AAP NEWS
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THE OFFICIAL NEWSMAGAZINE OF THE AMERICAN ACADEMY OF PEDIATRICS
VOLUME 20 NUMBER 4
April 2002

Save the dates!

Boston 2002

National Conference & Exhibition

October 19-23, 2002

Hynes Convention Center/Boston Marriott Copley Place
Boston, MA

For over 350 years, people have come to Boston for top quality education. Be part of this great tradition. Plan now to come to Boston in October for the best in pediatric CME at the AAP National Conference & Exhibition.

Great CME

The fuller schedule and new formats introduced last year have been designed to give you more choices, more sessions, and more interactive learning…in short, more top-quality CME.

- Simpler pricing provides attendees easy access to more sessions. For most attendees, that means the highest value at a low price.
- Two-hour sessions (instead of three) provide more educational opportunities for each attendee each day.
- Over 350 sessions, including repeats of traditionally sold-out sessions, provide greater access to education on high-demand topics.
- Breakfast and lunchtime meet-the-expert discussions offer small-group access to pediatric leaders and to more hours of CME each day.
- Interactive learning opportunities include more than 30 audience response case discussions and more than 50 workshops.

Education Highlights

From new diagnosis and treatment guidelines for common problems to the latest surgical techniques and genetic advancements, the 2002 AAP National Conference & Exhibition offers top quality education. Highlights include:

- programs on terrorism and disaster preparedness
- Tissue Engineering
- Solving Children's Sleep Problems
- New Vaccines & Vaccine Combinations
- 2002 CDC STD guidelines
- Complementary and Alternative Medicine
- Gastroesophageal Reflux Disease
- New Antibiotics, Antivirals, and Other Anti-Infectives
- A Complete Track on Developmental and Behavioral Pediatrics
- Bovine Spongiform Encephalopathy: Mad Cow Disease
- New Perspectives in the Management of DDH
- Reducing Medical Errors
- Pain Management
- Improve Your Bottom Line: Getting Paid for What You Do
- New Advances in the Management of Type 1 Diabetes

Why you should attend

- Network with your colleagues from across the country and around the world
- Discuss your most challenging cases
- Update your clinical skills and techniques
- Hear the latest from world-renowned pediatric experts
- Attend cutting-edge seminars, workshops, and sessions
- Earn valuable AMA PRA Category 1 credits
- Visit Boston, for the best from the colonial past and the cutting edge

BOSTON POPS!

The Best of Old and New

From Bunker Hill to the Back Bay, Boston has it all. Combining milestones of the nation's historic past with the best of contemporary culture; Boston is the perfect place to come for CME and so much more.

For a taste of history, walk the Freedom Trail and take in the Paul Revere House, Faneuil Hall and Quincy Market, the Old North Church, and the USS Constitution, or venture to Concord and Lexington for echoes of the shot heard 'round the world. For a moving look at the more recent past, take the "T" to the John F. Kennedy Library and Museum.

Back in town, stroll through the elegant streets of Beacon Hill, amble through the Boston Common, or float through the Public Garden in its famous swan boats. Visit Newberry Street for world-class shopping or the North End for tastes from old-world Italy. For high culture, the Museum of Fine Arts presents the treasures of one of the country's greatest collections, and the Boston Symphony Orchestra is a treasure all its own. For other grand institutions, cross the Charles River to Cambridge and visit Harvard and MIT; they're only two of the 60 universities and colleges that make Boston a leading center of learning and innovation.

The Best for Kids

From interactive museums to the nation's earliest history, Boston offers plenty especially for families. And if that's not enough, the AAP Family Tour Program will offer special rates to many of Boston's sights and attractions. Please refer to the registration program in the June issue of *AAP News* for specific tours and times.

Complete details, including registration materials, will appear in the June 2002 issue of AAP News. For program updates, visit the AAP Web site at www.aap.org/nce.htm.

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Zithromax®

(azithromycin for oral suspension)

Pfizer U.S. Pharmaceuticals

For older babies and toddlers,

A nutritionally balanced diet doesn't always come easily

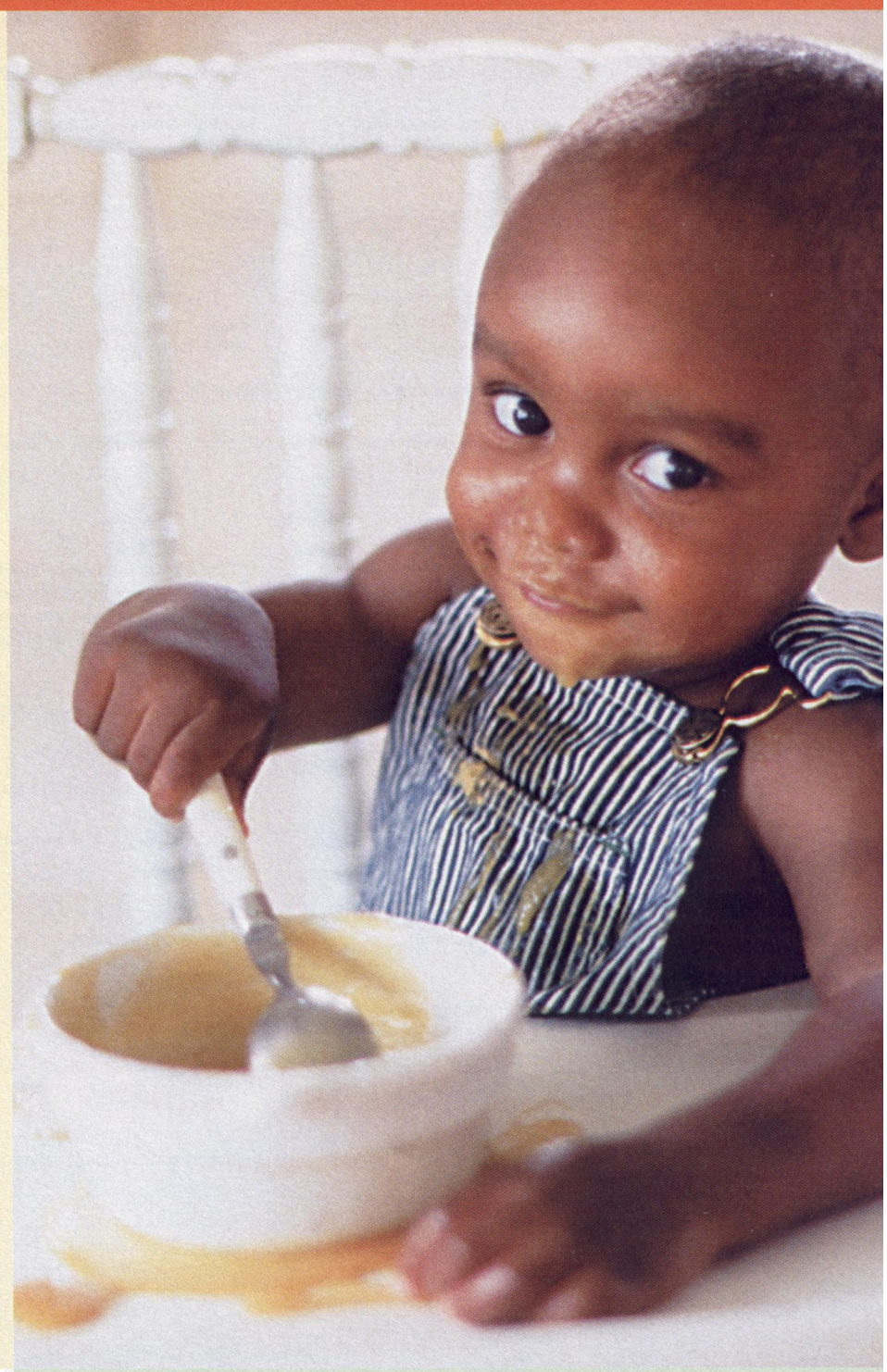
ISOMIL® 2 AND SIMILAC® 2 provide nutritional support as your young patients move to a broader diet.

A USDA study reveals that nutrient intakes don't always meet the recommended levels in children between the ages of 1 and 2.*

- More than 50% are not getting the RDA for iron and calcium
- More than 80% are not getting the RDA for zinc and vitamin E

And since nutritional needs change as babies grow, both Isomil 2 and Similac 2 have been designed to help promote complete, balanced nutrition.

- Isomil 2 contains 29% more calcium than Isomil® Soy Formula With Iron
- Similac 2 contains 50% more calcium than Similac® With Iron Infant Formula
- Both formulas are iron fortified** for growth and development



Recommend a cup a day.

Adding one cup of nutritionally complete Isomil 2 or Similac 2 to their daily diet can help one-year-olds meet the RDA for iron, calcium and other essential nutrients.

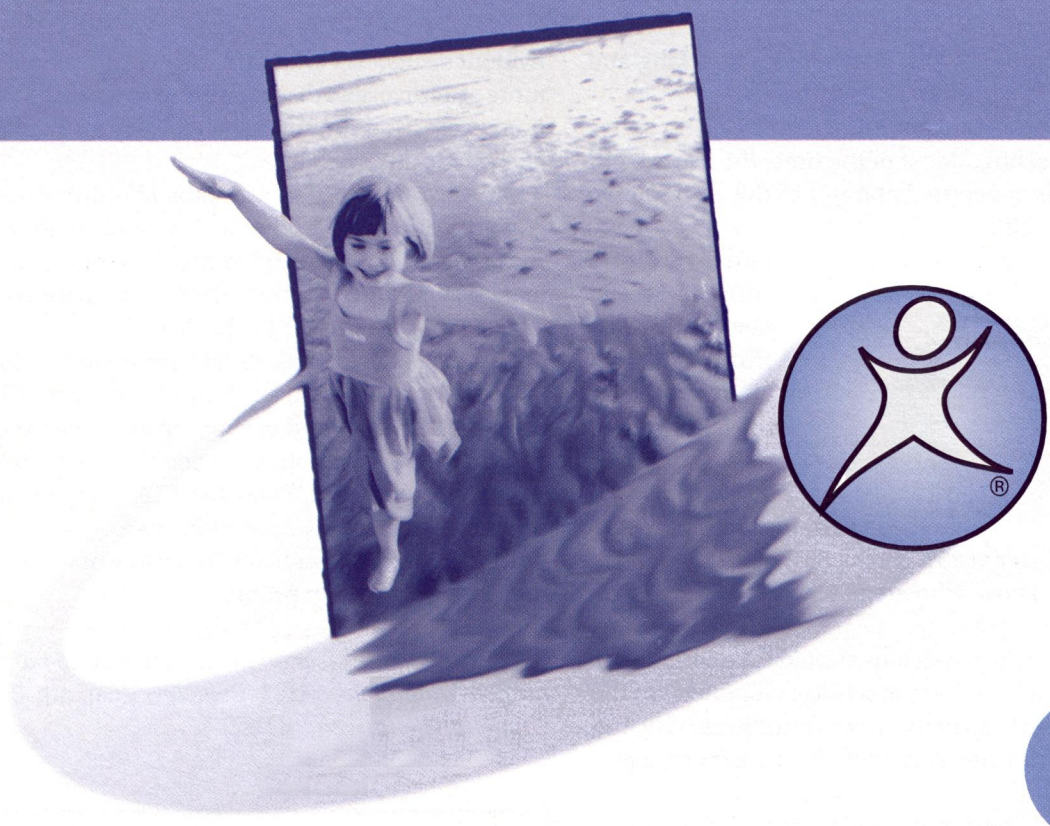
ROSS PEDIATRICS

B1033/March 2002

*US Department of Agriculture, Agricultural Research Service: Food and Nutrient Intakes by Children, 1994-1996, 1998. Table Set 17. (Numbers have been rounded. Percent based on Recommended Dietary Allowances, ed 10, 1989.) ARS Food Surveys Research Group, 1999.

**1.8 mg/100 Cal.

Pediatric patients need
Pediatric Medication.



PediaMed®
Pharmaceuticals, Inc.

Devoted to improving
the health of children

**Visit us at booth #312
at the AAP SuperCME 2002**

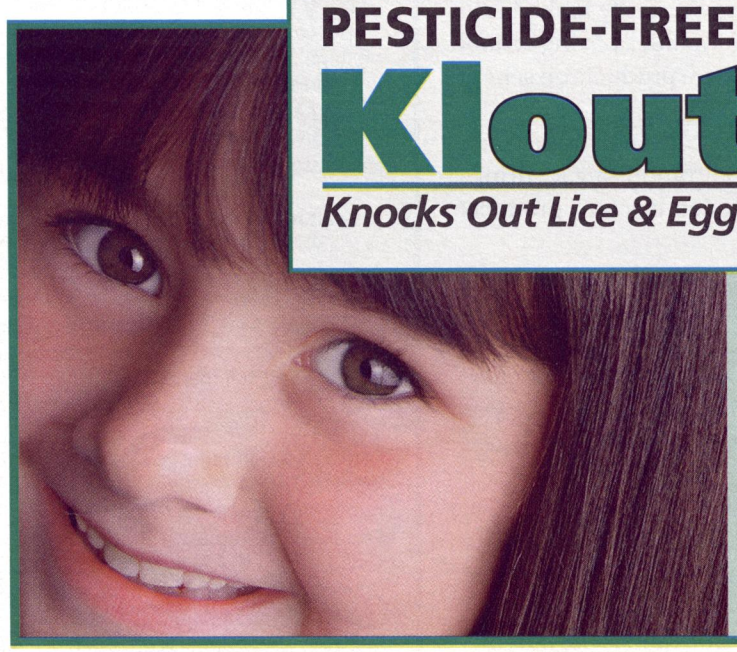
Convenient b.i.d. Dosing

Viravan®

(phenylephrine tannate,
pyrilamine tannate)

Give kids an advantage over allergic rhinitis or the common cold.

- Convenient b.i.d. Dosing
- Terrific Grape Taste
- Available in Both Chewable Tablet and Oral Suspension Formulations



PESTICIDE-FREE

Klout™

Knocks Out Lice & Eggs

Clinically proven 99% success rate

- Excellent safety profile
- So safe, can be used as often as necessary
- High-quality metal comb included in every kit

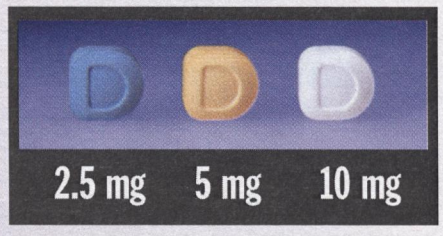
For more information about PediaMed and our product offerings, contact us toll-free at **1-866-KID-MEDS** (1-866-543-6337) or visit us at www.pediamedpharma.com

New FOR ADHD FROM THE MAKERS OF RITALIN®C II
(methylphenidate HCl)

THE RIGHT[1] HALF FOR THE EFFICACY THEY NEED

INTRODUCING FOCALIN™— ONLY THE EFFECTIVE ISOMER OF RITALIN

- **A refined form of Ritalin created by isolating the pharmacologically more active *d*-isomer, or right half[1,2]**
- **Safe and well tolerated in clinical trials[2]**
- **Short-acting for flexible dosing**
- **Recommended starting dose is 2.5 mg bid**



Please see brief summary of prescribing information, including **Contraindications** and **Boxed Warning,** on following page.

Focalin™ is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Focalin™ should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. (See Boxed Warning.)

New
Short-Acting
Focalin™ C II
dexmethylphenidate HCl tablets
2.5 mg, 5 mg, 10 mg

The ADHD Original. Refined.

References: 1. Anderson DM, ed. *Dorland's Illustrated Medical Dictionary.* 28th ed. Philadelphia, Pa: W.B. Saunders Co; 1994;455 (dexter [L.] right; a term denoting the right-hand one of two similar structures; or the one situated on the right side of the body). **2.** Data on file, Novartis Pharmaceuticals, Inc.

Kids preferred the great grape taste of Orapred® over Prelone® 2 to 1.[1]*

- The pleasant taste of Orapred may improve patient compliance.[2,3]
- In a survey of 500 parents, nearly 50% said that their children have refused to take medicine; bad taste was the #1 reason.[4]
- In a survey of 50 pediatricians, 88% characterized the taste of Prelone as a problem.[5]
- More than half of all pediatricians surveyed believed the bad taste had negatively affected their patients' outcome due to poor compliance.[5]
- Orapred has a unique, patented taste-masking system.

Orapred (prednisolone sodium phosphate oral solution) is not generically equivalent to Prelone (prednisolone syrup, USP).

Orapred has the 15 mg†/5 mL strength you need to treat inflammation.

As with all glucocorticoids, Orapred is contraindicated in persons with systemic fungal infections. Please refer to the brief summary of prescribing information for Orapred on the adjacent page for a complete listing of adverse events such as dermatologic and gastrointestinal disturbances.

Orapred must be kept refrigerated.

Orapred®

(prednisolone sodium phosphate oral solution) **15 mg†/5 mL**

Do your kids a flavor!

†Prednisolone base.

*Results of a blinded taste test conducted with 50 children, ages 4–11 years who, after tasting both Orapred and Prelone, were asked to state a preference.

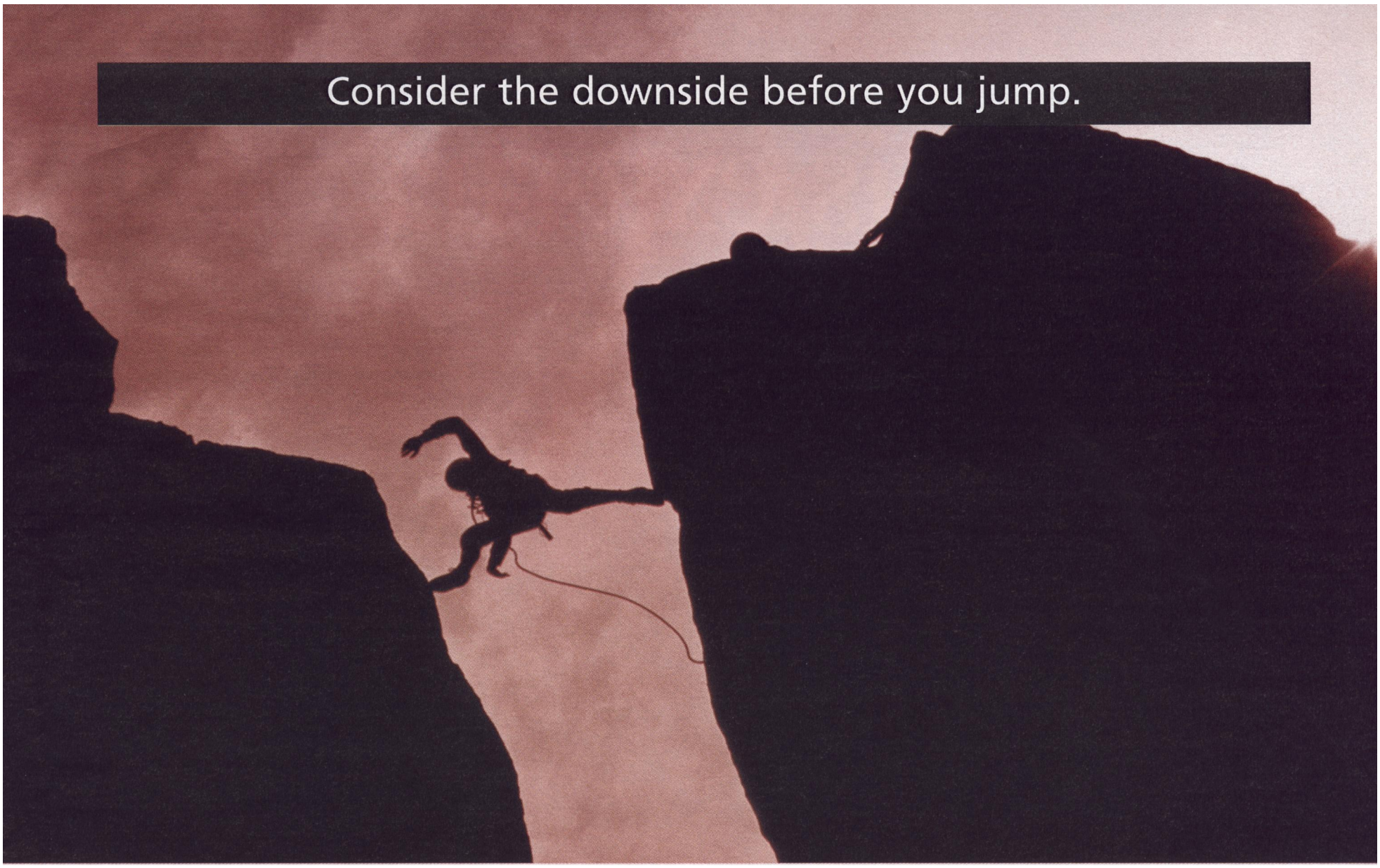
References: 1. (Taste test) Data on file, Ascent Pediatrics, 1999. **2.** Dajani AS. Adherence to physicians' instructions as a factor in managing streptococcal pharyngitis. *Pediatrics.* 1996;97(6, pt 2):976-980. **3.** Matsui DM. Drug compliance in pediatrics. Clinical research and issues. *Pediatr Clin North Am.* 1997;44:1-14. **4.** (Parents survey) Data on file, Ascent Pediatrics, 1997. **5.** (Pediatrician survey) Data on file, Ascent Pediatrics, 1999.

ASCENT PEDIATRICS, INC.

Medicine Just For Kids™

www.ascentpediatrics.com

AD0604 9/01

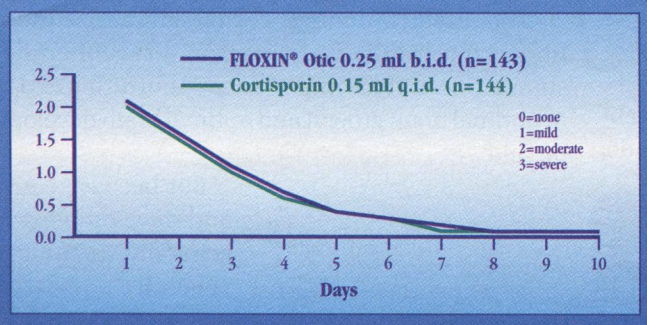


Often, what appears to be a short-cut can cost you dearly. Jumping for a "bargain" in medical malpractice insurance is a dangerous leap...a risky proposition for your practice and your future. As Illinois' leading medical professional liability insurer, we are dedicated to providing physicians and their practice entities superior protection with unparalleled service at affordable prices. It is easy to understand why physicians who choose ISMIE, stay with ISMIE. **Our outstanding record of proven results makes us the best insurance value in the business.** Call us today at 1-800-782-4767 or visit us at www.ismie.com.

NOW RATED A- (EXCELLENT) BY A.M.BEST!

ISMIE
The Physician-First Service Insurer
WHEN IT MATTERS MOST

Power to relieve pain
as fast as Cortisporin® otic solution‡, but without a steroid [1,2§]



‡Cortisporin is a registered trademark of Monarch Pharmaceuticals, Inc.

§Based on daily pain and discomfort assessment recorded by a parent or guardian for intent-to-treat pediatric population. Cortisporin otic solution contains neomycin, polymyxin B, and hydrocortisone.

Power against otitis externa
due to *Staphylococcus aureus* and *Pseudomonas aeruginosa* in patients ≥1 year of age

Percent eradicated

	100%
Pseudomonas aeruginosa	99%

Clinical cure rate[2]

Percentage of clinical cure

Staphylococcus aureus	100%
Pseudomonas aeruginosa	93%

Safe and well-tolerated *topical power*

Safety information

Most commonly reported adverse reactions in clinical trials in otitis externa patients treated twice daily with FLOXIN® Otic (n=229): pruritus (4%), application site reaction (3%), dizziness (1%), earache (1%), and vertigo (1%).

FLOXIN Otic is contraindicated in patients with a history of hypersensitivity to ofloxacin, other quinolones, or other ingredients of the medication, and should be discontinued at the first sign of allergic reaction. Patients who have not improved after 1 week of treatment should be evaluated by their doctor.

Safety and efficacy have not been established in patients <1 year of age with otitis externa.

First-line therapy

FLOXIN® (ofloxacin otic solution) 0.3% OTIC B.I.D.™

the power drop™

Please see brief summary below.

older, safety and effectiveness in infants below the age of one year have not been established. Although quinolones, including ofloxacin, have been shown to cause arthropathy in immature animals after systemic administration, young growing guinea pigs dosed in the middle ear with 0.3% ofloxacin otic solution for one month showed no systemic effects, quinolone-induced lesions, erosions of the cartilage in weight-bearing joints, or other signs of arthropathy.

ADVERSE REACTIONS

In the Phase III registration trials, a total of 885 subjects were treated with ofloxacin otic solution. This included 229 subjects with otitis externa (with intact tympanic membranes) and 656 subjects with acute otitis media with tympanostomy tubes or chronic suppurative otitis media with perforated tympanic membranes. The reported treatment-related adverse events are listed below:

Subjects with Otitis Externa

The following treatment-related adverse events occurred in 1% or more of the subjects with intact tympanic membranes.

Adverse Event	Frequency (n = 229)
Pruritus	4%
Application Site Reaction	3%
Dizziness	1%
Earache	1%
Vertigo	1%

The following treatment-related adverse events were each reported in a single subject: dermatitis, eczema, erythematous rash, follicular rash, rash, hypoaesthesia, tinnitus, dyspepsia, hot flushes, flushing, and otorrhagia.

Subjects with Acute Otitis Media with Tympanostomy Tubes and Subjects with Chronic Suppurative Otitis Media with Perforated Tympanic Membranes

The following treatment-related adverse events occurred in 1% or more of the subjects with non-intact tympanic membranes.

Adverse Event	Frequency (n = 656)
Taste Perversion	7%
Earache	1%
Pruritus	1%
Paraesthesia	1%
Rash	1%
Dizziness	1%

Other treatment-related adverse reactions reported in subjects with non-intact tympanic membranes included: diarrhea (0.6%), nausea (0.3%), vomiting (0.3%), dry mouth (0.5%), headache (0.3%), vertigo (0.5%), otorrhagia (0.6%), tinnitus (0.3%), fever (0.3%). The following treatment-related adverse events were each reported in a single subject: application site reaction, otitis externa, urticaria, abdominal pain, dysaesthesia, hyperkinesia, halitosis, inflammation, pain, insomnia, coughing, pharyngitis, rhinitis, sinusitis, and tachycardia.

DOSAGE AND ADMINISTRATION

Otitis Externa: The recommended dosage regimen for the treatment of otitis externa is: For pediatric patients (from 1 to 12 years old): Five drops (0.25 mL, 0.75 mg ofloxacin) instilled into the affected ear twice daily for ten days. For patients 12 years and older: Ten drops (0.5 mL, 1.5 mg ofloxacin) instilled into the affected ear twice daily for ten days. The solution should be warmed by holding the bottle in the hand for one or two minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. This position should be maintained for five minutes to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear.

Acute Otitis Media in pediatric patients with tympanostomy tubes: The recommended dosage regimen for the treatment of acute otitis media in pediatric patients (from one to 12 years old) with tympanostomy tubes is: Five drops (0.25 mL, 0.75 mg ofloxacin) instilled into the affected ear twice daily for ten days.

The solution should be warmed by holding the bottle in the hand for one or two minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. The tragus should then be pumped 4 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for five minutes. Repeat, if necessary, for the opposite ear.

Chronic Suppurative Otitis Media with perforated tympanic membranes: The recommended dosage regimen for the treatment of chronic suppurative otitis media with perforated tympanic membranes in patients 12 years or older is: Ten drops (0.5 mL, 1.5 mg ofloxacin) instilled into the affected ear twice daily for fourteen days.

The solution should be warmed by holding the bottle in the hand for one or two minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, before instilling the drops. The tragus should then be pumped 4 times by pushing inward to facilitate penetration into the middle ear. This position should be maintained for five minutes. Repeat, if necessary, for the opposite ear.

℞ Only

DAIICHI PHARMACEUTICAL CORPORATION
Montvale, NJ 07645
10/99
(FPI April 20, 1999)

References:

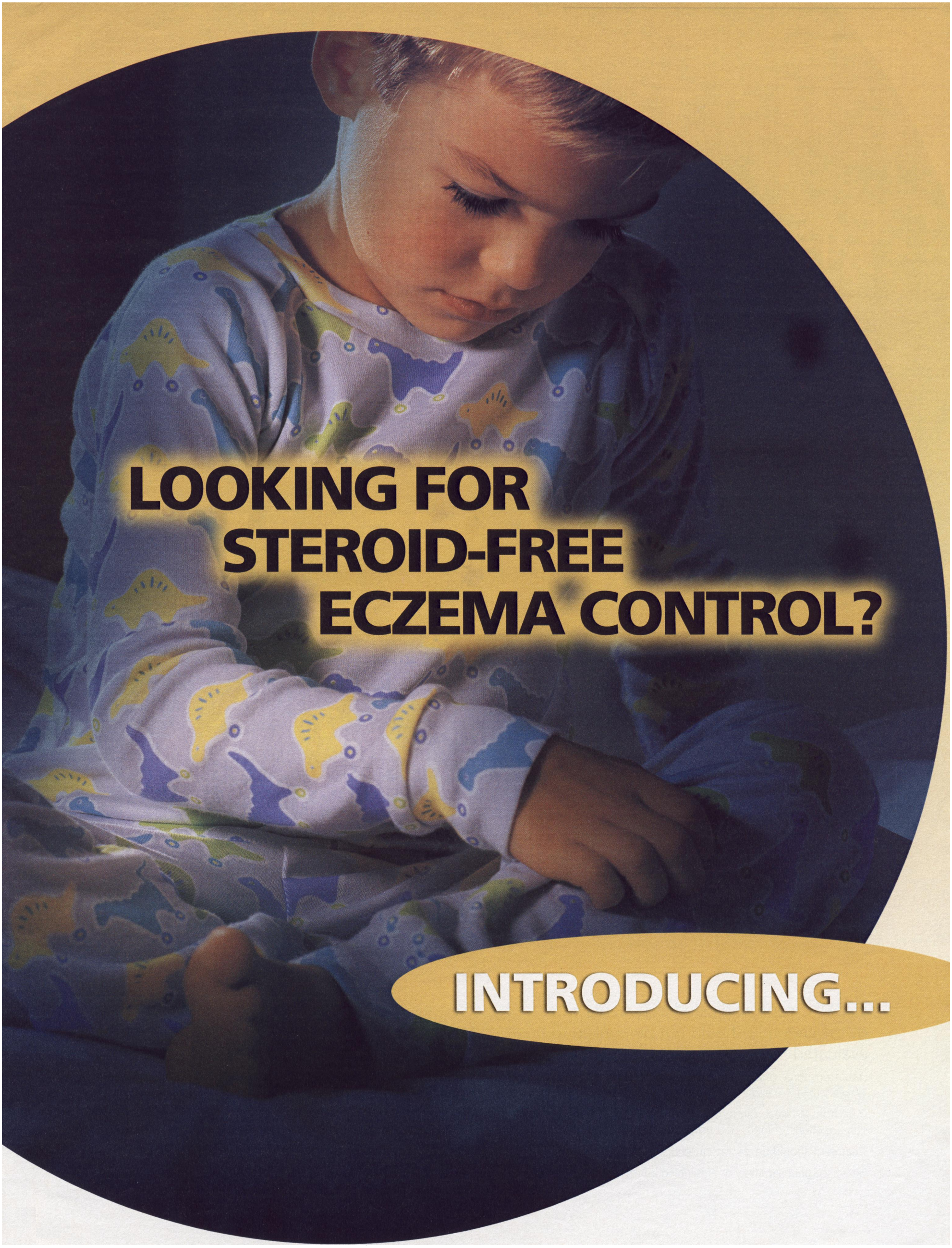
1. Jones RN, Milazzo J, Seidlin M. Ofloxacin otic solution for treatment of otitis externa in children and adults. *Arch Otolaryngol Head Neck Surg.* 1997;123:1193-1200.
2. Based on overall responses of twice-daily ofloxacin-treated patients in Phase III clinical trials (NDA 20-799).

ORTHO-McNEIL

DAIICHI Daiichi Pharmaceutical Corporation

McNeil Consumer Healthcare

FO-101-198 03/02


LOOKING FOR
STEROID-FREE
ECZEMA CONTROL?
INTRODUCING...

ELIDEL is contraindicated in patients who are hypersensitive to pimecrolimus or any of the components of the cream. It should not be applied to areas of active cutaneous infections. Use should be carefully evaluated if varicella zoster virus, herpes simplex virus, or eczema herpeticum infections are present.

† Data from three phase 3 randomized, placebo-controlled, multicenter, efficacy and safety studies conducted in pediatric patients aged 2 to 17 years (n=1114) and 1 active-controlled adult study (N=658).

‡ Data from a 1-year, randomized, multicenter, double-blind, placebo-controlled study in patients aged 2 to 17 years. An increased incidence of skin infections, rhinitis, and urticaria was found in patients using ELIDEL sequentially with topical corticosteroids as compared to ELIDEL alone.

§ Treatment should be discontinued upon resolution of disease. Patients should be re-evaluated if symptoms persist beyond 6 weeks.

Please see brief summary of Prescribing Information.

When you want or need to avoid corticosteroids for your mild to moderate patients*

ELIDEL® in control.

- The efficacy and safety of new ELIDEL have been evaluated in 1772 pediatric and adult patients[†1]
- New ELIDEL effectively relieves the itch, redness, inflammation, and excoriation of eczema flares
- New ELIDEL is proven safe in patients aged 2 years through adult
- In a 1-year pediatric safety study, 57% of ELIDEL patients had no flares requiring a corticosteroid[‡]
- New ELIDEL is an odor-free, easy-to-use cream that may be used on the face, neck, hands, and sensitive skin areas
- New ELIDEL should be used twice daily at the earliest signs or symptoms and for as long as they persist*[§]

*ELIDEL is indicated for short-term and intermittent long-term therapy for *mild to moderate* atopic dermatitis in non-immunocompromised patients 2 years of age and older, in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, inadequate clinical response, or patient intolerance of such therapies.

NEW Steroid-Free

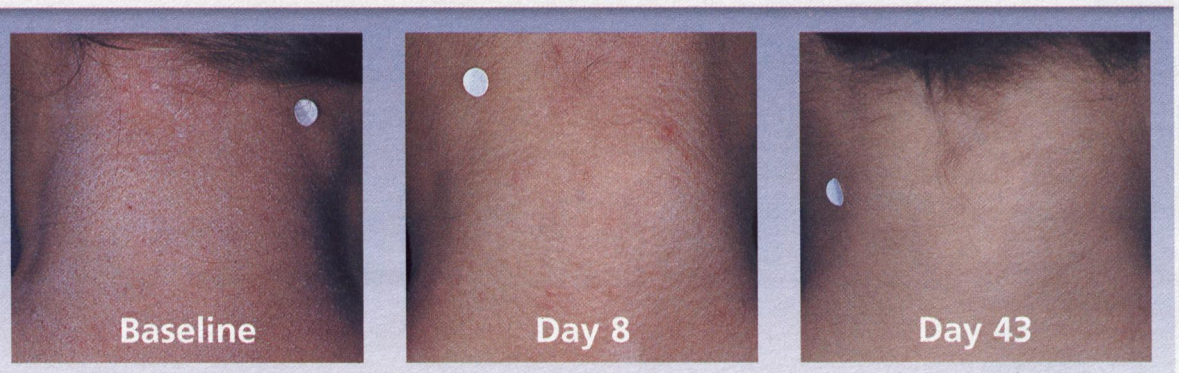
ELIDEL®

(pimecrolimus) Cream 1%

See eczema control with ELIDEL® for yourself[1]

8-year-old female Caucasian treated with ELIDEL for eczema on neck

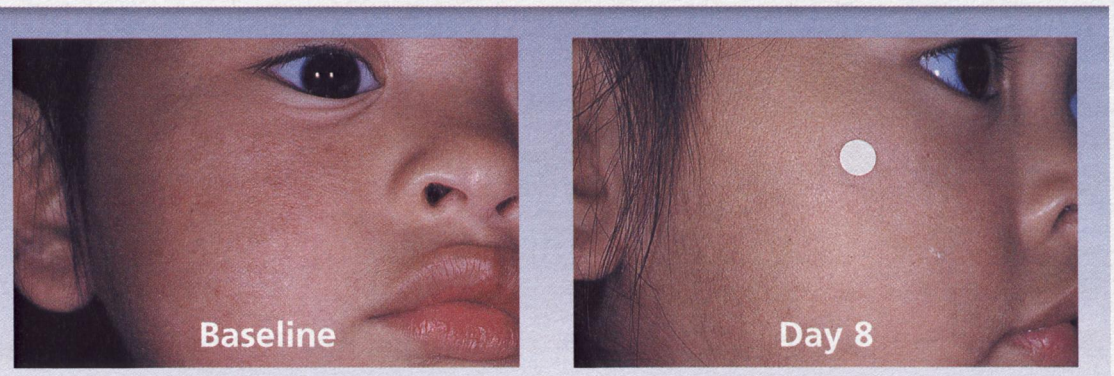
Subject's Assessment (Day 43):
Complete disease control



	Baseline	Day 8	Day 43
Severity of eczema (IGA)	moderate	mild	almost clear
EASI	9.6	3.2	0.2

2-year-old female Asian treated with ELIDEL for eczema on face

Subject's/Caregiver's Assessment (Day 8):
Complete disease control



	Baseline	Day 8
Severity of eczema (IGA)	moderate	almost clear
EASI	4.8	0.6

IGA=Investigator's Global Assessment. EASI=Eczema Area and Severity Index.[2]

- 35% of patients treated with ELIDEL were "clear or almost clear" of signs of atopic dermatitis at 6 weeks*
- Results described here may not be representative of entire patient population; individual results may vary

If patients have lymphadenopathy that is unresolved or of unclear etiology, discontinuation should be considered. Patients should minimize or avoid natural or artificial sunlight exposure. **ELIDEL should not be used with occlusive dressings.**

The most common adverse events seen in clinical studies included application-site burning, headache, pharyngitis, nasopharyngitis, cough, influenza, pyrexia, and viral infection.

In clinical studies, skin papilloma or warts were observed in 1% of ELIDEL patients.

The efficacy and safety of ELIDEL have not been studied beyond 1 year.

*Based on investigator's global assessment of disease severity in the 6-week, double-blind phases of two, 26-week, multicenter trials comparing ELIDEL to placebo cream in pediatric patients aged 2 to 17 years (n=403).

References: 1. Data on file, Novartis Pharmaceuticals Corporation. **2.** Hanifin JM, Thurston M, Omoto M, et al. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. *Exp Dermatol.* 2001;10:11-18.

Please see brief summary of Prescribing Information.

NOVARTIS

NEW Steroid-Free ELIDEL® (pimecrolimus) Cream 1%

Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936

 Printed in USA (3/02) C-ELI-1004-A Printed on recycled paper

an alternative to steroids

the first nonsteroid topical immunomodulator (TIM) for moderate to severe atopic dermatitis

- for short-term and intermittent long-term therapy
- 0.1% and 0.03% for adults; 0.03% for children aged 2 to 15 years
- for patients who:
  - should avoid the potential risks of conventional therapies
  - are not adequately responsive to conventional therapies
- apply anywhere—including face, neck, sensitive areas

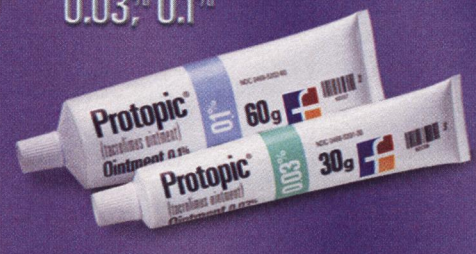
The most common adverse events associated with the use of Protopic Ointment included the sensation of skin burning, pruritus, flu-like symptoms, and headache. Local symptoms are most common during the first few days of application and typically improve as lesions heal.

Protopic Ointment is contraindicated in patients who are hypersensitive to tacrolimus or any of the other ingredients of Protopic.

Please see brief summary of prescribing information on the following page.

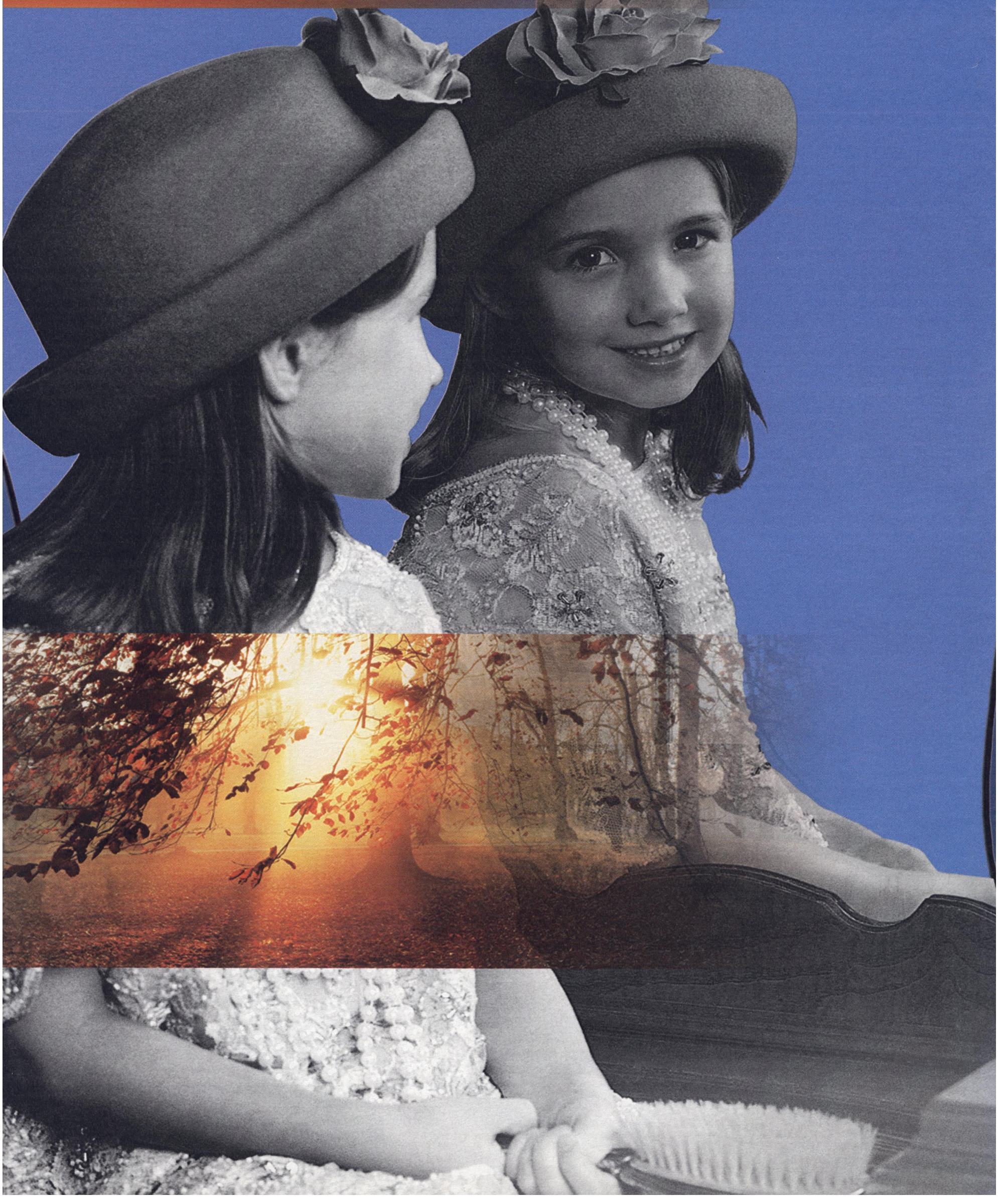
www.protopic.com

Protopic®
(tacrolimus) Ointment 0.03%, 0.1%



DRAMATICALLY DIFFERENT

NOW *approved in patients as young as 6 years...*



In β-agonist therapy

SINGLE-ISOMER TECHNOLOGY JUST RIGHT FOR HER.

- Now approved in two doses for children ages 6 to 11 years
- New lower dose...Xopenex 0.31 mg now available
- Important **new pediatric clinical data**—from one of the largest, well-controlled, pediatric trials conducted with a β-agonist[1]
- Proven safe at a low, effective dose
- Devoid of the unnecessary left isomer, (S)-albuterol

Xopenex®
(levalbuterol HCl)

*Inhalation Solution, 0.31 mg, 0.63 mg and 1.25 mg**

***Potency expressed as levalbuterol.**

Just right.

Important Safety Information

In patients aged 6 to 11 years, the adverse events occurring in ≥2% of patients and more frequently than with patients receiving placebo, were (0.31 mg Xopenex; 0.63 mg Xopenex; and placebo, respectively): headache (7.6%; 11.9%; 8.5%), pharyngitis (3%; 10.4%; 6.8%), rhinitis (6.1%; 10.4%; 1.7%), asthma (9.1%; 9%; 5.1%), fever (9.1%; 3%; 5.1%), viral infection (7.6%; 9%; 5.1%), rash (NA*; 7.5%; NA*), accidental injury (6.1%; 4.5%; 3.4%), diarrhea (1.5%; 6%; NA*), pain (3%; 1.5%; 3.4%), asthenia (3%; 3%; NA*), lymphadenopathy (3%; NA*; NA*), and urticaria (NA*; 3%; NA*).

In patients aged 12 years and older, the adverse events occurring in ≥2% of patients and more frequently than with patients receiving placebo, were (0.63 mg Xopenex; 1.25 mg Xopenex; and placebo, respectively): viral infection (6.9%; 12.3%; 9.3%), rhinitis (11.1%; 2.7%; 2.7%), nervousness (2.8%; 9.6%; NA*), tremor (NA*; 6.8%; NA*), sinusitis (4.2%; 1.4%; 2.7%), flu syndrome (4.2%; 1.4%; NA*), increased cough (1.4%; 4.1%; 2.7%), tachycardia (2.8%; 2.7%; NA*), pain (2.8%; 1.4%; 1.3%), turbinate edema (2.8%; 1.4%; NA*), dizziness (1.4%; 2.7%; 1.3%), dyspepsia (1.4%; 2.7%; 1.3%), leg cramps (NA*; 2.7%; 1.3%), accidental injury (NA*; 2.7%; NA*), anxiety (NA*; 2.7%; NA*), and migraine (NA*; 2.7%; NA*).

* Less than 2% reported.

Xopenex is contraindicated in patients with a history of hypersensitivity to levalbuterol HCl or racemic albuterol.

See reverse side for brief summary of Xopenex prescribing information and safety information concerning β-agonists.

Reference: 1. Milgrom H, Skoner DP, Bensch G, et al. Low-dose levalbuterol in children with asthma: safety and efficacy in comparison with placebo and racemic albuterol. *J Allergy Clin Immunol.* 2001;108:938-945.

Xopenex® (levalbuterol HCl) Inhalation Solution, 0.31 mg*, 0.63 mg*, 1.25 mg*

(zo´pə-neks´)

*Potency expressed as levalbuterol

BRIEF SUMMARY

INDICATIONS AND USAGE: Xopenex (levalbuterol HCl) Inhalation Solution is indicated for the treatment or prevention of bronchospasm in adults, adolescents and children 6 years of age and older with reversible obstructive airway disease.

CONTRAINDICATIONS: Xopenex (levalbuterol HCl) Inhalation Solution is contraindicated in patients with a history of hypersensitivity to levalbuterol HCl or racemic albuterol.

WARNINGS: 1. Paradoxical Bronchospasm: Like other inhaled beta-adrenergic agonists, Xopenex Inhalation Solution can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, Xopenex Inhalation Solution should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister or vial. 2. Deterioration of Asthma: Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of Xopenex Inhalation Solution than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids. 3. Use of Anti-Inflammatory Agents: The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen. 4. Cardiovascular Effects: Xopenex Inhalation Solution, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of Xopenex Inhalation Solution at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QT_c interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, Xopenex Inhalation Solution, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. 5. Do Not Exceed Recommended Dose: Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected. 6. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of racemic albuterol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving Xopenex Inhalation Solution.

PRECAUTIONS: General Levalbuterol HCl, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmias; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after the use of any beta-adrenergic bronchodilator. Large doses of intravenous racemic albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-adrenergic agonist medications, levalbuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Information for Patients The action of Xopenex (levalbuterol HCl) Inhalation Solution may last up to 8 hours. Xopenex Inhalation Solution should not be used more frequently than recommended. Do not increase the dose or frequency of dosing of Xopenex Inhalation Solution without consulting your physician. If you find that treatment with Xopenex Inhalation Solution becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek medical attention immediately. While you are taking Xopenex Inhalation Solution, other inhaled drugs and asthma medications should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, headache, dizziness, and tremor or nervousness. If you are pregnant or nursing, contact your physician about the use of Xopenex Inhalation Solution. Effective and safe use of Xopenex Inhalation Solution requires consideration of the following information in addition to that provided under Patient's Instructions for Use (see complete prescribing information): Xopenex Inhalation Solution single-use low-density polyethylene (LDPE) vials should be protected from light and excessive heat. Store in the protective foil pouch between 20°C and 25°C (68°F and 77°F). Do not use after the expiration date stamped on the container. Unused vials should be stored in the protective foil pouch. Once the foil pouch is opened, the vials should be used within two weeks. Vials removed from the pouch, if not used immediately, should be protected from light and used within one week. Discard any vial if the solution is not colorless.

The drug compatibility (physical and chemical), efficacy, and safety of Xopenex Inhalation Solution when mixed with other drugs in a nebulizer have not been established.

Drug Interactions Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should be used with caution with levalbuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

1. Beta-blockers: Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists such as Xopenex (levalbuterol HCl) Inhalation Solution, but may also produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

2. Diuretics: The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non-potassium sparing diuretics.

3. Digoxin: Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of racemic albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving levalbuterol HCl and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and Xopenex Inhalation Solution.

4. Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: Xopenex Inhalation Solution should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of levalbuterol HCl on the vascular system may be potentiated.

Carcinogenesis, Mutagenesis, and Impairment of Fertility No carcinogenesis or impairment of fertility studies have been carried out with levalbuterol HCl alone. However, racemic albuterol sulfate has been evaluated for its carcinogenic potential and ability to impair fertility. In a 2-year study in Sprague-Dawley rats, racemic albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately 2 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults and children on a mg/m² basis). In another study, this effect was blocked by the coadministration of propranolol, a nonselective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, racemic albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 500 mg/kg (approximately 260 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults and children on a mg/m² basis). In a 22-month study in the Golden hamster, racemic albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg (approximately 35 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults and children on a mg/m² basis). Levalbuterol HCl was not mutagenic in the Ames test or the CHO/HPRT Mammalian Forward Gene Mutation Assay. Although levalbuterol HCl has not been tested for clastogenicity, racemic albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay. Reproduction studies in rats using racemic albuterol sulfate demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 55 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m² basis).

Teratogenic Effects — Pregnancy Category C A reproduction study in New Zealand White rabbits demonstrated that levalbuterol HCl was not teratogenic when administered orally at doses up to 25 mg/kg (approximately 110 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m² basis). However, racemic albuterol sulfate has been shown to be teratogenic in mice and rabbits. A study in CD-1 mice given racemic albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m² basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately equal to the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m² basis). The drug did not induce cleft palate formation when administered subcutaneously at a dose of 0.025 mg/kg (less than the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m² basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with 2.5 mg/kg of isoproterenol (positive control). A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when racemic albuterol sulfate was administered orally at a dose of 50 mg/kg (approximately 110 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m² basis). A study in which pregnant rats were dosed with radiolabeled racemic albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus. There are no adequate and well-controlled studies of Xopenex Inhalation Solution in pregnant women. Because animal reproduction studies are not always predictive of human response, Xopenex Inhalation Solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. During marketing experience of racemic albuterol, various congenital anomalies, including cleft palate and limb defects, have been rarely reported in the offspring of patients being treated with racemic albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between racemic albuterol use and congenital anomalies has not been established.

Use in Labor and Delivery Because of the potential for beta-adrenergic agonists to interfere with uterine contractility, the use of Xopenex Inhalation Solution for the treatment of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Tocolysis Levalbuterol HCl has not been approved for the management of preterm labor. The benefit:risk ratio when levalbuterol HCl is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with $beta_2$-agonists, including racemic albuterol.

Nursing Mothers Plasma levels of levalbuterol after inhalation of therapeutic doses are very low in humans, but it is not known whether levalbuterol is excreted in human milk. Because of the potential for tumorigenicity shown for racemic albuterol in animal studies and the lack of experience with the use of Xopenex Inhalation Solution 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 Xopenex Inhalation Solution is administered to a nursing woman.

Pediatrics The safety and efficacy of Xopenex (levalbuterol HCl) Inhalation Solution have been established in pediatric patients 6 years of age and older in one adequate and well-controlled clinical trial. Use of Xopenex in children is also supported by evidence from adequate and well-controlled studies of Xopenex in adults, considering that the pathophysiology and the drugs's exposure level and effects in pediatric and adult patients are substantially similar. Safety and effectiveness of Xopenex in pediatric patients below the age of 6 years have not been established.

Geriatrics Data on the use of Xopenex in patients 65 years of age and older are very limited. A very small number of patients 65 years of age and older were treated with Xopenex Inhalation Solution in a 4-week clinical study (n=2 for 0.63 mg and n=3 for 1.25 mg). In these patients, bronchodilation was observed after the first dose on day 1 and after 4 weeks of treatment. There are insufficient data to determine if the safety and efficacy of Xopenex Inhalation Solution are different in patients < 65 years of age and patients 65 years of age and older. In general, patients 65 years of age and older should be started at a dose of 0.63 mg of Xopenex Inhalation Solution. If clinically warranted due to insufficient bronchodilator response, the dose of Xopenex Inhalation Solution may be increased in elderly patients as tolerated, in conjunction with frequent clinical and laboratory monitoring, to the maximum recommended daily dose.

ADVERSE REACTIONS (Adults and Adolescents ≥12 years old): Adverse events reported in ≥ 2% of patients receiving Xopenex Inhalation Solution or racemic albuterol and more frequently than in patients receiving placebo in a 4-week, controlled clinical trial are listed in **Table 1**.

Table 1: Adverse Events Reported in a 4-Week, Controlled Clinical Trial in Adults and Adolescents ≥ 12 years old

	Percent of Patients			
Body System Preferred Term	Placebo (n=75)	Xopenex1.25 mg (n=73)	Xopenex 0.63 mg (n=72)	Racemic albuterol 2.5 mg (n=74)
Body as a Whole				
Allergic reaction	1.3	0	0	2.7
Flu syndrome	0	1.4	4.2	2.7
Accidental injury	0	2.7	0	0
Pain	1.3	1.4	2.8	2.7
Back pain	0	0	0	2.7
Cardiovascular System				
Tachycardia	0	2.7	2.8	2.7
Migraine	0	2.7	0	0
Digestive System				
Dyspepsia	1.3	2.7	1.4	1.4
Musculoskeletal System				
Leg cramps	1.3	2.7	0	1.4
Central Nervous System				
Dizziness	1.3	2.7	1.4	0
Hypertonia	0	0	0	2.7
Nervousness	0	9.6	2.8	8.1
Tremor	0	6.8	0	2.7
Anxiety	0	2.7	0	0
Respiratory System				
Cough increased	2.7	4.1	1.4	2.7
Infection viral	9.3	12.3	6.9	12.2
Rhinitis	2.7	2.7	11.1	6.8
Sinusitis	2.7	1.4	4.2	2.7
Turbinate edema	0	1.4	2.8	0

The incidence of certain systemic beta-adrenergic adverse effects (e.g., tremor, nervousness) was slightly less in the Xopenex 0.63 mg group as compared to the other active treatment groups. The clinical significance of these small differences is unknown. Changes in heart rate 15 minutes after drug administration and in plasma glucose and potassium one hour after drug administration on day 1 and day 29 were clinically comparable in the Xopenex 1.25 mg and the racemic albuterol 2.5 mg groups (see **Table 2**). Changes in heart rate and plasma glucose were slightly less in the Xopenex 0.63 mg group compared to the other active treatment groups (see **Table 2**). The clinical significance of these small differences is unknown. After 4 weeks, effects on heart rate, plasma glucose, and plasma potassium were generally diminished compared with day 1 in all active treatment groups.

Table 2: Mean Changes from Baseline in Heart Rate at 15 Minutes and in Glucose and Potassium at 1 Hour after First Dose (Day 1) in Adults and Adolescents ≥12 years old

	Mean Changes (day 1)		
Treatment	Heart Rate (bpm)	Glucose (mg/dL)	Potassium (mEq/L)
Xopenex 0.63 mg, n=72	2.4	4.6	–0.2
Xopenex 1.25 mg, n=73	6.9	10.3	–0.3
Racemic albuterol 2.5 mg, n=74	5.7	8.2	–0.3
Placebo, n=75	–2.8	–0.2	–0.2

No other clinically relevant laboratory abnormalities related to administration of Xopenex Inhalation Solution were observed in this study. In the clinical trials, a slightly greater number of serious adverse events, discontinuations due to adverse events, and clinically significant ECG changes were reported in patients who received Xopenex 1.25 mg compared to the other active treatment groups. The following adverse events, considered potentially related to Xopenex, occurred in less than 2% of the 292 subjects who received Xopenex and more frequently than in patients who received placebo in any clinical trial:

Body as a Whole:	chills, pain, chest pain
Cardiovascular System:	ECG abnormal, ECG change, hypertension, hypotension, syncope
Digestive System:	diarrhea, dry mouth, dry throat, dyspepsia, gastroenteritis, nausea
Hemic and Lymphatic System:	lymphadenopathy
Musculoskeletal System:	leg cramps, myalgia
Nervous System:	anxiety, hypesthesia of the hand, insomnia, paresthesia, tremor
Special Senses:	eye itch

The following events, considered potentially related to Xopenex, occurred in less than 2% of the treated subjects but at a frequency less than in patients who received placebo: asthma exacerbation, cough increased, wheezing, sweating, and vomiting.

ADVERSE REACTIONS (Children 6 - 11 years old): Adverse events reported in ≥ 2% of patients in any treatment group and more frequently than in patients receiving placebo in a 3-week, controlled clinical trial are listed in **Table 3**.

Table 3: Most Frequently Reported Adverse Events (≥2% in Any Treatment Group) and More Frequently Than Placebo During the Double-Blind Period (ITT Population, 6 - 11 Years Old)

	Percent of Patients				
Body System Preferred Term	Placebo (n=59)	Xopenex 0.31 mg (n=66)	Xopenex 0.63 mg (n=67)	Racemic albuterol 1.25 mg (n=64)	Racemic albuterol 2.5 mg (n=60)
Body as a Whole					
Abdominal pain	3.4	0	1.5	3.1	6.7
Accidental injury	3.4	6.1	4.5	3.1	5.0
Asthenia	0	3.0	3.0	1.6	1.7
Fever	5.1	9.1	3.0	1.6	6.7
Headache	8.5	7.6	11.9	9.4	3.3
Pain	3.4	3.0	1.5	4.7	6.7
Viral Infection	5.1	7.6	9.0	4.7	8.3
Digestive System					
Diarrhea	0	1.5	6.0	1.6	0
Hemic and Lymphatic					
Lymphadenopathy	0	3.0	0	1.6	0
Musculoskeletal System					
Myalgia	0	0	1.5	1.6	3.3
Respiratory System					
Asthma	5.1	9.1	9.0	6.3	10.0
Pharyngitis	6.8	3.0	10.4	0	6.7
Rhinitis	1.7	6.1	10.4	3.1	5.0
Skin and Appendages					
Eczema	0	0	0	0	3.3
Rash	0	0	7.5	1.6	0
Urticaria	0	0	3.0	0	0
Special Senses					
Otitis Media	1.7	0	0	0	3.3

Note: Subjects may have more than one adverse event per body system and preferred term. Changes in heart rate, plasma glucose, and serum potassium are shown in **Table 4**. The clinical significance of these small differences is unknown.

Table 4: Mean Changes from Baseline in Heart Rate at 30 Minutes and in Glucose and Potassium at 1 Hour after First Dose (Day 1) and Last Dose (Day 21) in Children 6-11 years old

	Mean Changes (Day 1)		
Treatment	Heart Rate (bpm)	Glucose (mg/dL)	Potassium (mEq/L)
Xopenex 0.31 mg, n=66	0.8	4.9	–0.31
Xopenex 0.63 mg, n=67	6.7	5.2	–0.36
Racemic albuterol 1.25 mg, n=64	6.4	8.0	–0.27
Racemic albuterol 2.5 mg, n=60	10.9	10.8	–0.56
Placebo, n=59	–1.8	0.6	–0.05
	Mean Changes (Day 21)		
Treatment	Heart Rate (bpm)	Glucose (mg/dL)	Potassium (mEq/L)
Xopenex 0.31 mg, n=60	0	2.6	–0.32
Xopenex 0.63 mg, n=66	3.8	5.8	–0.34
Racemic albuterol 1.25 mg, n=62	5.8	1.7	–0.18
Racemic albuterol 2.5 mg, n=54	5.7	11.8	–0.26
Placebo, n=55	–1.7	1.1	–0.04

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