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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.
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*Ibuprofen is not indicated for treatment of pain in children under 12 years of age.
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Clinical studies prove 15 mg/kg acetaminophen as effective as 10 mg/kg ibuprofen.*[1,2] And Children's TYLENOL® has a superior safety profile to ibuprofen.[3-5]

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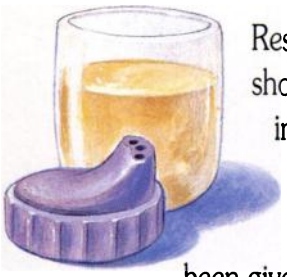

Research just published in *Pediatrics** shows white grape juice is easier for infants and toddlers to absorb than apple juice.

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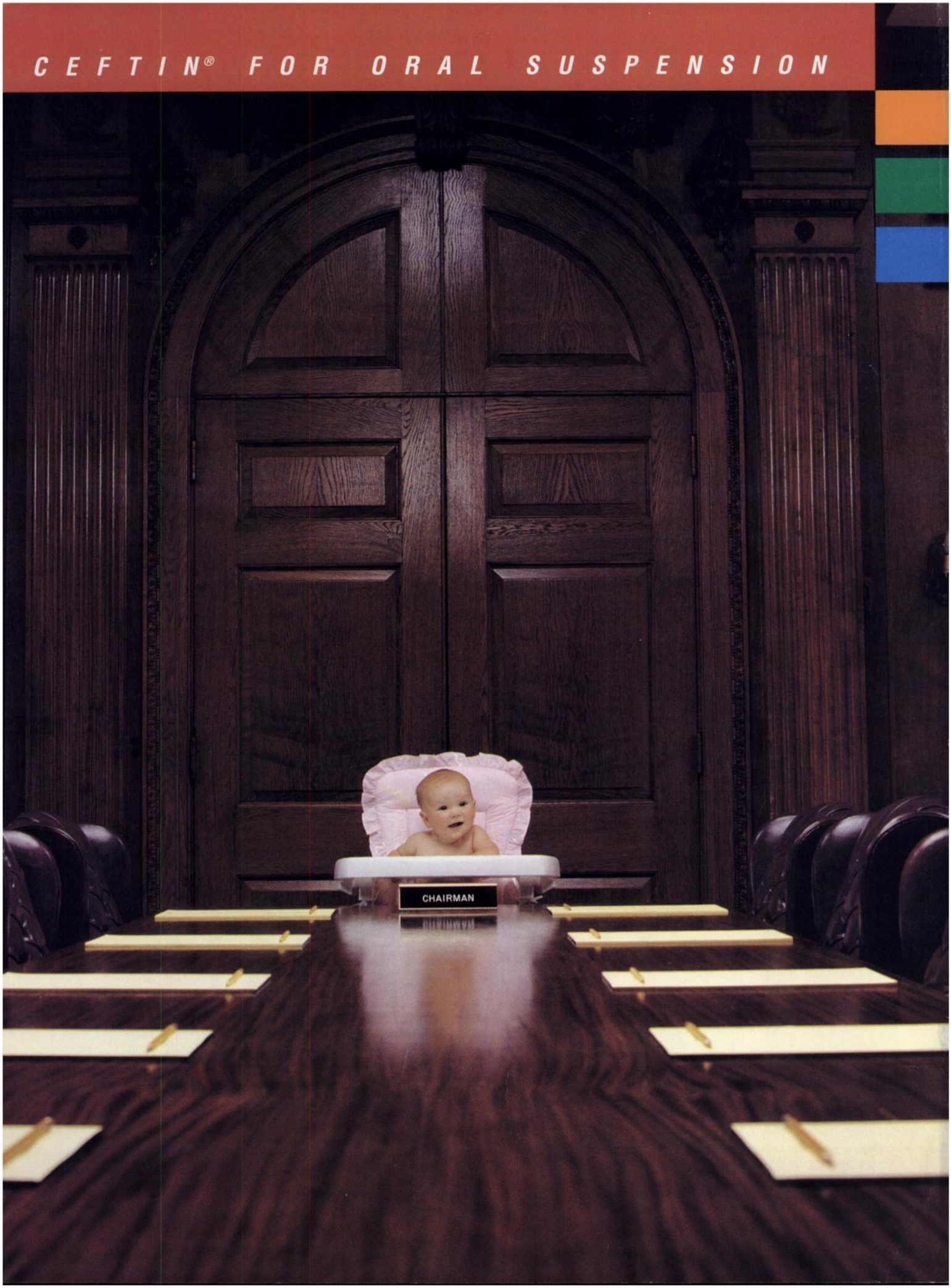
CEFTIN® FOR ORAL SUSPENSION



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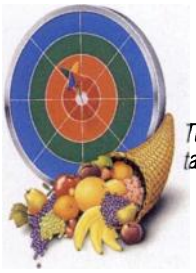

Tutti-frutti taste

The power of CEFTIN, now in a tutti-frutti–flavored suspension. So it's tough on ear infections but easy on kids.
CEFTIN for Oral Suspension is indicated for acute otitis media caused by *Haemophilus influenzae* and *Moraxella catarrhalis* (both including ß-lactamase–producing strains), *Streptococcus pneumoniae,* and *Streptococcus pyogenes.*

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.

In US controlled clinical trials with CEFTIN for Oral Suspension, the most commonly reported adverse event was diarrhea/loose stools at 8.6%. Other adverse events included diaper rash (3.4%) and nausea/vomiting (2.6%). 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. CEFTIN for Oral Suspension is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

And a convenient BID dosing schedule

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

* CEFTIN for Oral Suspension is indicated for the treatment of children 3 months to 12 years of age. CEFTIN for Oral Suspension and CEFTIN® (cefuroxime axetil) Tablets are not bioequivalent and are not substitutable on a mg/mg basis.

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

*The power of CEFTIN– now in suspension**

† 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/m²) 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/m²) 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

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July 1994
RL-128

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MANUSCRIPT PREPARATION: INSTRUCTIONS FOR AUTHORS

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- 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.
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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.

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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.

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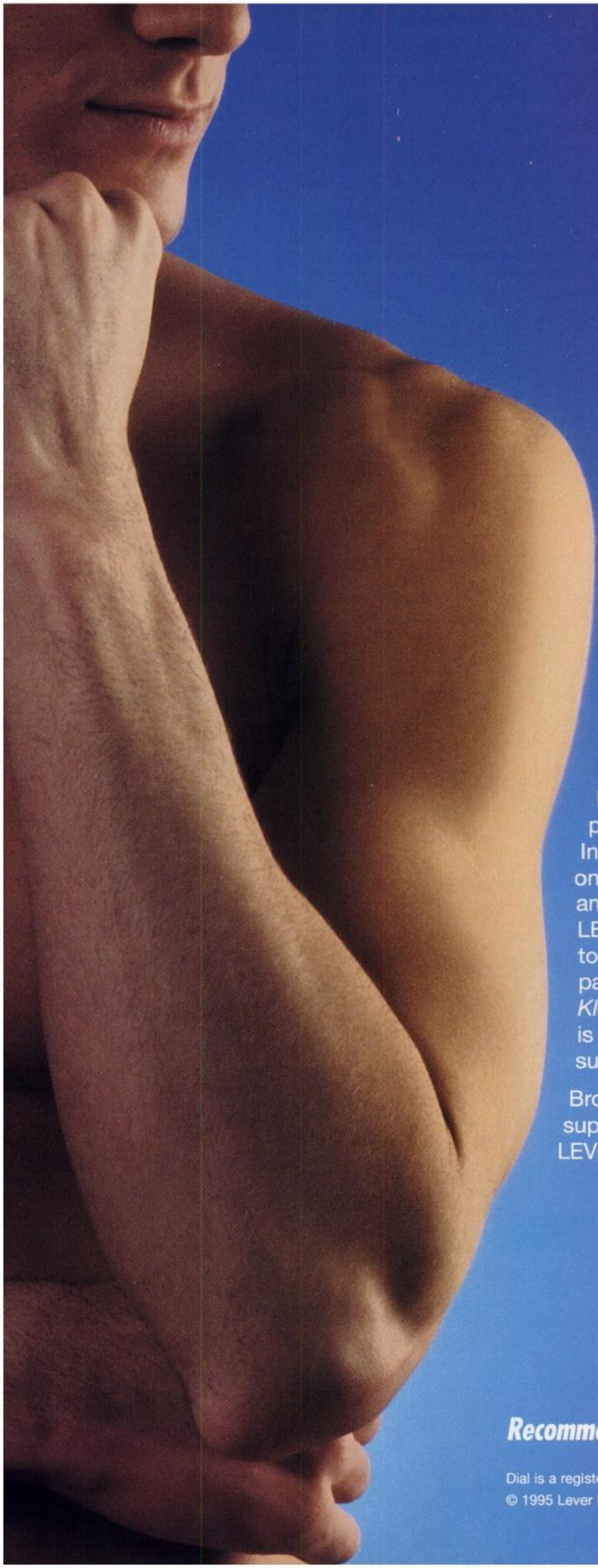

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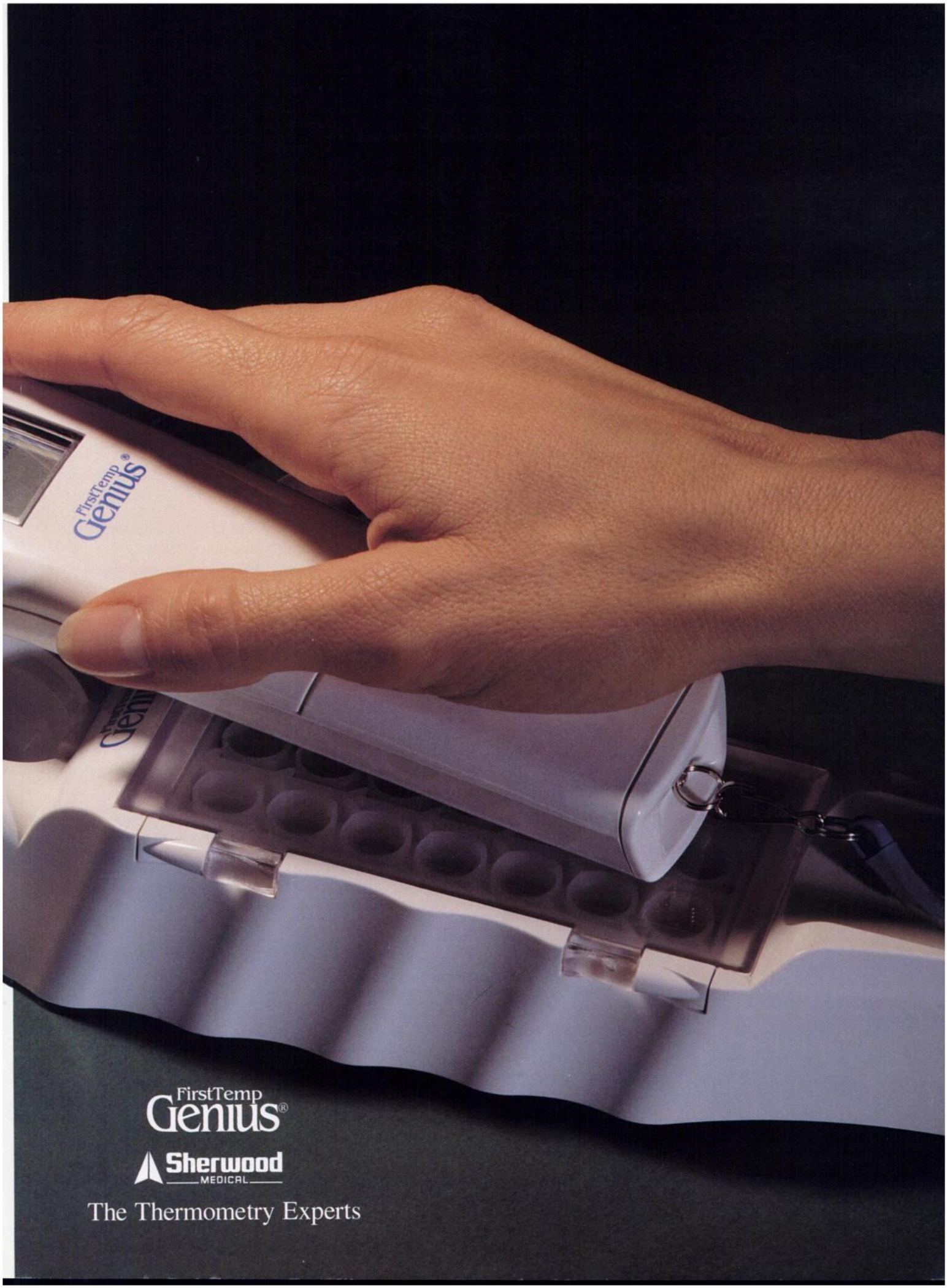
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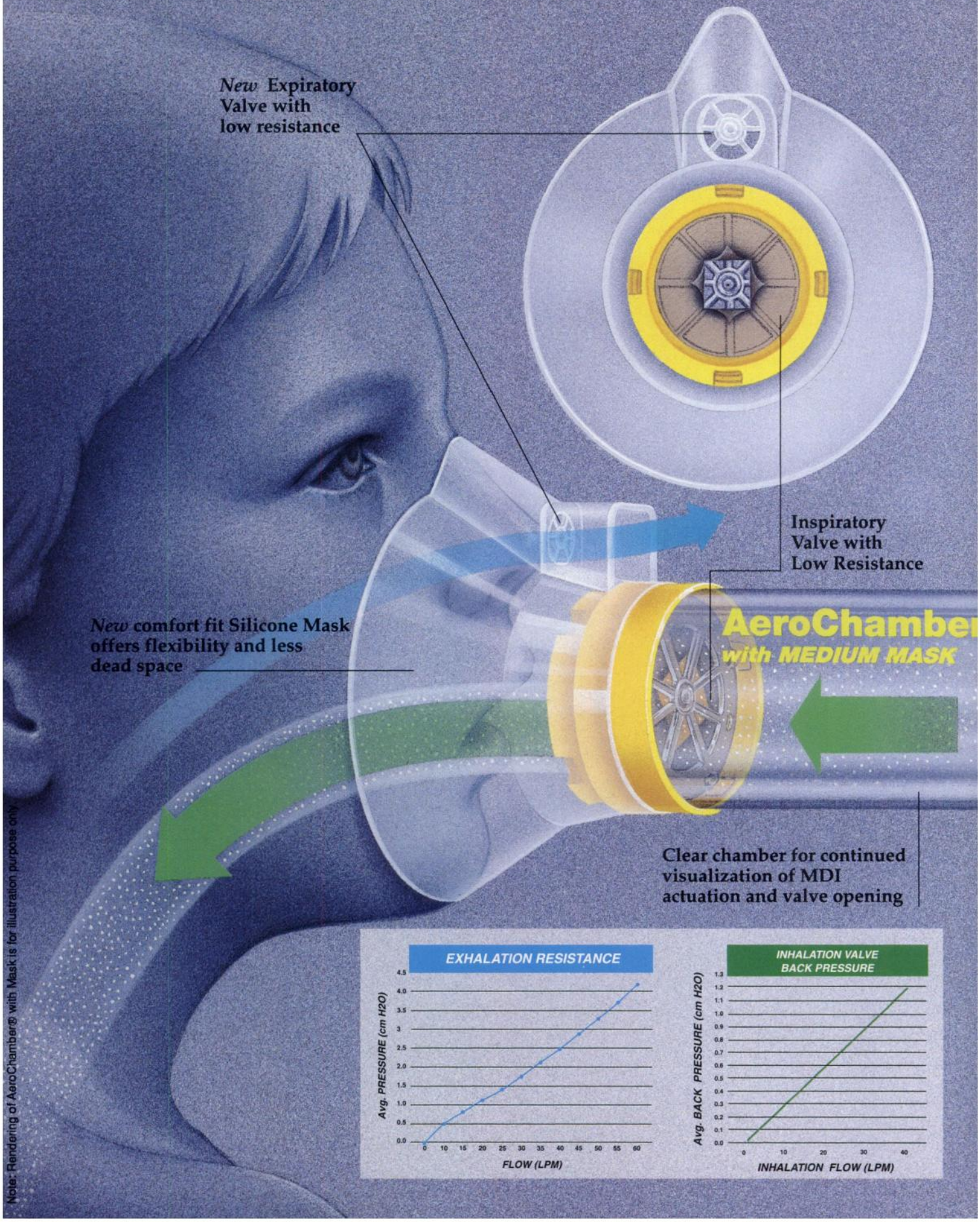

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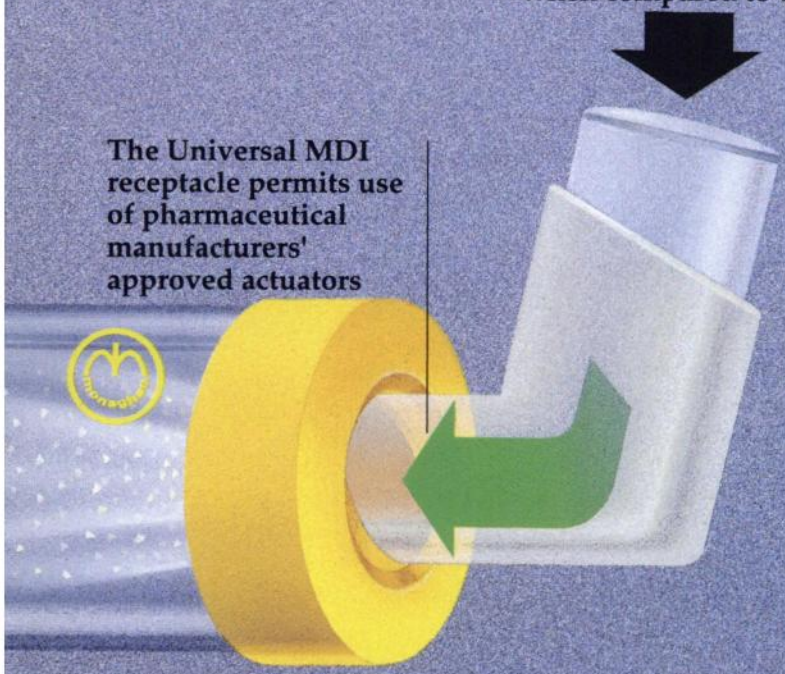

1. Drug delivery from holding chambers with attached facemaskML Everard et al, Archives of Disease in Children, Vol. 67, No. 5, May 1992

2. Substitution of Metered Dose Inhalers for Hand Held Nebulizers. Success and Cost Savings in a large, Acute Care Hospital, Bowton, DL, et al, Chest 101 (2) : 305-8, 1992 Feb.

3. Metered Dose Inhalers with Spacers vs Nebulizers for Bronchodilator Therapy in a Pediatric Emergency Department, Chou, KJ, et al, Am. J of Dis of Child. volume 147, No. 4 April 1993

4. Efficacy of Albuterol Administered by Nebulizer versus Spacer Device in Children with Accute Asthma, Karem, E., et al J. Ped 123 (2):313-7, 1993

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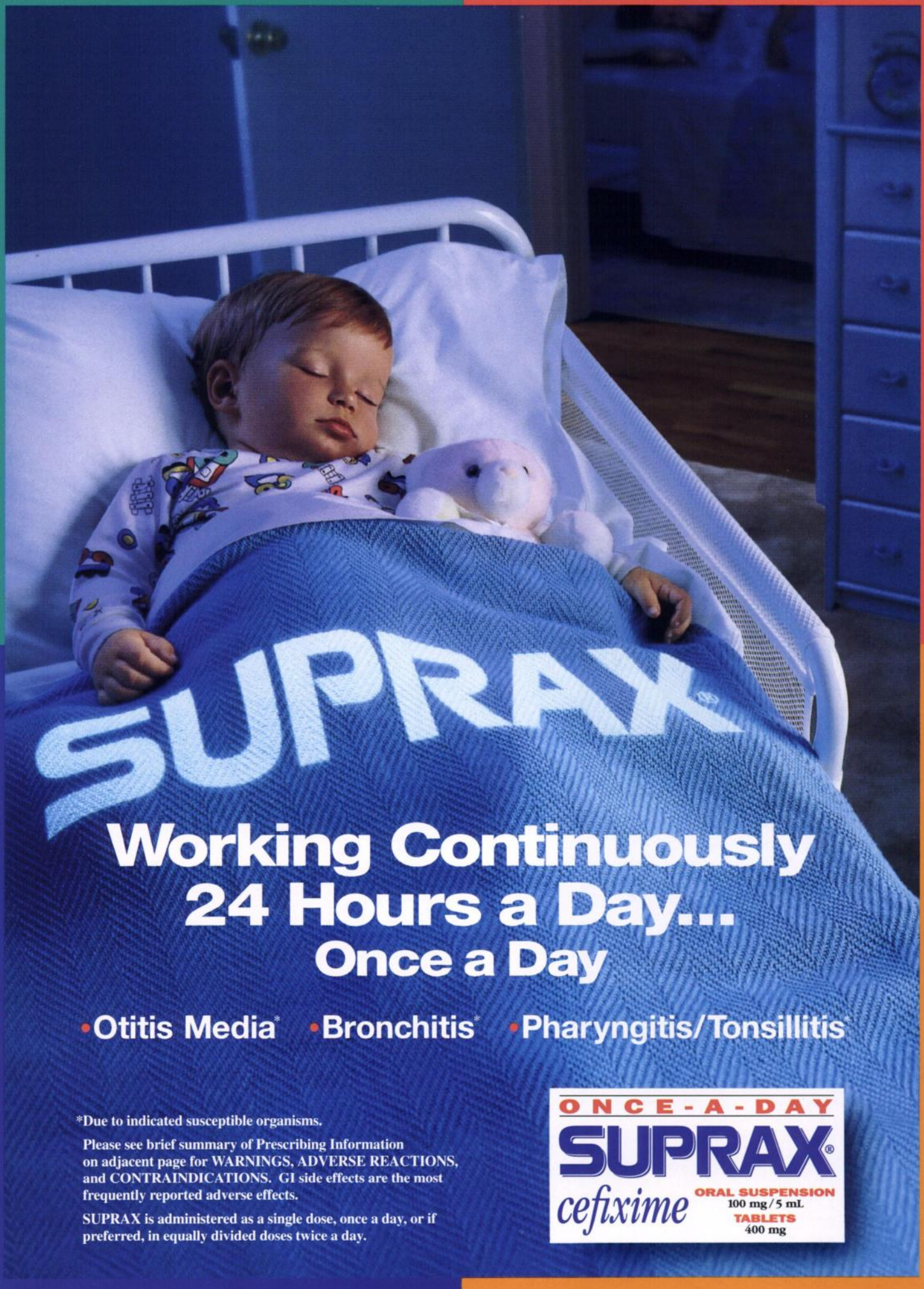

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INDICATIONS AND USAGE

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.

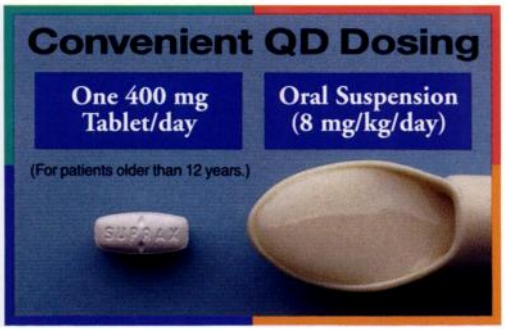
*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

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

[a] Number eradicated/number isolated.

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

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

CONTRAINDICATIONS

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

WARNINGS

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

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

Administer cautiously to allergic patients.

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

Renal: Transient elevations in BUN or creatinine.

Central Nervous System: Headaches or dizziness.

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

Other: Genital pruritus, vaginitis, candidiasis.

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

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

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

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

OVERDOSAGE

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

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No Lumbar Puncture in the Evaluation for Early Neonatal Sepsis: Will Meningitis Be Missed?

Thomas E. Wiswell, MD; Stephen Baumgart, MD; Catherine M. Gannon, MD; and Alan R. Spitzer, MD

ABSTRACT. *Objective.* **We performed this investigation to assess whether selective approaches to performing lumbar puncture (LP) in the early neonatal period will result in a missed or delayed diagnosis of bacterial meningitis.**

Design. **A retrospective review was conducted of the medical records of all neonates born in US Army hospitals from 1988 through 1992 who developed culture-positive meningitis during the first 72 hours of life.**

Results. **In total, 169 849 infants were born during the 5-year study period. The incidence of meningitis in the first 72 hours of life was 0.25 per 1000 live births. Forty-three infants had organisms isolated from their cerebrospinal fluid (30, group B streptococcus; 10, *Escherichia coli*; 1, *Listeria monocytogenes*; 1, *Streptococcus pneumoniae*; and 1, *Citrobacter diversus*). The median age of infants at evaluation was 12 hours, and the mean gestational age was 38.8 weeks (7 <37 weeks), whereas mean birth weight was 3163 g (7 <2500 g). If we had used currently advocated selective criteria as the basis for not performing an LP, the diagnosis of bacterial meningitis would have been missed or delayed in 16 of 43 infants (37%): 5 infants born prematurely with suspected respiratory distress syndrome, 3 asymptomatic infants born at term with positive blood cultures, and 8 infants born at term with no central nervous system symptoms and negative blood cultures.**

Conclusion. **If LPs are omitted as part of the early neonatal sepsis evaluation, the diagnosis of bacterial meningitis occasionally will be delayed or missed completely.** *Pediatrics* **1995;95:803–806;** ***bacterial meningitis, lumbar puncture, newborn infant.***

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The opinions or assertions contained herein are solely those of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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ABBREVIATIONS. CSF, cerebrospinal fluid; LP, lumbar puncture; GBS, group B streptococcal.

Bacterial meningitis occurs more frequently during the first month of life than at any other time during an individual's life.[1,2] Examination of the cerbrospinal fluid (CSF) obtained via a lumbar puncture (LP) is the only method of confirming the diagnosis of bacterial meningitis and identifying the causative organism. The LP has long been considered an integral part of the evaluation of neonates for suspected systemic infection. Nonetheless, several authors recently have proposed that the LP be eliminated from the evaluation of sepsis among newborns younger than 1 week of age.[3–9] Some of these studies contend that an LP may be reserved for infants with central nervous system symptoms or proven bacteremia.[3–5] Others assert that CSF examination is not indicated in asymptomatic neonates with antepartum risk factors for infection[5–8] or in the evaluation of infants born prematurely with or without respiratory distress.[4,5,8,9]

Many infants are born to mothers who have received intrapartum antibiotics for group B streptococcal (GBS) colonization of the lower vaginal tract[10] or for suspected chorioamnionitis.[11] Many antibiotics readily cross the placenta to the fetus and subsequently may interfere with the growth of bacteria in culture media. Furthermore, a substantial proportion of neonates with culture-proven bacterial meningitis (15% to 55%) have blood cultures from which no organisms are isolated.[9,12–18] Had a positive blood culture been used as a criterion for performing an LP, the diagnosis of bacterial meningitis may not have been made.

We performed this investigation to assess whether selective approaches to performing LPs as part of the early neonatal sepsis evaluation potentially could result in a missed or delayed diagnosis of bacterial meningitis.

difference in the choice, dosage, and duration of antibiotic therapy; (3) partially treated meningitis; and (4) a delay in the use of steroid therapy (among individual clinicians who use such therapy in neonates). With the use of newer technology, perhaps in the future, methods for better prediction of neonates with meningitis will be developed, allowing for the use of selective criteria to perform LPs. However, until that time, the benefits of early diagnosis and appropriate therapy outweigh the risks of this important procedure.

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WHAT PATIENTS CONTRIBUTE

Studies of medical outpatient consultations show that 86% of diagnosis depends entirely on what patients say, their own story. What doctors find on examination adds a further 6%; and technical investigations (x-rays, blood tests, etc) add another 8%.

Julian Tudor Hart citing Hampton JR, et al. Relative contributions of history-taking, physical examinations, and laboratory examination to diagnosis and management of medical outpatients. *Br Med J*. 1975;2:486–489.

Submitted by Student

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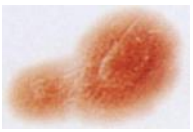
For many patients...

chickenpox.

now avoidable...



VARIVAX®

[VARICELLA VIRUS VACCINE LIVE (Oka/Merck)]

now available.

Vaccination with VARIVAX may not result in protection of all healthy, susceptible children, adolescents, and adults.

The duration of protection of VARIVAX is unknown at present and the need for booster doses is not defined.

Please read the Brief Summary of the Prescribing Information on the last page of this advertisement.

Before administering the vaccine, please read the full Prescribing Information for VARIVAX.

chickenpox. uncomfortable. unwelcome.

For many patients, VARIVAX® [Varicella Virus Vaccine Live (Oka/Merck)]:

efficacy

The majority of vaccinees in clinical studies who were exposed to wild-type virus were either completely protected from chickenpox or developed a milder form of the disease.

In controlled clinical trials in children: Compared to historical controls...

Single dose of VARIVAX in children	% difference from expected attack rates (natural exposure)	Breakthrough cases (vaccinees reporting chickenpox)
Results with current vaccine using 2,900 PFU to 9,000 PFU (n=1,164)	A reduction of approximately **93%**	**0.2% to 1.0%** per year (up to 3 years of follow-up)
In earlier trials with a vaccine using 1,000 PFU to 1,625 PFU (n=4,142)	A reduction of approximately **67%** (57% to 77%)	**2.1% to 3.6%** per year (up to 6 years of follow-up)

PFU = plaque-forming units

After household exposure...

▶ A single dose of VARIVAX reduced the incidence of chickenpox by 77% in pediatric vaccinees subsequently exposed to chickenpox in a household setting (n=259). 80% did not report chickenpox; 20% reported a mild form of the disease.

In a placebo-controlled trial...

▶ One dose of VARIVAX (at a formulation containing 17,000 PFU) protected 96% to 100% of children over the first 2 years postvaccination.

- **100%** calculated protection rate the first year: 0% contracted chickenpox with VARIVAX (n=491) compared to 8.5% with placebo (n=465)
- **96%** calculated protection rate the second year (n=163 VARIVAX; n=161 placebo)

VARIVAX is contraindicated in individuals with a history of hypersensitivity or anaphylactoid reaction to any component of the vaccine including gelatin or neomycin, blood dyscrasias, leukemia, lymphomas of any type, other malignant neoplasms affecting the bone marrow or lymphatic systems, febrile illness, and most primary or acquired immunodeficiency states; and in those receiving immunosuppressive therapy.

VARIVAX should not be administered during pregnancy. Pregnancy should be avoided for 3 months following vaccination.

For a Brief Summary of the Prescribing Information, please see the last page of this advertisement.

unavoidable...until now...

immunogenicity

In clinical trials, 1 dose maintained varicella antibodies in healthy children for at least 4 years.

Years post-vaccination	1	2	3	4
% vaccinees with detectable antibody level	**98.8%** (n=3,822)	**98.9%** (n=1,069)	**97.5%** (n=562)	**99.5%** (n=221)

Antibody presence over time in healthy children who received 1 dose of VARIVAX in clinical trials

- A boost in antibody levels was observed in vaccinees following exposure to natural chickenpox, which could account for this apparent persistence of antibody levels. However, the duration of protection from varicella obtained using VARIVAX in the absence of wild-type boosting is unknown.
- The relative contributions of humoral immunity and cell-mediated immunity to protection from chickenpox are unknown.

Introducing new

VARIVAX®

[VARICELLA VIRUS VACCINE LIVE (Oka/Merck)]

The First Vaccine Against Chickenpox Available In The U.S.

For a Brief Summary of the Prescribing Information, please see the last page of this advertisement.

VARIVAX® [Varicella Virus Vaccine Live (Oka/Merck)] generally well tolerated...

safety profile

In clinical trials of 11,102 children, adolescents, and adults
(at formulations ranging from 1,000 to 17,000 PFU)

Frequency of fever, local reactions, or rashes (%) in healthy children, adolescents, and adults monitored for up to 42 days after any dose of VARIVAX

Reaction (0–42 days)	CHILDREN after a single dose	ADOLESCENTS and ADULTS after first dose	ADOLESCENTS and ADULTS after second dose
Fever (≥ 102°F [39°C] oral for children, ≥ 100°F [37.7°C] oral for adolescents and adults)	14.7% (n=8,827)	10.2% (n=1,584)	9.5% (n=956)
Injection-site complaints	19.3% (n=8,916)	24.4% (n=1,606)	32.5% (n=955)
Varicella-like rash (injection site) Median number of lesions	3.4% (n=8,916) 2	3.0% (n=1,606) 2	1.0% (n=955) 2
Varicella-like rash (generalized) Median number of lesions	3.8% (n=8,916) 5	5.5% (n=1,606) 5	0.9% (n=955) 5.5

- Vaccine recipients should avoid close association with susceptible high-risk individuals (e.g., newborns, pregnant women, and immunocompromised persons). The potential risk of transmission of vaccine virus should be weighed against the risk of transmission of natural varicella virus in such circumstances.

- In children and adults, adverse experiences reported at ≥1% frequency included (without regard to causality): upper respiratory illness, cough, irritability/nervousness, fatigue, disturbed sleep, diarrhea, loss of appetite, vomiting, otitis, rash, headache, teething, malaise, abdominal pain, nausea, eye complaints, chills, lymphadenopathy, myalgia, stiff neck, arthralgia, lower respiratory illness, allergic reactions, constipation, itching, and cold/canker sores. In children, pneumonitis and febrile seizures have been reported rarely; a causal relationship has not been established.

  As with any vaccine, there is the possibility that broad use of VARIVAX could reveal adverse reactions not observed in clinical trials.

with several benefits.

Helps prevent disease and work loss

- Helps reduce costs of work time lost by family members who stay home to care for children with chickenpox.[1]

VARIVAX is indicated for vaccination against varicella in individuals 12 months of age or older

- For children 12 months to 12 years of age: **one 0.5 mL dose**, administered subcutaneously.
- For individuals 13 years of age and older: **two 0.5 mL doses**, administered subcutaneously (second dose 4 to 8 weeks after initial dose).

Ordering/Storage

- Call **1-800-MERCK-RX** (1-800-637-2579) to order VARIVAX.
- Call **1-800-9-VARIVAX** (1-800-982-7482) if you have any questions about VARIVAX or would like to obtain materials and information for your patients and practice.
- Lyophilized VARIVAX is available in single-dose vials packaged in boxes of 1 or 10 vials with accompanying diluent.
- Store vaccine frozen at an average temperature of +5°F (–15°C) or colder until reconstitution. Storage in a frost-free freezer with an average temperature of +5°F (–15°C) is acceptable.
- Store diluent separately at room temperature or in the refrigerator.

Reference:
1. Lieu, T.A. et al.: Cost-effectiveness of a routine varicella vaccination program for U.S. children. JAMA *271(5)*:375–381, 1994.

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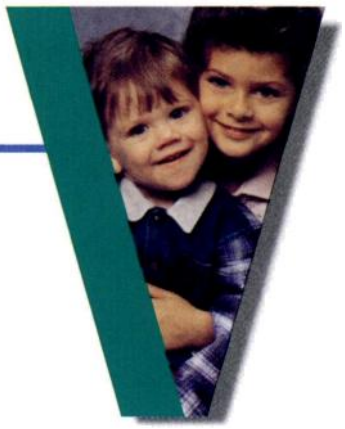

VARIVAX®

[VARICELLA VIRUS VACCINE LIVE (Oka/Merck)]

The First Vaccine Against Chickenpox Available In The U.S.

For a Brief Summary of the Prescribing Information, please see the last page of this advertisement.
Before administering the vaccine, please read the full Prescribing Information for VARIVAX.

BRIEF SUMMARY

Please read the full Prescribing Information for complete details.

INDICATIONS AND USAGE

VARIVAX® [Varicella Virus Vaccine Live (Oka/Merck)] is indicated for vaccination against varicella in individuals 12 months of age and older.

Revaccination

The duration of protection of VARIVAX is unknown at present and the need for booster doses is not defined. However, a boost in antibody levels has been observed in vaccinees following exposure to natural varicella as well as following a booster dose of VARIVAX administered four to six years post vaccination.

In a highly vaccinated population, immunity for some individuals may wane due to lack of exposure to natural varicella as a result of shifting epidemiology. Post-marketing surveillance studies are ongoing to evaluate the need and timing for booster vaccination.

Vaccination with VARIVAX may not result in protection of all healthy, susceptible children, adolescents, and adults (see CLINICAL PHARMACOLOGY section of the full Prescribing Information).

CONTRAINDICATIONS

A history of hypersensitivity to any component of the vaccine, including gelatin.

A history of anaphylactoid reaction to neomycin (each dose of reconstituted vaccine contains trace quantities of neomycin).

Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Individuals receiving immunosuppressive therapy. Individuals who are on immunosuppressant drugs are more susceptible to infections than healthy individuals. Vaccination with live attenuated varicella vaccine can result in a more extensive vaccine-associated rash or disseminated disease in individuals on immunosuppressant doses of corticosteroids.

Individuals with primary and acquired immunodeficiency states, including those who are immunosuppressed in association with AIDS or other clinical manifestations of infection with human immunodeficiency virus; cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states.

A family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated.

Active untreated tuberculosis.

Any febrile respiratory illness or other active febrile infection.

Pregnancy; the possible effects of the vaccine on fetal development are unknown at this time. However, natural varicella is known to sometimes cause fetal harm. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for 3 months following vaccination (see PRECAUTIONS, *Pregnancy*).

WARNINGS

Children and adolescents with acute lymphoblastic leukemia (ALL) in remission can receive the vaccine under an investigational protocol. More information is available by contacting the VARIVAX coordinating center, Bio-Pharm Clinical Services, Inc., 4 Valley Square, Blue Bell, PA 19422, (610) 283-0897.

PRECAUTIONS

General

Adequate treatment provisions, including epinephrine injection (1:1000), should be available for immediate use should an anaphylactoid reaction occur.

The duration of protection from varicella infection after vaccination with VARIVAX is unknown.

It is not known whether VARIVAX given immediately after exposure to natural varicella virus will prevent illness.

Vaccination should be deferred for at least 5 months following blood or plasma transfusions, or administration of immune globulin or varicella zoster immune globulin (VZIG).

Following administration of VARIVAX, any immune globulin, including VZIG, should not be given for 2 months thereafter unless its use outweighs the benefits of vaccination.

Vaccine recipients should avoid use of salicylates for 6 weeks after vaccination with VARIVAX as Reye's syndrome has been reported following the use of salicylates during natural varicella infection.

Individuals vaccinated with VARIVAX may potentially be capable of transmitting the vaccine virus to close contacts. Therefore, vaccine recipients should avoid close association with susceptible high-risk individuals (e.g., newborns, pregnant women, immunocompromised persons). The potential risk of transmission of vaccine virus should be weighed against the risk of transmission of natural varicella in such circumstances.

The safety and efficacy of VARIVAX have not been established in children and young adults who are known to be infected with human immunodeficiency viruses but who do not have overt clinical manifestations of immunosuppression.

Care should be taken by the healthcare provider for safe and effective use of VARIVAX.

The healthcare provider should question the patient, parent, or guardian about reactions to a previous dose of VARIVAX or a similar product.

The healthcare provider should obtain the previous immunization history of the vaccinee.

VARIVAX should not be injected into a blood vessel.

Vaccination should be deferred in patients with a family history of congenital or hereditary immunodeficiency until the patient's own immune system has been evaluated.

A separate sterile needle and syringe should be used for administration of each dose of VARIVAX to prevent transfer of infectious diseases.

Needles should be disposed of properly and should not be recapped.

Information for Patients

The healthcare provider should inform the patient, parent, or guardian of the benefits and risks of vaccination.

Patients, parents, or guardians should be instructed to report any adverse reactions to their healthcare provider.

Pregnancy should be avoided for 3 months following vaccination.

Drug Interactions

See PRECAUTIONS, *General*, regarding the administration of immune globulins, salicylates, and transfusions.

Use with Other Vaccines

Results from clinical studies indicate that VARIVAX can be administered concomitantly with M-M-R®II (Measles, Mumps, and Rubella Virus Vaccine Live, MSD).

Limited data from an experimental product containing varicella vaccine suggest that VARIVAX can be administered concomitantly with DTaP (diphtheria, tetanus, acellular pertussis) and PedvaxHIB® [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate), MSD] using separate sites and syringes (see CLINICAL PHARMACOLOGY, *Studies With Other Vaccines* in the full Prescribing Information). However, there are no data relating to simultaneous administration of VARIVAX with DTP or OPV.

Carcinogenesis, Mutagenesis, Impairment of Fertility

VARIVAX has not been evaluated for its carcinogenic or mutagenic potential, or its potential to impair fertility.

Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with VARIVAX. It is also not known whether VARIVAX can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, VARIVAX should not be administered to pregnant females; furthermore, pregnancy should be avoided for 3 months following vaccination (see CONTRAINDICATIONS).

Nursing Mothers

It is not known whether varicella vaccine virus is secreted in human milk. Therefore, because some viruses are secreted in human milk, caution should be exercised if VARIVAX is administered to a nursing woman.

Pediatric Use

No clinical data are available on safety or efficacy of VARIVAX in children less than one year of age, and administration to infants under 12 months of age is not recommended.

ADVERSE REACTIONS

In clinical trials, VARIVAX was administered to 11,102 healthy children, adolescents, and adults. VARIVAX was generally well tolerated.

In children, adolescents, and adults followed for up to 42 days, the adverse effects most frequently reported were as follows: fever (≥102°F [39°C] oral in children and ≥100°F [37.7°C] oral in adolescents and adults); injection site complaints (pain/soreness, swellings, and/or erythema, rash, pruritus, hematoma, induration, stiffness); and varicella-like rash (injection site and generalized).

In children, adolescents, and adults, adverse experiences reported at ≥1% frequency included, without regard to causality, upper respiratory illness, cough, irritability/nervousness, fatigue, disturbed sleep, diarrhea, loss of appetite, vomiting, otitis, diaper rash/contact rash, headache, teething, malaise, abdominal pain, other rash, nausea, eye complaints, chills, lymphadenopathy, myalgia, stiff neck, arthralgia, lower respiratory illness, allergic reaction (including allergic rash, hives), constipation, itching, heat rash/prickly heat, eczema/dry skin, dermatitis, and cold/canker sore. In children, pneumonitis (<1%) and febrile seizures (<0.1%) have been reported rarely; a causal relationship has not been established.

As with any vaccine, there is the possibility that broad use of the vaccine could reveal adverse reactions not observed in clinical trials.

DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION

Do not inject intravenously.

Children 12 months to 12 years of age should receive a single 0.5 mL dose administered subcutaneously. Adolescents and adults 13 years of age and older should receive a 0.5 mL dose administered subcutaneously at elected date and a second 0.5 mL dose 4 to 8 weeks later.

VARIVAX MUST BE KEPT FROZEN AT AN AVERAGE TEMPERATURE OF +5°F (–15°C) OR COLDER UNTIL IT IS RECONSTITUTED FOR INJECTION. STORAGE IN A FROST-FREE FREEZER WITH AN AVERAGE TEMPERATURE OF +5°F (–15°C) OR COLDER IS ACCEPTABLE. THE DILUENT SHOULD BE STORED SEPARATELY AT ROOM TEMPERATURE OR IN THE REFRIGERATOR. IT IS RECOMMENDED THAT THE VACCINE BE ADMINISTERED IMMEDIATELY AFTER RECONSTITUTION, TO MINIMIZE LOSS OF POTENCY. DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 30 MINUTES.

Do not freeze reconstituted vaccine.

Do not give immune globulin including Varicella Zoster Immune Globulin concurrently with VARIVAX (see also PRECAUTIONS).

VARIVAX®

[VARICELLA VIRUS VACCINE LIVE (Oka/Merck)]

MERCK
Vaccine Division

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clarithromycin
For Oral Suspension

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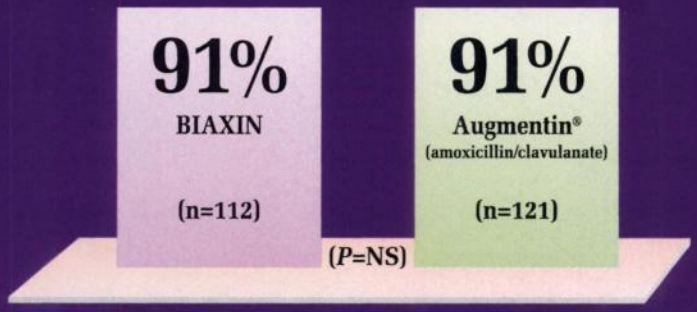
SPANS THE SPECTRUM™

Proven clinical success* in acute otitis media[1,2]
due to *H influenzae, M catarrhalis,* and *S pneumoniae*



- ✓ **Significantly lower incidence of diarrhea vs Augmentin®** (amoxicillin/clavulanate) in two well-controlled studies ($P<.001$)[1]
- ✓ **Very well tolerated: low incidence of adverse events,**[1] including diarrhea 6%, vomiting 6%, abdominal pain 3%, rash 3%, headache 2%
- ✓ **Dosing:** 15 mg/kg/day divided BID for 10 days
- ✓ **Low cost** vs Augmentin†[3]

* Clinical success = clinical cure or improvement.

† 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 10-day course of therapy for acute otitis media. Comparison is between BIAXIN and Augmentin® (amoxicillin/clavulanate), a registered trademark of SmithKline Beecham Pharmaceuticals.

References:
1. Biaxin package insert, Abbott Laboratories.
2. Data on file, Integrated Summary of Effectiveness, Abbott Laboratories.
3. *Red Book®* Update. Montvale, NJ: Medical Economics Data;1994;13(9).

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PLEASE SEE BRIEF SUMMARY OF PRESCRIBING INFORMATION ON FOLLOWING PAGE.

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clarithromycin
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January 1995

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BRIEF SUMMARY
FOR USE IN RESPIRATORY AND SKIN INFECTIONS
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

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-hydroxy-clarithromycin 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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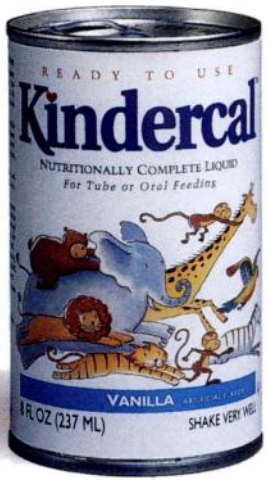

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nary right-to-left shunting,[13] or both. They also could have been caused by broken apnea, ie, by a sequence of two or three apneic pauses of less than 20 seconds interrupted by one or two single breaths. Whatever the mechanism, the clinically relevant fact is that they would not have been detected by cardiorespiratory monitors.

We were also unable to determine whether episodes occurred during sleep or quiet wakefulness. From a clinical viewpoint, however, it seems irrelevant whether an infant is awake or asleep when he or she becomes hypoxemic; in either case, it is important to detect the hypoxemia as early as possible. In addition, we are reasonably certain that the episodes were not associated with periods of gross body movements (eg, crying), because this invariably would have resulted in a disturbed pulse waveform signal and, therefore, in the exclusion of the episode from analysis. Although this procedure may have resulted in an underestimation of the true incidence of desaturation episodes in our patients (there is evidence that a proportion of hypoxemic episodes in preterm infants is associated with "squirming" motor activity[14]), we thought that it would not be appropriate to include hypoxemic episodes for analysis during which there were unreliable measurement conditions for SpO_2 throughout. Finally, we used a fixed threshold (100 bpm) for defining bradycardia. Although it seems somewhat more physiologic to use a relative decrement in heart rate when defining bradycardia, eg, a fall by greater than 30% of an infant's baseline heart rate, it is as yet standard practice in most neonatal units to use a fixed bradycardia threshold, and the latter was, therefore, also used in this study.

In conclusion, we have shown that apparently well preterm infants may exhibit episodes of severe prolonged hypoxemia that are not accompanied by prolonged apneic pauses or bradycardia and are thus difficult to detect if only breathing movements and heart rates are monitored in these infants. We suggest that the use of pulse oximeters, $TcPo_2$ monitors, or both should be considered in all preterm infants undergoing special care.

ACKNOWLEDGMENTS

We are grateful to the parents and hospital staff, in particular Drs Meeks, Lewis, Bonavia, and Wyatt, at the Royal Sussex Childrens Hospital (Brighton, UK) Crawley General District Hospital, (Crawley, UK) the New East Surrey Hospital (Redhill, UK) and University College Hospital (London, UK) for allowing us to perform this study on their infants and for their help with the recordings, to S. Neale, who obtained the recordings, and to J. Kelly, who analyzed the recordings.

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LOOK AHEAD THROUGH THE REAR-VIEW MIRROR

The best qualification of a prophet is to have a good memory.

—Marquess of Halifax

Submitted by Student

pharyngeal intubation in a spontaneously breathing child, which are limitations pertaining to capnometry in general[10,12] and not only to this monitor.

We think that some form of carbon dioxide monitoring would make transport of intubated patients safer, and that it would be better if this were part of the monitoring equipment. A quantitative capnometer with capnographs and a numerical display may be much more helpful in the treatment of patients. Of course, when in doubt regarding ETT position, direct laryngoscopy provides immediate clarification of the tube position.

CONCLUSIONS

The Biochem 520 breath indicator is reliable in confirming ETT position during transport of critically ill infants and children but was found to be inconvenient to use in this setting. Further improvements in this area of noninvasive technology, eg, making the equipment smaller and easier to secure or incorporating it into the cardiorespiratory monitor, would make it much more practical for use during interhospital transport.

ACKNOWLEDGMENTS

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DARWIN ON METHOD

The line of argument pursued throughout my theory is to establish a point as a probability by induction, and to apply it as a hypothesis to other points and see whether it will solve them.

Darwin, quoted by Wright R. *The Moral Animal*. NY: Panthgon; 1994.

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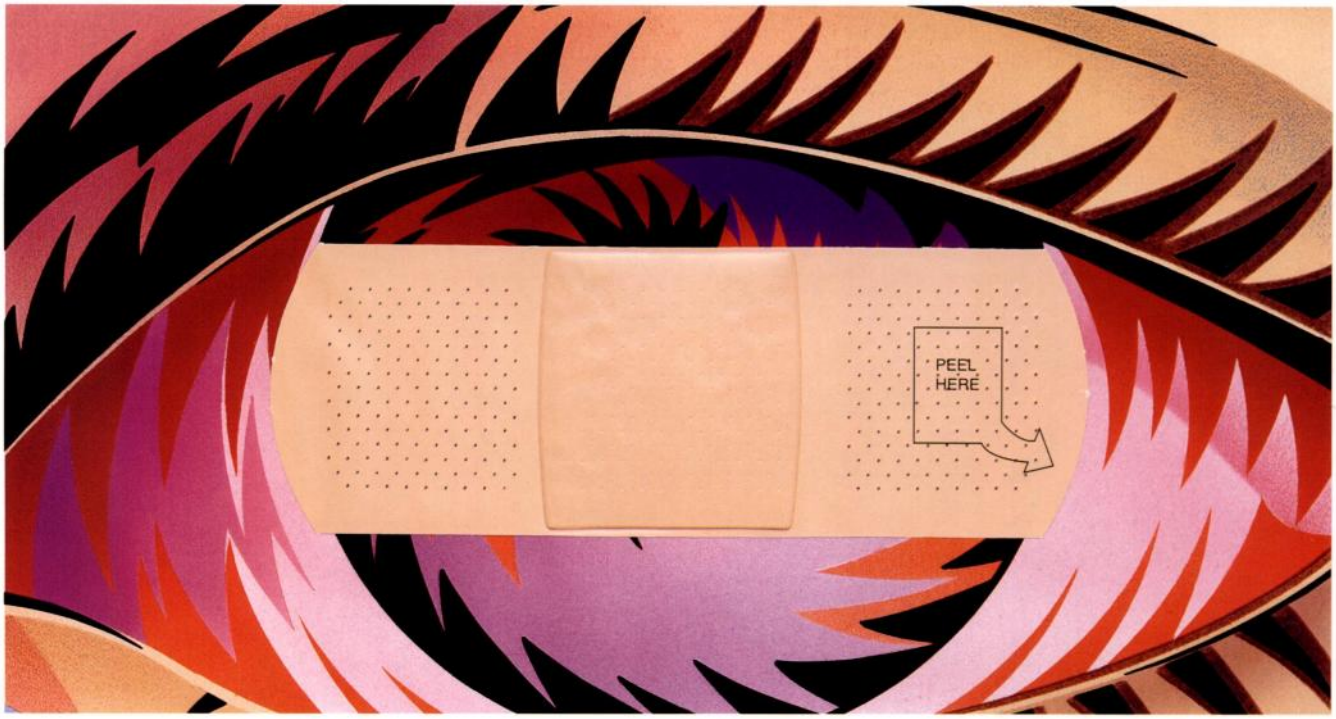

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Common Respiratory Disorders of the Newborn—Kopelman and Mathew

Index of Suspicion—McCarthy, Tuite, and Connors

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CONTRAINDICATION: Known hypersensitivity to DDAVP Nasal Spray

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1 For intranasal use only

2 In very young and elderly patients in particular, fluid intake should be adjusted downward in order to decrease the potential occurrence of water intoxication and hyponatremia Particular attention should be paid to the possibility of the rare occurrence of an extreme decrease in plasma osmolality that may result in seizures which could lead to coma

PRECAUTIONS:

General: DDAVP Nasal Spray at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure

DDAVP Nasal Spray should be used with caution in patients with conditions associated with fluid and electrolyte imbalance, such as cystic fibrosis, because these patients are prone to hyponatremia

Rare severe allergic reactions have been reported with DDAVP Anaphylaxis has been reported with intravenous administration of DDAVP Injection, but not with DDAVP intranasal

Central Cranial Diabetes Insipidus: Since DDAVP Nasal Spray is used intranasally, changes in the nasal mucosa such as scarring, edema, or other disease may cause erratic, unreliable absorption in which case DDAVP Nasal Spray should not be used For such situations, DDAVP Injection should be considered

Primary Nocturnal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result DDAVP Nasal Spray should be discontinued until the nasal problems resolve

Information for Patients: Patients should be informed that the bottle accurately delivers 50 doses of 10 mcg each Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug No attempt should be made to transfer remaining solution to another bottle Patients should be instructed to read accompanying directions on use of the spray pump carefully before use

Laboratory Tests: Laboratory tests for following the patient with central cranial diabetes insipidus or post-surgical or head trauma-related polyuna and polydipsia include urine volume and osmolality In some cases plasma osmolality may be required For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days

Drug Interactions: Although the pressor activity of DDAVP Nasal Spray is very low compared to the antidiuretic activity, use of large doses of DDAVP Nasal Spray with other pressor agents should only be done with careful patient monitoring

Carcinogenesis, Mutagenesis, Impairment of Fertility: Teratology studies in rats have shown no abnormalities No further information is available

Pregnancy-Category B: Reproduction studies performed in rats and rabbits with doses up to 12 5 times the human intranasal dose (*i e* about 125 times the total adult human dose given systemically) have revealed no evidence of harm to the fetus due to desmopressin acetate There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported, however, no controlled studies in pregnant women have been carried out Published reports stress that, as opposed to preparations containing the natural hormones, DDAVP Nasal Spray (desmopressin acetate) in antidiuretic doses has no uterotonic action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case

Nursing Mothers: There have been no controlled studies in nursing mothers A single study in a post-partum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP Nasal Spray in breast milk following an intranasal dose of 10 mcg

Pediatric Use: Primary Nocturnal Enuresis: DDAVP Nasal Spray has been used in childhood nocturnal enuresis Short-term (4-8 weeks) DDAVP Nasal Spray administration has been shown to be safe and modestly effective in children aged 6 years or older with severe childhood nocturnal enuresis Adequately controlled studies with DDAVP Nasal Spray in primary nocturnal enuresis have not been conducted beyond 4-8 weeks The dose should be individually adjusted to achieve the best results

Central Cranial Diabetes Insipidus: DDAVP Nasal Spray has been used in children with diabetes insipidus Use in infants and children will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication The dose must be individually adjusted to the patient with attention in the very young to the danger of an extreme decrease in plasma osmolality with resulting convulsions Dose should start at 0 05 mL or less

Since the spray cannot deliver less than 0 1 mL (10 mcg), smaller doses should be administered using the rhinal tube delivery system Do not use the nasal spray in pediatric patients requiring less than 0 1 mL (10 mcg) per dose

There are reports of an occasional change in response with time, usually greater than 6 months Some patients may show a decreased responsiveness, others a shortened duration of effect There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide

ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps These symptoms disappeared with reduction in dosage Nosebleed, sore throat, cough and upper respiratory infections have also been reported

The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis

ADVERSE REACTION	PLACEBO (N=59) %	DDAVP 20 mcg (N=60) %	DDAVP 40 mcg (N=61) %
BODY AS A WHOLE			
Abdominal Pain	0	2	2
Asthenia	0	0	2
Chills	0	0	2
Headache	0	2	5
Throat Pain	2	0	0
NERVOUS SYSTEM			
Depression	2	0	0
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	2	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2	0	0
Rash	2	0	0
SPECIAL SENSES			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

OVERDOSAGE: See adverse reactions above In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition There is no known specific antidote for DDAVP Nasal Spray

An oral LD_{50} has not been established An intravenous dose of 2 mg/kg in mice demonstrated no effect

CAUTION: Federal (U S A) law prohibits dispensing without prescription

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REFERENCES: 1. Rittig S, Knudsen UB, Sorensen S Long-term double-blind cross-over study of desmopressin intranasal spray in the management of nocturnal enuresis In Meadow SR, ed *Desmopressin in Nocturnal Enuresis Proceedings of an international symposium* England Horus Medical Publications, 1988 43-54 **2. Miller K,** Klauber GT Desmopressin acetate in children with severe primary nocturnal enuresis *Clin Ther* 1990 12(4) 357-366 **3. Aladjem M,** Wohl R, Boichis H, et al Desmopressin in nocturnal enuresis *Arch Dis Child* 1982 57 137-140 **4. Bloom DA:** The American experience with desmopressin *Clin Pediatr* July 1993, Special Edition 28-31

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by Tan in 1977.[5] In vitro genotoxicity of light in the 400- to 500-nm range[13] may not be predictive of human risk.[14] The amount of light to which one is exposed[11] during phototherapy is minute compared with the exposure later in life, even during the first year.[1]

The fluid bed acts as a thermal reservoir, smoothing out the temperature fluctuations. The fluid absorbs and dissipates the heat generated by the light source, allowing the close proximity necessary for the high irradiance of 26 to 30 $\mu W/cm^2$ per nanometer. The close proximity of the light source below the cot also reduces the scatter and glare of the blue light, decreasing the inconvenience to the attending personnel.[15]

The infants tolerated the fluid bed well. It is softer, probably more physiological and comfortable for the newborn infant than a hard mattress or the perspex floor of a bassinet.

The system we have described is simple, easy to assemble using equipment available in most neonatal units. The modifications are reversible and can be done by the maintenance department of any hospital; thus the additional cost is virtually nil. These factors take greater importance when the financial outlay for new high-technology equipment and their spare parts, along with the waiting period for servicing, is considered in the current cost-cutting environment, especially in developing countries.

The efficacy and ease of HIDS phototherapy on the fluid bed may be further enhanced by a better light source and a disposable custom-made plastic fluid bed. We recommend HIDS phototherapy on the fluid bed as the treatment of choice during critical periods of hyperbilirubinemia, when rapid control of hyperbilirubinemia is desirable.

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ETHICAL DECISIONS

Of the many theories that have been propounded for ethical decision-making, three are particularly useful in helping us think through the twin rights of moral dilemmas:

1) *Ends-Based Thinking*: Do whatever produces the greatest good for the greatest number;
2) *Rule-Based Thinking*: Follow only the principle that you want everyone else to follow; and
3) *Care-Based Thinking*: Do to others what you would like them to do to you.

Kidder RK. *How Good People Make Tough Choices*. NY: Harper Row; 1995.

Submitted by Student

Alkhobar and King Faisal University
Dammam, Saudi Arabia

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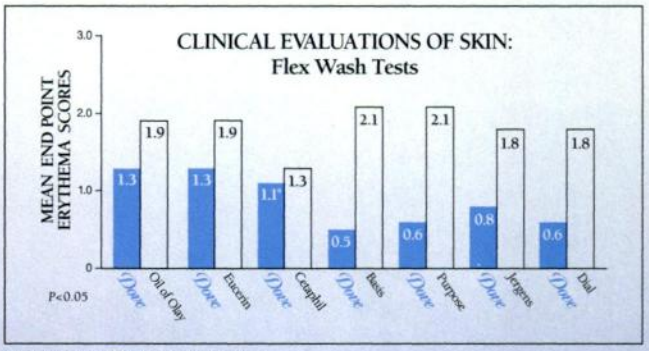

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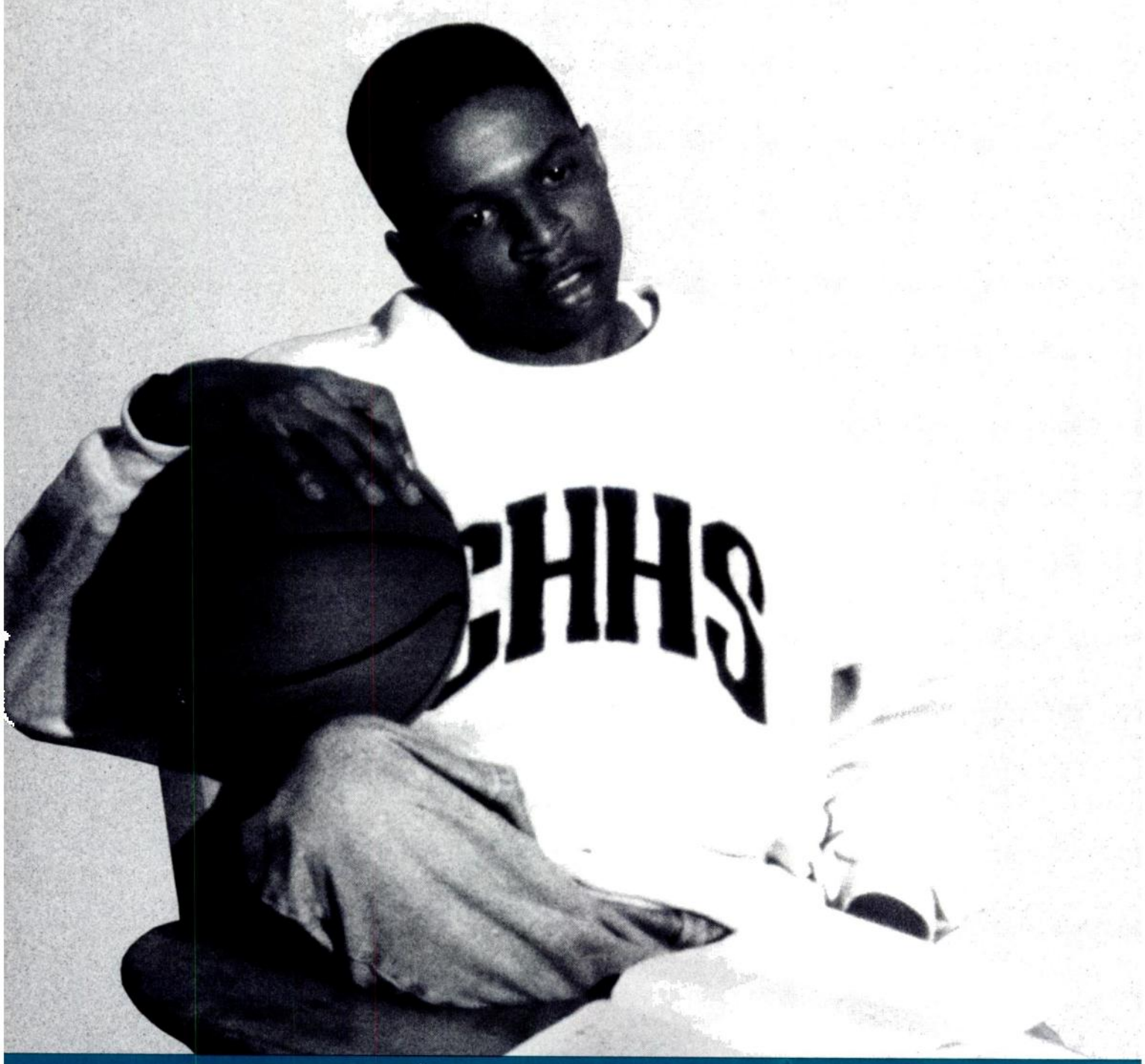

Serevent® (salmeterol xinafoate)

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:
IMPORTANT INFORMATION: SEREVENT® INHALATION AEROSOL SHOULD NOT BE INITIATED IN PATIENTS WITH SIGNIFICANTLY WORSENING OR ACUTELY DETERIORATING ASTHMA, WHICH MAY BE A LIFE-THREATENING CONDITION. Serious acute respiratory events, including fatalities, have been reported, both in the US and worldwide, when Serevent Inhalation Aerosol has been initiated in this situation.

Although it is not possible from these reports to determine whether Serevent Inhalation Aerosol contributed to these adverse events or simply failed to relieve the deteriorating asthma, the use of Serevent Inhalation Aerosol in this setting is inappropriate.

SEREVENT INHALATION AEROSOL SHOULD NOT BE USED TO TREAT ACUTE SYMPTOMS. It is crucial to inform patients of this and prescribe a short-acting, inhaled $beta_2$-agonist for this purpose as well as warn them that increasing inhaled $beta_2$-agonist use is a signal of deteriorating asthma.

SEREVENT INHALATION AEROSOL IS NOT A SUBSTITUTE FOR INHALED OR ORAL CORTICOSTEROIDS. Corticosteroids should not be stopped or reduced when Serevent Inhalation Aerosol is initiated.

(See PRECAUTIONS: Information for Patients section of the full prescribing information and the separate PATIENT'S INSTRUCTIONS FOR USE leaflet.)

1. Do Not Introduce Serevent Inhalation Aerosol as a Treatment for Acutely Deteriorating Asthma: Serevent Inhalation Aerosol is intended for the maintenance treatment of asthma (see INDICATIONS and USAGE section of the full prescribing information) and should not be introduced in acutely deteriorating asthma, which is a potentially life-threatening condition. There are no data demonstrating that Serevent Inhalation Aerosol provides greater efficacy than or additional efficacy to short-acting, inhaled $beta_2$-agonists in patients with worsening asthma. Serious acute respiratory events, including fatalities, have been reported, both in the US and worldwide, in patients receiving Serevent Inhalation Aerosol. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications, increasing need for inhaled short-acting $beta_2$-agonists, increasing need for systemic corticosteroids, significant increase in symptoms, recent emergency room visits, sudden or progressive deterioration in pulmonary function). However, they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether Serevent Inhalation Aerosol contributed to these events or simply failed to relieve the deteriorating asthma.

2. Do Not Use Serevent Inhalation Aerosol to Treat Acute Symptoms: A short-acting, inhaled $beta_2$-agonist, not Serevent Inhalation Aerosol, should be used to relieve acute asthma symptoms. When prescribing Serevent Inhalation Aerosol, the physician must also provide the patient with a short-acting, inhaled $beta_2$-agonist (e.g., albuterol) for treatment of symptoms that occur acutely, despite regular twice daily (morning and evening) use of Serevent Inhalation Aerosol.

When beginning treatment with Serevent Inhalation Aerosol, patients who have been taking short-acting, inhaled $beta_2$-agonists on a regular basis (e.g., q.i.d.) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief if they develop acute asthma symptoms while taking Serevent Inhalation Aerosol (see PRECAUTIONS: Information for Patients).

3. Watch for Increasing Use of Short-Acting, Inhaled $Beta_2$-Agonists, Which Is a Marker of Deteriorating Asthma: Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's short-acting, inhaled $beta_2$-agonist becomes less effective or the patient needs more inhalations than usual, this may be a marker of destabilization of asthma. In this setting, the patient requires immediate re-evaluation with reassessment of the treatment regimen, giving special consideration to the possible need for corticosteroids. If the patient uses four or more inhalations per day of a short-acting, inhaled $beta_2$-agonist for 2 or more consecutive days, or if more than one canister (200 inhalations per canister) of short-acting, inhaled $beta_2$-agonist is used in an 8-week period in conjunction with Serevent Inhalation Aerosol, then the patient should consult the physician for re-evaluation. **Increasing the daily dosage of Serevent Inhalation Aerosol in this situation is not appropriate. Serevent Inhalation Aerosol should not be used more frequently than twice daily (morning and evening) at the recommended dose of two inhalations.**

4. Do Not Use Serevent Inhalation Aerosol as a Substitute for Oral or Inhaled Corticosteroids: There are no data demonstrating that Serevent Inhalation Aerosol has a clinical anti-inflammatory effect and could be expected to take the place of, or reduce the dose of corticosteroids. Patients who already require oral or inhaled corticosteroids for treatment of asthma should be continued on this type of treatment even if they feel better as a result of initiating Serevent Inhalation Aerosol. Any change in corticosteroid dosage should be made ONLY after clinical evaluation (see PRECAUTIONS: Information for Patients).

5. Do Not Exceed Recommended Dosage: As with other inhaled $beta_2$-adrenergic drugs, Serevent Inhalation Aerosol should not be used more often or at higher doses than recommended. 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 interval, which has the potential for producing ventricular arrhythmias.

6. Paradoxical Bronchospasm: As with other inhaled asthma medication, 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.

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

8. Upper Airway Symptoms: Symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported rarely in patients receiving Serevent Inhalation Aerosol.

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 leaflet. **SHAKE WELL BEFORE USING.**

It is important that patients understand how to use Serevent Inhalation Aerosol appropriately and how it should be used in relation to other asthma medications they are taking. Patients should be given the following information:

1. Shake well before using.

2. The recommended dosage (two inhalations twice daily, morning and evening) should not be exceeded.

3. Serevent Inhalation Aerosol is not meant to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with a short-acting, inhaled $beta_2$-agonist such as albuterol (the physician should provide the patient with such medication and instruct the patient in how it should be used).

4. The physician should be notified immediately if any of the following situations occur, which may be a sign of seriously worsening asthma.

- Decreasing effectiveness of short-acting, inhaled $beta_2$-agonists
- Need for more inhalations than usual of short-acting, inhaled $beta_2$-agonists
- Use of four or more inhalations per day of a short-acting $beta_2$-agonist for 2 or more days consecutively
- Use of more than one canister of a short-acting, inhaled $beta_2$-agonist in an 8-week period (i.e., canister with 200 inhalations)

5. Serevent Inhalation Aerosol should not be used as a substitute for oral or inhaled corticosteroids. The dosage of these medications should not be changed and they should not be stopped without consulting the physician, even if the patient feels better after initiating treatment with Serevent Inhalation Aerosol.

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

7. In patients receiving Serevent Inhalation Aerosol, other inhaled medications should be used only as directed by the physician.

8. When using Serevent Inhalation Aerosol to prevent exercise-induced bronchospasm, patients should take the dose 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 $1^1/_2$ 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 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 forced expiratory volume in 1 second (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, angioedema, 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 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.

Postmarketing Experience: In extensive US and worldwide postmarketing experience, serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating (see WARNINGS no. 1), but they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether Serevent Inhalation Aerosol contributed to these events or simply failed to relieve the deteriorating asthma.

Postmarketing experience includes rare reports of upper airway symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking.

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

December 1994
RL-164
OM.BS.S1

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SEREVENT protected against exercise-induced bronchospasm (EIB) for up to 12 hours in the majority of patients[1-3]

SEREVENT is indicated for prevention of exercise-induced bronchospasm (EIB) in patients 12 years of age and older.

Dosing should be two puffs (42 µg) at least 30 to 60 minutes before exercise.

Patients being treated with SEREVENT twice daily, morning and evening, approximately 12 hours apart, should not use additional SEREVENT before exercising.

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(salmeterol xinafoate)

Inhalation Aerosol

Morning and Evening Inhalation for Active Days and Restful Nights

Please consult Brief Summary of Prescribing Information on the preceding pages.

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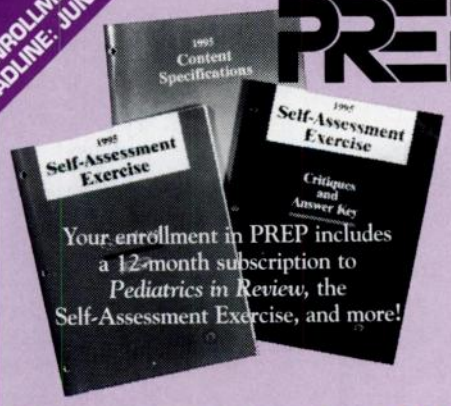

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ment, although one child was suspected to have this problem in infancy, only to improve later in childhood. That child also had cerebral palsy. The children in our study have been followed-up not only by the ophthalmologist, but the majority of them have also had their growth and development assessed by an experienced follow-up team. It is unlikely that we would have missed any blind children from cortical visual impairment.

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Foreign Bodies of the Lower Airway: Sunflower Seed Alert!

To the Editor.—

Jackson and Jackson,[1] in their landmark text, describe over 3000 foreign bodies of the air and food passages removed during their careers. Of these, 565 were vegetative and from the tracheobronchial tree. In their detailed list of foreign body types, sunflower seeds are not mentioned. A review of airway foreign bodies removed from children in the last 4 years at St. Christopher's Hospital for Children, the Jacksons' main operative hospital for children, showed a remarkable change. Sunflower seeds now comprised 16% (6/38) of all airway foreign bodies, second only to peanuts (12/38) in their recovery from the lower airway. Reviewing series from the last three decades, the percentage of sunflowers seeds retrieved appears to be rapidly rising. Law and Kosloske[2] reported a 4% (3/76) incidence in 1976, while a large 1991 series[3] marked a rise to 13% (50/400).

Like peanuts, sunflower seeds are ideal airway foreign bodies. They are often pleasantly salted and so are held in the oral cavity for prolonged pleasure. During a sudden inspiration, these thin, bullet-shaped missiles are then ready to roar down between the vocal folds. In addition, there appears to be a tendency for these flat, wide seeds to lodge in the subglottis or trachea.[4] In either location, they may elude detection as they are radiolucent and produce atypical physical signs.[5] In the subglottis, an irritative seed may cause edema and imitate "croup." If trapped in the trachea, a sunflower seed may not produce the usual signs of unilateral hyperinflation on chest radiographs seen with bronchial foreign bodies.[6]

Most parents seem to be aware of the dangers of feeding nuts, especially peanuts, to young children, but a similar awareness of the risk of sunflower seeds seems to be lacking. Parental desires to provide their children with "health foods" may in some cases be placing them at increased risk.[7] Parents should be warned that sunflower seeds are inappropriate for small children.

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A TALE OF TWO STATES

When Oregon decided to stop paying for transplants until all people below the poverty line had basic health care, the criticism was volcanic. Colby Howard, denied a transplant, died on the front page of America's newspapers. Yet it is instructive to compare what California did when confronted with a similar choice. California voted to pay for transplants. Then, one week later, they knocked 270,000 low-income Californians off the Medicaid rolls. The *New England Journal of Medicine* documents that California killed far more people than Oregon did—but Oregon got all the criticism.

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Submitted by Student