefold higher, on average, than the values observed when terfenadine was administered alone. The pharmacokinetics of clarithromycin and the 14-hydroxyclarithromycin were not significantly affected by coadministration of terfenadine once clarithromycin reached steady-state conditions. The increase in the QT interval seen in association with the elevated terfenadine acid metabolite level is unlikely to be of clinical significance in healthy individuals. Clarithromycin should not be given to patients receiving terfenadine therapy who have preexisting cardiac abnormalities (arrhythmia, bradycardia, QT interval prolongation, ischemic heart disease, congestive heart failure, etc.) or electrolyte disturbances. (See **CONTRAINDICATIONS.**)

Simultaneous oral administration of BIAXIN tablets and zidovudine to HIV-infected adult patients resulted in decreased steady-state zidovudine concentrations. When 500 mg of clarithromycin were administered twice daily, steady-state zidovudine AUC was reduced by a mean of 12% (n=4). Individual values ranged from a decrease of 34% to an increase of 14%.

Spontaneous reports in the post-marketing period suggest that concomitant administration of clarithromycin and oral anticoagulants may potentiate the effects of the oral anticoagulants. Prothrombin times should be carefully monitored while patients are receiving clarithromycin and oral anticoagulants simultaneously.

Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in post-marketing surveillance. Serum digoxin levels should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

The following drug interactions, other than increased serum concentrations of carbamazepine and active acid metabolite of terfenadine, have not been reported in clinical trials with clarithromycin; however, they have been observed with erythromycin products:

Concurrent use of erythromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

Erythromycin has been reported to decrease the clearance of triazolam and, thus, may increase the pharmacologic effect of triazolam.

The use of erythromycin in patients concurrently taking drugs metabolized by the cytochrome P450 system may be associated with elevations in serum levels of these other drugs. There have been reports of interactions of erythromycin with carbamazepine, cyclosporine, hexobarbital, phenytoin, alfentanil, disopyramide, lovastatin, bromocriptine, valproate, terfenadine, and astemizole. Serum concentrations of drugs metabolized by the cytochrome P450 system should be monitored closely in patients concurrently receiving erythromycin.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The following *in vitro* mutagenicity tests have been conducted with clarithromycin: *Salmonella*/Mammalian Microsomes Test, Bacterial Induced Mutation Frequency Test, *In Vitro* Chromosome Aberration Test, Rat Hepatocyte DNA Synthesis Assay, Mouse Lymphoma Assay, Mouse Dominant Lethal Study, and Mouse Micronucleus Test.

All tests had negative results except the *In Vitro* Chromosome Aberration Test which was weakly positive in one test and negative in another.

In addition, a Bacterial Reverse-Mutation Test (Ames Test) has been performed on clarithromycin metabolites with negative results.

Fertility and reproduction studies have shown that daily doses of up to 160 mg/kg/day (1.3 times the recommended maximum human dose based on mg/m^2) to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring. Plasma levels in rats after 150 mg/kg/day were 2 times the human serum levels.

In the 150 mg/kg/day monkey studies, plasma levels were 3 times the human serum levels. When given orally at 150 mg/kg/day (2.4 times the recommended maximum human dose based on mg/m^2), clarithromycin was shown to produce embryonic loss in monkeys. This effect has been attributed to marked maternal toxicity of the drug at this high dose.

In rabbits, *in utero* fetal loss occurred at an intravenous dose of 33 mg/m^2, which is 17 times less than the maximum proposed human oral daily dose of 618 mg/m^2.

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of clarithromycin.

Pregnancy: Teratogenic Effects. Pregnancy Category C.
Four teratogenicity studies in rats (three with oral doses and one with intravenous doses up to 160 mg/kg/day administered during the period of major organogenesis) and two in rabbits at oral doses up to 125 mg/kg/day (approximately 2 times the recommended maximum human dose based on mg/m^2) or intravenous doses of 30 mg/kg/day administered during gestation days 6 to 18 failed to demonstrate any teratogenicity from clarithromycin. Two additional oral studies in a different rat strain at similar doses and similar conditions demonstrated a low incidence of cardiovascular anomalies at doses of 150 mg/kg/day administered during gestation days 6 to 15. Plasma levels after 150 mg/kg/day were 2 times the human serum levels. Four studies in mice revealed a variable incidence of cleft palate following oral doses of 1000 mg/kg/day (2 and 4 times the recommended maximum human dose based on mg/m^2, respectively) during gestation days 6 to 15. Cleft palate was also seen at 500 mg/kg/day. The 1000 mg/kg/day exposure resulted in plasma levels 17 times the human serum levels. In monkeys, an oral dose of 70 mg/kg/day (an approximate equidose of the recommended maximum human dose based on mg/m^2) produced fetal growth retardation at plasma levels that were 2 times the human serum levels.

There are no adequate and well-controlled studies in pregnant women. Clarithromycin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS.**)

Nursing Mothers: It is not known whether clarithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when clarithromycin is administered to a nursing woman. It is known that clarithromycin is excreted in the milk of lactating animals and that other drugs of this class are excreted in human milk. Preweaned rats, exposed indirectly via consumption of milk from dams treated with 150 mg/kg/day for 3 weeks, were not adversely affected, despite data indicating higher drug levels in milk than in plasma.

Pediatric Use: Safety and effectiveness of clarithromycin in children under 6 months of age have not been established. Neonatal and juvenile animals tolerated clarithromycin in a manner similar to adult animals. Young animals were slightly more intolerant to acute overdosage and to subtle reductions in erythrocytes, platelets and leukocytes but were less sensitive to toxicity in the liver, kidney, thymus, and genitalia.

Geriatric Use: In a steady-state study in which healthy elderly subjects (age 65 to 81 years old) were given 500 mg every 12 hours, the maximum serum concentrations and area under the curves of clarithromycin and 14-OH clarithromycin were increased compared to those achieved in healthy young adults. These changes in pharmacokinetics parallel known age-related decreases in renal function. In clinical trials, elderly patients did not have an increased incidence of adverse events when compared to younger patients. Dosage adjustment should be considered in elderly patients with severe renal impairment.

ADVERSE REACTIONS:
The majority of side effects observed in clinical trials were of a mild and transient nature. Fewer than 3% of adult patients and fewer than 2% of pediatric patients discontinued therapy because of drug-related side effects.

The most frequently reported events in adults were diarrhea (3%), nausea (3%), abnormal taste (3%), dyspepsia (2%), abdominal pain/discomfort (2%), and headache (2%). In pediatric patients, the most frequently reported events were diarrhea (6%), vomiting (6%), abdominal pain (3%), rash (3%), and headache (2%). Most of these events were described as mild or moderate in severity. Of the reported adverse events, only 1% was described as severe.

In pneumonia studies conducted in adults comparing clarithromycin to erythromycin base or erythromycin stearate, there were fewer adverse events involving the digestive system in clarithromycin-treated patients compared to erythromycin-treated patients (13% vs 32%; p<0.01). Twenty percent of erythromycin-treated patients discontinued therapy due to adverse events compared to 4% of clarithromycin-treated patients.

In two U.S. studies of acute otitis media comparing clarithromycin to amoxicillin/potassium clavulanate in pediatric patients, there were fewer adverse events involving the digestive system in clarithromycin-treated patients compared to amoxicillin/potassium clavulanate-treated patients (21% vs. 40%, p<0.001). One-third as many clarithromycin-treated patients reported diarrhea as did amoxicillin/potassium clavulanate-treated patients.

Post-Marketing Experience: Allergic reactions ranging from urticaria and mild skin eruptions to rare cases of anaphylaxis and Stevens-Johnson syndrome have occurred. Other spontaneously reported adverse events include glossitis, stomatitis, oral moniliasis, vomiting, dizziness, and insomnia. Hepatic dysfunction, including cholestasis, with or without jaundice has also been reported.

Adverse events reported with erythromycin products but not in clinical trials of clarithromycin include: Rarely, erythromycin has been associated with ventricular arrhythmias, including ventricular tachycardia and torsades de pointes, in individuals with prolonged QT intervals.

Changes in Laboratory Values: Changes in laboratory values with possible clinical significance were as follows:
Hepatic - elevated SGPT (ALT) < 1%; SGOT (AST) < 1%; GGT < 1%; alkaline phosphatase <1%; LDH < 1%; total bilirubin < 1%
Hematologic - decreased WBC < 1%; elevated prothrombin time 1%
Renal - elevated BUN 4%; elevated serum creatinine < 1%
GGT, alkaline phosphatase, and prothrombin time data are from adult studies only.

Ref. 03-4452-R5 Revised: July 1994

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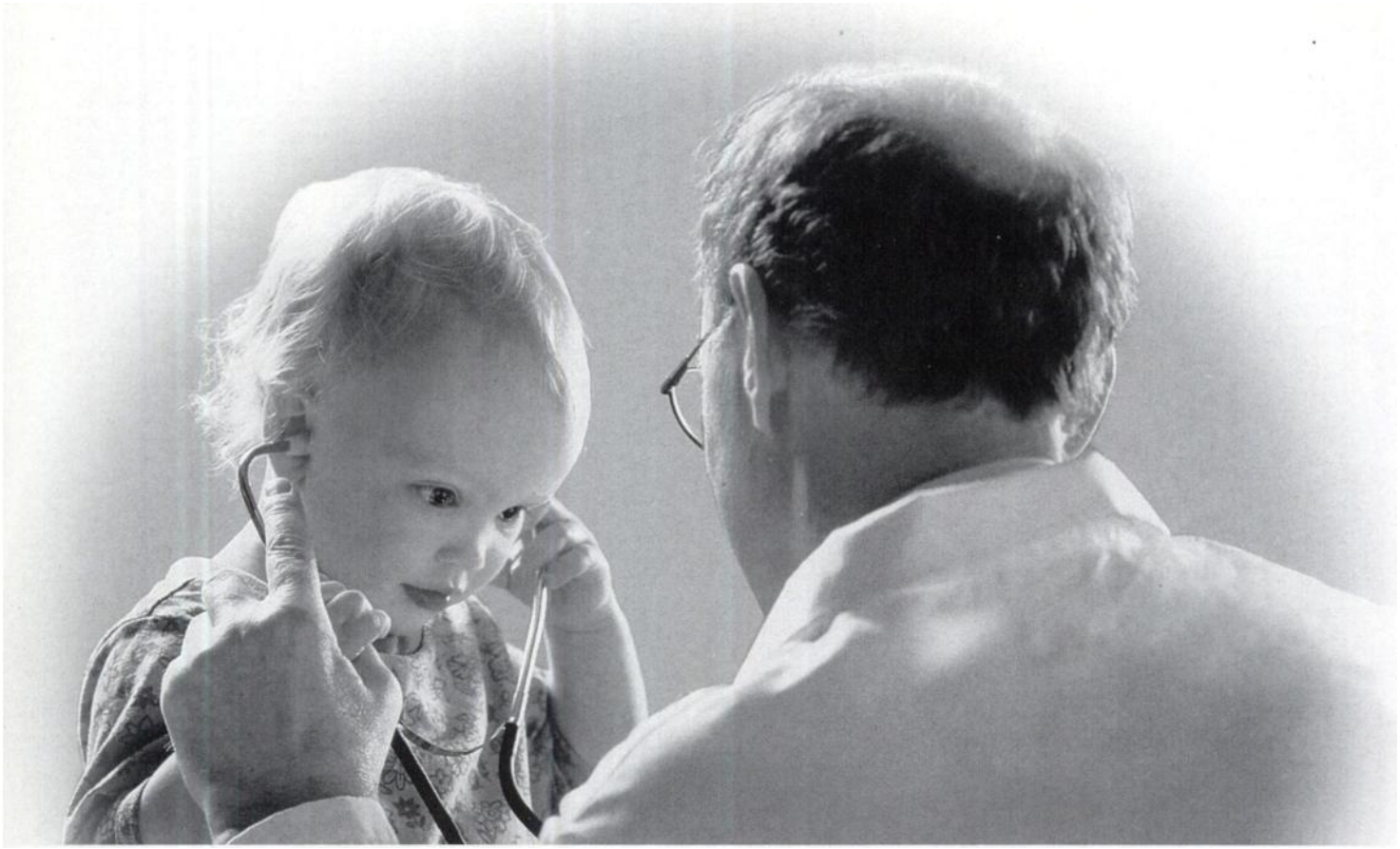

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of injury for infants who fall with their caretakers is fall from a height, then this could account for the relative severity of injuries in this subgroup of patients.

CONCLUSIONS

When young children fall down stairs, the injury is likely to be superficial and involve only one body region, most commonly the head and neck. Injuries to the extremities and trunk occur occasionally. Significant injuries including concussion, skull fracture, cerebral contusion, intracranial hemorrhage, and cervical spine fracture can occur, and were observed in 22% of the patients in this series. Small infants who fall with their caretaker while being carried on the stairs require an especially close evaluation for significant head injury.

Severe head injury is compatible with a stairway-related fall. However, injuries involving multiple body regions, or severe truncal or extremity injuries should prompt a search for an alternate mechanism, including intentional trauma.

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NOTICE REGARDING THE AMERICAN ACADEMY OF PEDIATRICS NUTRITION AWARD 1995

Nominations for the 1995 American Academy of Pediatrics (AAP) Nutrition Award are now being solicited.

Nominations must be in writing and should be limited to one per nominator. The letter should contain a description of the nominee's achievements and state clearly the basis for the recommendation (including references to the literature that describes his/her work). It is requested that the nominee's bibliography be submitted with the nominating letter, together with copies of available reprints. Letters supporting the nomination (no more than five) are to be solicited and screened by the nominator and forwarded to the attention of:

Edgar O. Ledbetter, MD, Director
Department of Maternal, Child
and Adolescent Health
American Academy of Pediatrics
141 Northwest Point Bouvelard
PO Box 927
Elk Grove Village, IL 60009-0927

Please note that the deadline for award nominations is December 14, 1994.

The Academy appreciates your effort to assist in the appropriate selection of a deserving person for this award.

Nutrition Award Stipulations

The Nutrition Award of the American Academy of Pediatrics was established in 1944. The award is made possible by a grant from the Infant Formula Council.

The Nutrition Award provides an honorarium of $3000 to be awarded under the following stipulations:

1. That the award will be made for outstanding achievement in research relating to the nutrition of infants and children.
2. That the award be made for research, which has been completed and publicly reported.
3. That the award be made for research, conducted by residents of the United States and Canada.
4. That the award be made to one individual or for one project.
5. That the award is open to all regardless of age. In fact, it is hoped that younger persons will be considered for the award. No current member of the Committee on Nutrition shall be eligible for the award.

The Nutrition Award also includes round trip tourist class airfare as well as two days lodging at $150 per diem for the recipient and another person of his/her choice to attend the Annual Meeting of the Academy.

The selection of the Award recipient is made by the Committee on Nutrition of the American Academy of Pediatrics, and is presented at the Annual Meeting of the Academy.

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THE AMERICAN ACADEMY OF PEDIATRICS 1995 AWARDS FOR EXCELLENCE IN PEDIATRIC RESEARCH

Each year two American Academy of Pediatrics Awards for Excellence in Pediatric Research will be made available by the American Academy of Pediatrics and are awarded under the following stipulations:

1. These awards are two in number. Each award provides an honorarium of $5000, a plaque, and travel expenses for the recipient and his/her spouse to and from the Annual Meeting of the American Academy of Pediatrics at which the Award is presented.
2. The Awards shall be given only at times when an individual's research work is considered outstanding and worthy of Academy recognition.
3. To be eligible for the 1995 Award, nominees must have been graduated from medical school within the twenty year period before July 1, 1995.
4. The Awards shall not be limited to members of the Academy, but to physicians in the Americas who have completed a pediatrics residency, or have passed the Pediatric Board Examination, or have fellowship in the Academy, or hold a full-time primary academic position in a Department of Pediatrics for at least two years before the nomination, and have demonstrated a continuing commitment to pediatric research.
5. The Awards shall be made for research work currently published, preferably coming to fruition or recognition during the past three years.
6. The Awards shall be presented at the Annual Meeting of the American Academy of Pediatrics by the President of the Academy or his/her designee.
7. Selection of the Awards recipient shall be the sole responsibility of the American Academy of Pediatrics Committee on Awards for Excellence in Pediatric Research and the Board of Directors.

Each year in September, deans of medical schools, heads of departments of pediatric education, and chiefs of hospital staff are informed of the stipulations for the American Academy of Pediatrics Awards for Excellence in Pediatric Research and are asked to submit nominations for these Awards. Individual nominators are encouraged to limit their nomination to one individual.

The Director of Department of Maternal, Child and Adolescent Health of the American Academy of Pediatrics will prepare and distribute such notices and will receive the nominations for the Awards Committee. All nominations must be received before January 31, 1995. The committee will select the Award winners before May 1, 1995 so that the announcement may appear in the program for the Annual Meeting.

A nomination letter, nomination form, curriculum vitae, reprints and five letters of support for each nominee should be mailed to: Edgar O. Ledbetter, MD, Director, Department of Maternal, Child and Adolescent Health, American Academy of Pediatrics, PO Box 927, Elk Grove Village, IL 60009-0927. To obtain a copy of written stipulations and a nomination form, please call (708) 228-5005 ext. 6785.

In Acute Otitis Media*

Delivers The Gram-negative Activity You Depend On...

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*In mild to moderate infections in children (aged 6 months through 12 years) caused by *Streptococcus pneumoniae, Haemophilus influenzae* (including β-lactamase–producing strains), or *Moraxella catarrhalis*.

Vantin® *Oral Suspension and Tablets*

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Highly stable in the presence of β-lactamase enzymes

Many organisms resistant to penicillins and some cephalosporins due to the presence of β-lactamases in acute otitis media may be susceptible to *Vantin*.

Generally well tolerated by children[1]

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 ß-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 ß-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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American Academy of Pediatrics

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Pediatric Update

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For discounted air and ground transportation, contact the AAP Travel Office at 800/433-9016.

The American Academy of Pediatrics gratefully acknowledges support for its continuing medical education courses in the form of educational grants from the following companies:
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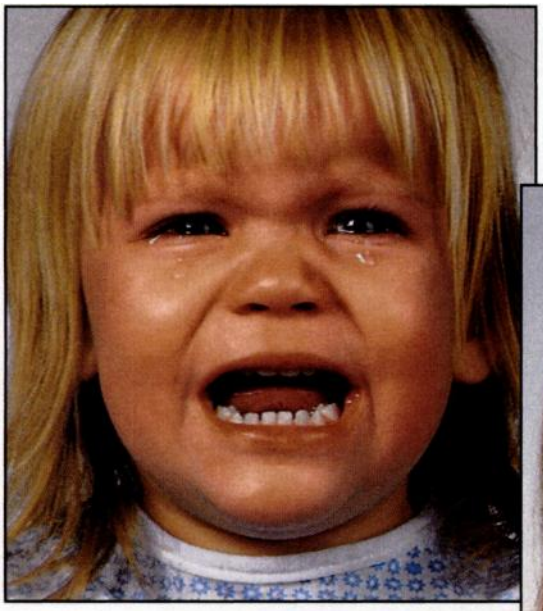
Painful needle procedures often require patience, understanding...



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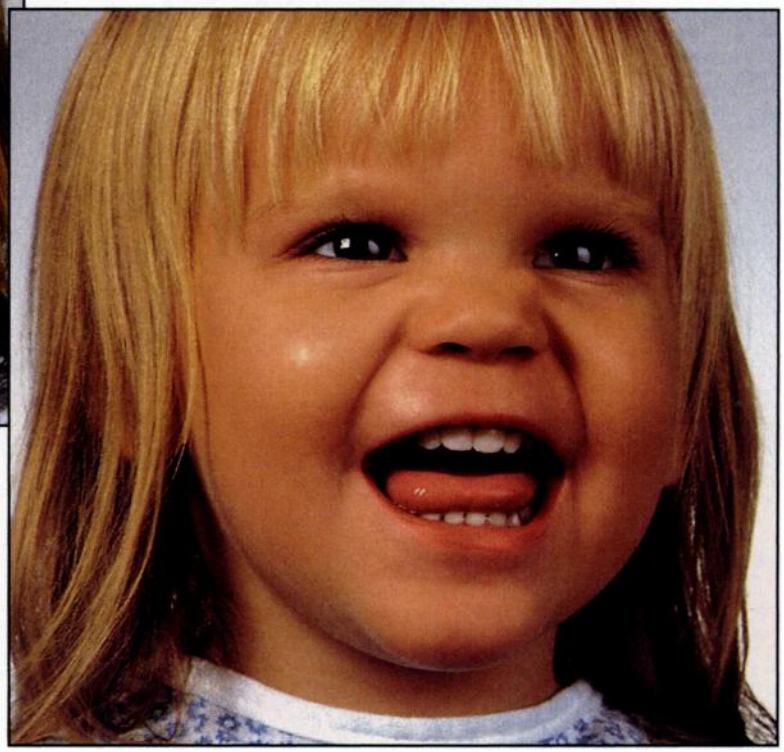

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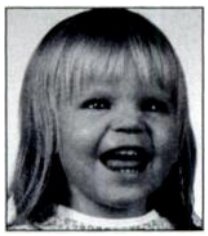

EMLA®
CREAM (lidocaine 2.5% and prilocaine 2.5%)

CONTRAINDICATIONS
EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) is contraindicated in patients with a known history of sensitivity to local anesthetics of the amide type or to any other component of the product.

WARNINGS
Application of EMLA Cream to larger areas or for longer times than those recommended could result in sufficient absorption of lidocaine and prilocaine resulting in serious adverse effects (see Individualization of Dose).

Studies in laboratory animals (guinea pigs) have shown that EMLA Cream has an ototoxic effect when instilled into the middle ear. In these same studies, animals exposed to EMLA Cream in the external auditory canal only, showed no abnormality. EMLA Cream should not be used in any clinical situation in which its penetration or migration beyond the tympanic membrane into the middle ear is possible.

Methemoglobinemia: EMLA Cream should not be used in those rare patients with congenital or idiopathic methemoglobinemia and in infants under the age of twelve months who are receiving treatment with methemoglobin-inducing agents.

Very young patients or patients with glucose-6-phosphate deficiencies are more susceptible to methemoglobinemia.

Patients taking drugs associated with drug-induced methemoglobinemia such as sulfonamides, acetaminophen, acetanilid, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, quinine, are also at greater risk for developing methemoglobinemia.

A methemoglobinemia value of 28% (of total hemoglobin) developed in a three-month old male infant (5.3 kg) who had 5 grams of EMLA Cream under an occlusive dressing applied to the back of the hands and in the cubital regions for 5 hours. The methemoglobinemia was successfully treated with IV methylene blue. The patient was concomitantly receiving trimethoprim (16 mg/day) and sulfamethoxazole (80 mg/day) for a urinary tract infection.

PRECAUTIONS
General: Repeated doses of EMLA Cream may increase blood levels of lidocaine and prilocaine. EMLA Cream should be used with caution in patients who may be more sensitive to the systemic effects of lidocaine and prilocaine including acutely ill, debilitated, or elderly patients.

EMLA Cream coming in contact with the eye should be avoided because animal studies have demonstrated severe eye irritation. Also the loss of protective reflexes can permit corneal irritation and potential abrasion. Absorption of EMLA Cream in conjunctival tissues has not been determined. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.

Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine and/or prilocaine, however, EMLA Cream should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain.

Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations of lidocaine and prilocaine.

Information for Patients: When EMLA Cream is used, the patient should be aware that the production of dermal analgesia may be accompanied by the block of all sensations in the treated skin. For this reason, the patient should avoid inadvertent trauma to the treated area by scratching, rubbing, or exposure to extreme hot or cold temperatures until complete sensation has returned.

Drug Interactions: EMLA Cream should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic.

Prilocaine may contribute to the formation of methemoglobin in patients treated with other drugs known to cause this condition (see Methemoglobinemia subsection of WARNINGS).

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Carcinogenesis: Metabolites of both lidocaine and prilocaine have been shown to be carcinogenic in laboratory animals. In the animal studies reported below, doses or blood levels are compared to the Single Dermal Administration (SDA) of 60 g of EMLA Cream to 400 cm^2 for 3 hours to a small person (50 kg). The typical application for one or two treatments for venipuncture sites (2.5 or 5 g) would be 1/24 or 1/12 of that dose in an adult or about the same mg/kg dose in an infant.

A two-year oral toxicity study of 2,6-xylidine, a metabolite of lidocaine, has shown that in both male and female rats 2,6-xylidine in daily doses of 900 mg/m^2 (60 times SDA) resulted in carcinomas and adenomas of the nasal cavity. With daily doses of 300 mg/m^2 (20 times SDA), the increase in incidence of nasal carcinomas and/or adenomas in each sex of the rat were not statistically greater than the control group. In the low dose (90 mg/m^2; 6 times SDA) and control groups, no nasal tumors were observed. A rhabdomyosarcoma, a rare tumor, was observed in the nasal cavity of both male and female rats at the high dose of 900 mg/m^2. In addition, the compound caused subcutaneous fibromas and/or fibrosarcomas in both male and female rats and neoplastic nodules of the liver in the female rats with a significantly positive trend test; pairwise comparisons using Fisher's Exact Test showed significance only at the high dose of 900 mg/m^2. The animal study was conducted at oral doses of 15, 50, and 150 mg/kg/day. The dosages have been converted to mg/m^2 for the SDA calculations above.

Chronic oral toxicity studies of *ortho*-toluidine, a metabolite of prilocaine, in mice (900 to14,400 mg/m^2; 60 to 960 times SDA) and rats (900 to 4,800 mg/m^2; 60 to 320 times SDA) have shown that *ortho*-toluidine is a carcinogen in both species. The tumors included hepatocarcinomas/adenomas in female mice, multiple occurrences of hemangiosarcomas/hemangiomas in both sexes of mice, sarcomas of multiple organs, transitional-cell carcinomas/papillomas of urinary bladder in both sexes of rats, subcutaneous fibromas/fibrosarcomas and mesotheliomas in male rats, and mammary gland fibroadenomas/adenomas in female rats. The lowest dose tested (900 mg/m^2; 60 times SDA) was carcinogenic in both species. Thus the no-effect dose must be less than 60 times SDA. The animal studies were conducted at 150 to 2,400 mg/kg in mice and at 150 to 800 mg/kg in rats. The dosages have been converted to mg/m^2 for the SDA calculations above.

Mutagenesis: The mutagenic potential of lidocaine HCl has been tested in the Ames Salmonella/mammalian microsome test and by analysis of structural chromosome aberrations in human lymphocytes *in vitro*, and by the mouse micronucleus test *in vivo*. There was no indication in these three tests of any mutagenic effects.

The mutagenicity of 2,6-xylidine, a metabolite of lidocaine, has been studied in different tests with mixed results. The compound was found to be weakly mutagenic in the Ames test only under metabolic activation conditions. In addition, 2,6-xylidine was observed to be mutagenic at the thymidine kinase locus, with or without activation, and induced chromosome aberrations and sister chromatid exchanges at concentrations at which the drug precipitated out of the solution (1.2 mg/mL). No evidence of genotoxicity was found in the *in vivo* assays measuring unscheduled DNA synthesis in rat hepatocytes, chromosome damage in polychromatic erythrocytes or preferential killing of DNA repair-deficient bacteria in liver, lung, kidney, testes and blood extracts from mice. However, covalent binding studies of DNA from liver and ethmoid turbinates in rats indicate that 2,6-xylidine may be genotoxic under certain conditions *in vivo*.

Ortho-toluidine, a metabolite of prilocaine, (0.5 μg/mL) showed positive results in *Escherichia coli* DNA repair and phage-induction assays. Urine concentrates from rats treated with *ortho*-toluidine (300 mg/kg orally; 300 times SDA) were mutagenic for *Salmonella typhimurium* with metabolic activation. Several other tests on *ortho*-toluidine, including reverse mutations in five different *Salmonella typhimurium* strains with or without metabolic activation and with single strand breaks in DNA of V79 Chinese hamster cells, were negative.

Impairment of Fertility: See Use in Pregnancy.

Use in Pregnancy: Teratogenic Effects: Pregnancy Category B.
Reproduction studies with lidocaine have been performed in rats and have revealed no evidence of harm to the fetus (30 mg/kg subcutaneously; 22 times SDA). Reproduction studies with prilocaine have been performed in rats and have revealed no evidence of impaired fertility or harm to the fetus (300 mg/kg intramuscularly; 188 times SDA). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, EMLA Cream should be used during pregnancy only if clearly needed.

Reproduction studies have been performed in rats receiving subcutaneous administration of an aqueous mixture containing lidocaine HCl and prilocaine HCl at 1:1 (w/w). At 40 mg/kg each, a dose equivalent to 29 times SDA lidocaine and 25 times SDA prilocaine, no teratogenic, embryotoxic or fetotoxic effects were observed.

Labor and Delivery: Neither lidocaine nor prilocaine are contraindicated in labor and delivery. Should EMLA Cream be used concomitantly with other products containing lidocaine and/or prilocaine, total doses contributed by all formulations must be considered.

Nursing Mothers: Lidocaine, and probably prilocaine, are excreted in human milk. Therefore, caution should be exercised when EMLA Cream is administered to a nursing mother since the milk:plasma ratio of lidocaine is 0.4 and is not determined for prilocaine.

Pediatric Use: Controlled studies of EMLA Cream in children under the age of seven years have shown less overall benefit than in older children or adults. These results illustrate the importance of emotional and psychological support of younger children undergoing medical or surgical procedures.

EMLA Cream should be used with care in patients with conditions or therapy associated with methemoglobinemia (see Methemoglobinemia subsection of WARNINGS).

When using EMLA Cream in young children, care must be taken to insure that application of the cream is limited to the intended site (see DOSAGE AND ADMINISTRATION). Accidental ingestion may lead to dose related toxicity.

In children weighing less than 20 kg, the area and duration should be limited (see TABLE 2 in Individualization of Dose).

ADVERSE REACTIONS
Localized Reactions: During or immediately after treatment with EMLA Cream, the skin at the site of treatment may develop erythema or edema or may be the locus of abnormal sensation. In clinical studies involving over 1,300 EMLA Cream-treated subjects, one or more such local reactions were noted in 56% of patients, and were generally mild and transient, resolving spontaneously within 1 or 2 hours. There were no serious reactions which were ascribed to EMLA Cream.

In patients treated with EMLA Cream, local effects observed in the trials included: paleness (pallor or blanching) 37%, redness (erythema) 30%, alterations in temperature sensations 7%, edema 6%, itching 2% and rash, less than 1%.

Allergic Reactions: Allergic and anaphylactoid reactions associated with lidocaine or prilocaine can occur. They are characterized by urticaria, angioedema, bronchospasm, and shock. If they occur they should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Systemic (Dose Related) Reactions: Systemic adverse reactions following appropriate use of EMLA Cream are unlikely due to the small dose absorbed (see Pharmacokinetics subsection of CLINICAL PHARMACOLOGY). Systemic adverse effects of lidocaine and/or prilocaine are similar in nature to those observed with other amide local anesthetic agents including CNS excitation and/or depression (light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest). Excitatory CNS reactions may be brief or not occur at all, in which case the first manifestation may be drowsiness merging into unconsciousness. Cardiovascular manifestations may include bradycardia, hypotension and cardiovascular collapse leading to arrest.

OVERDOSAGE
Peak blood levels following a 60 g application to 400 cm^2 for 3 hours are 0.05 to 0.16 μg/mL for lidocaine and 0.02 to 0.10 μg/mL for prilocaine. Toxic levels of lidocaine (>5 μg/mL) and/or prilocaine (>6 μg/mL) cause decreases in cardiac output, total peripheral resistance and mean arterial pressure. These changes may be attributable to direct depressant effects of these local anesthetic agents on the cardiovascular system. In the absence of massive topical overdose or oral ingestion, evaluation should include evaluation of other etiologies for the clinical effects or overdosage from other sources of lidocaine, prilocaine or other local anesthetics. Consult the package inserts for parenteral Xylocaine (lidocaine HCl) or Citanest (prilocaine HCl) for further information for the management of overdose.

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Manufactured for:

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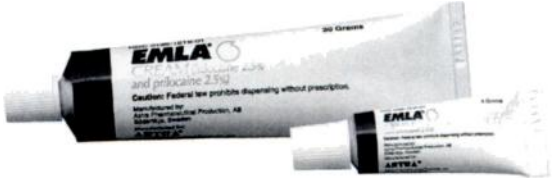

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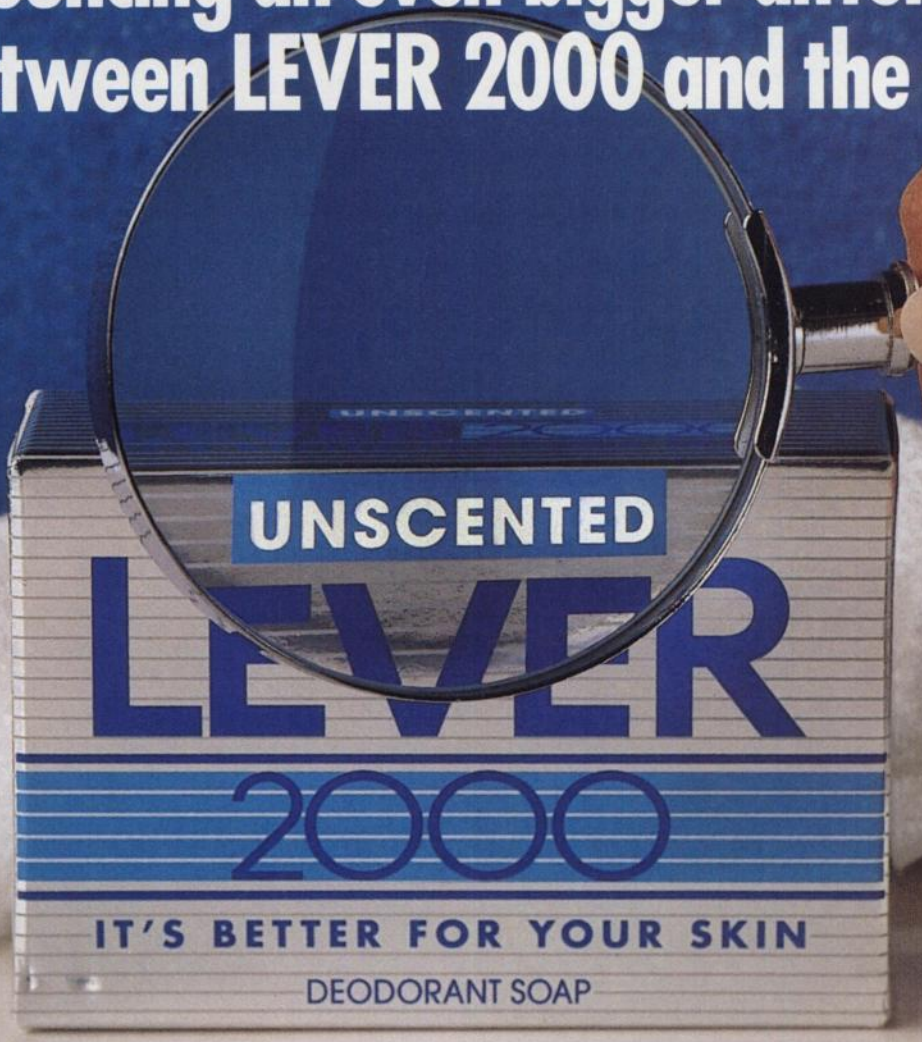

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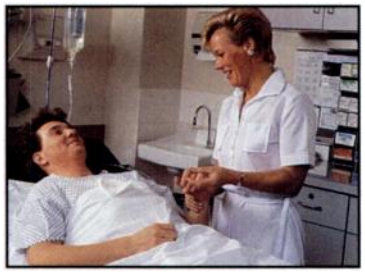

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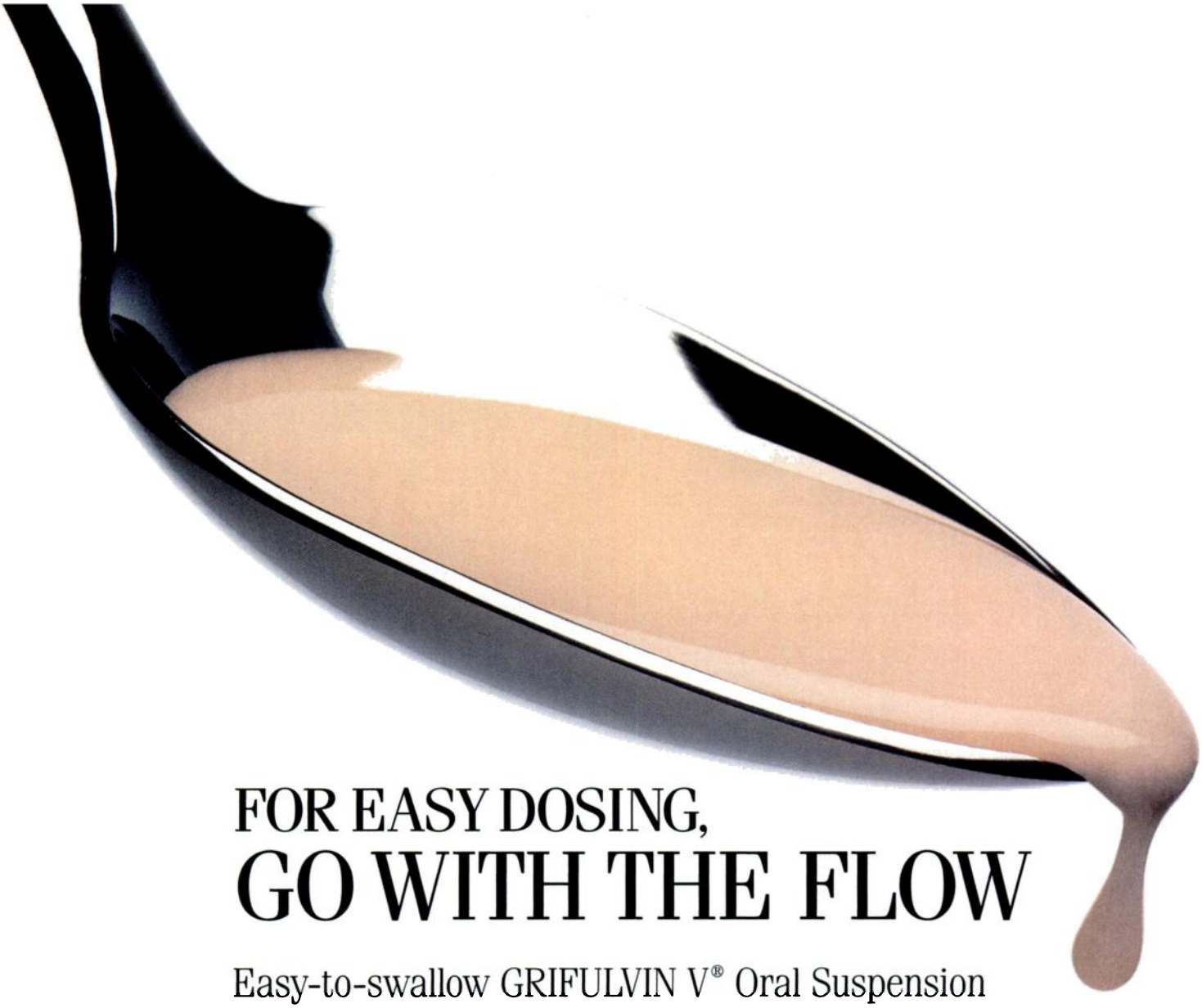

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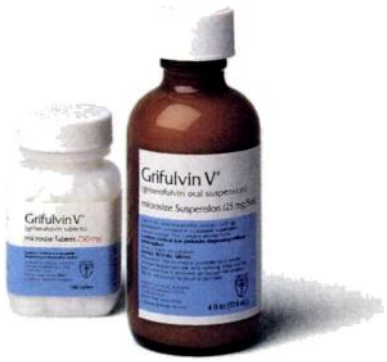
Easy-to-swallow GRIFULVIN V® Oral Suspension may help patients get the full course of therapy you prescribe.

GRIFULVIN V®

(griseofulvin oral suspension)
microsize Suspension 125mg/5mL
(griseofulvin tablets)
microsize Tablets 250mg or 500mg

First in griseofulvin suspension



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

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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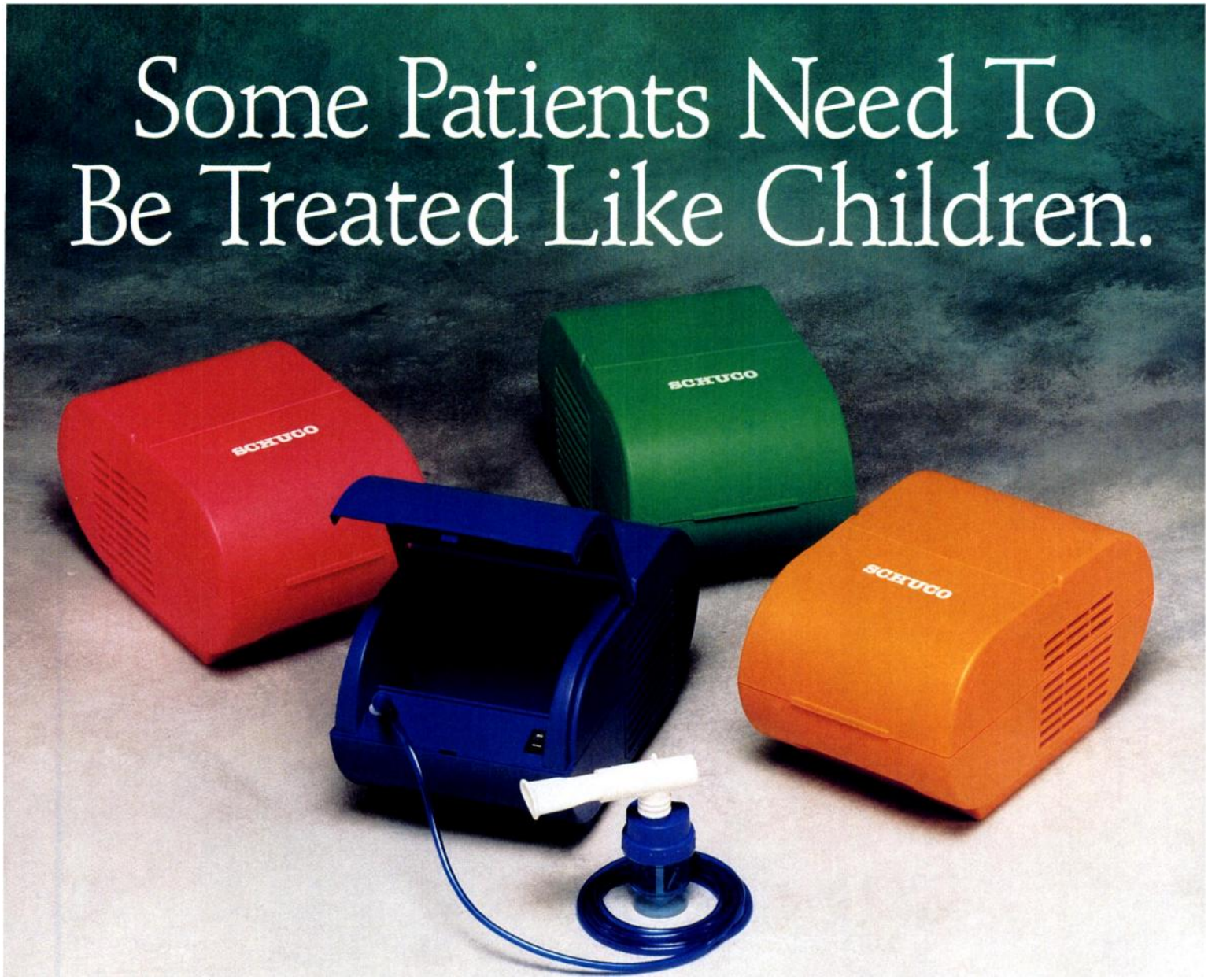
Some Patients Need To Be Treated Like Children.



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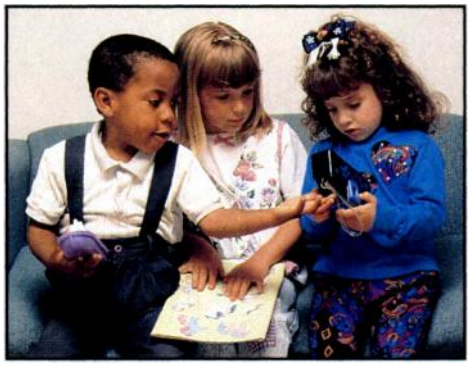

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Data on file.

For Patients With Asthma

Twice-Daily

Serevent®

(salmeterol xinafoate)

Inhalation Aerosol

Morning and Evening Inhalation for Active Days and Restful Nights

SEREVENT is indicated for maintenance treatment of asthma and prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma, who require regular treatment with inhaled, short-acting β_2-agonists.

Dosing should be two puffs (42 µg) of SEREVENT Inhalation Aerosol, twice daily, morning and evening, approximately 12 hours apart.

IMPORTANT: *SEREVENT should not be used to relieve acute asthma symptoms.*

The most common drug-related adverse events reported in clinical trials were headache (10%), tremor (3%), and cough (3%).[1]

Please consult Brief Summary of Prescribing Information on adjacent pages.

Serevent®
(salmeterol xinafoate)
Inhalation Aerosol

BRIEF SUMMARY

Bronchodilator Aerosol
For Oral Inhalation Only

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

CONTRAINDICATIONS: Serevent® Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to any of the components.

WARNINGS: 1. Not for Use to Treat Acute Symptoms; Watch for Increased Need for Short-Acting $Beta_2$-Agonists: Serevent® Inhalation Aerosol should not be used to relieve acute asthma symptoms. If the patient's short-acting, inhaled $beta_2$-agonist becomes less effective, e.g., the patient needs more inhalations than usual, medical evaluation must be obtained immediately and increasing use of Serevent Inhalation Aerosol in this situation is inappropriate. Serevent Inhalation Aerosol should not be used more frequently than twice daily (morning and evening) at the recommended dose. When prescribing Serevent Inhalation Aerosol, patients must be provided with a short-acting, inhaled $beta_2$-agonist (e.g., albuterol) for treatment of symptoms that occur despite regular twice-daily (morning and evening) use of Serevent.

Asthma may deteriorate acutely over a period of hours or chronically over several days. In this setting, increased use of inhaled, short-acting $beta_2$-agonists is a marker of destabilization of asthma and requires re-evaluation of the patient and consideration of alternative treatment regimens, especially inhaled or systemic corticosteroids. If the patient uses four or more inhalations per day of a short-acting $beta_2$-agonist on a regular basis, or if more than one canister (200 inhalations per canister) is used in an 8-week period, then the patient should see the physician for re-evaluation of treatment.

2. Use With Short-Acting $Beta_2$-Agonists: When patients begin treatment with Serevent Inhalation Aerosol, those who have been taking short-acting, inhaled $beta_2$-agonists on a regular daily basis should be advised to discontinue their regular daily-dosing regimen and should be clearly instructed to use short-acting, inhaled $beta_2$-agonists only for symptomatic relief if they develop asthma symptoms while taking Serevent Inhalation Aerosol (see PRECAUTIONS: Drug Interactions).

3. Serevent Inhalation Aerosol Is Not a Substitute for Oral or Inhaled Corticosteroids: Patients must be warned not to stop or reduce corticosteroid therapy without medical advice, even if they feel better when they are being treated with Serevent.

4. Do Not Exceed Recommended Dose: As with other beta-adrenergic aerosols, Serevent Inhalation Aerosol should not be used in excess. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QT_C interval, which has the potential for producing ventricular arrhythmias.

5. Paradoxical Bronchospasm: As with other inhaled asthma medications, paradoxical bronchospasm (which can be life-threatening) has been reported following the use of Serevent Inhalation Aerosol. If it occurs, treatment with Serevent Inhalation Aerosol should be discontinued immediately and alternative therapy instituted.

6. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of Serevent Inhalation Aerosol, as demonstrated by rare cases of urticaria, rash, and bronchospasm.

PRECAUTIONS:

General: 1. Use with Spacer or Other Devices: The safety and effectiveness of Serevent® Inhalation Aerosol when used with a spacer or other devices have not been adequately studied.

2. Cardiovascular and Other Effects: No effect on the cardiovascular system is usually seen after the administration of inhaled salmeterol in recommended doses, but the cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can occur after use of Serevent Inhalation Aerosol and may require discontinuation of the drug. Salmeterol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other beta-adrenergic agonist bronchodilators, clinically significant changes in systolic and/or diastolic blood pressure, pulse rate, and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with salmeterol.

3. Metabolic Effects: Doses of the related $beta_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. No effects on glucose have been seen with Serevent Inhalation Aerosol at recommended doses. Administration of $beta_2$-adrenoceptor agonists may cause a decrease in serum potassium, possibly through intracellular shunting, which has the potential to increase the likelihood of arrhythmias. The decrease is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were seen rarely during clinical studies with long-term administration of Serevent Inhalation Aerosol at recommended doses.

Information for Patients: See illustrated Patient's Instructions for Use. **SHAKE WELL BEFORE USING.** Patients should be given the following information:

1. Not for Use to Treat Acute Symptoms: Serevent Inhalation Aerosol is not meant to relieve acute asthmatic symptoms. Acute symptoms should be treated with an inhaled, short-acting bronchodilator that has been prescribed by a physician for symptom relief.

2. Do Not Exceed Recommended Dose: The bronchodilator action of salmeterol usually lasts for at least 12 hours. Therefore it should not be used more often than every 12 hours.

3. Use with Other Medications: While using Serevent Inhalation Aerosol, other inhaled medicines should be taken only as directed by the physician.

4. Use with Short-Acting, Inhaled Beta-Agonists: While using Serevent Inhalation Aerosol, medical attention should be sought immediately if the short-acting bronchodilator treatment becomes less effective for symptom relief, if more inhalations than usual are needed, or if more than the maximum number of inhalations of short-acting bronchodilator treatment prescribed for a 24-hour period are needed. If the patient uses four or more inhalations per day of a short-acting $beta_2$-agonist on a regular basis, or if more than one canister (200 inhalations per canister) is used in an 8-week period, then the patient should see the physician for re-evaluation of treatment.

Patients should be cautioned regarding potential adverse cardiovascular effects, such as palpitations or chest pain, related to the use of additional $beta_2$-agonist.

5. Use of Systemic or Inhaled Steroids: Serevent Inhalation Aerosol does not replace oral or inhaled corticosteroids; the dosage of these medicines should not be changed and they should not be stopped without consulting the physician, even if the patient feels better.

6. Use for Exercise-Induced Bronchospasm: When using Serevent Inhalation Aerosol to prevent exercise-induced bronchospasm, the dose should be administered at least 30 to 60 minutes before exercise.

Drug Interactions: ***Short-Acting Beta-Agonists:*** In the two 3-month, repetitive-dose clinical trials (n=184), the mean daily need for additional $beta_2$-agonist use was 1 to 1½ inhalations per day, but some patients used more. Eight percent of patients used at least eight inhalations per day at least on one occasion. Six percent used 9 to 12 inhalations at least once. There were 15 patients (8%) who averaged over four inhalations per day. Four of these used an average of 8 to 11 inhalations per day. In these 15 patients there was no observed increase in frequency of cardiovascular adverse events. The safety of concomitant use of more than eight inhalations per day of short-acting $beta_2$-agonists with Serevent® (salmeterol xinafoate) Inhalation Aerosol has not been established. In 15 patients who experienced worsening of asthma while receiving Serevent Inhalation Aerosol, nebulized albuterol (one dose in most) led to improvement in FEV_1 and no increase in occurrence of cardiovascular adverse events.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: Salmeterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants because the action of salmeterol on the vascular system may be potentiated by these agents.

Corticosteroids and Cromoglycate: In clinical trials, inhaled corticosteroids and/or inhaled cromolyn sodium did not alter the safety profile of Serevent Inhalation Aerosol when administered concurrently.

Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving Serevent Inhalation Aerosol has not been completely evaluated. In one clinical trial, 87 patients receiving Serevent Inhalation Aerosol 42 mcg twice daily concurrently with a theophylline product had adverse event rates similar to those in 71 patients receiving Serevent Inhalation Aerosol without theophylline. Resting heart rates were slightly higher in the patients on theophylline but were little affected by Serevent Inhalation Aerosol therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In an 18-month oral carcinogenicity study in CD-mice, salmeterol xinafoate caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, and leiomyomas of the uterus and a dose-related increase in the incidence of cysts in the ovaries. A higher incidence of leiomyosarcomas was not statistically significant; tumor findings were observed at oral doses of 1.4 and 10 mg/kg, which gave 9 and 63 times, respectively, the human exposure based on rodent:human AUC comparisons.

Salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts in Sprague Dawley rats in a 24-month inhalation/oral carcinogenicity study. Tumors were observed in rats receiving doses of 0.68 and 2.58 mg/kg per day (about 55 and 215 times the recommended clinical dose [mg/m^2]). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

No significant effects occurred in mice at 0.2 mg/kg (1.3 times the recommended clinical dose based on comparisons of the AUCs) and in rats at 0.21 mg/kg (15 times the recommended clinical dose on a mg/m^2 basis).

Salmeterol xinafoate produced no detectable or reproducible increases in microbial and mammalian gene mutation *in vitro*. No blastogenic activity occurred *in vitro* in human lymphocytes or *in vivo* in a rat micronucleus test. No effects on fertility were identified in male and female rats treated orally with salmeterol xinafoate at doses up to 2 mg/kg orally (about 160 times the recommended clinical dose on a mg/m^2 basis).

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** No significant effects of maternal exposure to oral salmeterol xinafoate occurred in the rat at doses up to the equivalent of about 160 times the recommended clinical dose on a mg/m^2 basis. Dutch rabbit fetuses exposed to salmeterol xinafoate *in utero* exhibited effects characteristically resulting from beta-adrenoceptor stimulation; these included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at 0.6 mg/kg given orally (12 times the recommended clinical dose based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at 10 mg/kg given orally (approximately 1,600 times the recommended clinical dose on a mg/m^2 basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to use in humans. There are no adequate and well-controlled studies with Serevent Inhalation Aerosol in pregnant women. Serevent Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Labor and Delivery: There are no well-controlled human studies that have investigated effects of salmeterol on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of Serevent Inhalation Aerosol during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Nursing Mothers: Plasma levels of salmeterol after inhaled therapeutic doses are very low (85 to 200 pg/mL) in humans. In lactating rats dosed with radiolabeled salmeterol, levels of radioactivity were similar in plasma and milk. In rats, concentrations of salmeterol in plasma and milk were similar. The xinafoate moiety is also transferred to milk in rats at concentrations of about half the corresponding level in plasma. However, since there is no experience with use of Serevent Inhalation Aerosol by nursing mothers, 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. Caution should be exercised when salmeterol xinafoate is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of Serevent Inhalation Aerosol in children younger than 12 years of age have not been established.

Geriatric Use: Of the total number of patients who received Serevent Inhalation Aerosol in all clinical studies, 241 were 65 years and older. Geriatric patients (65 years and older) with reversible obstructive airway disease were evaluated in four well-controlled studies of 3 weeks' to 3 months' duration. Two placebo-controlled, crossover studies evaluated twice-daily dosing with salmeterol for 21 to 28 days in 45 patients. An additional 75 geriatric patients were treated with salmeterol for 3 months in two large parallel-group, multicenter studies. These 120 patients experienced increases in AM and PM peak expiratory flow rate and decreases in diurnal variation in peak expiratory flow rate similar to responses seen in the total populations of the two latter studies. The adverse event type and frequency in geriatric patients were not different from those of the total populations studied.

No apparent differences in the efficacy and safety of Serevent Inhalation Aerosol were observed when geriatric patients were compared with younger patients in clinical trials. As with other $beta_2$-agonists, however, special caution should be observed when using Serevent Inhalation Aerosol in elderly patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug. Based on available data, no adjustment of salmeterol dosage in geriatric patients is warranted.

ADVERSE REACTIONS: Adverse reactions to salmeterol are similar in nature to reactions to other selective $beta_2$-adrenoceptor agonists, i.e., tachycardia; palpitations; immediate hypersensitivity reactions, including urticaria, rash, bronchospasm (see WARNINGS); headache; tremor; nervousness; and paradoxical bronchospasm (see WARNINGS).

Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of Serevent® Inhalation Aerosol in patients 12 years of age and older with asthma. The following table reports the incidence of adverse events in these two studies.

Serevent® (salmeterol xinafoate) Inhalation Aerosol

Adverse Experience Incidence in Two Large 12-Week Clinical Trials*

Adverse Event Type	Percent of Patients		
	Placebo n=187	Serevent 42 mcg b.i.d. n=184	Albuterol 180 mcg q.i.d. n=185
Ear, nose, and throat			
Upper respiratory tract infection	13	14	16*
Nasopharyngitis	12	14	11
Disease of nasal cavity/sinus	4	6	1
Sinus headache	2	4	<1
Gastrointestinal			
Stomachache	0	4	0
Neurological			
Headache	23	28	27
Tremor	2	4	3
Respiratory			
Cough	6	7	3
Lower respiratory infection	2	4	2

* The only adverse experience classified as serious was one case of upper respiratory tract infection in a patient treated with albuterol.

The table above includes all events (whether considered drug related or nondrug related by the investigator) that occurred at a rate of over 3% in the Serevent® (salmeterol xinafoate) Inhalation Aerosol treatment group and were more common in the Serevent Inhalation Aerosol group than in the placebo group.

Pharyngitis, allergic rhinitis, dizziness/giddiness, and influenza occurred at 3% or more but were equally common on placebo. Other events occurring in the Serevent Inhalation Aerosol treatment group at a frequency of 1% to 3% were as follows:

Cardiovascular: Tachycardia, palpitations.
Ear, Nose, and Throat: Rhinitis, laryngitis.
Gastrointestinal: Nausea, viral gastroenteritis, nausea and vomiting, diarrhea, abdominal pain.
Hypersensitivity: Urticaria.
Mouth and Teeth: Dental pain.
Musculoskeletal: Pain in joint, back pain, muscle cramp/contraction, myalgia/myositis, muscular soreness.
Neurological: Nervousness, malaise/fatigue.
Respiratory: Tracheitis/bronchitis.
Skin: Rash/skin eruption.
Urogenital: Dysmenorrhea.

In small dose-response studies, tremor, nervousness, and palpitations appeared to be dose related.

OVERDOSAGE: Overdosage with salmeterol may be expected to result in exaggeration of the pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead to clinically significant prolongation of the QT_C interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

In these cases, therapy with Serevent® Inhalation Aerosol and all beta-adrenergic–stimulant drugs should be stopped, supportive therapy provided, and judicious use of a beta-adrenergic blocking agent should be considered, bearing in mind the possibility that such agents can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

As with all sympathomimetic pressurized aerosol medications, cardiac arrest and even death may be associated with abuse of Serevent Inhalation Aerosol.

Rats and dogs survived the maximum practicable inhalation doses of salmeterol of 2.9 and 0.7 mg/kg, respectively. The maximum nonlethal oral doses in mice and rats were approximately 150 mg/kg and >1,000 mg/kg, respectively.

Dialysis is not appropriate treatment for overdosage of Serevent Inhalation Aerosol.

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

February 1994
RL-096

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

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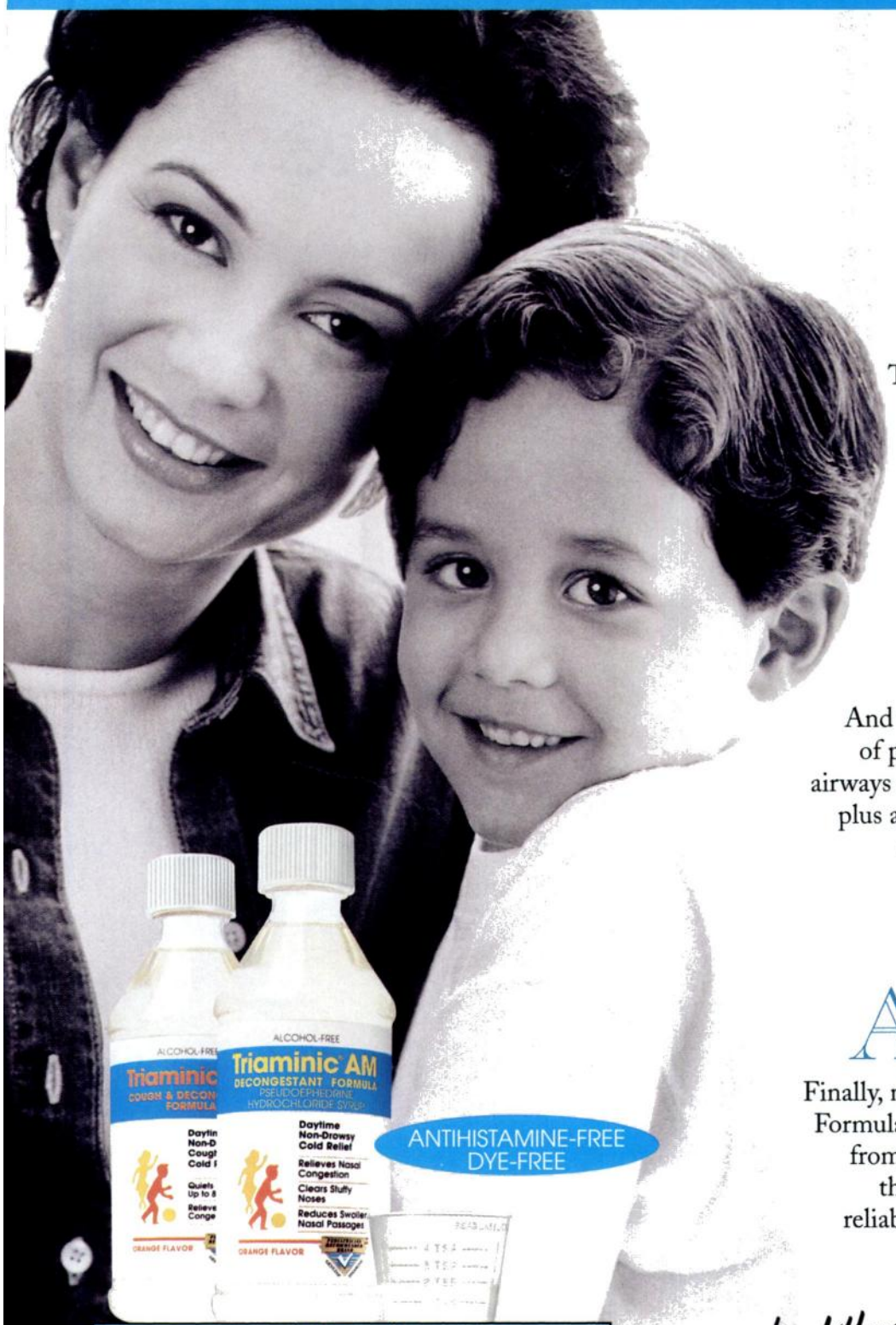

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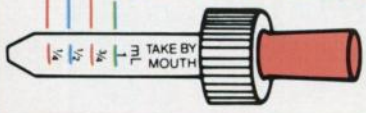
1 mL . . . 10 months or more (21 lbs or more)



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

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AMERICAN ACADEMY OF PEDIATRICS 1995 MEDICAL EDUCATION AWARDS

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The American Academy of Pediatrics (AAP) is pleased to announce that nominations are now being accepted for the 1995 Medical Education Awards. Nominations must be submitted by January 27, 1995. The awards will be presented at the Academy's Annual Meeting in San Francisco, California, October 14–18, 1995.

The AAP Medical Education Awards, sponsored by Ross Products Division of Abbott Laboratories, annually recognize excellence in pediatric education, and are offered in three categories: the Professional Education Award for innovative and effective programs in the education of medical students, residents, nurses, and pediatricians; the Lay Education Award for programs that educate parents, teachers, children, and others in aspects of child health; and the Lifetime Achievement Award for lifetime achievements in pediatric medical education.

The 1994 Award Recipients are: Neil A. Izenberg, MD, Director, Nemours Center for Biomedical Communications, Alfred I. duPont Institute—winner of the Lay Education Award for his production of two videos: "It Wasn't Supposed to Happen" and "Baby Talk"; Avroy Fanaroff, MD, Professor of Pediatrics, Rainbow Babies & Children's Hospital (Cleveland)—winner of the Professional Education Award for his development of educational materials in neonatal/perinatal medicine; Waldo E. Nelson, MD, Emeritus Professor of Pediatrics, Temple University—one of the winners of the Lifetime Achievement Award for his outstanding teaching qualities and as editor of *The Textbook of Pediatrics*; and Obstetrics and Gynecology, and Physiology, Hospital of the University of Pennsylvania—also a winner of the Lifetime Achievement Award for her outstanding research and clinical practice skills.

CRITERIA FOR AWARDS: Selection of awards will be based on originality, educational quality, program/project effectiveness, and the potential for utilization in other programs or practices. Nominees are restricted to pediatricians who are members of the Academy. Nominees for professional or lay medical education awards should be actively involved in the program for which they are being considered, and the program should have come to fruition within the last two to three years. Previous nominees may be resubmitted for consideration.

For additional information, or to obtain nomination forms, contact: Linda Wetzel, Program Coordinator, AAP Department of Education, 141 Northwest Point Blvd, PO Box 927, Elk Grove Village, IL 60009-0927, 800/433-9016, ext 6793.

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

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REFERENCES:

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Tablets–250 mg and 500 mg
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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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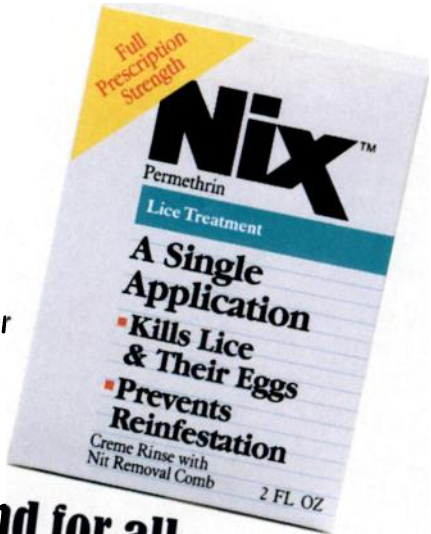

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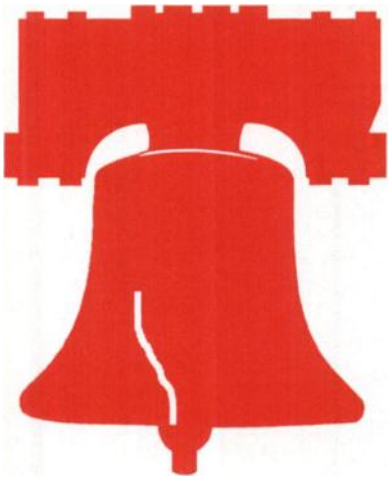

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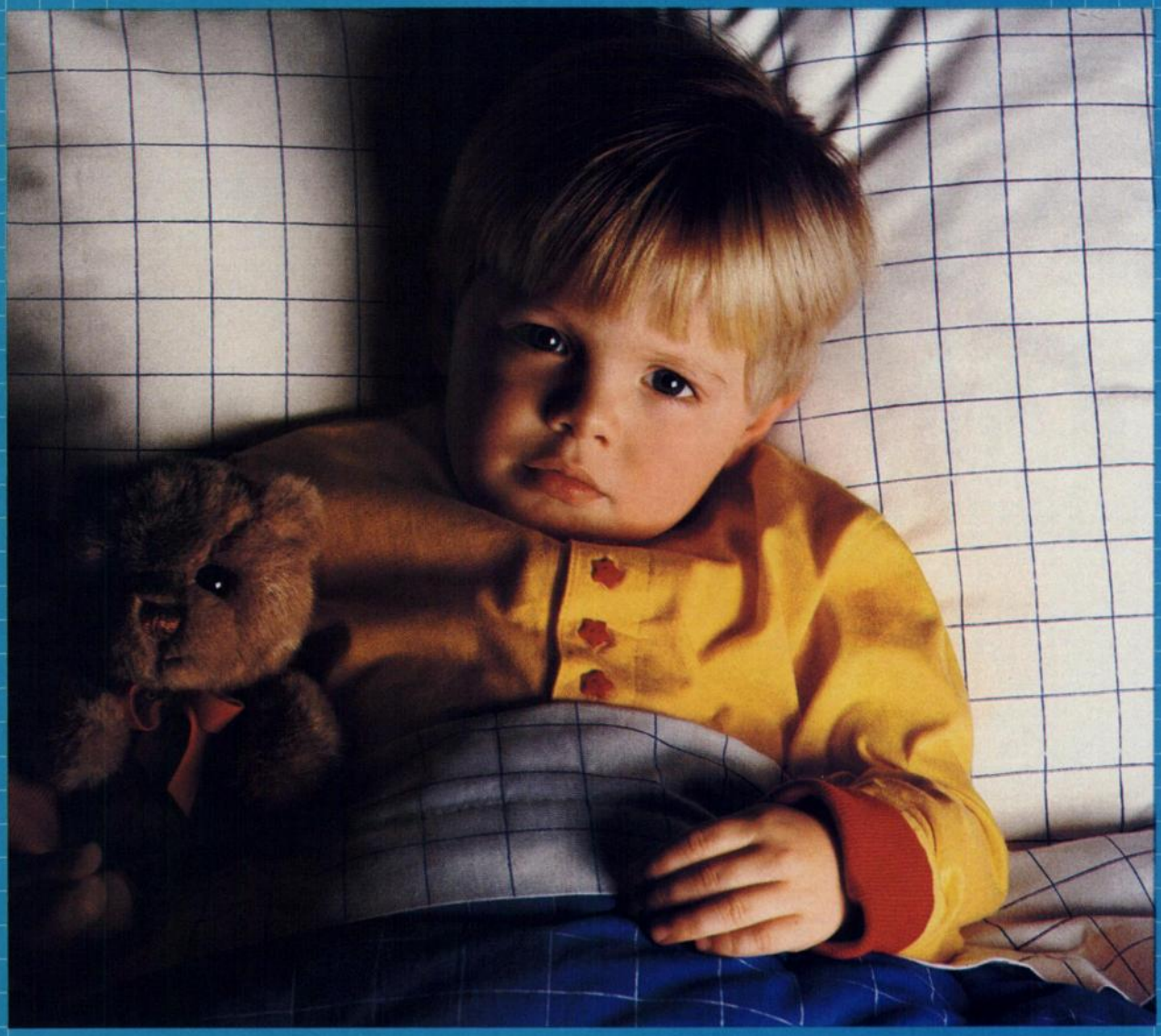

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CONTRAINDICATIONS: Hypersensitivity to ibuprofen. Do not give to patients with all or part of the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risks of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In clinical trials occurrence of serious GI toxicity is about 1% after 3-6 months of therapy; 2%-4% after one year.

Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, no factors have been associated with increased risk. Elderly or debilitated patients tolerate ulceration or bleeding less well and have more fatal GI events.

PRECAUTIONS: General: Serious GI tract ulceration and bleeding can occur without warning symptoms; follow chronically treated patients for signs/symptoms of ulceration and bleeding.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints discontinue the drug and have an ophthalmologic examination performed.

Fluid retention and edema have been reported, therefore, use with caution in patients with history of cardiac decompensation or hypertension.

Ibuprofen can inhibit platelet aggregation, although less than aspirin does, and prolong bleeding time (but within the normal range). Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have their therapy tapered slowly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Liver Effects: Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Evaluate patients with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, for evidence of more severe hepatic reactions while on ibuprofen therapy. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, discontinue ibuprofen.

Hemoglobin Levels: Small decreases (usually not exceeding one gram) in hemoglobin and hematocrit with an apparent dose response relationship have been observed following chronic administration. If there are no signs of bleeding it is probably not clinically important.

In two ibuprofen postmarketing studies a decrease in hemoglobin of 1 gm or more was observed.

Aseptic Meningitis: While rare, aseptic meningitis with fever and coma has occurred in patients on ibuprofen. Although more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in adults without an underlying chronic disease. If signs or symptoms of meningitis develop in a patient on ibuprofen, consider the possibility of its being related to ibuprofen.

Renal Effects: Like other NSAIDs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome have been reported. A second form of renal toxicity is seen in patients with prerenal conditions leading to reduction in renal blood flow or blood volume. In these patients, NSAIDs may cause a dose-dependent reduction in prostaglandin formation and precipitate overt renal failure; patients with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly are at greatest risk. Monitor renal function in patients at high risk who take ibuprofen chronically if they have signs or symptoms of azotemia. Discontinuation of NSAIDs is typically followed by recovery. Since ibuprofen is eliminated primarily by the kidneys, closely monitor patients with significant renal impairment and anticipate a dosage reduction to avoid drug accumulation.

Information for Patients: Physicians may wish to discuss potential risks (see **WARNINGS, PRECAUTIONS, ADVERSE REACTIONS**) and likely benefits with patients.

Drug Interactions: *Coumarin-type Anticoagulants:* Short-term studies did not show a significant effect of ibuprofen on a variety of clotting factors when given with coumarin-type anticoagulants. However, bleeding has been reported when ibuprofen or other NSAIDs were administered to patients on these medications; use caution when administering ibuprofen to such patients.

Aspirin: In animal studies, concomitant aspirin/NSAID therapy yielded a net decrease in anti-inflammatory activity with lowered NSAID blood levels. Single dose bioavailability studies in normal volunteers failed to show an effect of aspirin on ibuprofen levels.

Methotrexate: In vitro studies indicate that ibuprofen could enhance the toxicity of methotrexate. Use caution if ibuprofen is administered concomitantly.

H_2 Antagonists: In human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant ibuprofen therapy, observe the patient closely for signs of renal failure and to assure diuretic efficacy.

Lithium: Ibuprofen elevated plasma lithium levels (15%) and reduced renal lithium clearance (19%) in normal volunteers. Observe patients carefully for lithium toxicity. Read lithium package insert before its use.

Diabetes: Each 5 mL of CHILDREN'S ADVIL® SUSPENSION contains 2.5 g of sucrose; consider this when treating patients with impaired glucose tolerance. It also contains sorbitol, 350 mg/5 mL. Although in clinical trials CHILDREN'S ADVIL® SUSPENSION was not associated with more diarrhea than controls, if diarrhea develops, the physician may wish to review other sources of sorbitol in the patient's diet.

Pregnancy/Nursing Mothers: Administration of ibuprofen is not recommended during pregnancy or for use by nursing mothers.

Infants: Safety and efficacy in children < 6 months old have not been established.

ADVERSE REACTIONS: The most frequent type of adverse reaction is gastrointestinal (GI). In adult clinical trials involving chronic ibuprofen administration, 4%-16% of patients reported one or more GI complaints.

Incidence Greater Than 1% (but < 3%) During Controlled Clinical Trials in Adults, Probable Causal Relationship: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence); dizziness,* headache, nervousness; rash* (including maculopapular type), pruritus; tinnitus; decreased appetite; edema, fluid retention (generally responds promptly to drug discontinuation, see **PRECAUTIONS**).

Precise Incidence Unknown (but < 1%), Probable Causal Relationship (see **PRECAUTIONS**): Gastric or duodenal ulcer with bleeding and/or perforation, GI hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests, pancreatitis; depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision); neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coomb's positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; syndrome of abdominal pain, fever, chills, nausea and vomiting, anaphylaxis, bronchospasm (see **CONTRAINDICATIONS**); acute renal failure, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; dry eyes and mouth, gingival ulcers, rhinitis.

Precise Incidence Unkown (but < 1%), Causal Relationship Unknown: Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; toxic epidermal necrolysis, photoallergic skin reactions; conjunctivitis, diplopia, optic neuritis, cataracts; bleeding episodes (eg., epistaxis, menorrhagia); gynecomastia, hypoglycemic reactions, acidosis; arrhythmias (sinus tachycardia, sinus bradycardia); serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis, angioedema; renal papillary necrosis.

**Reactions occurring in 3%-9% of adult patients treated with ibuprofen. Reactions occurring in < 3% are unmarked.*

OVERDOSAGE: Induce emesis or perform gastric lavage. Oral activated charcoal may be useful in addition to supportive therapy. Because the drug is acidic and excreted in the urine, administration of alkali and induction of diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Do not exceed 3200 mg total daily dose. Fever: Children 6 months to 12 years of age—5 mg/kg if baseline temperature is 102.5°F or below, or 10 mg/kg if baseline temperature is greater than 102.5°F, every 6-8 hours; Adults—400 mg every 4-6 hours. Mild to moderate pain in adults: 400 mg every 4 to 6 hours prn. Juvenile Arthritis: 30-40 mg/kg/day in 3 or 4 divided doses. RA and OA: 1200-3200 mg daily in 3 or 4 divided doses (adults). Dysmenorrhea: 400 mg every 4 hours prn.

CI 4123-1 5/7/91

References:

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2. Kauffman RE, Sawyer LA, Scheinbaum ML. Antipyretic efficacy of ibuprofen vs acetaminophen. *Am J Dis Child.* 1992;146:622-625.
3. Kelley MT, Walson PD, Edge JH, et al. Pharmacokinetics and pharmacodynamics of ibuprofen isomers and acetaminophen in febrile children. *Clin Pharmacol Ther.* 1992;52:181-189.
4. Prescribing information, Children's Tylenol® (acetaminophen) Elixir.
5. Prescribing information, Children's Advil® (ibuprofen) Suspension 100 mg/5 mL.

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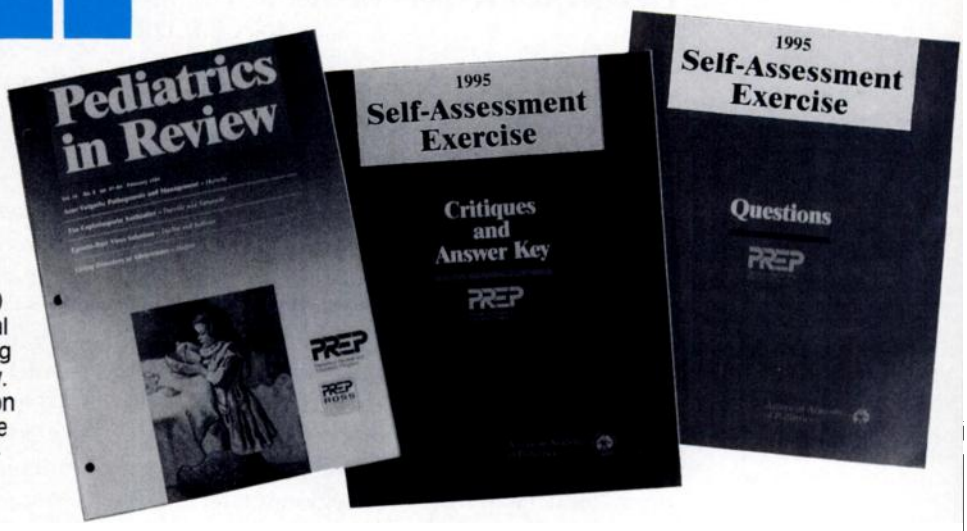

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