PEDIATRICS

American Academy of Pediatrics

MAY 1994
VOLUME 93
NUMBER 5

ARTICLES

SPECIAL ARTICLE

COMMENTARIES

EXPERIENCE AND REASON

SECTION REPORT

Committee Statements—For Contents See Page A13


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References: 1. Amadio P Jr. Am J Med. 1984;77 (3A):17-26. 2. Aspirin or paracetamol? Lancet. 1981; 2:287-289. 3. Settipane GA. Am J Med. 1983;74(6A): 102-109. 4. Walson PD et al. AJDC. 1992;146:626-632.
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1. Morales D, Craig LD, MacLean WC: Dietary management of malnourished children with a new enteral feeding. *J Am Diet Assoc* 1991;91:1233-1238.
2. Ross Study, CP#AD14 EXT, June 1992. Data available on request, Ross Laboratories, Pediatric Nutrition Research & Development, Columbus, Ohio.
3. Ross Study, CP#AD32, June 1992. Data available on request, Ross Laboratories, Pediatric Nutrition Research & Development, Columbus, Ohio.
4. National Research Council: *Recommended Dietary Allowances*, ed 10. Washington, DC: National Academy Press, 1989.

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

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References

1. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J.* 1991; 302:338-341
2. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *N Engl J Med.* 1991;324:424-428
3. Ad Hoc Working Group for Critical Appraisal of the Medical Literature. A proposal for more informative abstracts of clinical articles. *Ann Intern Med.* 1987;106:598-604
4. Iverson C, Dan BB, Glitman P, et al. *American Medical Association Manual of Style*. 8th ed. Baltimore, MD: Williams & Wilkins; 1988
5. Lundberg GD. SI unit implementation: the next step. *JAMA.* 1988;260: 73-76
6. Système International conversion factors for frequently used laboratory components. *JAMA.* 1991;266:45-47

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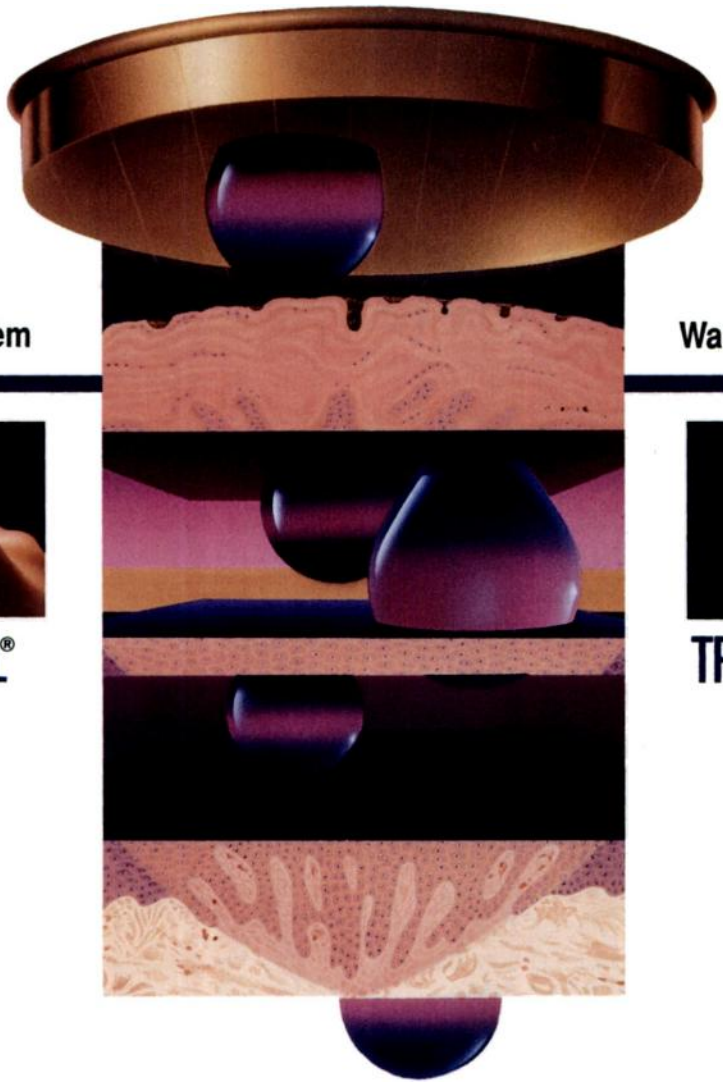

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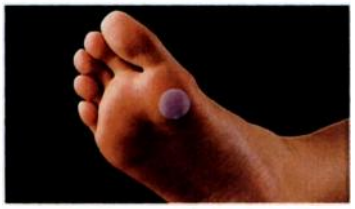

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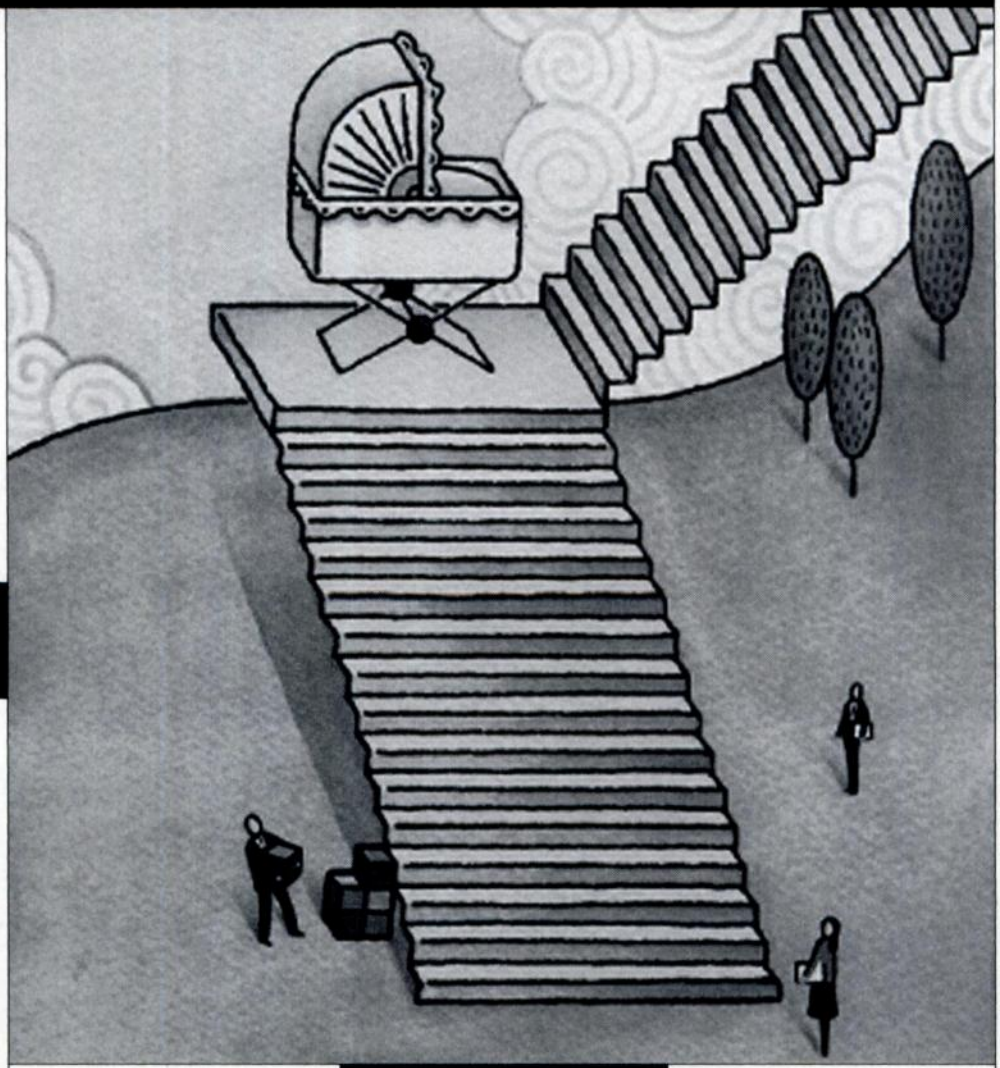

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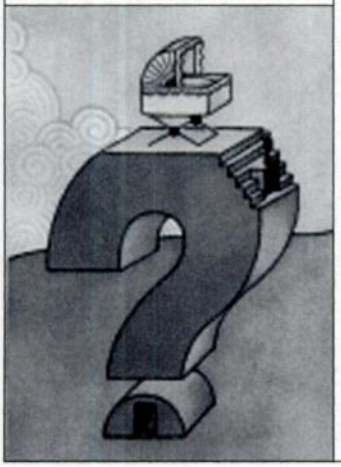

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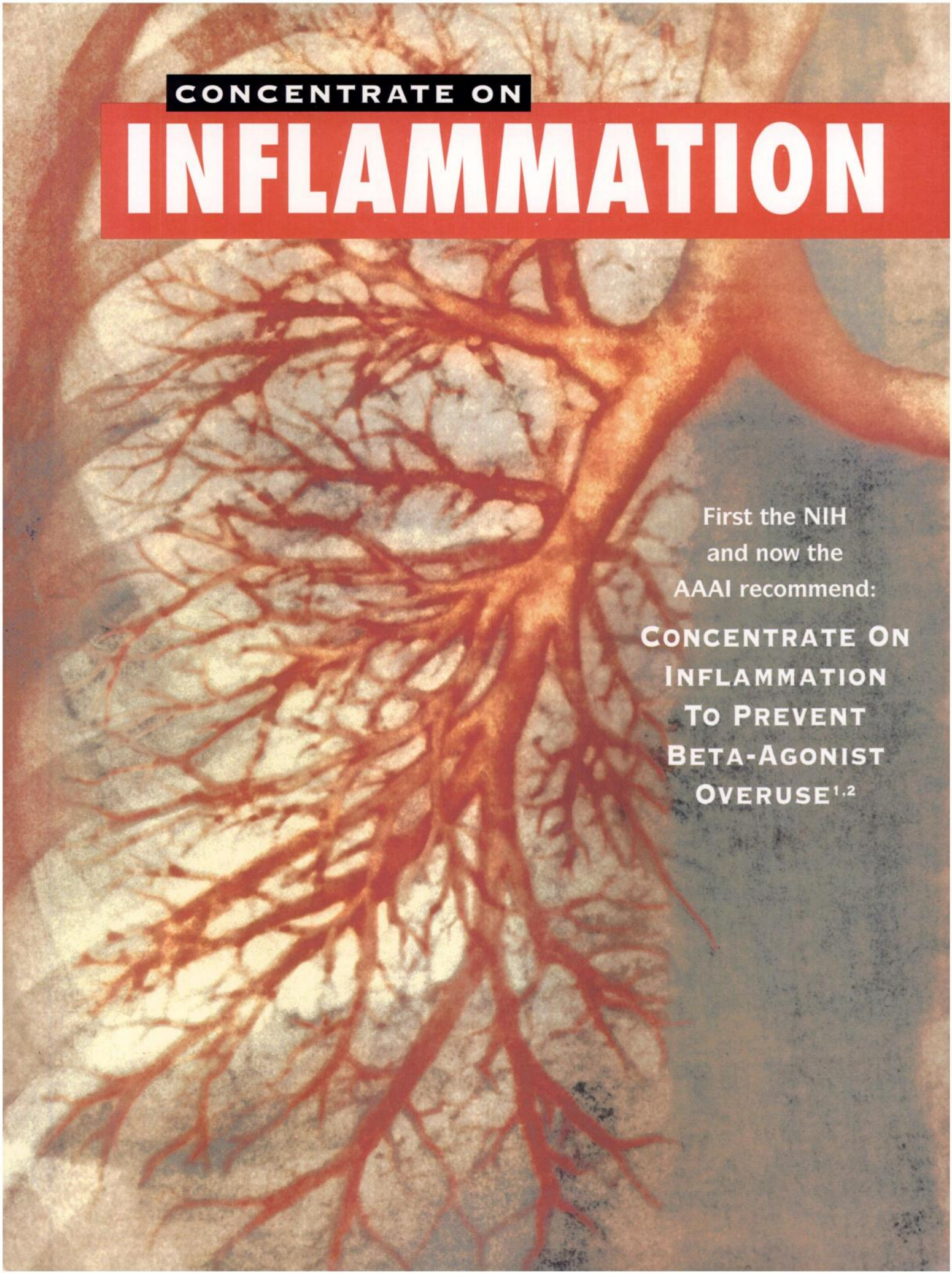
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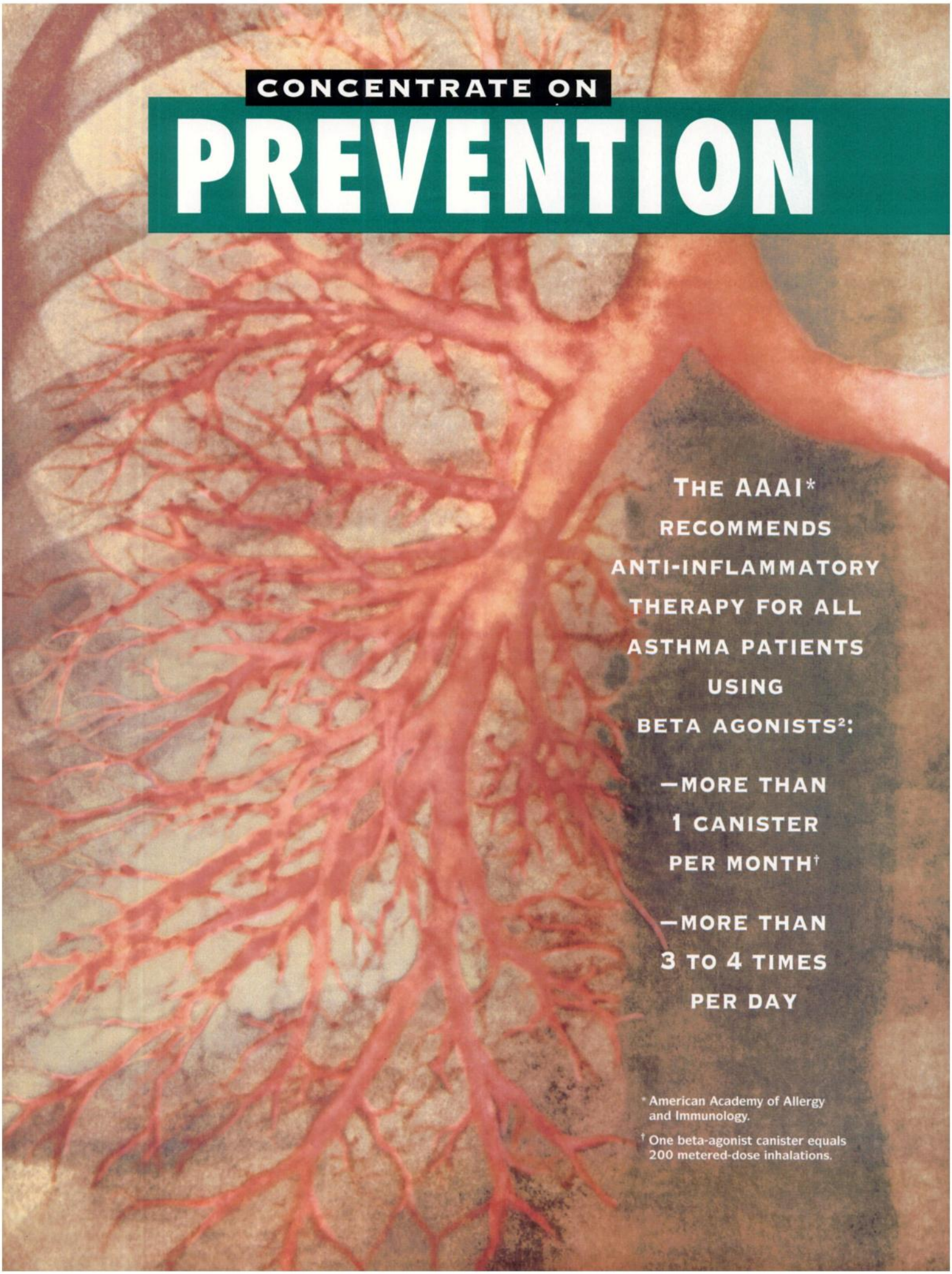
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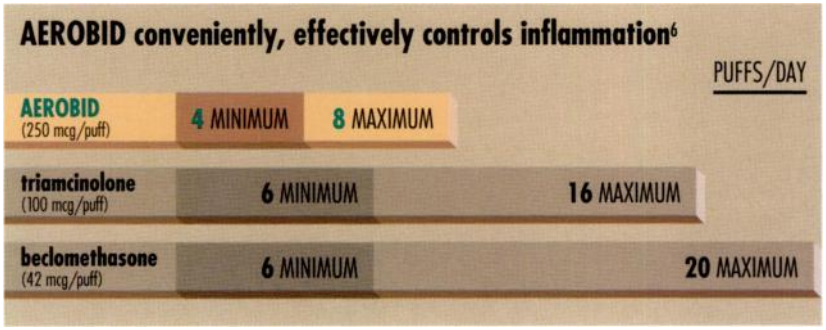

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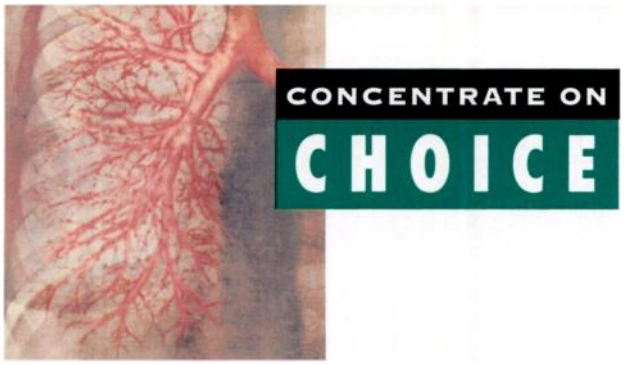
AEROBID®-M

(flunisolide) ***250 mcg/puff***

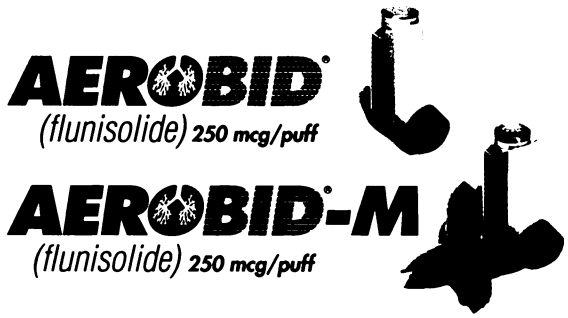


AEROBID: highly concentrated inhaled steroid therapy

- Effectively controls airway inflammation[6]
- Reduces beta-agonist dependence/use[2,4,7]
- Highly concentrated formulation—250 mcg/puff[5]
- Excellent safety profile—in adults *and* children[2-4,6]

AEROBID-M: the pleasant-tasting mint alternative

- All the benefits of original AEROBID
- Pleasant mint taste



Not recommended for chronic use with alternate prednisone regimens.

CAUTION: ADRENAL INSUFFICIENCY MAY OCCUR WHEN TRANSFERRING PATIENTS FROM SYSTEMIC STEROIDS (SEE WARNINGS).

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AEROBID®/AEROBID®-M (flunisolide)
Inhaler system for oral inhalation only
Brief summary of prescribing information

CONTRAINDICATIONS

AEROBID Inhaler is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS

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

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

Localized infections with *Candida albicans* or *Aspergillus niger* have occurred in the mouth and pharynx and occasionally in the larynx. Positive cultures for oral *Candida* may be present in up to 34% of patients. Although the frequency of clinically apparent infection is considerably lower, these infections may require treatment with appropriate antifungal therapy or discontinuance of treatment with **AEROBID** (flunisolide) Inhaler.

AEROBID Inhaler is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

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

There is no evidence that control of asthma can be achieved by administration of the drug in amounts greater than the recommended doses, which appear to be the therapeutic equivalent of approximately 10 mg/day of oral prednisone. Theoretically, the use of inhaled corticosteroids with alternate day prednisone systemic treatment should be accompanied by more HPA suppression than a therapeutically equivalent regimen of either alone.

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

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

PRECAUTIONS

General: Because of the relatively high molar dose of flunisolide per activation in this preparation, and because of the evidence suggesting higher levels of systemic absorption with flunisolide than with other comparable inhaled corticosteroids (see CLINICAL PHARMACOLOGY section), patients treated with **AEROBID** (flunisolide) should be observed carefully for any evidence of systemic corticosteroid effect, including suppression of bone growth in children. Particular care should be taken in observing patients post-operatively or during periods of stress for evidence of a decrease in adrenal function. During withdrawal from oral steroids, some patients may experience symptoms of systemically active steroid withdrawal, e.g., joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement of respiratory function (see DOSAGE AND ADMINISTRATION for details).

In responsive patients, flunisolide may permit control of asthmatic symptoms without suppression of HPA function. Since flunisolide is absorbed into the circulation and can be systemically active, the beneficial effects of **AEROBID** Inhaler in minimizing or preventing HPA dysfunction may be expected only when recommended dosages are not exceeded.

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

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

Pulmonary infiltrates with eosinophilia may occur in patients on **AEROBID (flunisolide)** Inhaler therapy. Although it is possible that in some patients this state may become manifest because of systemic steroid withdrawal when inhalational steroids are administered, a causative role for the drug and/or its vehicle cannot be ruled out.

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

Carcinogenesis: Long-term studies were conducted in mice and rats using oral administration to evaluate the carcinogenic potential of the drug. There was an increase in the incidence of pulmonary adenomas in mice, but not in rats.

Female rats receiving the highest oral dose had an increased incidence of mammary adenocarcinoma compared to control rats. An increased incidence of this tumor type has been reported for other corticosteroids.

Impairment of Fertility: Female rats receiving high doses of flunisolide (200 mcg/kg/day) showed some evidence of impaired fertility. Reproductive performance in the low (8 mcg/kg/day) and mid-dose (40 mcg/kg/day) groups was comparable to controls.

Pregnancy: Pregnancy Category C. As with other corticosteroids, flunisolide has been shown to be teratogenic in rabbits and rats at doses of 40 and 200 mcg/kg/day respectively. It was also fetotoxic in these animal reproductive studies. There are no adequate and well-controlled studies in pregnant women. Flunisolide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when flunisolide is administered to nursing women.

ADVERSE REACTIONS

Adverse events reported in controlled clinical trials and long-term open studies in 514 patients treated with **AEROBID (flunisolide)** are described below. Of those patients, 463 were treated for 3 months or longer, 407 for 6 months or longer, 287 for 1 year or longer, and 122 for 2 years or longer.

Musculoskeletal reactions were reported in 35% of steroid-dependent patients in whom the dose of oral steroid was being tapered. This is a well-known effect of steroid withdrawal.

Incidence 10% or greater

Gastrointestinal: diarrhea (10%), nausea and/or vomiting (25%), upset stomach (10%); *General:* flu (10%); *Mouth and Throat:* sore throat (20%); *Nervous System:* headache (25%); *Respiratory:* cold symptoms (15%), nasal congestion (15%), upper respiratory infection (25%); *Special Senses:* unpleasant taste (10%).

Incidence 3-9%

Cardiovascular: palpitations; *Gastrointestinal:* abdominal pain, heartburn; *General:* chest pain, decreased appetite, edema, fever; *Mouth and Throat: Candida* infection; *Nervous System:* dizziness, irritability, nervousness, shakiness; *Reproductive:* menstrual disturbances; *Respiratory:* chest congestion, cough,* hoarseness, rhinitis, runny nose, sinus congestion, sinus drainage, sinus infection, sinusitis, sneezing, sputum, wheezing*; *Skin:* eczema, itching (pruritus), rash; *Special Senses:* ear infection, loss of smell or taste.

Incidence 1-3%

General: chills, increased appetite and weight gain, malaise, peripheral edema, sweating, weakness; *Cardiovascular:* hypertension, tachycardia; *Gastrointestinal:* constipation, dyspepsia, gas; *Hemic/Lymph:* capillary fragility, enlarged lymph nodes; *Mouth and Throat:* dry throat, glossitis, mouth irritation, pharyngitis, phlegm, throat irritation; *Nervous System:* anxiety, depression, faintness, fatigue, hyperactivity, hypoactivity, insomnia, moodiness, numbness, vertigo; *Respiratory:* bronchitis, chest tightness,* dyspnea, epistaxis, head stuffiness, laryngitis, nasal irritation, pleurisy, pneumonia, sinus discomfort; *Skin:* acne, hives, or urticaria; *Special Senses:* blurred vision, earache, eye discomfort, eye infection.

Incidence less than 1%, judged by investigators as possibly or probably drug-related: abdominal fullness, shortness of breath.

*The incidences as shown of cough, wheezing, and chest tightness were judged by investigators to be possibly or probably drug-related. In placebo-controlled trials, the *overall* incidences of these adverse events (regardless of investigators' judgment of drug relationship) were similar for drug and placebo-treated groups. They may be related to the vehicle or delivery system.

Caution: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

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DDAVP® Nasal Spray
(desmopressin acetate) 5mL

Dry Nights For Good Mornings

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

ADVERSE REACTION	PLACEBO (N=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.
HOW SUPPLIED: A 5-mL bottle with spray pump delivering 50 doses of 10 mcg (NDC 0075-2450-02). Also available as 2.5 mL per vial, packaged with two rhinal tube applicators per carton (NDC 0075-2450-01). Keep refrigerated at 2°-8°C (36°-46°F). When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 22°C (72°F).
CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.
Please see full prescribing information in product circular.

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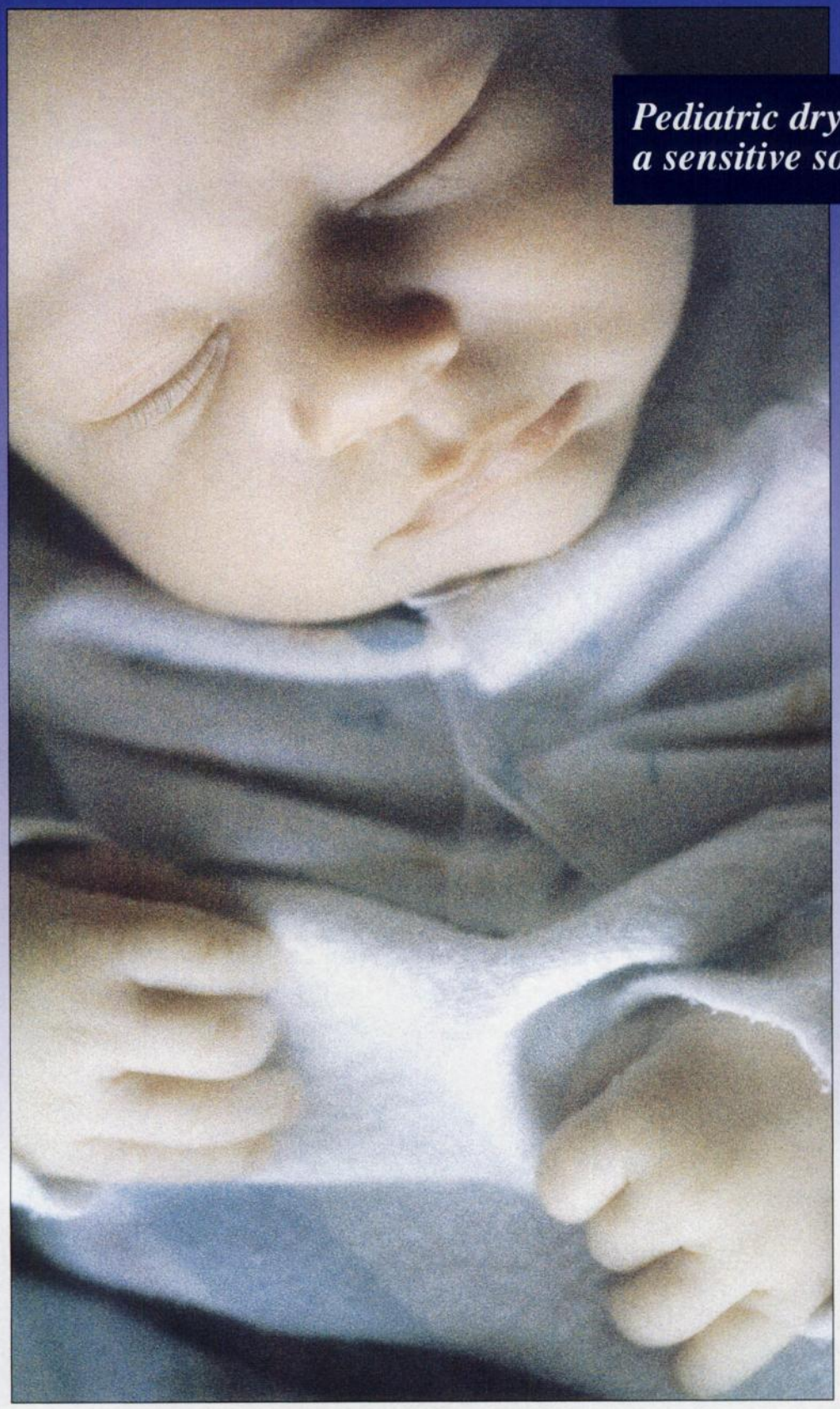

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FACULTY SCHOLARS' AWARDS

Each year the William T. Grant Foundation makes awards to up to five investigators whose research contributes to understanding the development and well-being of children, adolescents and youths. Awards are for five (5) years, totaling $175,000 including indirect costs.

The goal of the Faculty Scholars' Program is to promote children's development to healthy and productive adulthood by supporting investigators in a variety of fields on topics such as problem behaviors in school-age children. Applicants should be junior or pre-tenure, not established investigators (with a record of publication), in tenure-track positons. Award recipients will be called William T. Grant Faculty Scholars. Applicant institutions and individuals should obtain the brochure outlining the application procedure from Faculty Scholars Program, William T. Grant Foundation, 515 Madison Avenue, New York, New York 10022-5403. Deadline for applications for the 1995 awards is July 1, 1994.

nization with little or no out-of-pocket charges to their members, this suggests an economic influence on adoption. Other possibilities are that uniform educational efforts to providers within HMOs, as well as internal immunization policies, have an effect. Previous studies have demonstrated the crucial role of organizational factors in the implementation of practice recommendations.[9]

For many practitioners, recent changes in immunization recommendations have been difficult to understand and problematic to incorporate into customary practice. The situation is exacerbated by fragmented and staggered schedules of recommendation announcements from the CDC, AAP, and AAFP, as which occurred with the hepatitis B vaccine recommendation. Liaison representatives from these groups communicate with each other regarding the content of new immunization recommendations; coordinated announcement of these recommendations is a practical, viable way to reduce confusion and have a greater and more consistent impact on practitioners.

ACKNOWLEDGMENTS

Partial funding for this project was provided by SmithKline Beechum Pharmaceuticals and Merck Sharp & Dohme. Drs Freed and Konrad are supported in part by grant R01-5-51986 from the Agency for Health Care Policy and Research.

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CHILDHOOD MYOSITIS PATIENTS NEEDED FOR STUDY

The Laboratory of Molecular Immunology of the Food and Drug Administration is seeking referral of childhood myositis patients for a study that consists of completing a questionnaire and collecting a blood sample. We are interested in patients with any form of inflammatory muscle disease whose disease onset occurred at <18 years of age. This would include patients diagnosed as having juvenile dermatomyositis, polymyositis, myositis associated with another connective tissue disease, inclusion body myositis and cancer-associated myositis. We are also recruiting, as controls, children with other muscle disorders, rheumatic diseases without myositis, interstitial lung disease, or inflammatory skin diseases.

For further information please contact: Lisa G. Rider, M.D. or Frederick W. Miller, M.D., Ph.D., Laboratory of Molecular Immunology, CBER, FDA, Building 29, Room 507, HFM-521, Bethesda, MD 20892. Phone: 301-496-6913; FAX: 301-496-7027.

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KIDS AND CAMELS

Yet another study has found that cigarette advertisements with cartoon characters are highly effective in reaching adolescents.

A study published yesterday in Tobacco Control, a British Medical Association quarterly, found that ads featuring Joe Camel, R.J. Reynolds's stylish cartoon dromedary, are by far the most popular cigarette ads with seventh and eighth graders. Nearly three-quarters of the students liked the Camels ads, while 43% of the students liked ads with human models.

The study, of 243 teenagers in Chicago, found that students who liked the ads said they would likely buy Camels if they smoked. They said Joe Camel was "cool" and "fun," while the Marlboro man was "tough" and "macho."

Eighty-five percent of the students surveyed recalled seeing a cigarette ad within the previous week.

A spokeswoman for R.J. Reynolds, a unit of **RJR Nabisco Holdings** Corp., said there was no indication that liking or recognizing an ad leads to the use of a product.

Kids and Camels. *The Wall Street Journal*. February 5, 1993.

For problem gas, recommend the simple solution.

INFANTS' MYLICON® DROPS

simethicone/antiflatulent

Sig. 0.3 mL q.i.d.

Johnson & Johnson • MERCK
CONSUMER PHARMACEUTICALS CO.
Fort Washington, PA 19034

January 1994

Books Received

Atlas of Dermatology, Third Ed. G. Rassner. Philadelphia, PA: Lea & Febiger; 1994, $85.00 (hardcover), 382 pp.

Atlas of Pediatric Dermatology. B. Cohen, MD. St. Louis, MO: Mosby-Year Book; 1993, price N/A (hardcover), 232 pp.

Development in Jeopardy: Clinical Responses to Infants and Families. Editors: E. Fenichel & S. Provence. Madison, CT: International Universities Press Inc; 1993, $45.00 (hardcover), 314 pp.

Disorders of Hair Growth: Diagnosis and Treatment. E. Olsen. New York: McGraw-Hill; 1993, $115.00 (hardcover), 426 pp.

Everyday Pediatrics. E. Grossman, MD. Philadelphia, PA: W. B. Saunders; 1994, $25.00 (paperback), 321 pp.

Implementing Early Interventions: From Research to Effective Practice. Edited by D. Bryant & M. Graham. New York: The Guilford Press; 1993, $35.00 (hardcover), 358 pp.

Promoting Social and Emotional Development in Deaf Children: The PATHS Project. M. Greenberg & C. Kusché. Seattle, WA: University of Washington Press; 1994, $50.00 (hardcover), 248 pp.

The Silent Petition. T. Ming. Hong Kong: Icon Media Co, Ltd; 1993, $10.00 (paperback), 108 pp.

The Vulnerable Child, Volume 1. Edited by: T. Cohen, M. Etezady, & B. Pacella. Madison, CT: International Universities Press Inc; 1994, $40.00 (hardcover), 275 pp.

Pediatrics in Review: May 1994 Contents

In Acute Otitis Media*

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

The Gram-positive Coverage You Want

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

Vantin® *Oral Suspension and Tablets*

cefpodoxime proxetil

Please see brief summary of prescribing information on reverse side of this advertisement.

Vantin® Oral Suspension and Tablets
cefpodoxime proxetil

Delivers The Gram-negative Activity You Depend On…

The Gram-positive Coverage You Want

Highly stable in the presence of β-lactamase enzymes

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

Generally well tolerated by children[1]

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

Simple BID dosing schedule

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

Reference

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

Upjohn USJ 1156.00 December 1993

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

CONTRAINDICATIONS. Known allergy to cefpodoxime or to cephalosporins.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Caution: Federal law prohibits dispensing without a prescription.

Licensed from Sankyo Company, Ltd, Japan, and manufactured by Upjohn S.A., Puurs, Belgium, for **The Upjohn Company,** Kalamazoo, MI 49001, USA O-SB-2-S

The authors thank Marie-Christine Godefroy and Roland Eschenlauer for their experimental collaborations. They gratefully acknowledge the constructive comments of Professor L.C. Johnson.

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[Humankind] is the skin disease of the earth.

—Ambassador William Bullitt Quoted by George Will.

Submitted by Student

Your Ace Reliever

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

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

When you need a choice for fever relief

McNEIL

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

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

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

Children's Motrin®

Ibuprofen Suspension 100 mg/5 ml

The following is a brief summary only. Before prescribing, see complete prescribing information in **Children's Motrin** labeling.

INDICATIONS AND USAGE: Children's Motrin is indicated for the reduction of fever in patients aged 6 months and older and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CLINICAL PHARMACOLOGY: Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 10-15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F, both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In those children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

CONTRAINDICATIONS: Children's Motrin should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving **Children's Motrin**, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

Children's Motrin, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, **Children's Motrin** should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on **Children's Motrin** should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

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

As with other nonsteroidal anti-inflammatory drugs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pre-treatment state.

Those patients at high risk who chronically take ibuprofen should have renal function monitored if they have signs or symptoms which may be consistent with mild azotemia, such as malaise, fatigue, loss of appetite, etc. Occasional patients may develop some elevation of serum creatinine and BUN levels without signs or symptoms.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with **Children's Motrin**. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), **Children's Motrin** should be discontinued.

Safety and efficacy of **Children's Motrin** in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of **Children's Motrin** is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. *Adverse reactions occurring in 1% to 3% of patients:* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5°F or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain in adults.

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than 400 mg dose.

HOW SUPPLIED: Children's Motrin Ibuprofen Suspension 100 mg/5 ml (teaspoon) – orange, berry-vanilla flavored

Bottles of 4 oz (120 ml)	NDC 0045-0801-04
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SHAKE WELL BEFORE USING. Store at room temperature.

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NUTRITIONAL ASPECTS OF AMBULATORY CARE

OXYGEN RADICALS AND DISEASE—No. I

The first organisms which evolved in the early anoxic atmosphere utilized fermentative processes in order to generate energy; i.e., they broke down existing chemical compounds and captured the energy released.[1,2] Later, solar energy was employed through the photosynthetic process yielding free oxygen. As atmospheric oxygen levels increased slowly over eons, selective pressure on the existing biota gave rise to organisms which could merely tolerate molecular oxygen; eventually new forms appeared which had the ability to use oxygen through respiration for a higher energy yield.[1] However, the shuffling of electrons which is intrinsic to the process of respiration placed these organisms at a new risk: damage from oxygen-derived free radicals.

Free radicals are defined as molecules which have an unpaired or odd number of electrons in their outer orbital. Since the chemical reactivity of a molecule is dependent upon this outer orbital conformation (with its reactivity directly proportional to the ease with which it can accept or donate one or more electrons), the unpaired electron makes the radical highly reactive as it seeks to acquire or give up a single electron to achieve stability. Because of the extreme level of reactive potential possessed by most free radicals, it is theorized that they played a seminal role in the origin of life from simple components of the primitive atmosphere.[3] Aerobic organisms thus developed defenses against these substances, but oxygen remains lethal for modern obligate anaerobic bacteria lacking these neutralizing systems.[4]

Molecular oxygen (O_2) has two unpaired electrons in its outer orbitals and is technically a free (bi) radical. It would thus appear to easily accept a pair of electrons from another compound, reducing oxygen and oxidizing the other compound. However, because oxygen's two outer electrons are orbiting with a parallel spin, the direct reduction of molecular oxygen with the addition of two electrons would result in two electrons spinning in the same direction in the same orbit: an impossibility according to quantum theory. Therefore, reduction of oxygen in biologic systems requires electrons to be added one at a time. It is this process that generates free oxygen radicals.

When a single electron is added to O_2, the superoxide radical, O_2^- is generated. Adding another electron and two hydrogen ions yields hydrogen peroxide (H_2O_2); combining H_2O_2 with O_2^- results in the formation of the hydroxyl radical, $OH^\cdot$. The hydroxyl radical is the most active of all the free radicals in biologic systems, reacting as soon as it is formed with any nearby compound. It is a high priority of all aerobic cells to avoid the generation of this radical.

Another reactive species of oxygen, singlet oxygen, while not technically a free radical, behaves as one. Singlet oxygen has the same number of electrons present as molecular oxygen, but the spin restriction referred to above is removed as the two outer electrons now spin in opposite directions.

The importance of free radical reactions in the rancidification of fats and oils was first appreciated in the 1940s.[5] Their presence in biologic systems was debated for years until an enzyme, superoxide dismutase (SOD), was reported in 1969[6] providing evidence that cells had the means to deal with the superoxide radical.

Although the fact that free radicals exist in biologic systems is now beyond debate, their importance in specific disease states such as atherosclerosis, cancer, cataracts, ischemic injury, Parkinson's disease, rheumatoid arthritis and the aging process itself as primary or secondary etiologic agents is the subject of intense investigation, discussion and debate.[5,7]

Free radicals also have a positive role to play in the phagocytic defense against microbial invaders. The respiratory burst of neutrophils produces the superoxide and hydroxyl radicals which kill the engulfed bacterium. It has also been proposed that free radical damage may "tag" neoplastic cells for removal by the immune system.[5]

SOURCES OF FREE RADICALS

On a quantitative basis, the most important source of free oxygen radicals from normal metabolic processes takes place within the mitochondria (see Table I).

TABLE I. SOURCES OF FREE RADICALS WITHIN CELLS

ENDOGENOUS SOURCES

- MITOCHONDRIAL ELECTRON TRANSPORT CHAIN
- MICROSOMAL ELECTRON TRANSPORT CHAIN
- OXIDANT ENZYMES
  - XANTHINE OXIDASE
  - INDOLAMINE DIOXYGENASE
  - TRYPTOPHAN DIOXYGENASE
  - GALACTOSE OXIDASE
  - CYCLOOXYGENASE
  - LIPOXYGENASE
  - MONOAMINE OXIDASE
- PHAGOCYTIC CELLS
  - NEUTROPHILS
  - MONOCYTES AND MACROPHAGES
  - EOSINOPHILS
  - ENDOTHELIAL CELLS
- AUTO-OXIDATION REACTIONS (FOR EXAMPLE, FE^{++}, EPINEPHRINE)

EXOGENOUS SOURCES

- REDOX-CYCLING SUBSTANCES (FOR EXAMPLE, PARAQUAT, DIQUAT, ALLOXAN, DOXORUBICIN)
- DRUG OXIDATION (FOR EXAMPLE, ACETAMINOPHEN, CCl_4)
- CIGARETTE SMOKE
- IONIZING RADIATION
- SUNLIGHT
- HEAT SHOCK
- SUBSTANCES THAT OXIDIZE GLUTATHIONE
- NITROGEN DIOXIDE & OZONE (AIR POLLUTANTS)
- NITROUS OXIDE

Adapted from Halliwell B. Free radicals: aging and disease. In: Cross CE, moderator. Oxygen radicals and human disease. *Ann Intern Med.* 1987;107:528, with permission of author and publisher.

However, under normal conditions, the cytochrome system, in transferring electrons and generating ATP within the safety of the specialized mitochondrial membranes, is able to keep the great majority of the radicals away from other vital cytoplasmic structures.

Additional metabolic sources of free radicals include the oxidant enzymes such as cyclooxygenase (involved in the synthesis of prostaglandins from arachidonic acid) and the auto-oxidation of the catecholamines. In addition to their formation under these normal circumstances, increased free radical production accompanies certain pathologic processes such as the activation of phagocytic cells and the reperfusion of ischemic tissue.[8,9]

Important exogenous sources of free radicals are ionizing radiation (a direct source of hydroxyl radicals), sunlight (which generates singlet oxygen), cigarette smoke, alcohol, air pollutants and certain anti-cancer drugs.

CELLULAR COMPONENTS AT RISK

While all major organic constituents of the cell are at risk for oxidative damage from free radicals, two of the most important are lipid membrane peroxidation and damage to DNA.

TABLE II – CELLULAR COMPONENTS DAMAGED BY FREE RADICALS

LIPIDS:	PEROXIDATION OF POLYUNSATURATED FATTY ACIDS IN ORGANELLES, PLASMA MEMBRANES
PROTEINS:	OXIDATION OF SULFHYDRYL-CONTAINING ENZYMES – > INACTIVATION OF ENZYMES
CARBOHYDRATES:	POLYSACCHARIDE DEPOLYMERIZATION
NUCLEIC ACIDS:	BASE HYDROXYLATION, "NICKING," CROSS-LINKAGE, SCISSION OF DNA STRANDS (CAUSING MUTATION AND INHIBITION OF PROTEIN, NUCLEOTIDE, AND FATTY ACID SYNTHESIS)

Reprinted from Southorn PA, Powis G. Free radicals in medicine I. Chemical nature and biologic reactions. *Mayo Clin Proc.* 1988;63:386, with permission of author and publisher.

The lipid bilayers that compose the cellular membranes and those of the intracellular organelles are subject to a particularly damaging peroxidative insult. The initial interaction with a free radical sets off a chain reaction in the membrane which can lead to extensive cellular damage. The lipid peroxides that form can inhibit many enzymes,[10] cause a loss in membrane fluidity and receptor site alignment[11] and lead to the lysis of organelles and eventually the cell itself.[8]

DNA can be damaged at either the sugar (resulting in strand breaks) or the purine or pyrimidine base (resulting in an altered base).[12] Both of these kinds of DNA damage can be repaired by nuclear enzymes.

NATURAL DEFENSES AGAINST FREE RADICALS

Although cytochrome oxidase is not a specific defense against free radicals, in sequestering the great majority of consumed oxygen it prevents most of the O_2 from forming the free radicals in vulnerable areas.[13] However, small amounts of free radicals may reach the cytoplasm from the mitochondria through a "univalent leak"[2] in addition to the other endogenous and exogenous sources noted above. Thus, cells have an array of both genetically programmed and nutritionally derived substances which are needed in both their aqueous and lipid compartments for protection from free radicals, whatever their source.

Two distinct types of superoxide dismutase exist in cells to intercept the superoxide radical before it can react with other compounds. The mitochondria have a manganese-based SOD, whereas the free cytoplasmic form of the enzyme uses copper and zinc at the active sites. The amino acid sequences of the two SODs are distinct, supporting a convergent evolutionary pathway for these proteins and emphasizing the importance of this defense for aerobic organisms. SOD converts O_2^- to H_2O_2, a non-radical, but a powerful oxidizing agent which the cell needs to dispose of.

Small amounts of H_2O_2 can be handled by reduced glutathione peroxidase, but once higher levels accumulate, the enzyme catalase becomes more important.[13] Water and O_2 are formed in this key step in cellular defense, otherwise the hydrogen peroxide generated from the superoxide radical in the presence of ferrous or cupric ions, would lead to the formation of the hydroxyl radical.

Another aqueous-based scavenger of free radicals is ascorbic acid (vitamin C), which may be especially important in extracellular fluids where the above-mentioned enzymes are essentially absent.

Evidence supports vitamin C's role in reacting directly with aqueous lipid peroxides, the superoxide radical and singlet oxygen.[14] A recent study suggests that ascorbate in human plasma is the most important first line of defense against peroxy radical-mediated damage to lipids.[15]

In the lipid phase of the cell, the most important antioxidant appears to be alpha-tocopherol, or vitamin E.[16] Here, the lipid-soluble vitamin E is capable of breaking the self-propagating chain reaction of lipid peroxidation, thus preventing damage to the plasma membrane.[10] It is interesting to note that vitamin C helps restore the antioxidant properties of vitamin E itself after the latter reacts with a free radical.[14]

Beta-carotene (pro-vitamin A), is acknowledged as one of the most effective quenchers of singlet oxygen.[17] In addition to this function, it appears that beta-carotene is also an effective anti-oxidant with unusual properties: it is most effective at lower oxygen tensions, a situation that exists at the organelle level.[17]

Future papers in this series will discuss the possible role of free radicals in the pathogenesis of various diseases and strategies which may offer protection from their effects.

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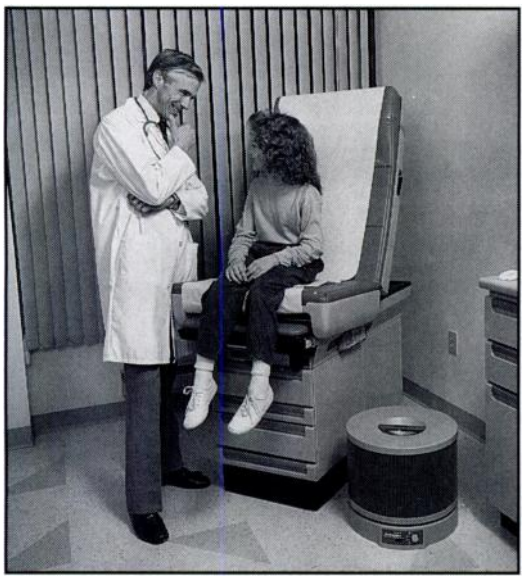

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International Health Exchange. *J R Soc Med.* 1992:85;584.

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A Dutch Doctor. Quoted by Payer L in: *Medicine and Culture.* New York: Penguin; 1988.

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References: 1. Brunette MG, Lands L, Thibodeau LP. Childhood asthma: prevention of attacks with short-term corticosteroid treatment of upper respiratory tract infection. *Pediatrics.* 1988;81(5):624-629. **2.** Chapman KR, Verbeek PR, White JG, et al. Effect of a short course of prednisone in the prevention of early relapse after the emergency room treatment of acute asthma. *N Engl J Med.* 1991;324(12):788-794. **3.** Tal A, Levy N, Bearman JE. Methylprednisolone therapy for acute asthma in infants and toddlers: a controlled clinical trial. *Pediatrics.* 1990;86(3):350-356. **4.** Harris JB, Weinberger MM, Nassif E, et al. Early intervention with short courses of prednisone to prevent progression of asthma in ambulatory patients incompletely responsive to bronchodilators. *J Pediatr.* 1987;110(4):627-633.

Please see adjacent page for brief summary of prescribing information.

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BRIEF SUMMARY

CONTRAINDICATIONS: Systemic fungal infections

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Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Use in pregnancy. Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancies, nursing mothers or women of childbearing potential requires that the possible benefits of the drug be weighted against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy, should be carefully observed for signs of hypoadrenalism.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

While on corticosteroid therapy, patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high dose, because of possible hazards of neurological complications and a lack of antibody response.

The use of ***PRELONE® Syrup*** in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS: Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection: diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer, renal insufficiency; hypertension, osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See DOSAGE AND ADMINISTRATION.)

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Information for Patients: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

ADVERSE REACTIONS: Fluid and Electrolyte Disturbances: Sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, hypertension. **Musculoskeletal:** Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathologic fracture of long bones. **Gastrointestinal:** Peptic ulcer with possible perforation and hemorrhage, pancreatitis, abdominal distention, ulcerative esophagitis. **Dermatologic:** Impaired wound healing, thin fragile skin, petechiae and ecchymoses, facial erythema, increased sweating, may suppress reactions to skin tests. **Metabolic:** Negative nitrogen balance due to protein catabolism. **Neurological:** Increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment, convulsions, vertigo, headache. **Endocrine:** Menstrual irregularities, development of Cushingoid state, secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness, suppression of growth in children, decreased carbohydrate tolerance, manifestations of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetics. **Ophthalmic:** Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos. **Other:** Urticaria and other allergic, anaphylactic or hypersensitivity reactions.

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For moderate to severe asthma

UNFOLD THE MANY BENEFITS OF BECLOVENT

Compatible with a variety of spacer devices

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

Minimal systemic absorption

BECLOVENT has minimal systemic absorption at recommended doses.

Dosing options

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

*Available in limited quantities.

Cut costs

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

Weigh the potency

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

Examine the record

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

Beclovent®

(BECLOMETHASONE DIPROPIONATE, USP)

INHALATION AEROSOL AND REFILL

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

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

Please consult Brief Summary of Prescribing Information on adjacent page.

Allen & Hanburys
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a world leader in respiratory care
Research Triangle Park, NC 27709

No. 2 in a series

Breathing Easier

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

The asthma trigger control plan

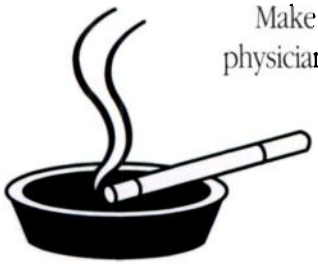
What are asthma triggers?

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

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

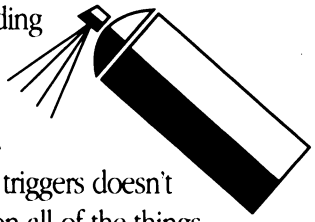
How do I know what *my* asthma triggers are?

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



What can I do about my asthma triggers?

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



What else can I do to help manage my asthma?

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

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

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

Physician's name and phone number

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Please consult Brief Summary of Prescribing Information on adjacent page.

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

BRIEF SUMMARY

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

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

Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Allen & Hanburys
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Research Triangle Park, NC 27709

November 1993
RL-090

References:

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

BEV365R1 Printed in USA January 1994

PAEDIATRIC WEEK HOLLAND

JUNE 29–JULY 6, 1994

ROTTERDAM, THE NETHERLANDS

European Society for Paediatric Research (ESPR)
European Respiratory Society • Paediatric Assembly (ERS)
Eur. Soc. of Paediatric Allergy and Clinical Immunology (ESPACI)
Eur. Soc. for Paediatric Haematology and Immunology (ESPHI)
Eur. Soc. for the Study and Prevention of Infant Death (ESPID)
Dutch Soc. of Psychosocial Consultation in Paediatrics (DSPCP)
European Paediatric Respiratory Society (EPRS)
Eur. Soc. for Paediatric Infectious Diseases (ESPID)
European Society of Paediatric Intensive Care (ESPIC)
British Association of Paediatric Surgeons (BAPS)
European Society for Paediatric Dermatology (ESPD)
Dutch Belgian Soc. for Paediatric Dermatology (DBSPD)

PRELIMINARY PROGRAMME

MONDAY 04.07.94

Plenary:
H. Galjaard (NL) *Gene Technology and Social Acceptance*/**D.J.P. Barker** (UK) *Critical Periods in Early Life—Long-term Effects*/**A.J. Sameroff** (USA) *Critical Periods in Early Childhood—Psychological Aspects*

Symposia:
Long-term Outcome of VLBW Children:
U. de Vonderweid (I), A.D. Milner (GB)
Nitric Oxide:
F. van Bel (NL), J.R. Fineman (USA), F.P. Nijkamp (NL)
Neonatal Lung Damage:
M. Silverman (GB), F. Marchal (F), K.O. Raivio (F)
Towards Basic Defects in Asthma:
A.J. Woolcock (AU), P. Scheinmann (F)
Clinical Application of Growth Factors:
G. Prindull (D), K. Welte (D), A.G. Tehernia (F)
Host Defense Mechanisms in Infections with Encapsulated Bacteriae:
D.A. Watson (USA), R.G. Feldman (UK), G.T. Rijkers (NL)
Childhood Trauma 1:
A.H. Green (USA), S.R. Meadow (GB)
Paediatric Dermatology and Internal Disease:
N.S. Prose (USA), R.J.J. Koopman (NL), J.H. Sillevis Smitt (NL)
Transplantation:
J.B. Otte (B), J.P. Vacanti (USA)

Psychiatric Sessions:
1. *The Role of the Psychiatrist in Paediatric Practice*
2. *Treatment Strategies*

Special Lecture:
D.G. Nathan (USA)
Haematopoietic Growth Factors

TUESDAY 05.07.94

Plenary:
R.K. Chandra (CAN) *Nutritional Aspects of Host Defense*/**P.J. Graham** (UK) *Development of Psychological Defense*/**R.E. Ballieux** (NL) *Psychological Influences on Immunological Defense*

Symposia:
Nutrition in Infancy:
V.P. Carnielli (I), A. Gil (BS), S.C. Kalhan (USA), A. Plaut (USA)
Periventricular Leukomalacia:
A. Leviton (USA), C.L. Pawer (CH), F. Groenendaal (NL)
Steroids and Growth:
O.D. Wolthers (DK), P.H. Burri (CH)
New Treatments for CF Lung Disease:
R. Williamson (UK), J.O. Warner (UK)
T-Lymphocyte Differentiation and Selection:
G.A. Holländer (CH), H.C. Clevers (NL), W. van Ewijk (NL)
Development of Allergy, Early Intervention:
U. Wahn (C), J.O. Warner (UK)
Management of Neonatal Infections:
B.K. English (USA), J. Levy (B)
Childhood Trauma 2:
B.A. van der Kolk (USA), S. van Deursen (NL)
Long-term Morbidity of Congenital Anomalies:
I. Louhimo (SF), E.R. Howard (UK)

Psychiatric Sessions:
3. *Multi-disciplinary Treatment of Chronic Paediatric Illnesss*
4. *Long-term Adaptation of Children with Physical Illness*

Special Lecture:
H.K.A. Visser (NL)
Ethical Aspects in Paediatrics: Clinical Care and Research

WEDNESDAY 06.07.94

Plenary:
A.H. Jobe (USA) *Fetal Lung Maturation: Present and Future Approaches*/**L.M. Taussig** (USA) *Early Determinants of Chronic Lung Disease*/**D. Bootsma** (NL) *DNA Repair and Congenital Abnormalities*

Symposia:
Mineral Metabolism and Body Composition:
F. Bronner (USA), J. Verhoef (NL)
Neurometabolic Disorders:
P.G. Barth (NL), J. Jaeken (B), P. Burgard (G)
Non-immunological Lung Defense:
O.D. Saugstad (N), M.G. van Golde (NL)
Developments in Immunodeficiency Syndromes:
L.D. Notarangelo (I), C.M. Roifman (CAN), M.J.D. van Tol (NL)
Meningitis:
U.B. Schaad (G), J. Eskola (SP), M. Tarlow (UK)
Tuberculosis:
J.M. Watson (GB), R.F. Jacobs (USA) P.W.M. Hermans (NL)
Bone Marrow Transplantation:
D. Valerio (NL), D.J.A. Gerritsen (NL)
Atopic Dermatitis:
A. Taieb (F), A.P. Oranje (NL), J. Ring (D)
Development of Respiratory Control and SIDS:
A. Kahn (B), C.I. Gaultier (F), P. Johnson (UK)

DEADLINE for early registration:
15 May 1994

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