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PEDIAU 83(1) pp. 1–151 (1989)

NEW

CHILDREN'S NyQuil®

More of what puts cough and congestion to rest

For the cough and congestion that always seem to be at their worst at bedtime, now there's new CHILDREN'S NYQUIL. It's so effective at relieving symptoms that it lets children rest comfortably through the night.

CHILDREN'S NYQUIL has the maximum allowable dosage of three effective medicines: 15 mg dextromethorphan for cough control, 30 mg pseudoephedrine for decongestion, and 2 mg chlorpheniramine for rhinorrhea.

All in a great-tasting, cherry-flavored liquid that children themselves prefer 7 to 1 over the leading cough suppressant/expectorant.

For children ages 6-11, the recommended dosage is one tablespoon every 6-8 hours; ages 2-5, ½ tablespoon; under age 2, dose at your discretion.

CHILDREN'S NYQUIL.
Just what children need when they need it most.

NEW

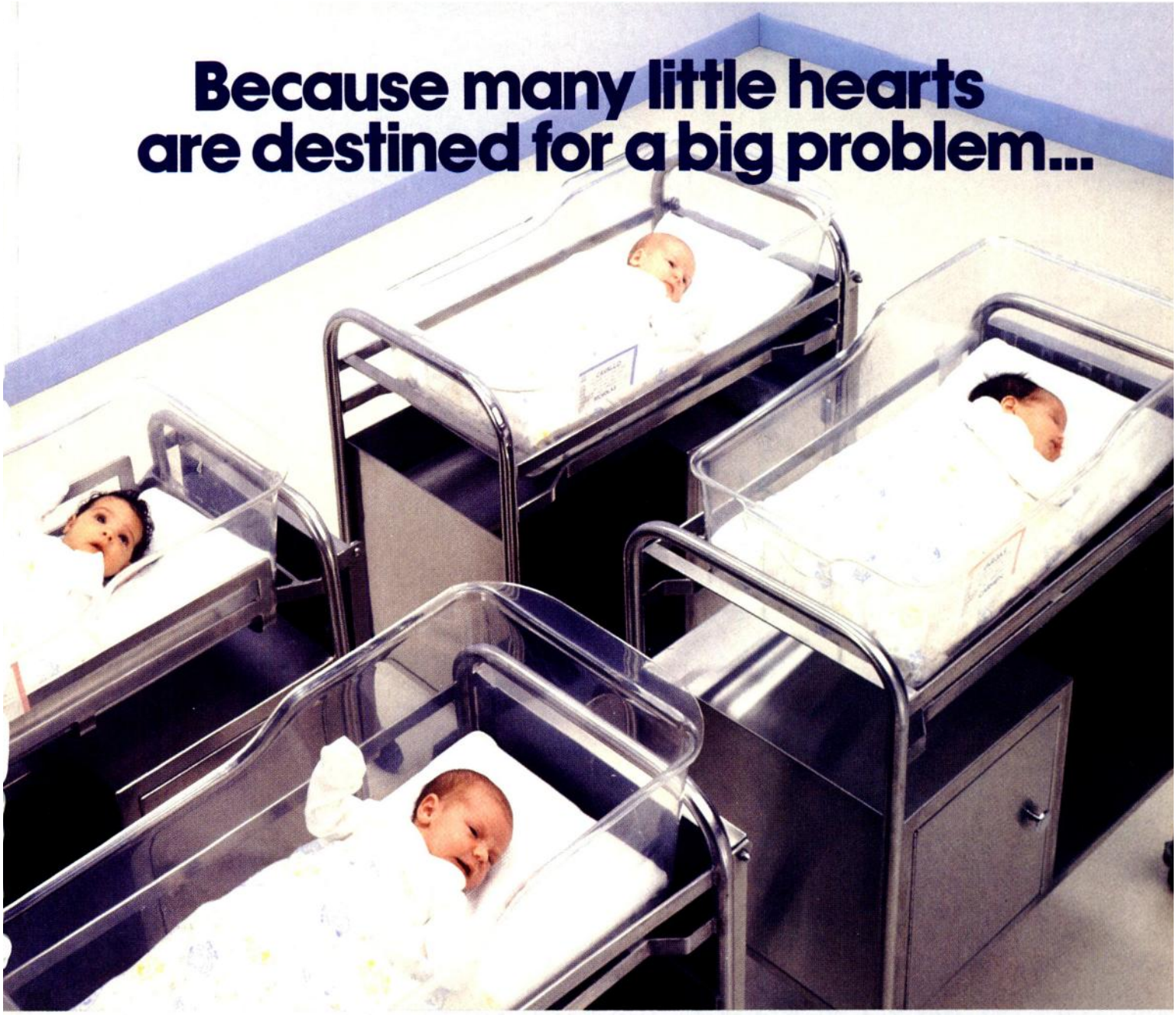
ALCOHOL-FREE
ASPIRIN-FREE

6-8 hours of symptomatic relief from each easy-to-measure dose

maximum children's dosage for restful relief

For further information about CHILDREN'S NYQUIL, call toll-free: 1-800-358-8707 (in Ohio, call 1-800-346-9101).

Because many little hearts are destined for a big problem...



Fatty streaks in the aortas of 3-year-olds Fatty streaks have been found even in the aortas of 3-year-olds. Aortic fatty streaks have been strongly related to both total- and LDL-cholesterol levels and inversely to the HDL/LDL + VLDL ratio. Expert advice suggests that a rational approach to the prevention of CVD should begin early in life.[1]

SMA® maintains high levels of cardio-protective HDL Wyeth's SMA, with a lipid profile virtually identical to mother's milk, provides infants with HDL-cholesterol plasma levels that closely approximate those found in breast-fed infants. And, like breast milk, SMA has more than twice the level of monounsaturates than the other two leading formulas. High levels of monounsaturates have been associated with higher levels of cardio-protective HDL.[2] Start them early...and start them right... with SMA.

References: 1. Newman WP III, *et al:* Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis. *N Engl J Med 314*:138-144, 1986. **2.** Mattson FH, Grundy SM: Comparison of effects of dietary saturated, monounsaturated and polyunsaturated fatty acids on plasma lipids and lipoproteins in man. *J Lipid Res 26*:194-202, 1985.

S·M·A™
Infant Formula

A first step in good cardiovascular nutrition

Important Notice. Breast milk is best for babies. Infant formula is intended to replace or supplement breast milk when breast-feeding is not possible or is insufficient, or when mothers elect not to breast-feed.
Good maternal nutrition is important for the preparation and maintenance of breast-feeding. Extensive or prolonged use of partial bottle-feeding, before breast-feeding has been well established, could make breast-feeding difficult to maintain. A decision not to breast-feed could be difficult to reverse.
Professional advice should be followed on the need for and proper method of use of infant formula and on all matters of infant feeding. Infant formula should always be prepared and used as directed. Unnecessary or improper use of infant formula could present a health hazard. Social and financial implications should be considered when selecting the method of infant feeding.

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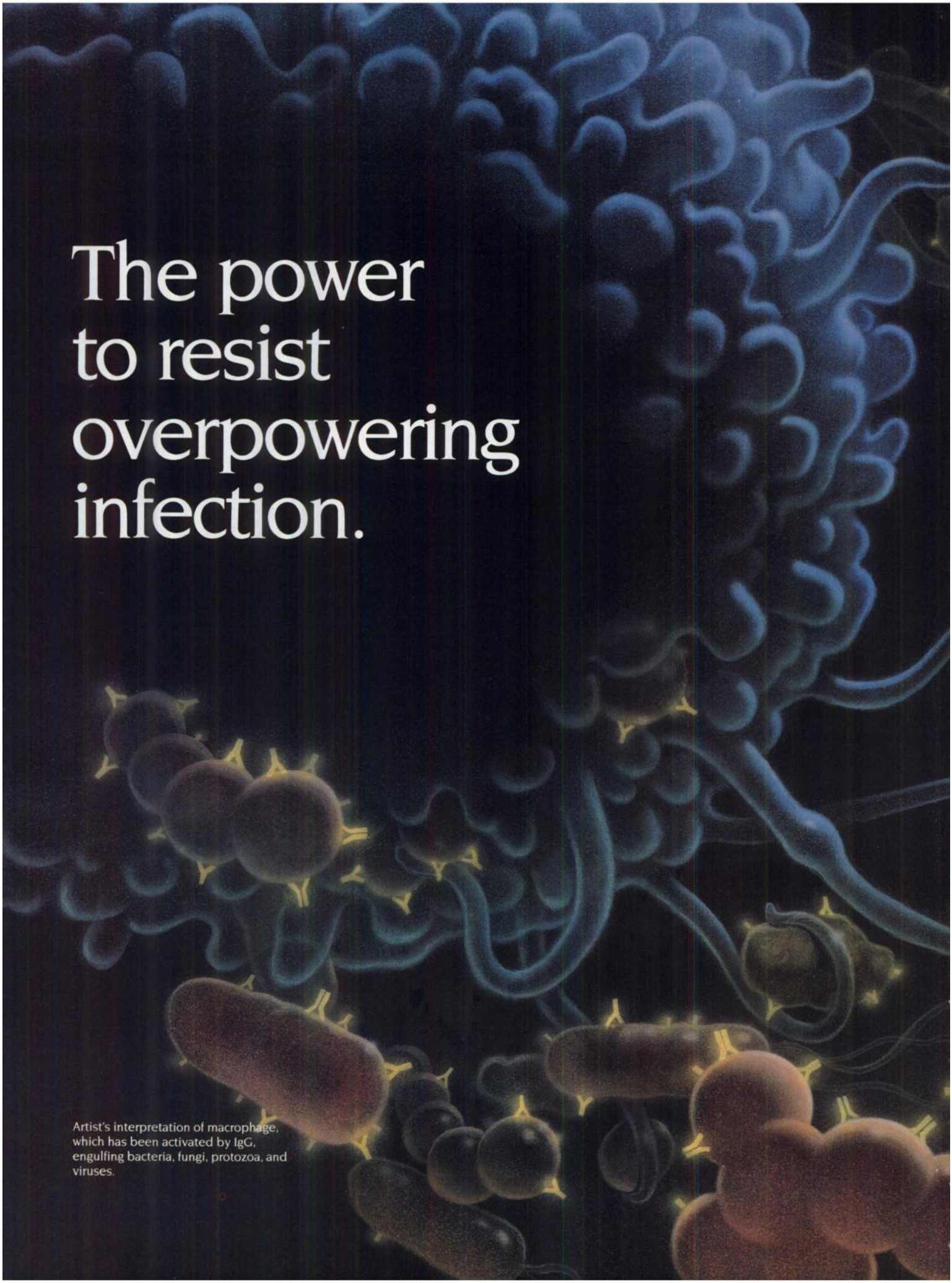
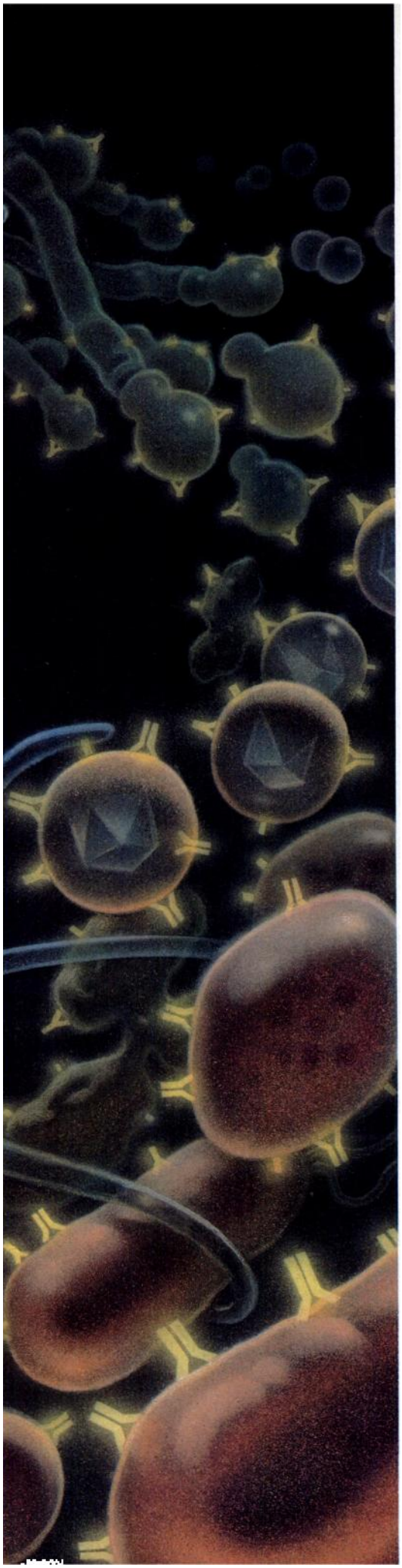
The power to resist overpowering infection.



Artist's interpretation of macrophage, which has been activated by IgG, engulfing bacteria, fungi, protozoa, and viruses.



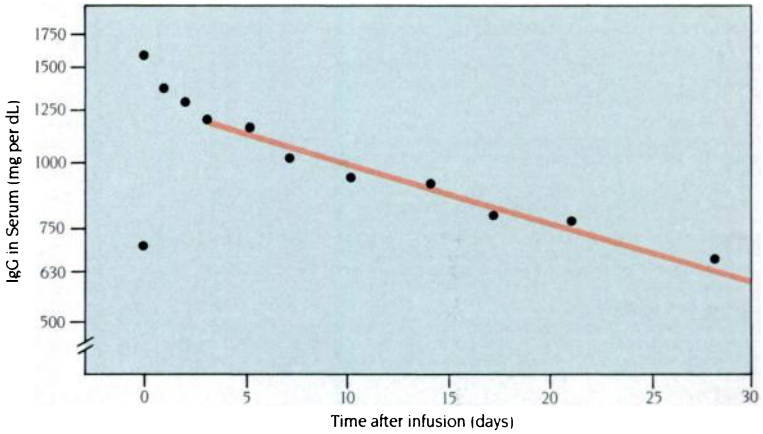
New

For the treatment of primary immunodeficiencies

Venoglobulin®-I

Immune Globulin Intravenous (Human)

- Demonstrated purity of not less than 97% IgG (excluding albumin and nonprotein components) with a natural distribution of all four subclasses
- 13.9% higher trough (pre-infusion) serum IgG levels than historical controls treated with other brands of IgG
- Long-serum half-life — 29 ± 7.6 days (mean of 6 patients, ± 1 S.D.)



- Reduces infection rate, need for antibiotics, and hospitalization
- Production process inactivates and/or removes up to 13 logs of HIV
- Well tolerated during long-term studies
- Supported by the world's largest private plasma collection organization

alpha™
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Providing Intravenous Care and Technology

Please see next page for brief summary of prescribing information.

This One
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IMMUNE GLOBULIN INTRAVENOUS (HUMAN)
VENOGLOBULIN ® -I
Lyophilized

BRIEF SUMMARY

CLINICAL PHARMACOLOGY

Venoglobulin ® -I [Immune Globulin Intravenous (Human)] supplies a broad spectrum of IgG antibodies against bacterial, viral, parasitic and mycoplasma antigens. These antibodies have retained full biological function for the prevention or attenuation of a wide variety of infectious disease, including their abilities to promote opsonization, fix complement and neutralize microbes and their toxins.

The IgG half-life as well as the amount of immunoglobulin administered per dose is important in determining the frequency of administration of the drug for each patient. The mean half-life of serum Venoglobulin ® -I, when given intravenously, is 29 days with a standard deviation of 7.6 days.[1] Appropriate doses of Venoglobulin ® -I will restore abnormally low IgG levels to the normal range. With the intravenous route of administration, essentially 100% of the dose is immediately available in the patient's circulation. A relatively rapid fall in serum IgG level in the first week post-infusion is to be expected; this decrease averages 40% of the peak level achieved immediately post-infusion and is mainly due to the equilibration of IgG between the plasma and the extravascular space.[1–4]

Intravenous administration of Albumin (Human) and D-Mannitol, used to stabilize the IgG protein in Venoglobulin ® -I, is considered safe.

Among 32 immunodeficient patients receiving periodic infusions of Venoglobulin ® -I and 24 immunocompetent patients treated for immune thrombocytopenia, no seroconversion to positivity for Anti-HIV was detected.[1]

INDICATIONS AND USAGE

Venoglobulin ® -I is indicated for the maintenance treatment of patients with primary immunodeficiency syndromes such as congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, severe combined immunodeficiency, and Wiskott-Aldrich syndrome.[5]

Venoglobulin ® -I is especially useful in treating patients who require an immediate and substantial increase in intravascular immunoglobulin levels, in patients with limited muscle mass, and in patients with bleeding tendencies for whom intramuscular injections are contraindicated. Venoglobulin ® -I may be of benefit in severe combined immunodeficiency, even though the cellular immunodeficit in this disease will not be corrected.

CONTRAINDICATIONS

Venoglobulin ® -I is contraindicated in individuals with a history of anaphylactic or severe systemic response to immune globulin intramuscular or intravenous preparations. As with all blood products containing IgA, Venoglobulin ® -I is contraindicated in patients with selective IgA deficiency.[6]

WARNINGS

Patients with agamma- or extreme hypogammaglobulinemia, who have never before received immunoglobulin substitution therapy or whose time from last treatment is greater than 8 weeks, may be at risk of developing inflammatory reactions on infusion of Venoglobulin ® -I. Such reactions appear to be related to the rate of infusion and are manifested by a rise in temperature, chills, nausea, and vomiting. The rate of administration specified in DOSAGE AND ADMINISTRATION should be closely followed, at least until the physician has had sufficient experience with a given patient. Vital signs should be monitored continuously and the patient should be carefully observed throughout the infusion.

IF ANAPHYLACTIC OR SEVERE ANAPHYLACTOID REACTIONS OCCUR, THE INFUSION SHOULD BE DISCONTINUED IMMEDIATELY. Epinephrine should be available for the treatment of any acute anaphylactoid reaction.

PRECAUTIONS

General

After reconstitution, Venoglobulin ® -I should be administered as soon as possible. Discard any unused reconstituted solution. The solution contains no preservative and should not be saved for later use. If large volumes are to be administered it may be advisable to warm the solution to near body temperature prior to infusion.

Drug Interactions

Specific drug interactions and incompatibilities have not been studied. Venoglobulin ® -I should be infused via a separate intravenous line. Do not add any medications, such as antibiotics, or other intravenous drugs to the Venoglobulin ® -I infusion container. Do not dilute with Dextrose solutions or other I.V. fluids with acidic pH as this may cause instability.

Venoglobulin ® -I should be reconstituted only with Sterile Water for Injection, USP. Do not reconstitute with Bacteriostatic Water for Injection, USP.

Pregnancy Category C: Animal reproduction studies have not been conducted with Venoglobulin ® -I. It is also not known whether Venoglobulin ® -I can cause fetal harm when administered to pregnant women or can affect reproductive capacity. Venoglobulin ® -I should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

Agammaglobulinemic or hypogammaglobulinemic patients who have never before received immunoglobulin substitution therapy or whose time from last treatment is greater than 8 weeks may experience adverse reactions if the initial infusion rate exceeds 0.02 mL/kg/minute.

If an adverse reaction occurs, it will generally become apparent only 30 minutes to one hour after the beginning of the infusion. Adverse reactions may include back pain, chills, headache, muscle pain, malaise, joint pain, fever, nausea, flushing, and tightness of the chest. Other reactions, occurring in less than 0.2% of infusions, were diaphoresis, hypotension, dizziness, cyanosis, and wheezing. If an adverse reaction occurs, the infusion rate should be decreased or temporarily stopped until the symptoms have subsided. In clinical trials with Venoglobulin ® -I, mild or moderate reactions were observed in approximately 7% of the infusions.[1]

Immediate anaphylactoid and hypersensitivity reactions, due to previous sensitization of the recipient to certain antigens, most commonly IgA, may be observed in exceptional cases (see CONTRAINDICATIONS).[6]

DOSAGE AND ADMINISTRATION

Adult and Pediatric Substitution Therapy: The usual dose of Venoglobulin ® -I in immunodeficiency syndromes is 200 mg immunoglobulin G per kg of body weight, usually administered once per month by intravenous infusion. If the clinical response is inadequate or the level of serum IgG achieved is felt to be insufficient, the dose may be increased to 300 – 400 mg/kg monthly or the infusion may be repeated more frequently than once per month. The minimum serum concentration of IgG necessary for protection has not been established.[3,7]

Venoglobulin ® -I should be infused at a rate of 0.01 – 0.02 mL/kg body weight per minute for the first thirty minutes. If the patient does not experience any discomfort, the rate may be increased to 0.04 mL/kg/minute. If tolerated, subsequent infusions to the same patient may be at the higher rate. If adverse effects occur, the rate should be reduced or the infusion interrupted until the symptoms subside. The infusion may then be resumed at a rate which is tolerated by the patient.

If large doses are to be administered, several reconstituted vials of Venoglobulin ® -I may be pooled in an empty sterile I.V. infusion container. Use aseptic technique. Do not dilute with Dextrose solutions or other I.V. fluids with acidic pH as this may cause instability.

Clinical investigations have confirmed that Venoglobulin ® -I is well tolerated and not likely to produce side effects when infused at these rates. However, the first infusion of Venoglobulin ® -I in previously untreated agamma- globulinemic and hypogammaglobulinemic patients may lead to systemic side effects. Some of the effects may occur as a result of the reaction between the antibodies administered and free antigens in the blood and tissues of the immunodeficient recipient.

Venoglobulin ® -I should be administered only intravenously as the intramuscular and subcutaneous routes have not been evaluated.

CAUTION

Federal law prohibits dispensing without prescription.

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1. Data on file at Alpha Therapeutic Corporation.
2. Pirofsky B, Campbell SM, Montaro A: Individual patient variation in the kinetics of intravenous immunoglobulin administration. J Clin Immunol 2 (2): 75–145, 1982.
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6. Burks AW, Sampson HA, Buckley RH: Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia. NEJM 314(9): 560–564, 1986.
7. Dwyer JM: Thirty years of supplying the missing link: History of gamma globulin therapy for immunodeficient disease. Am J Med 76: 46–52, 1984.

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VEN-230A/MD1

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1. Starzl TE, Klintmalm GBG, Porter KA, et al: Liver transplantation with use of cyclosporin A and prednisone. *N Engl J Med* 1981; 305:266–269

Book

1. Kavet J: Trends in the utilization of influenza vaccine: An examination of the implementation of public policy in the United States, in Selby P (ed): *Influenza: Virus, Vaccines, and Strategy*. New York, Academic Press Inc, 1976, pp 297–308

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Revised, July 1985

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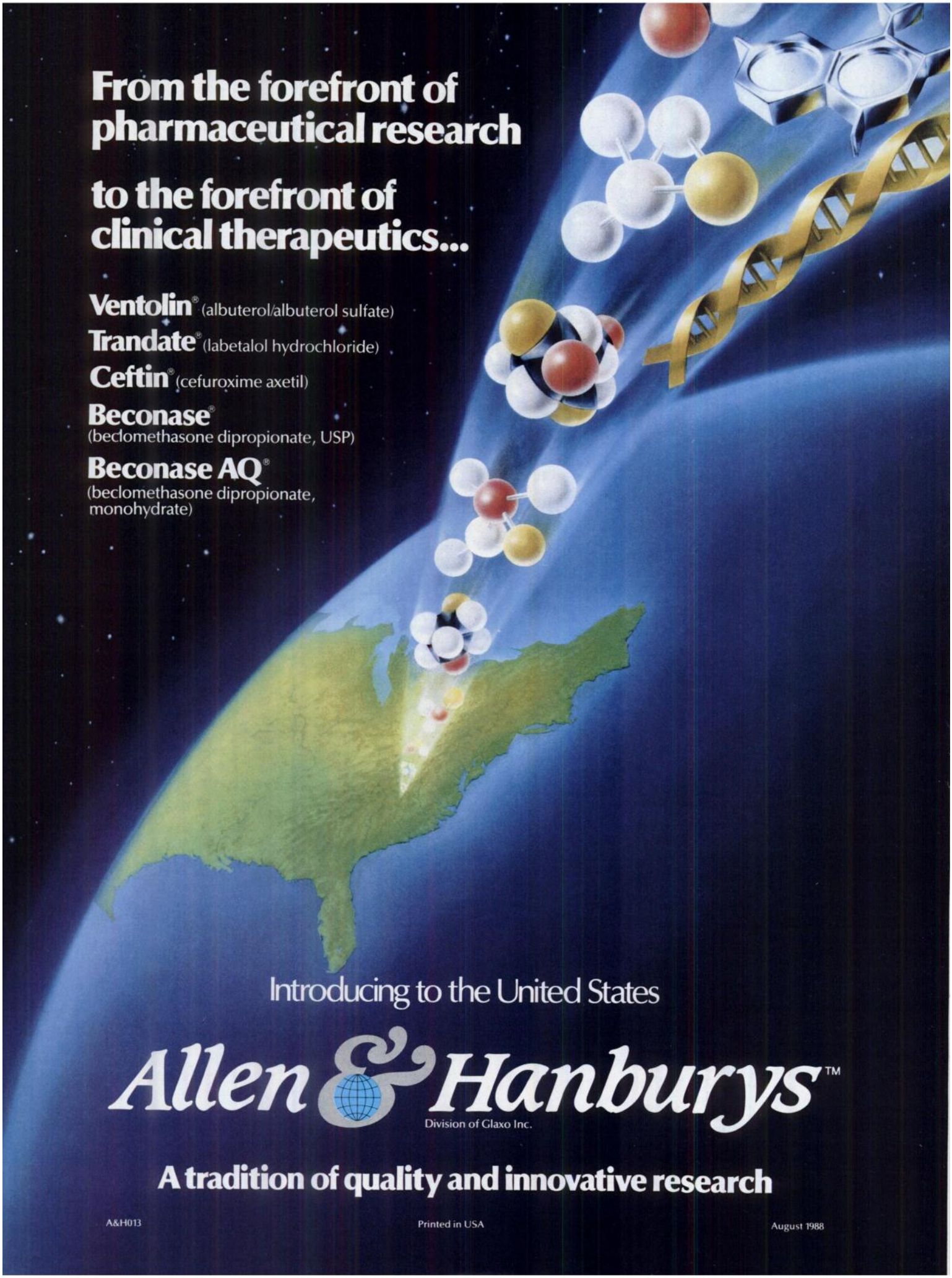
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For Brief Summary, please see following page.

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DURICEF® (CEFADROXIL)

Penetration plus Duration in Oral Cephalosporin Therapy

INDICATIONS: DURICEF (cefadroxil) is indicated for the treatment of the following infections when caused by susceptible strains of the designated microorganisms: Urinary tract infections caused by *E. coli, P. mirabilis,* and *Klebsiella* species. Skin and skin structure infections caused by staphylococci and/or streptococci. Pharyngitis and tonsillitis caused by Group A beta-hemolytic streptococci. (Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. DURICEF is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of DURICEF in the subsequent prevention of rheumatic fever are not available at present.)

Note—Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

CONTRAINDICATIONS: DURICEF is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNING: IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF PENICILLINS AND CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated a history of some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary. No exception should be made with regard to DURICEF (cefadroxil). **Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.** Treatment with broad spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*. Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should also be considered.

PRECAUTIONS: Patients should be followed carefully so that any side-effects or unusual manifestations of drug idiosyncrasy may be detected. If a hypersensitivity reaction occurs, the drug should be discontinued and the patient treated with the usual agents (e.g., epinephrine or other pressor amines, antihistamines, or corticosteroids).

DURICEF (cefadroxil) should be used with caution in the presence of markedly impaired renal function (creatinine clearance rate of less than 50 ml/min/1.73M²). (See Dosage and Administration section of Prescribing Information.) In patients with known or suspected renal impairment, careful clinical observation and appropriate laboratory studies should be made prior to and during therapy.

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

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug. DURICEF should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy: Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to 11 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefadroxil. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Caution should be exercised when cefadroxil is administered to a nursing mother.

ADVERSE REACTIONS: *Gastrointestinal*—Symptoms of pseudomembranous colitis can appear during antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity—Allergies (in the form of rash, urticaria, and angioedema) have been observed. These reactions usually subsided upon discontinuation of the drug.

Other reactions have included genital pruritus, genital moniliasis, vaginitis, and moderate transient neutropenia.

Before prescribing or administering, see package insert.

J-V23-1-89

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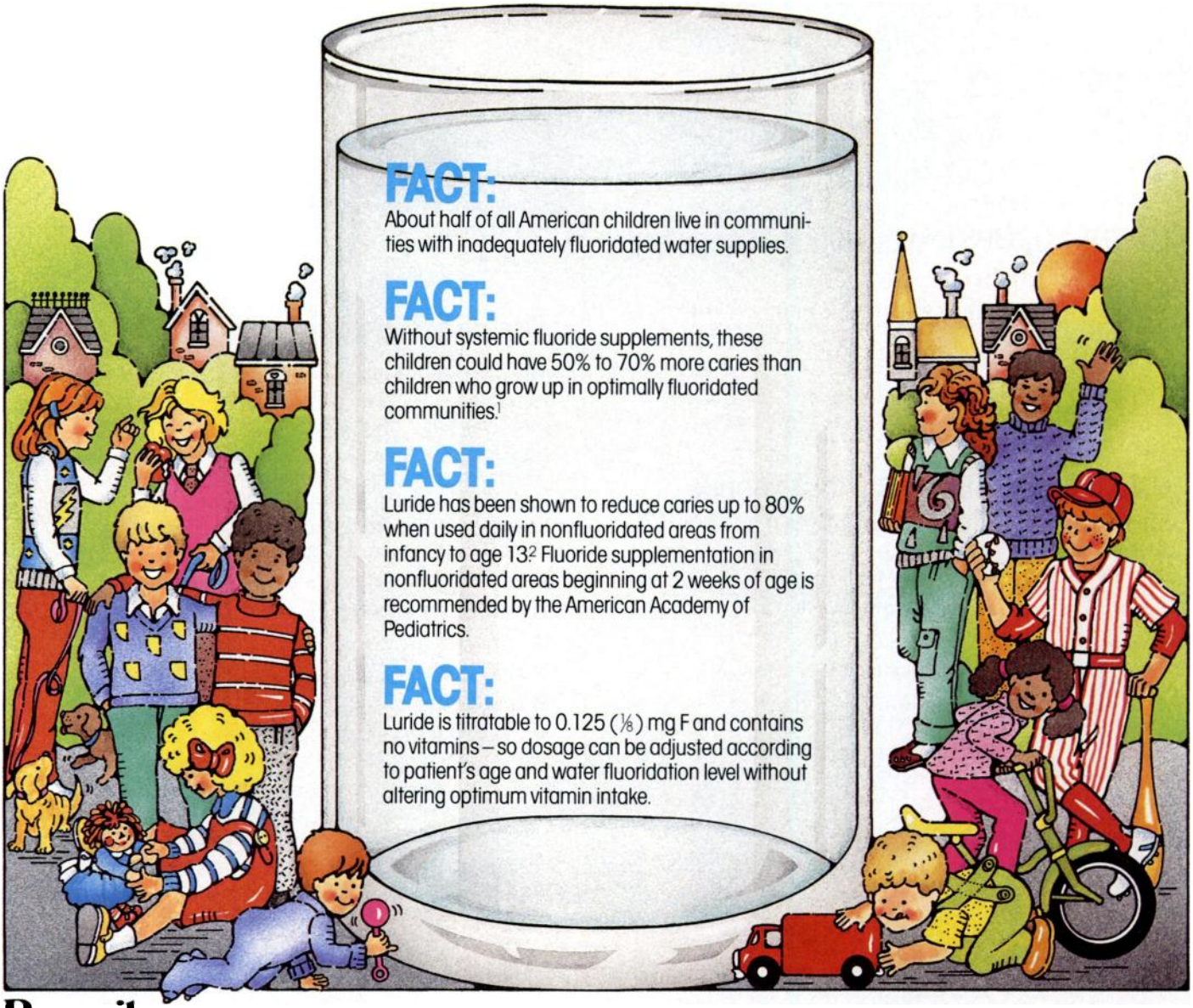

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[1] Gambowski, D. The effects of fluoridation on dental care demand. Comp. Cont. Ed. 5(8):689, 1984. [2] Aasenden, R., and T.C. Peebles. Effects of fluoride supplementation from birth on human deciduous and permanent teeth. Arch. Oral Biol. 19:321, 1978.

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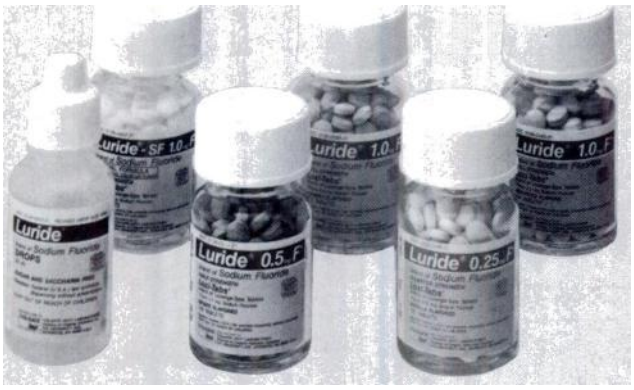

LURIDE® DROPS let you adjust dosage to 0.125 (⅛) mg. F.

One study showed that fluoride supplements such as Luride drops and tablets, used daily, prevented caries as effectively as fluoridated water.[1] Luride Drops and Lozi-Tabs have been shown to reduce caries up to 80% when used on a daily basis in non-fluoridated areas.[2] (Luride DMFS = 1.57, Control = 7.93)

Luride drops are sugar-free and saccharin-free, unlike many fluoride-vitamin combinations. And you can adjust dosage to the nearest 0.125 mg. F—to a single ⅛ mg. drop.

LURIDE® LOZI-TABS® TABLETS: 3 fluoride strengths, 7 child-pleasing flavors.

For children old enough to chew a tablet or let it dissolve in the mouth, Luride tablets are the logical choice. A variety of delicious fruit flavors (including our unique 4-flavor assorted package) encourages the habit of consistent, continuous use. Three strengths available—1.0 mg. F, 0.5 mg. F, and 0.25 mg. F.

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DESCRIPTION and HOW SUPPLIED:
All LURIDE systemic fluoride products are free of sugar and saccharin.

Product	Strength (F ION)	Package Size	Flavor
DROPS	Approx. 0.125 mg. per drop	30 ml.	peach
0.25 F TABLETS	0.25 mg. per tablet (quarter-strength)	120	vanilla
0.5 F TABLETS	0.5 mg. per tablet (half-strength)	120 1200*	grape grape
1.0 F TABLETS	1.0 mg. per tablet (full-strength)	120 1000* 5000*	cherry & assorted (cherry, orange, lemon, lime) cherry, assorted cherry
SF 1.0 F TABLETS	1.0 mg. per tablet (full-strength)	120	Special Formula, no artificial flavor or color.

*For dispensing only in quantities containing 120 mg. F. or less.
CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

ADMINISTRATION AND DOSAGE FLEXIBILITY:
Adjustable dose LURIDE gives you the flexibility to prescribe optimal DAILY dosage (based on age and fluoride content of water).

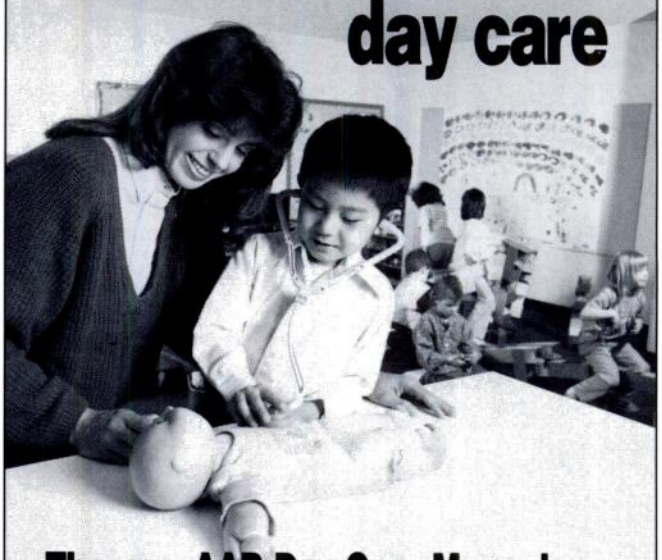
F-Content of Drinking Water	Daily Dosage (Fluoride Ion)* Birth to Age 2	Age 2-3	Age 3-13
less than 0.3 ppm	0.25 mg. tab or 2 drops	0.5 mg. tab or 4 drops	1.0 mg. tab or 8 drops
0.3 to 0.7 ppm	one-half above dosage		
over 0.7 ppm	Fluoride dietary supplements contraindicated		

*American Dental Association, Accepted Dental Therapeutics, Edition 40 1984, page 401. American Academy of Pediatrics, Committee on Nutrition, Fluoride supplementation: revised dosage schedule. Pediatrics 63:150-152, 1979.

PRECAUTIONS: Recommended dosage should not be exceeded since prolonged overdosage may result in dental fluorosis.

REFERENCES:
(1) Arnold F.A. Jr., McClure, F.J., and White, C.L. Sodium fluoride tablets for children. D. Progress 1:8-12, 1960.
(2) Aasenden, R., and Peebles, T.C. Effects of fluoride supplementation from birth on human deciduous and permanent teeth. Arch. Oral Biol. 19:321-326, 1974; 23:111-115, 1978.

State-of-the-health day care



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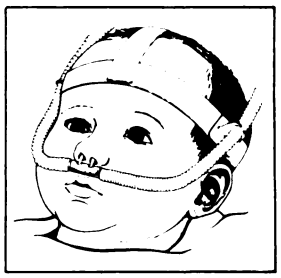

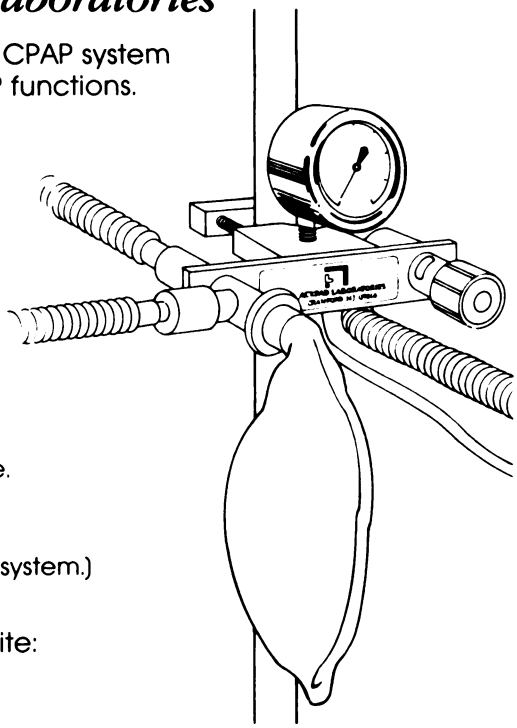

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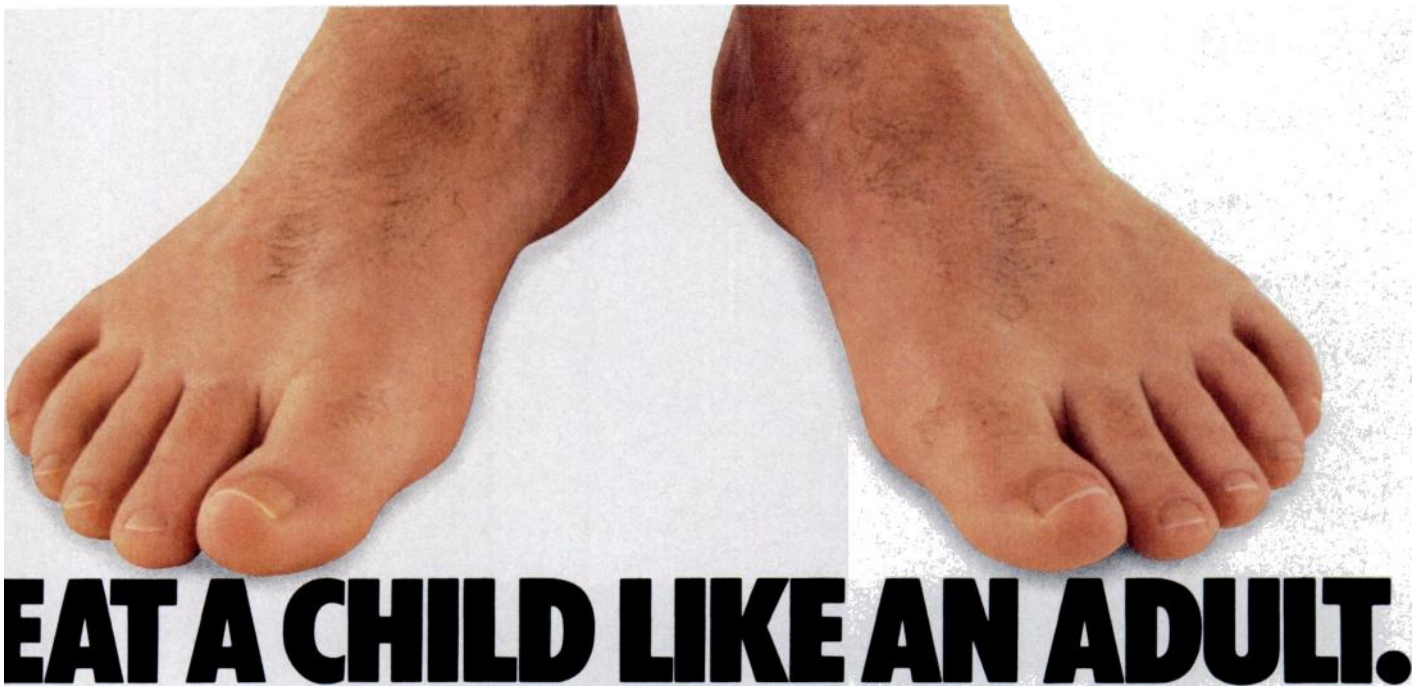

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Please see next page for Brief Summary of Prescribing Information.

References: 1. Lotrisone full Prescribing Information. 2. Mycolog-II full Prescribing Information.

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For Dermatologic Use Only
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DESCRIPTION: MYCOLOG-II Cream and Ointment (Nystatin and Triamcinolone Acetonide Cream USP and Ointment) for dermatologic use provide 100,000 units of the antifungal agent nystatin and 1.0 mg of the synthetic corticosteroid triamcinolone acetonide per gram.

CONTRAINDICATIONS: This preparation is contraindicated in those patients with a history of hypersensitivity to any of its components.

PRECAUTIONS: General—Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions that augment systemic absorption include application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Therefore, patients receiving a large dose of any potent topical steroid applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests, and for impairment of thermal homeostasis. If HPA axis suppression or elevation of the body temperature occurs, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function and thermal homeostasis are generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see PRECAUTIONS, Pediatric Use).

If irritation or hypersensitivity develops with the combination nystatin and triamcinolone acetonide, treatment should be discontinued and appropriate therapy instituted.

Laboratory Tests—If there is a lack of therapeutic response, appropriate microbiological studies (e.g., KOH smears and/or cultures) should be repeated to confirm the diagnosis and rule out other pathogens, before instituting another course of therapy.

A urinary free cortisol test and ACTH stimulation test may be helpful in evaluating hypothalamic-pituitary-adrenal (HPA) axis suppression due to corticosteroid.

Carcinogenesis, Mutagenesis, and Impairment of Fertility—Long-term animal studies have not been performed to evaluate carcinogenic or mutagenic potential, or possible impairment of fertility in males or females.

Pregnancy Category C—There are no teratogenic studies with combined nystatin and triamcinolone acetonide. Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. Therefore, any topical corticosteroid preparation should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Topical preparations containing corticosteroids should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers—It is not known whether any component of this preparation is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised during use of this preparation by a nursing woman.

Pediatric Use—In clinical studies of a limited number of pediatric patients ranging in age from two months through 12 years, nystatin-triamcinolone cream formulation cleared or significantly ameliorated the disease state in most patients.

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced hypothalamic-pituitary-adrenal (HPA) axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.

HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS: A single case (approximately one percent of patients studied) of acneform eruption occurred with use of combined nystatin and triamcinolone acetonide in clinical studies.

Nystatin is virtually nontoxic and nonsensitizing and is well tolerated by all age groups, even during prolonged use. Rarely, irritation may occur.

The following local adverse reactions are reported infrequently with topical corticosteroids (reactions are listed in an approximate decreasing order of occurrence): burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermitidis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

OVERDOSAGE: Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS, General); however, acute overdosage and serious adverse effects with dermatologic use are unlikely.

DOSAGE AND ADMINISTRATION: The use of these preparations should be discontinued if symptoms persist after 25 days of therapy (see PRECAUTIONS, Laboratory Tests). MYCOLOG-II Cream and Ointment should *not* be used with occlusive dressings.

HOW SUPPLIED: MYCOLOG-II Cream (Nystatin and Triamcinolone Acetonide Cream USP) is supplied in 15 g, 30 g, and 60 g tubes and 120 g jars.

MYCOLOG-II Ointment (Nystatin and Triamcinolone Acetonide Ointment) is supplied in 15 g, 30 g, and 60 g tubes and 120 g jars.

Storage—Store at room temperature; avoid freezing cream.

(J4-019A, J4-024)

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A dramatic 40-minute video and a clear, concise book provide a complete, frank and authoritative guide to breastfeeding, giving mothers the information they need to know. The video was produced by an award-winning film producer together with eminent medical authorities. The book was written by a pediatrician, nurse lactation consultant and a nurse childbirth educator. It is recommended for mothers who are breastfeeding, intend to breastfeed or are just thinking about it.

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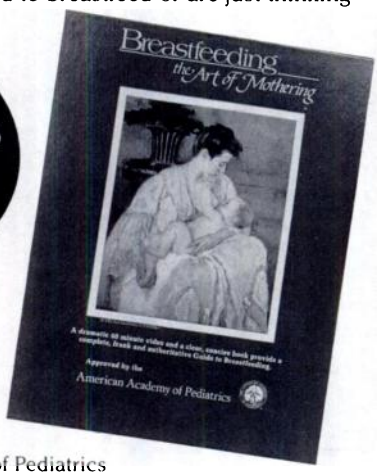

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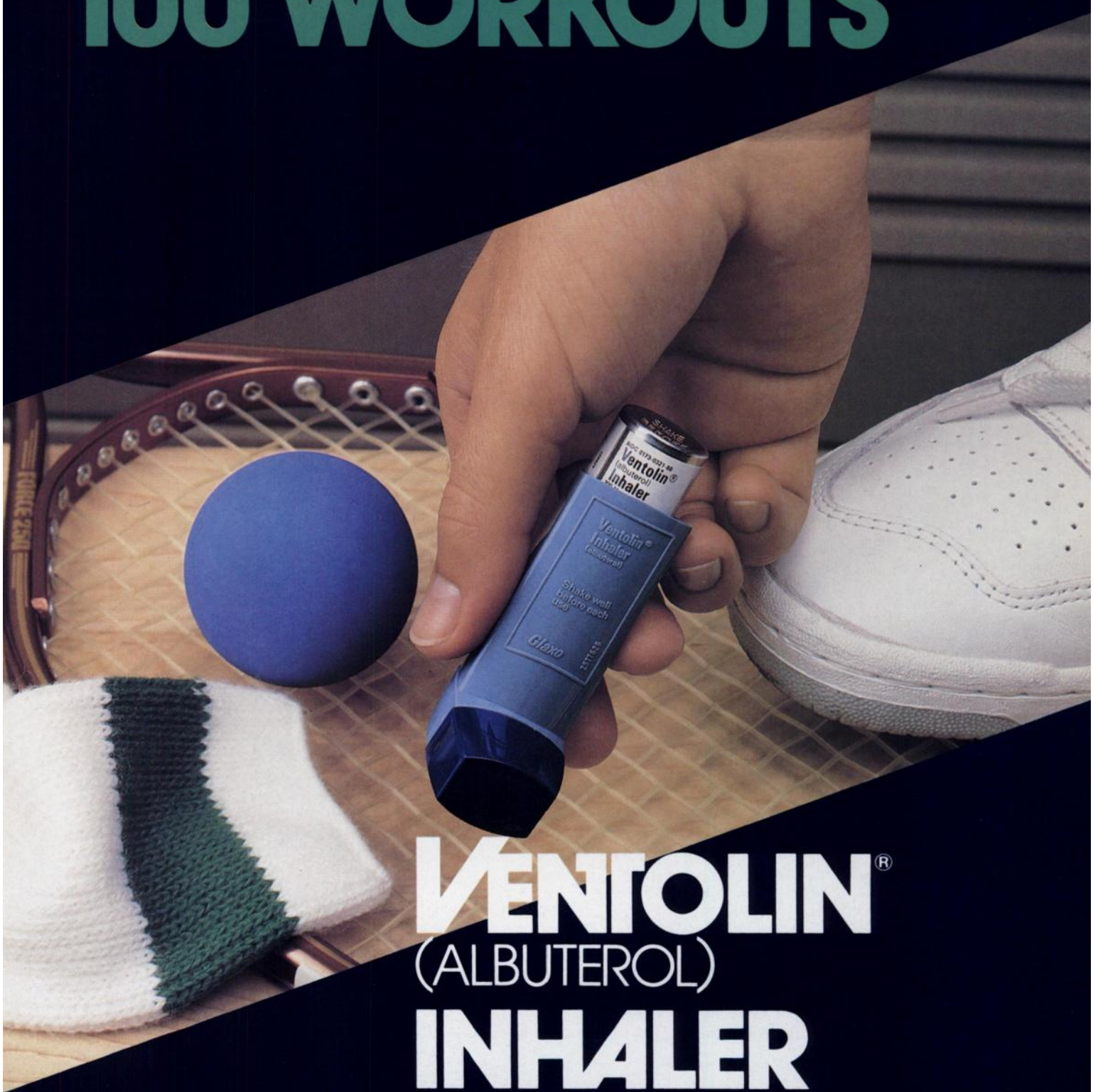

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*Sympathomimetic amines should be used with caution in patients with cardiovascular disorders.

VIN 315R • Printed in USA • October 1988

VENTOLIN® (albuterol) Inhaler
Bronchodilator Aerosol
For Oral Inhalation Only

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in VENTOLIN® Inhaler product labeling.

CONTRAINDICATIONS: VENTOLIN® Inhaler is contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS: As with other inhaled beta-adrenergic agonists, VENTOLIN® Inhaler can produce paradoxical bronchospasm that can be life-threatening. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. The exact cause of death is unknown, but cardiac arrest following the unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

Immediate hypersensitivity reactions may occur after administration of albuterol inhaler, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

The contents of VENTOLIN® Inhaler are under pressure. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of reach of children.

PRECAUTIONS: General: Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension, in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.

Large doses of intravenous albuterol have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. Additionally, beta-agonists, including albuterol, given intravenously may cause a decrease in serum potassium, possibly through intracellular shunting. The decrease is usually transient, not requiring supplementation. The relevance of these observations to the use of VENTOLIN® Inhaler is unknown, since the aerosol dose is much lower than the doses given intravenously.

Although there have been no reports concerning the use of VENTOLIN Inhaler during labor and delivery, it has been reported that high doses of albuterol administered intravenously inhibit uterine contractions. Although this effect is extremely unlikely as a consequence of aerosol use, it should be kept in mind.

Information For Patients: The action of VENTOLIN Inhaler may last up to six hours, and therefore it should not be used more frequently than recommended. Do not increase the number or frequency of doses without medical consultation. If recommended dosage does not provide relief of symptoms or symptoms become worse, seek immediate medical attention. While taking VENTOLIN Inhaler, other inhaled drugs should not be used unless prescribed.

See illustrated Patient's Instructions for Use.

Drug Interactions: Other sympathomimetic aerosol bronchodilators should not be used concomitantly with albuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

Albuterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants because the action of albuterol on the vascular system may be potentiated.

Beta-receptor blocking agents and albuterol inhibit the effect of each other.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Albuterol sulfate, like other agents in its class, caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium in a two-year study in the rat, at doses corresponding to 111, 555, and 2,800 times the maximum human inhalational dose. In another study this effect was blocked by the coadministration of propranolol. The relevance of these findings to humans is not known. An 18-month study in mice and a lifetime study in hamsters revealed no evidence of tumorigenicity. Studies with albuterol revealed no evidence of mutagenesis. Reproduction studies in rats revealed no evidence of impaired fertility.

Pregnancy: *Teratogenic Effects: Pregnancy Category C:* Albuterol has been shown to be teratogenic in mice when given in doses corresponding to 14 times the human dose. There are no adequate and well-controlled studies in pregnant women. Albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A reproduction study in CD-1 mice given albuterol subcutaneously (0.025, 0.25, and 2.5 mg/kg, corresponding to 1.4, 14, and 140 times the maximum human inhalational dose, respectively) showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg. None was observed at 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5%) fetuses treated with 2.5 mg/kg isoproterenol (positive control). A reproduction study with oral albuterol in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses at 50 mg/kg, corresponding to 2,800 times the maximum human inhalational dose of albuterol.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in animal studies, 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.

Pediatric Use: Safety and effectiveness in children below 12 years of age have not been established.

ADVERSE REACTIONS: The adverse reactions to albuterol are similar in nature to reactions to other sympathomimetic agents, although the incidence of certain cardiovascular effects is less with albuterol. A 13-week double-blind study compared albuterol and isoproterenol aerosols in 147 asthmatic patients. The results of this study showed that the incidence of cardiovascular effects was: palpitations, less than 10 per 100 with albuterol and less than 15 per 100 with isoproterenol; tachycardia, 10 per 100 with both albuterol and isoproterenol; and increased blood pressure, less than 5 per 100 with both albuterol and isoproterenol. In the same study, both drugs caused tremor or nausea in less than 10 patients per 100, and dizziness or heartburn in less than 5 per 100 patients. Nervousness occurred in less than 10 per 100 patients receiving albuterol and in less than 15 per 100 patients receiving isoproterenol.

Rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema have been reported after the use of inhaled albuterol.

In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vomiting, vertigo, central nervous system stimulation, insomnia, headache, unusual taste, and drying or irritation of the oropharynx.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

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RB2-211
February 1988

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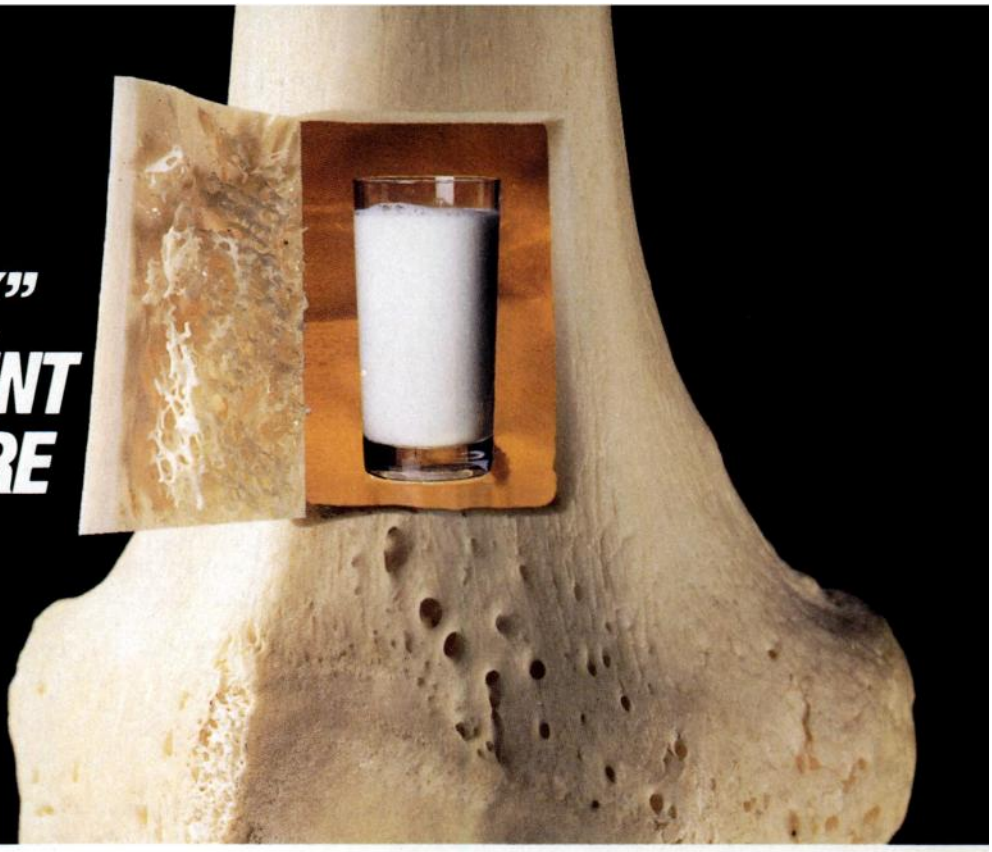
THE "BONE BANK" AN INVESTMENT IN THE FUTURE



Calcium: a disappearing element

Higher calcium intake is indicated during preadolescence and puberty than during childhood because of the demands of rapid skeletal growth.[1] Nevertheless, with the increasing popularity of carbonated drinks and so-called junk food over recent years, as well as peer pressure among females to be thin, many adolescents and preadolescents may not consume all the calcium they need. For example, a U.S. government study[2] found that the mean daily calcium intake for girls 12 to 14 years of age was 72% of the RDA, which is 1,200 mg per day.[3] The intake for girls aged 15 to 17 was even less—only 64% of the RDA.

Calcium in adolescence to build and maintain the "bone bank"

Calcium consumed during adolescence may also have far-reaching consequences throughout life, since both men and women lose bone mass with age.[4,5] To build and maintain an adequate "bone bank," it is logical to begin osteoporosis prevention programs, which include adequate calcium intake, during the active bone-forming years in both sexes.[4,5] A recent study has indicated, for example, that higher milk consumption through adolescence may be associated with greater bone density in the later decades.[6]

Dairy products...versatile calcium source

Since dairy products are the chief source of calcium in the American food supply,[7] and since they are available in a wide variety of good-tasting forms with different fat contents to meet the needs of different patients, it makes excellent sense to recommend dairy products to adolescent and preadolescent patients as their major dietary source of calcium. The fat content of available forms of milk, for example, ranges from a trace in skim milk through 1%, 2%, and to at least 3.25% in whole milk. Richer dairy products (eg, cheeses, ice cream) can be consumed in moderation when appropriate. For lactose-intolerant adolescents, yogurt with active cultures or lactose-free dairy products are available.

DAIRY PRODUCTS TO BUILD AND MAINTAIN THE "BONE BANK"

References: 1. Avioli LV, in Goodhart RS, Shils MR (eds): *Modern Nutrition in Health and Disease*, ed 6. Philadelphia, Lea & Febiger, 1980, pp 194-309. 2. *Second National Health and Nutrition Examination Survey (NHANES II). Dietary Intake Source Data: United States, 1976-80.* National Center for Health Statistics, Public Health Service. Washington, DC, U.S. Government Printing Office, March 1983. 3. *Recommended Dietary Allowances*, ed 9. Washington, DC, National Academy of Sciences, 1980. 4. Rubin K: *Pediatr By-Line* 1985;4(3):1,4-6. 5. Heidrich F, Thompson RS: *J Fam Pract* 1987;25(1):33-39. 6. Sandler RB, Slemenda CW, LaPorte RE, et al: *Am J Clin Nutr* 1985;42:270-274. 7. Marston R, Raper N: *National Food Review* 1987;36:18-23.

Some valuable information for your patients

If you would like a free kit containing patient education materials on dairy calcium's role in adolescent nutrition, please clip and mail this coupon to: Adolescent Nutrition, National Dairy Board, P.O. Box 1063, Fairview, NJ 07022-9763. Please print or type.

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BOOKS RECEIVED

AIDS: A Guide for the Primary Physician. K. K. Holmes and A. G. Motulsky (eds). Seattle, University of Washington Press, 1988, $15, 66 pp.

Allergy: Principles and Practice, ed 3, vol 1 and 2. E. Middleton, Jr, C. E. Reed, E. F. Ellis, et al (eds). St Louis, CV Mosby Co, 1988, $165, 1597 pp.

Assessing the Skeletal Maturity of the Hand-Wrist: Fels Method. A. F. Roche, W. C. Chumlea, and D. Thissen. Springfield, IL, Charles C Thomas, Publisher, 1988, $57.50, 339 pp.

Boston Children's Hospital The New Child Health Encyclopedia: The Complete Guide for Parents. F. H. Lovejoy, Jr (med ed). New York, Dell Publishing Co, Inc, 1987, $39.95 (hardcover). $19.95 (Delta trade paperback), 800 pp.

The Challenge of Epidemiology: Issues and Selected Readings. C. Buck, A. Llopis, E. Najera, et al. Albany, NY, Pan American Health Organization Publications Center, 1988, $30, 989 pp.

Childbirth in America: Anthropological Perspectives. K. L. Michaelson and Contributors. Granby, MA, Bergin & Garvey Publishers, 1988, $49.95 (cloth), $18.95 (paper), 304 pp.

Children With Asthma: A Manual for Parents, ed 2. T. F. Plaut, with parents, patients, and physicians. Amherst, MA, Pedipress, Inc, 1988, $11.95, 291 pp.

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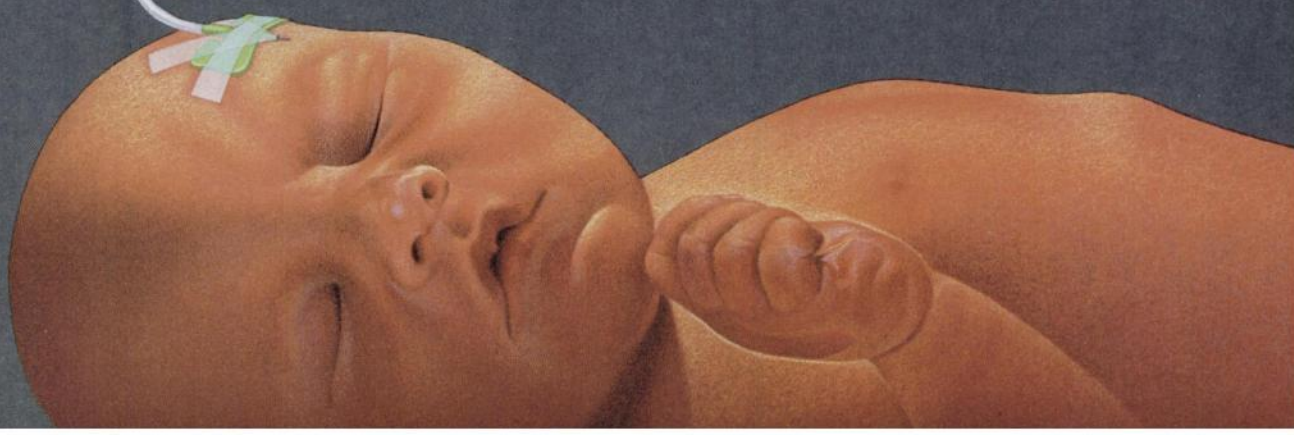
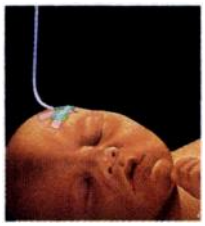
PEDIATRICS IN REVIEW: March 1989 Contents

INFECTIOUS DISEASE & THE BOTTOM LINE.




q8h/q12h

The right antibiotic at the right time. The bottom line in infectious disease.



For six years, Claforan® has been the right antibiotic for countless patients—with q8h dosing for moderate-to-severe infections, and q12h dosing for uncomplicated infections. From meningitis in neonates to pneumonia in the elderly, it has established an outstanding record of success. And, Claforan® provides the flexibility of q6-8h dosing for severe infections, and q4h dosing for life-threatening infections.

The efficacy and safety of Claforan® are uncompromised. In neonates it has the potential for less of an impact on fecal flora than ceftriaxone or cefoperazone.[1] That's why Claforan® is preferred by leading pediatric authorities.[2-4] In patients of all ages, it has not been shown to cause coagulation abnormalities, disulfiram-like reactions, nephrotoxicity, ototoxicity, or seizures.

Right for cost containment with q8h/q12h dosing. The bottom line in today's hospital environment.

Claforan® saves money as well, with economical q12h dosing in uncomplicated infections and q8h dosing in moderate-to-severe infections. In fact, data on over 2,000 cases show that Claforan® q8h for moderate-to-severe infections and q12h for uncomplicated infections consistently maintained a high level of efficacy.[5]

Clearly, what's best about cephalosporins is what you get with Claforan®

STERILE & INJECTION

Claforan®

(cefotaxime sodium)

Please see following page for references and brief summary of prescribing information.

The bottom line.

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Brief Summary

INDICATIONS AND USAGE

Treatment

Claforan is indicated for the treatment of patients with serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below.

(1) **Lower respiratory tract infections,** including pneumonia, caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*), *Streptococcus pyogenes*† (Group A streptococci) and other streptococci (excluding enterococci, e.g., *Streptococcus faecalis*), *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Escherichia coli*, *Klebsiella* species, *Haemophilus influenzae* (including ampicillin-resistant strains), *Haemophilus parainfluenzae*, *Proteus mirabilis*, *Serratia marcescens*†, *Enterobacter* species, indole-positive *Proteus* and *Pseudomonas* species (including *P. aeruginosa*).

(2) **Genitourinary infections.** Urinary tract infections caused by *Enterococcus* species, *Staphylococcus epidermidis*, *Staphylococcus aureus*† (penicillinase and non-penicillinase producing), *Citrobacter* species, *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Proteus mirabilis*, *Proteus vulgaris*†, *Proteus inconstans* Group B, *Morganella morganii*†, *Providencia rettgeri*†, *Serratia marcescens*, and *Pseudomonas* species (including *P. aeruginosa*). Also, uncomplicated gonorrhea of single or multiple sites caused by *Neisseria gonorrhoeae*, including penicillinase producing strains.

(3) **Gynecologic infections,** including pelvic inflammatory disease, endometritis and pelvic cellulitis caused by *Staphylococcus epidermidis*, *Streptococcus* species, *Enterococcus* species, *Enterobacter* species†, *Klebsiella* species†, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides* species (including *Bacteroides fragilis*†), *Clostridium* species, anaerobic cocci (including *Peptostreptococcus* species and *Peptococcus* species) and *Fusobacterium* species (including *F. nucleatum*†).

(4) **Bacteremia/Septicemia** caused by *Escherichia coli*, *Klebsiella* species, *Serratia marcescens*, *Staphylococcus aureus*, and *Streptococcus* species (including *S. pneumoniae*).

(5) **Skin and skin structure infections** caused by *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Staphylococcus epidermidis*, *Streptococcus pyogenes* (Group A streptococci) and other streptococci, *Enterococcus* species, *Acinetobacter* species†, *Escherichia coli*, *Citrobacter* species (including *C. freundii*†), *Enterobacter* species, *Klebsiella* species, *Proteus mirabilis*, *Proteus vulgaris*†, *Morganella morganii*, *Providencia rettgeri*†, *Pseudomonas* species, *Serratia marcescens*, *Bacteroides* species, and anaerobic cocci (including *Peptostreptococcus*† species and *Peptococcus* species).

(6) **Intra-abdominal infections** including peritonitis caused by *Streptococcus* species†, *Escherichia coli*, *Klebsiella* species, *Bacteroides* species, anaerobic cocci (including *Peptostreptococcus*† species and *Peptococcus*† species), *Proteus mirabilis*†, and *Clostridium* species†.

(7) **Bone and/or joint infections** caused by *Staphylococcus aureus* (penicillinase and non-penicillinase producing strains), *Streptococcus* species (including *S. pyogenes*†), *Pseudomonas* species (including *P. aeruginosa*†), and *Proteus mirabilis*†.

(8) **Central nervous system infections,** e.g., meningitis and ventriculitis, caused by *Neisseria meningitidis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*†, and *Escherichia coli*†.

† Efficacy for this organism, in this organ system, has been studied in fewer than 10 infections.

Although many strains of enterococci (e.g., *S. faecalis*) and *Pseudomonas* species are resistant to cefotaxime sodium *in vitro*, Claforan has been used successfully in treating patients with infections caused by susceptible organisms.

Specimens for bacteriologic cultures should be obtained prior to therapy in order to isolate and identify causative organisms and to determine their susceptibilities to Claforan. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

Prevention

The administration of Claforan preoperatively reduces the incidence of certain infections in patients undergoing surgical procedures (e.g., abdominal or vaginal hysterectomy, gastrointestinal and genitourinary tract surgery) that may be classified as contaminated or potentially contaminated.

In patients undergoing cesarean section, intraoperative (after clamping the umbilical cord) and postoperative use of Claforan may also reduce the incidence of certain postoperative infections. (See **DOSAGE AND ADMINISTRATION** section.)

Effective use for elective surgery depends on the time of administration. To achieve effective tissue levels, Claforan should be given ½ to 1½ hours before surgery. (See **DOSAGE AND ADMINISTRATION** section.)

For patients undergoing gastrointestinal surgery, preoperative bowel preparation by mechanical cleansing as well as with a non-absorbable antibiotic (e.g., neomycin) is recommended.

If there are signs of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapy may be instituted.

CONTRAINDICATIONS

Claforan is contraindicated in patients who have shown hypersensitivity to cefotaxime sodium or the cephalosporin group of antibiotics.

WARNINGS

BEFORE THERAPY WITH CLAFORAN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOTAXIME SODIUM, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN WITH CAUTION TO PATIENTS WITH TYPE I HYPERSENSITIVITY REACTIONS TO PENICILLIN. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CLAFORAN OCCURS, DISCONTINUE TREATMENT WITH THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*.

Mild cases of colitis may respond to drug discontinuance alone.

Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should also be considered.

PRECAUTIONS

Claforan® (cefotaxime sodium) should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Claforan has not been shown to be nephrotoxic; however, because high and prolonged serum antibiotic concentrations can occur from usual doses in patients with transient or persistent reduction of urinary output because of renal insufficiency, the total daily dosage should be reduced when Claforan is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organism.

Although there is no clinical evidence supporting the necessity of changing the dosage of cefotaxime sodium in patients with even profound renal dysfunction, it is suggested that, until further data are obtained, the dose of cefotaxime sodium be halved in patients with estimated creatinine clearances of less than 20 mL/min/1.73 m².

When only serum creatinine is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

$$\text{Males: } \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine}}$$

$$\text{Females: } 0.85 \times \text{above value}$$

As with other antibiotics, prolonged use of Claforan may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Drug Interactions: Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.

Carcinogenesis, Mutagenesis: Long-term studies in animals have not been performed to evaluate carcinogenic potential. Mutagenic tests included a micronucleus and an Ames test. Both tests were negative for mutagenic effects.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to 30 times the usual human dose and have revealed no evidence of impaired fertility or harm to the fetus because of cefotaxime sodium. However, there are no well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: Use of the drug in women of childbearing potential requires that the anticipated benefit be weighed against the possible risks.

In perinatal and postnatal studies with rats, the pups in the group given 1200 mg/kg of Claforan were significantly lighter in weight at birth and remained smaller than pups in the control group during the 21 days of nursing.

Nursing Mothers: Claforan is excreted in human milk in low concentrations. Caution should be exercised when Claforan is administered to a nursing woman.

ADVERSE REACTIONS

Claforan is generally well tolerated. The most common adverse reactions have been local reactions following IM or IV injection. Other adverse reactions have been encountered infrequently.

The most frequent adverse reactions (greater than 1%) are:

Local (4.3%)—Injection site inflammation with IV administration. Pain, induration, and tenderness after IM injection.

Hypersensitivity (2.4%)—Rash, pruritus, fever, and eosinophilia.

Gastrointestinal (1.4%)—Colitis, diarrhea, nausea, and vomiting.

Symptoms of pseudomembranous colitis can appear during or after antibiotic treatment.

Nausea and vomiting have been reported rarely.

Less frequent adverse reactions (less than 1%) are:

Hemic and Lymphatic System—Granulocytopenia, transient leukopenia, eosinophilia, neutropenia, and thrombocytopenia have been reported. Some individuals have developed positive direct Coombs Tests during treatment with the cephalosporin antibiotics.

Genitourinary System—Moniliasis, vaginitis.

Central Nervous System—Headache.

Liver—Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase levels have been reported.

Kidney—As with some other cephalosporins, transient elevations of BUN have been occasionally observed with Claforan.

DOSAGE AND ADMINISTRATION

Adults

Dosage and route of administration should be determined by susceptibility of the causative organisms, severity of the infection, and the condition of the patient (see table for dosage guidelines). Claforan may be administered IM or IV after reconstitution. Premixed Claforan Injection is intended for IV administration after thawing. The maximum daily dosage should not exceed 12 grams.

GUIDELINES FOR DOSAGE OF CLAFORAN

Type of Infection	Daily Dose (grams)	Frequency and Route
Gonorrhea	1	1 gram IM (single dose)
Uncomplicated infections	2	1 gram every 12 hours IM or IV
Moderate to severe infections	3-6	1-2 grams every 8 hours IM or IV
Infections commonly needing antibiotics in higher dosage (e.g., septicemia)	6-8	2 grams every 6-8 hours IV
Life-threatening infections	up to 12	2 grams every 4 hours IV

To prevent postoperative infection in contaminated or potentially contaminated surgery, the recommended dose is a single 1 gram IM or IV administered 30 to 90 minutes prior to start of surgery.

Cesarean Section Patients

The first dose of 1 gram is administered intravenously as soon as the umbilical cord is clamped. The second and third doses should be given as 1 gram intravenously or intramuscularly at 6 and 12 hours after the first dose.

Neonates, Infants, and Children

The following dosage schedule is recommended:

Neonates (birth to 1 month):

0-1 week of age — 50 mg/kg IV q12h

1-4 weeks of age — 50 mg/kg IV q8h

It is not necessary to differentiate between premature and normal gestational age infants.

Infants and Children (1 month to 12 years): For body weights less than 50 kg, the recommended daily dose is 50 to 180 mg/kg IM or IV of body weight divided into four to six equal doses. The higher dosages should be used for more severe or serious infections, including meningitis. For body weights 50 kg or more, the usual adult dosage should be used; the maximum daily dosage should not exceed 12 grams.

Impaired Renal Function—see **PRECAUTIONS** section.

NOTE: As with antibiotic therapy in general, administration of Claforan should be continued for a minimum of 48 to 72 hours after the patient defervesces or after evidence of bacterial eradication has been obtained; a minimum of 10 days of treatment is recommended for infections caused by Group A beta-hemolytic streptococci in order to guard against the risk of rheumatic fever or glomerulonephritis; frequent bacteriologic and clinical appraisal is necessary during therapy of chronic urinary tract infection and may be required for several months after therapy has been completed; persistent infections may require treatment of several weeks and doses smaller than those indicated above should not be used.

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Help make the common cold less common.

Recent research indicates: Colds are "caught"...by hand.

Today we know that we are far more likely to catch a cold from our fingers than from a sneeze or a cough.[1] Rhinovirus on a cold sufferer's hands can be easily passed on to other hands. And when contaminated fingers probe a nose or rub an eye, the result is often a common cold infection.

The importance of fomites is more clearly understood.

Contaminated surfaces—or fomites—also help to transmit common cold infections. When a child touches a fomite (which could be a favorite toy), and then goes on to touch his eyes or nose...a cold may follow.

Lysol® Spray: Meets the need for a virucidal agent...

Some experts recommend the use of a virucidal agent to help curb the spread of rhinovirus from fomites to fingers.[1,2] In laboratory studies with human volunteers, LYSOL Spray has been shown to virtually eliminate rhinovirus when applied to contaminated surfaces.[3]

Works to interrupt the chain of transmission

In separate tests involving human volunteers, the use of LYSOL Spray on contaminated tiles actually resulted in a *21% reduction* in common cold infections.[4]

Lysol® Spray: An important part of a patient prevention program

Throughout the year—and *especially* at the first sign of a cold—recommend frequent hand washing...avoidance of finger-to-eye and finger-to-nose contact...and widespread use of LYSOL Spray—to help eliminate rhinovirus on household surfaces, help make the common cold less common.

Please send me a free copy of the informative patient booklet, "Common Cold Facts," to review for use in my practice.

Mail to: Lysol® Common Colds Fact Book, P.O. Box 5440, Westbury, NY 11592

Name _____

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City _____ State _____ Zip _____

Offer Expires 8/31/89

References:

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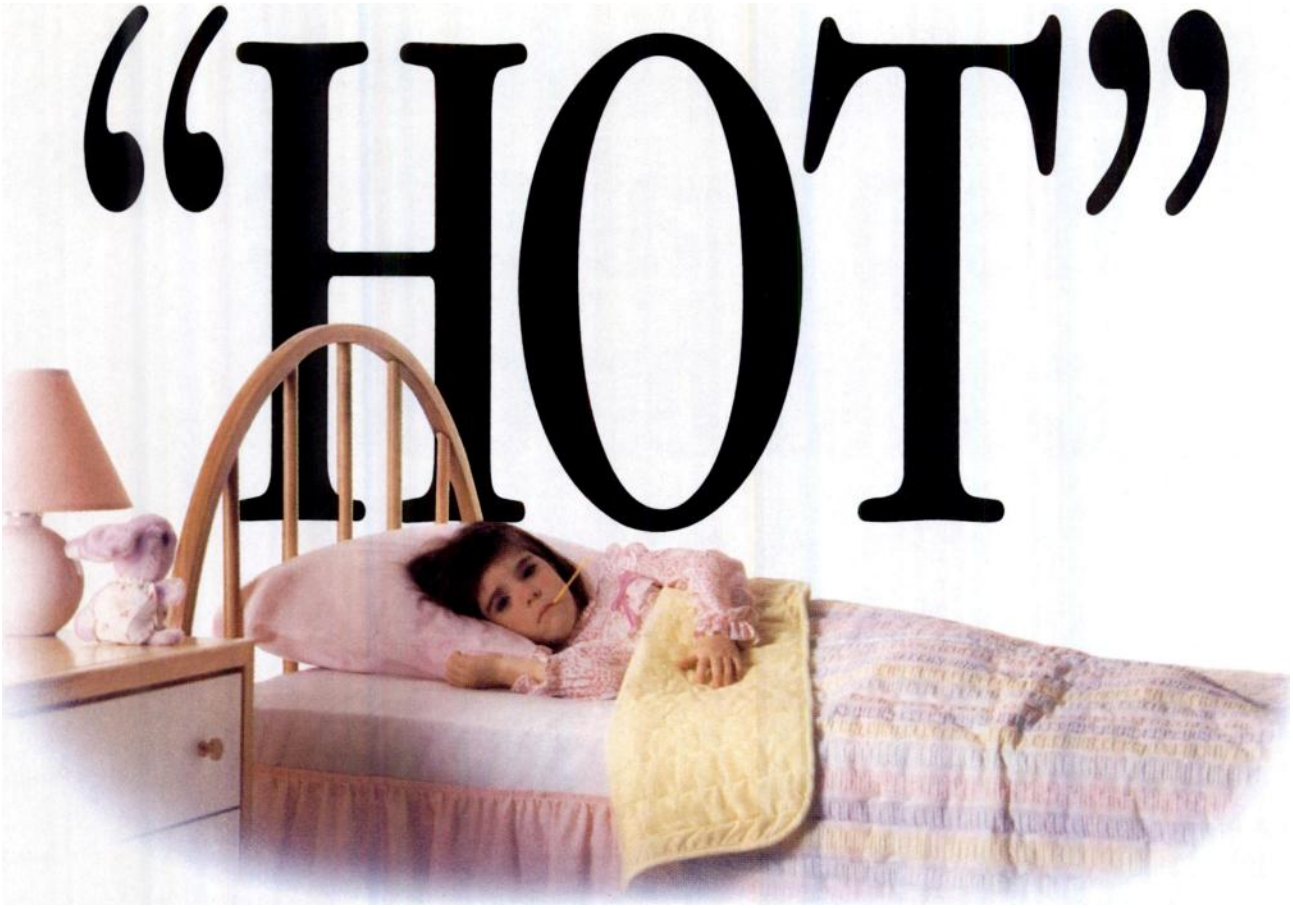

Cool her fever with the brand that offers the most dosage choices

When your patients need fever relief, Children's TYLENOL® acetaminophen should be your first choice. TYLENOL® offers you more dosage choices than any other acetaminophen brand, so your patients get the right medicine in a form and flavor that's right for every child's needs:

- ☐ Alcohol-free Infants' Drops
- ☐ Alcohol-free Children's Elixir in Cherry and *New Grape* flavors
- ☐ Children's 80 mg Chewables in *both* Grape and Fruit flavors
- ☐ Easy-to-swallow 160 mg Junior Strength Coated Caplets for 6- to 14-year-olds

Remember, TYLENOL® is clinically proven as effective an antipyretic as aspirin, with a superior safety profile.[1,2] And parents can easily find your recommendation, because TYLENOL® products are more widely available in food and drug stores than any other brand.[3] So next time a little patient is "Hot!" with fever, make your first choice TYLENOL® acetaminophen.

References: 1. Tarlin L, et al: *Am J Dis Child* 1972;124:880-882. **2.** Aspirin or paracetamol? *Lancet* 1981;II:287-289. **3.** Data on file, McNeil Consumer Products Company.

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acetaminophen

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University Associates in Psychiatry, 1986
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STIPULATIONS AMERICAN ACADEMY OF PEDIATRICS RESIDENCY FELLOWSHIPS, 1989

To enable young physicians to complete their pediatric training, the American Academy of Pediatrics will grant a small number of fellowships of $500 to $3,000 each to pediatric interns and residents for the year beginning July 1. Candidates must meet the following requirements:

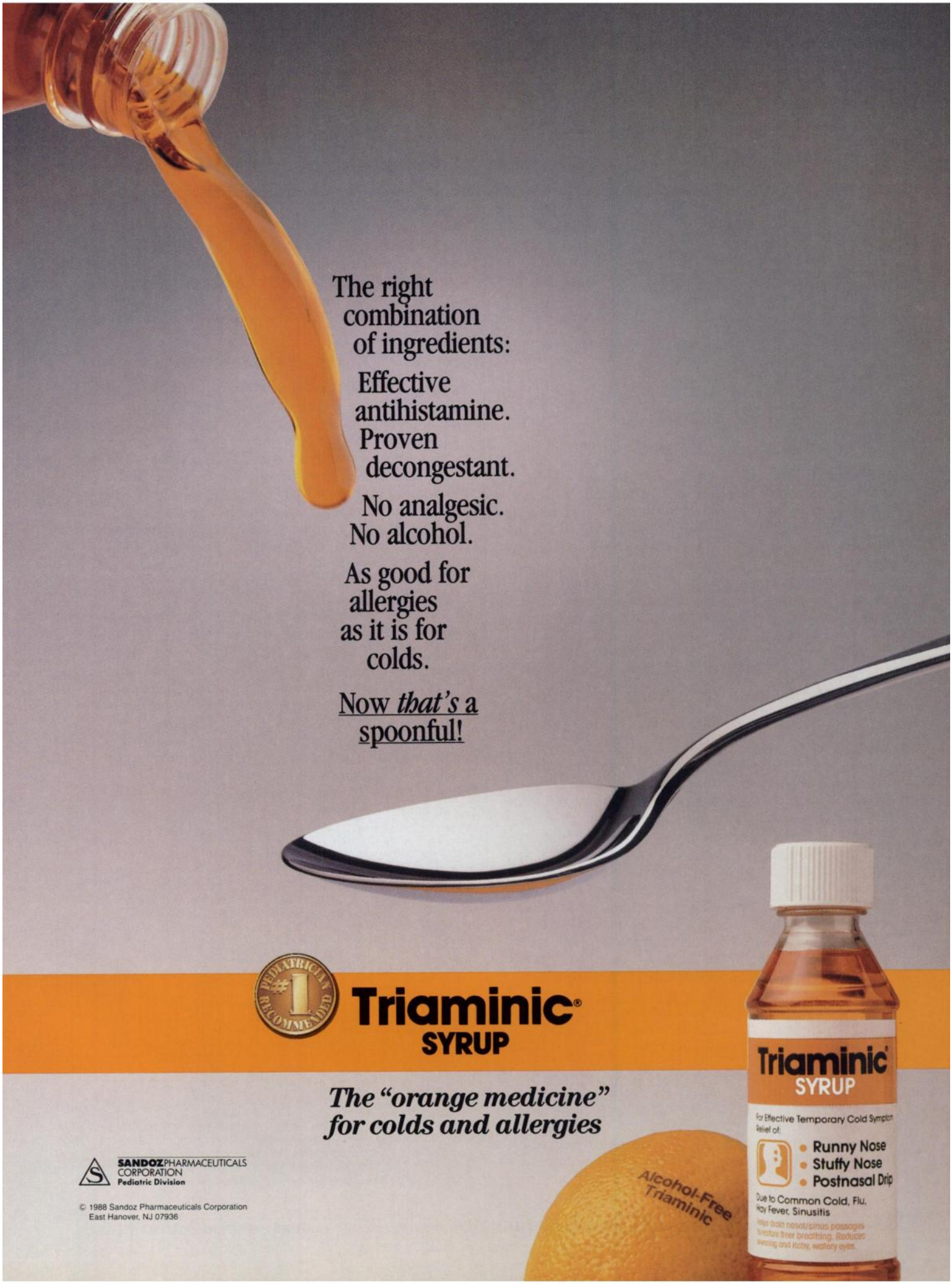
1. Be legal residents of the United States or Canada.
2. Have completed, or will have completed by July 1, a qualifying approved internship (PI-0) or have completed a PI-1 program and have a definite commitment for a first-year pediatric residency (PI-1 or PI-2) acceptable to the American Board of Pediatrics; or
3. Be pediatric residents (PI-1, PI-2, or PI-3) in a training program and have made a definite commitment for another year of residency (not fellowship) in a program acceptable to the American Board of Pediatrics;
4. Have a real need of financial assistance; and
5. Support their applications with a letter from the Chief of Service substantiating the above requirements, especially the financial need; if a change in residency program is contemplated (ie, moving to another institution), a letter from the Chief of this Service certifying acceptance to this program will also be necessary.

Although the fellowships awards are intended primarily for the support of first- and second-year pediatric residents, it is also recognized that some physicians may desire a third or fourth year of pediatric residency. Up to 25% of the fellowships may be awarded to persons in this category.

The fellowships have been provided through grants to the American Academy of Pediatrics by Mead Johnson Nutritional Division, the Gerber Products Company, and the McNeil Consumer Products Company.

The Committee on Residency Fellowships of the American Academy of Pediatrics will make the final decision on the granting of the awards. Those interested in applying may write to Edgar O. Ledbetter, MD, Director, Department of Maternal, Child and Adolescent Health, American Academy of Pediatrics, PO Box 927, Elk Grove Village, IL 60009-0927, for application forms.

The applications and letters must be returned by March 1, 1989, in order to be eligible.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THE VINDICATION OF LACTOSE

Decreased lactase levels are not as common as once believed: lactose actually helps resolve diarrhea often attributed to formula intolerance

Background

Though it is still common practice for physicians to recommend a lactose-free formula for infants with chronic nonspecific or postinfectious diarrhea, studies demonstrate that lactose is rarely the offending agent. In fact, recent clinical evidence shows that formula containing lactose may actually be helpful in resolving diarrhea.

Lactose routinely excluded from soy-based formula without intrinsic cause

Acute gastroenteritis in infants is often followed by chronic diarrhea. Conventional treatment for this involves delaying the reintroduction of usual feedings, and often withholding cow's milk or milk-based formula. Soy-based formulas are often substituted to eliminate the suspect protein. These formulas also replace lactose with sucrose and/or corn syrup for the carbohydrate source; this once seemed a good idea because congenital lactase deficiency, now regarded as extremely rare,[1] was formerly thought to be common in infants.

Protein, not lactose, is agent in most formula intolerance: guilt by association?

Most cases of lactose intolerance are temporary, secondary to protein-induced gastroenteritis, and quickly resolve as soon as the offending protein is withdrawn.[2] Liu et al[3] demonstrated convincingly that most infants initially intolerant of both milk and lactose could tolerate lactose after milk protein was eliminated from the diet. Lactose seems to play a role in formula intolerance only when associated with an offending protein. Gerrard[2] found that infants with confirmed allergy to cow's milk protein showed no signs of lactose intolerance when returned to breast milk. Also, clinical experience suggests that human milk frequently is well tolerated when other foods are not,[4,5] even though the carbohydrate of breast milk is entirely lactose. Groothuis et al[6] found that lactose formula did not prolong mild gastroenteritis in infants, but that these infants recovered as quickly as those fed formulas containing sucrose or maltodextrin.

Lactose helps resolve diarrhea

The most recent data indicate that lactose may actually resolve some of the symptoms formerly attributed to lactose intolerance or protein intolerance.[7] Forty infants were chosen who, following an initial presentation of acute gastroenteritis, were diagnosed as having chronic diarrhea and, presumably, formula intolerance. The infants were divided into three groups and fed formulas that were identical except for the carbohydrate source. Within four days, improvement was observed in 86% of the infants fed the formula containing lactose, compared with only 20% and 19% of those fed maltodextrin- or sucrose-containing formulas.

Lactose vindicated

Lactose is the carbohydrate of breast milk, the ideal infant nutritional source, and aids in the absorption of calcium,[8] magnesium, and zinc.[9] It causes beneficial biochemical and microbiological changes in the lower parts of the intestine,[10] helps establish favorable colonic flora,[11] and its galactose portion may be important in the rapid formation of brain lipids.[12] As described above, lactose may also take part in a specific mechanism for the inhibition of water and electrolyte losses through the bowel.[7] This beneficial energy source should not be eliminated from infant formulas because of outdated misinformation. The American Academy of Pediatrics Committee on Nutrition clearly states that "The current data do not suggest that lactose be routinely eliminated from the diet of infants recovering from diarrhea."[8] While the apparent hypoallergenicity of soy-based formulas may seem to make them suitable for infants with a family history of atopy, they contain no lactose; a more desirable alternative is the lactose-containing GOOD START H.A.™ Iron Fortified Hypoallergenic Infant Formula recently developed by Carnation Nutritional Products. For a product monograph write Carnation Nutritional Products, ACS, 4144 Howard Ave, Kensington, MD 20895.

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PHENERGAN® (promethazine HCl) RECTAL SUPPOSITORIES
In Brief

Indications: Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery. Active and prophylactic treatment of motion sickness. Antiemetic effect in postop patients. Phenergan® suppositories are not recommended for children under 2 years of age.

Contraindications: Contraindicated in individuals known to be hypertensive or to have had idiosyncratic reaction to promethazine or other phenothiazines.
Contraindicated in treatment of lower respiratory tract symptoms including asthma.

Warnings: May cause marked drowsiness. Caution ambulatory patients against activities like driving or operating machinery until it is known they do not become drowsy or dizzy from promethazine.
The sedative action of promethazine is additive to sedative effects of CNS depressants; therefore, agents such as alcohol, narcotic analgesics, sedatives, hypnotics, and tranquilizers should be eliminated or given in reduced dosage in presence of promethazine. When given concomitantly with promethazine, reduce dose of barbiturates by at least ½, and dose of analgesic depressants, such as morphine or meperidine, by ¼ to ½ Promethazine may lower seizure threshold. This should be taken into consideration when administering to persons with known seizure disorders or when giving in combination with narcotics or local anesthetics which may also affect seizure threshold. Avoid sedatives or CNS depressants in patients with history of sleep apnea. Antihistamines should be used with caution in patients with narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, and urinary bladder obstruction due to symptomatic prostatic hypertrophy and narrowing of the bladder neck. Administration of promethazine has been associated with reported cholestatic jaundice.

Precautions: GENERAL: Use cautiously in persons with cardiovascular disease or impairment of liver function.
INFORMATION FOR PATIENTS: May cause marked drowsiness or impair mental and/or physical abilities required for potentially hazardous tasks, e.g., driving or operating machinery. Ambulatory patients should be told to avoid engaging in such activities until it is known they do not become drowsy or dizzy from Phenergan. Children should be supervised to avoid potential harm in bike riding or other hazardous activities.
The concomitant use of alcohol or other CNS depressants, including narcotic analgesics, sedatives, hypnotics, and tranquilizers, may have an additive effect and should be avoided or their dosage reduced.
Patients should be advised to report any involuntary muscle movements or unusual sensitivity to sunlight.
DRUG INTERACTIONS: The sedative action of promethazine is additive to sedative effects of other CNS depressants, including alcohol, narcotic analgesics, sedatives, hypnotics, tricyclic antidepressants, and tranquilizers; therefore, these agents should be avoided or given in reduced dosage to patients receiving promethazine.
DRUG/LABORATORY TEST INTERACTIONS: Following tests may be affected in patients receiving promethazine:
Pregnancy Tests: Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.
Glucose Tolerance Test: Increase in blood glucose has been reported in patients receiving promethazine.
CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Long-term animal studies have not been performed to assess carcinogenic potential of promethazine, nor are there other animal or human data concerning carcinogenicity, mutagenicity, or impairment of fertility. Promethazine was nonmutagenic in the *Salmonella* test system of Ames.
PREGNANCY: *Teratogenic Effects–Pregnancy Category C:* Teratogenic effects have not been demonstrated in rat-feeding studies at doses of 6.25 and 12.5 mg/kg. These doses are from about 2.1 to 4.2 times maximum recommended total daily dose of promethazine for a 50-kg subject, depending on indication for the drug. Specific studies to test action of the drug on parturition, lactation, and development of the animal neonate were not done, but a general preliminary study in rats indicated no effect on these parameters. Although antihistamines, including promethazine, have been found to produce fetal mortality in rodents, the pharmacological effects of histamine in the rodent do not parallel those in man. There are no adequate and well-controlled studies of promethazine in pregnant women. Phenergan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nonteratogenic Effects: Promethazine taken within 2 weeks of delivery may inhibit platelet aggregation in the newborn.
NURSING MOTHERS: It is not known if promethazine is excreted in human milk. Caution should be exercised when promethazine is given to a nursing woman.
PEDIATRIC USE: Should not be used in children under 2 years because safety is not established.

Adverse Reactions: *Nervous System*–Sedation, sleepiness, occasional blurred vision, dryness of mouth, dizziness; rarely confusion, disorientation, and extrapyramidal symptoms such as oculogyric crisis, torticollis, and tongue protrusion (usually in association with parenteral injection or excessive dosage).
Cardiovascular–Increased or decreased blood pressure.
Dermatologic–Rash, rarely photosensitivity.
Hematologic–Rarely leukopenia, thrombocytopenia, agranulocytosis (1 case).
Gastrointestinal–Nausea and vomiting.

Overdosage: Signs and symptoms of overdosage range from mild CNS and cardiovascular system depression to profound hypotension, respiratory depression, and unconsciousness. Stimulation may be evident, especially in children and geriatric patients. Convulsions may rarely occur. A paradoxical reaction has been reported in children with single doses of 75 mg to 125 mg orally, characterized by hyperexcitability and nightmares. Atropine-like signs and symptoms–dry mouth, fixed, dilated pupils, flushing, as well as GI symptoms, may occur.
TREATMENT: Treatment of overdosage is essentially symptomatic and supportive. Only in cases of extreme overdosage of individual sensitivity do vital signs including respiration, pulse, blood pressure, temperature, and EKG need to be monitored. Activated charcoal orally or by lavage may be given, or sodium or magnesium sulfate orally as a cathartic. Attention should be given to re-establishment of adequate respiratory exchange through provision of patent airway and institution of assisted or controlled ventilation. Diazepam may be used to control convulsions. Acidosis and electrolyte losses should be corrected. Note that any depressant effects of promethazine are not reversed by naloxone. Avoid analeptics which may cause convulsions.
Severe hypotension usually responds to administration of norepinephrine or phenylephrine. EPINEPHRINE SHOULD NOT BE USED, since its use in patients with partial adrenergic blockade may further lower the blood pressure.
Limited experience with dialysis indicates it is not helpful.

Composition: 12.5 and 25 mg promethazine HCl with ascorbyl palmitate, silicon dioxide, white wax, and cocoa butter.

See full prescribing information.

3/6/87

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Produced in cooperation with the American Academy of Pediatrics, this 65-minute videotape and companion book provide vital information to keep your infant or young child safe and secure.

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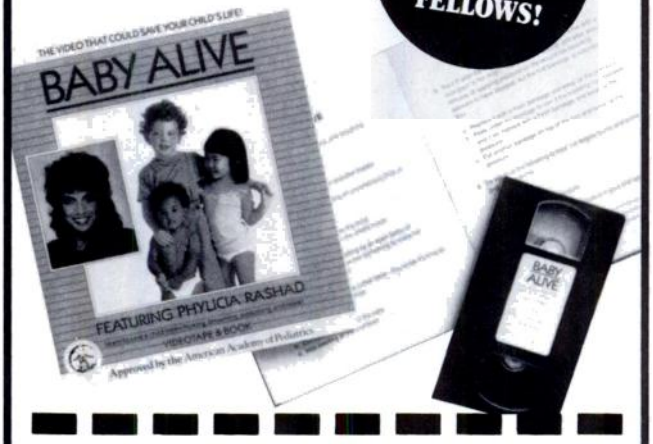

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Until now, even the best in-vitro Strep A diagnostic tests have left you and your staff unhappy. Clumsy extraction procedures, multiple steps and reagents, extensive hands-on time—all this adds up to make in-office Strep A testing an unpleasant chore. That was yesterday. Now there's CHROMAGEN™, the new enzyme screening assay that:

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*Data on file, Abbott Laboratories. Flavor evaluations conducted with 20 adult volunteers. Evaluations compared EryPed 200 and 400 to Barre's formulation of erythromycin ethylsuccinate oral suspension, USP 200 mg base/5 ml and 400 mg base/5 ml, respectively.

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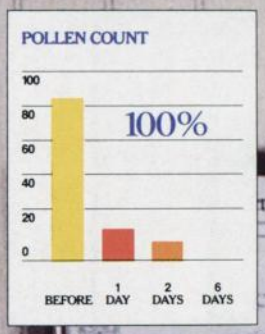

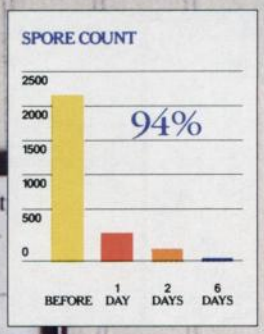

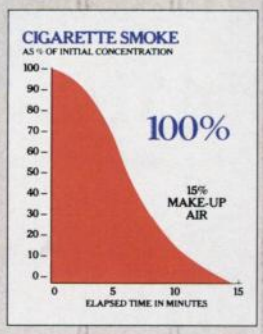

One therapy provides the same fast relief for both pediatric and adult patients: the Newtron Air Cleaner. The Newtron electrostatic air cleaner helps eliminate major causes of seasonal respiratory allergy. The Newtron has demonstrated that it is capable of removing up to 100% of pollen and up to 94% of mold spores from indoor air in a typical home. The Newtron is also highly effective against other airborne irritants such as household dust.

The Newtron is a time-proven therapy with no "side-effects." It cleans the air by generating natural static electricity, which traps airborne irritants in a patented configuration of five highly static-prone materials. And it works without producing ozone, without consuming electricity, without the bother of replacement media, powerpacks or other costly complications.

The Newtron Electrostatic Air Cleaner offers families and businesses consistent and reliable performance while providing cleaner, healthier indoor air, without expensive installation or tedious maintenance…at about half the cost of electronic air cleaners. Installation takes just minutes; cleaning is required every 60-90 days and is accomplished by a simple water rinse. Unlike ordinary air filters, the Newtron will not unduly restrict air flow or cause undue stress on heating and air conditioning systems.

If you recommend air cleaners in your practice, ask about Newtron's Evaluation Program.

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The Physician's Choice℠

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The Newtron cleans in minutes with plain water

Independent tests performed under real-life conditions. Pollen and spore count tests performed on 1" unit; cigarette smoke on 2" unit. Results may vary, depending on the location and heating system.

When the flu upsets stomachs, make the safe call. Emetrol®

Emetrol® safely relieves nausea associated with upset stomach of intestinal flu and food indiscretions.

There are no antihistimine side effects with Emetrol®.

- No drowsiness.
- No alcohol.
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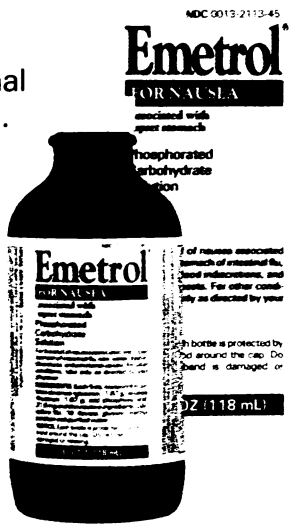
Safe for children of all ages.



Emetrol® does not mask symptoms of underlying pathology. It works almost immediately by local action on contact with the hyperactive G.I. tract.

Convenient. Ideal for telephone recommendations. No Rx required.

Available in 4 and 16 oz. sizes plus the NEW 8 oz. Family Size.

Carnation® introduces

A BREAKTHROUGH HYPOALLERGENIC INFANT FORMULA

Introducing

THE FIRST HYPOALLERGENIC FORMULA MADE FROM HYDROLYZED WHEY PROTEIN

Available in easy-to-dissolve powder, in 12-oz cans.

If you would like samples, call toll-free 1-800-628-BABY (2229).

Because of increasing recognition of the sensitivity to soy,[1] Carnation has developed the first truly hypoallergenic formula made from hydrolyzed whey protein.

Carnation® GOOD START H.A. effectively resolves symptoms in infants suffering from formula intolerance. And, it may prevent allergic manifestations in infants with a family history of allergy.

No curd formation and rapid gastric emptying make GOOD START H.A. easy to digest and may cause less spitting up. Because of its whey base, it's a high-quality protein source for optimal growth. Parents will like its pleasant taste and aroma. And, it's moderately priced for long-term use.

The GOOD START H.A. formulation has been thoroughly researched in clinical trials and safely fed to more than 25,000 infants over the past 3 years in Europe.

Hypoallergenicity Supported By Clinical Data

In four studies of 362 infants from atopic families, no allergic reaction was observed with the GOOD START H.A. hypoallergenic formulation.[2-5]

Carnation®

New **GOOD START H.A.**™

Hypoallergenic Infant Formula

. . . a change for the better

INSTEAD OF SOY, CHANGE TO NEW GOOD START H.A.™

Sensitivity to soy increasingly recognized[1]

About one fourth of infants who are sensitive to cow's milk protein are also intolerant of soy protein.[7,8]

If you would like samples, call toll-free 1-800-628-BABY (2229).

Recommend GOOD START H.A.™ for:

Formula Intolerance, Instead of Soy

Resolves symptoms of formula intolerance such as spitting up, skin rash, runny nose, colic, and sleeplessness.

Routine Feeding of Atopic Infants

May prevent allergic manifestations in infants with a family history of allergy[2]

Routine Feeding of Normal Infants

Nutritionally complete for optimal growth and development

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7. Gerrard JW, Lubos MC, Hardy LW, et al: Milk allergy: Clinical picture and familial incidence. *Can Med Assoc J* 1967;97:780-785.

NOTE: Although the protein in GOOD START H.A. is specially processed to be truly hypoallergenic, no formula is completely nonallergenic. In cases of severe allergy symptoms (e.g., excessive vomiting, bloody stools), direct physician supervision is necessary. If anaphylactic shock has already occurred, GOOD START H.A. should not be used.

Carnation®

New **GOOD START H.A.**™

Hypoallergenic Infant Formula

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GOOD START H.A.™

Hypoallergenic Infant Formula

A CHANGE FOR THE BETTER

Nutritionally close to breast milk

Amino acid balance close to breast milk

The added fat blend is 100% vegetable oil, high in monounsaturates:

GOOD START H.A.—44.5% of the fatty acid component is monounsaturated

Breast milk—40.2% of the fatty acid component is monounsaturated

Polyunsaturated-to-saturated ratio is similar to breast milk:

GOOD START H.A. P/S ratio = 0.31

Breast milk P/S ratio = 0.28–0.35*

Carbohydrate content is 70% lactose (the *only* carbohydrate in breast milk), for better absorption of calcium, magnesium, and zinc:

30% of the carbohydrate content is maltodextrin, which is easily digested and helps keep osmolarity low to protect against osmotic diarrhea

NOTE: GOOD START H.A. should not be used for infants with galactosemia.

*Varies with individual.

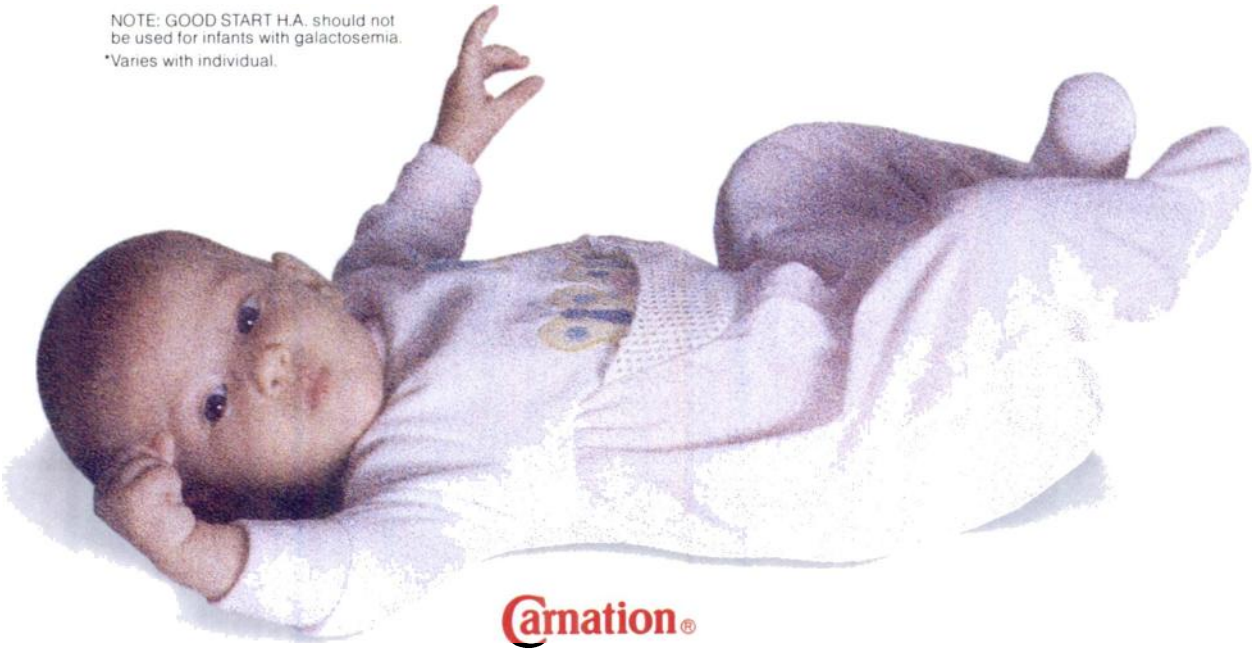

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TABLE. Episodes of Decreases in Systolic Blood Pressure in Infants Receiving Captopril Therapy*

Patient No.	Duration of Elevated BP (d)	BP (mm Hg) Prior to Therapy	BP After Therapy		Duration of BP Decrease (h)	Oliguria	Neurologic Manifestations
			Lowest BP (mm Hg)	% Decrease			
1	8	148	86	42	10	+	+
	28†	112†	60	46	2	−	−
2	53	122	70	43	24	+	+
	130	130	60	54	24	+	+
	160	96	38	60	76	+	+
3	40	138	60	56	24	+	+
	101	144	40	72	32	+	+
	134	121†	65	46	3	−	−
	154	120†	50	58	8	−	−
4	140	132	55	58	6	+	+
	156	100†	48	52	2	−	−
5	46	116†	58	50	5	−	−
	54	120†	60	50	4	−	−
6	36	114†	60	47	3	−	−
7	49	134†	52	61	1	−	−
8	69	144†	68	52	4	−	−
9	239	185†	110	40	2	−	+

* Symbols: +, presence; −, absence.
† Decreased BP unassociated with renal or neurologic manifestations.

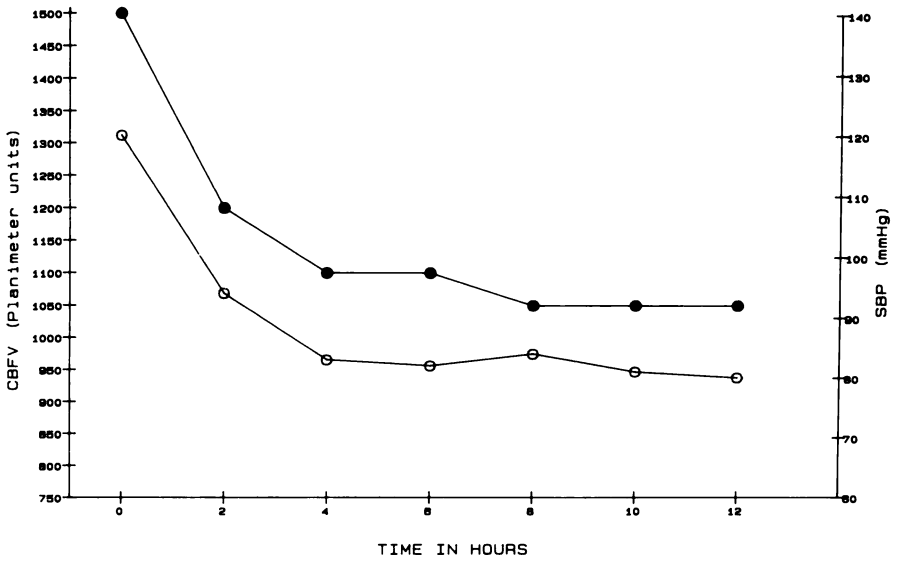

Fig 1. Case 1. Simultaneous systolic BP (SBP) (●) and cerebral blood flow velocity (CBFV) (○) measurements obtained from infant following treatment with captopril. Note decrease in cerebral blood flow velocity that parallels decrease in systolic BP.

BP, ie, a 46% decrease, from a mean of 112 to 60 mm Hg, which, however, persisted for only two hours and was not associated with oliguria or neurologic manifestations.

A cranial ultrasound scan performed on the third postnatal day demonstrated a small left subependymal hemorrhage. A repeat ultrasound scan performed at the time of the clinical deterioration following the onset of oliguria showed resolution of the subependymal hemorrhage. A third ultrasound scan, performed ten days following the clinical deterioration, appeared markedly abnormal. A large echogenic lesion, extending from the left frontal to the parietal-occipital regions, with associated mass effect and shift of the midline structures to the right, was noted. These findings were considered to be most consistent with an infarct. A CT scan on the same day demonstrated a large area of lucency involving the same regions with midline shift to the right (Fig 2). The appearance was that of a large infarct.

The infant's subsequent clinical course was characterized by resolution of the hypertension and the captopril was discontinued by the sixth postnatal month. She continues, however, to have a right-sided hemiparesis.

Case 2

This was an 1,100-g, 28-week, appropriate-for-gestational age infant delivered by repeat cesarean section.

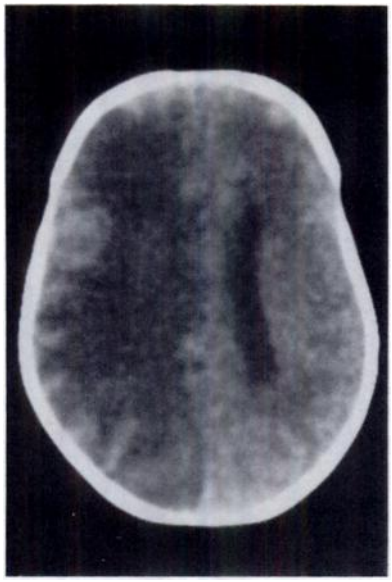

Fig 2. Case 1. CT scan shows large area of lucency in left hemisphere extending from frontal to parietooccipital region with slight shift of midline structures to right.

The Apgar scores were 8 at one minute and 9 at five minutes. The infant's clinical course was characterized by severe hyaline membrane disease which progressed to bronchopulmonary dysplasia. The latter was complicated by recurrent bronchospasm and cor pulmonale. She was treated with digoxin, furosemide, aldactazide, and bronchodilators. The initial cranial ultrasound scans demonstrated bilateral subependymal hemorrhages which subsequently resolved.

Hypertension was initially documented during the second postnatal month. The hypertension was presumed to be secondary to a right renal arterial thrombus demonstrated by renal ultrasonography. Mean renin values were 75 ng/mL/h. Because of a persistently elevated systolic BP, ie, >130 mm Hg, treatment was initiated with apresoline without appreciable benefit. Captopril was then begun on day 110 of life and was immediately effective. The systolic BP was decreased by a mean of 20% following each dose. Three days after initiating the captopril therapy, the infant had a 44% decrease in BP (from a mean systolic BP of 122 to 70 mm Hg). The systolic BP remained at this lower value for approximately 24 hours and was unaccompanied by a change in heart rate. The decrease in systolic BP was accompanied by anuria. Within 16 hours following the onset of decreased systolic BP and anuria, the infant had seizure activity characterized by multifocal clonic movements of all extremities with associated lip-smacking and tonic horizontal eye deviation. Serum electrolyte, glucose, and calcium concentrations were normal, and theophylline levels were within the therapeutic range. No abnormalities of CSF were noted. The seizures were treated successfully with a combination of phenobarbital and phenytoin. An EEG performed within three days was considered to be mildly abnormal because of an excessive amount of slow and sharp activity with a left posterior predominance.

Following this episode, the infant improved and during the subsequent 3 months remained alert without abnormal neurologic signs. On day 180 of life, the infant had another striking decrease in systolic BP following captopril therapy; the mean systolic BP decreased by 53% from 130 to 60 mm Hg and persisted at this level for approximately 24 hours and was unaccompanied by a change in heart rate. The decrease in systolic BP was accompanied by anuria. Therapy undertaken in an attempt to restore the systolic BP included volume reexpansion and the administration of both dopamine and isoproterenol. Within 18 hours following the onset of the decreased systolic BP and anuria, the infant had seizure activity characterized by lip-smacking and multifocal clonic movements of all extremities. The seizures were treated with phenobarbital, 20 mg/kg, and the abnormal movements stopped. Serum electrolyte, calcium, and glucose concentrations were normal, and a theophylline level was in the therapeutic range. An EEG performed 2 weeks later appeared severely abnormal because of recurring episodes of left hemispheral seizure activity and relative suppression of voltage in the right hemisphere throughout the recording. A CT scan performed at the same time demonstrated mildly enlarged ventricles with diffuse prominence of the sulci, consistent with cerebral atrophy.

On day 210 of life the infant had a 60% decrease in mean systolic BP (from 96 to 38 mm Hg). The hypotension persisted for 72 hours and was unresponsive to therapy. Anuria developed and continued for a total of 76 hours. Seizures, noted within 14 hours following the onset of anuria, were characterized by clonic movements of all extremities, lip-smacking, and horizontal eye deviation and persisted for 16 hours. Phenobarbital and phenytoin were required to control the seizures. The infant had a cardiorespiratory arrest during the eighth postnatal month and died. Permission for an autopsy was denied.

Case 3

This was a 660-g, 25-week, appropriate-for-gestational age infant delivered by cesarean section. The Apgar scores were 2 at one minute and 5 at five minutes. The clinical course was characterized by severe hyaline membrane disease which progressed to bronchopulmonary dysplasia, cor pulmonale, and reactive airway disease. Management included the use of digoxin, aldactazide, furosemide, theophylline, and aerosol therapy. Several cranial ultrasound scans performed in the first weeks of life appeared normal.

In the third postnatal month, the infant was noted to be hypertensive. The hypertension was presumed to be secondary to a left renal arterial thrombus, demonstrated by renal ultrasound scan. Systolic BP consistently ranged from 140 to 160 mm Hg. Antihypertensive therapy, ie, apresoline, was begun without a significant response. Because of the persistent hypertension and because of elevated renin levels (mean 47 ng/mL/h), captopril was begun. After approximately 1 month of therapy, the infant had a profound decrease in systolic BP following his usual maintenance dose, ie, mean decreased 56% from a peak of 138 to 60 mm Hg. This was unaccompanied by a change in heart rate. The decrease in BP persisted for

24 hours and was accompanied by oliguria. Attempts to increase the BP included the use of volume reexpanders and dopamine. Within 18 hours following the onset of the decreased systolic BP and oliguria, the infant had seizures, characterized by multifocal clonic movements of all extremities and horizontal eye deviation to the right. Phenobarbital administration led to cessation of the abnormal movements. Serum electrolyte, calcium, glucose, and CSF values were normal, and a theophylline level was within the therapeutic range. An EEG performed two days later was most notable for the presence of more than 20 electrographic seizure discharges, each lasting about 4 to 5 seconds and consisting of 3 to 4 Hz rhythmic activity which was maximum in the right temporal area but which spread to the right central region. On several occasions similar discharges were noted on the left. The infant's neurologic status improved during the next 24 hours, and he continued to receive captopril.

Two months later he had a profound decrease in systolic BP, ie, 74% (from a mean of 144 to 40 mm Hg) which was not associated with a change in heart rate. The decreased systolic BP persisted for 32 hours despite repeated attempts to increase the pressure. Within 14 hours of the onset he had seizures, characterized by multifocal clonic movements, predominantly involving the right arm and leg, horizontal eye movements to the left, and lip-smacking. Anticonvulsant therapy with phenobarbital, phenytoin, and lorazepam led to cessation of seizure activity. A CT scan performed 1 week later demonstrated mild dilation of the lateral ventricular system with increased lucency noted in the left frontal white matter. No other focal abnormalities were detected. The infant has had no further seizure activity.

During the next 2 months, two additional episodes of decreases in systolic BP, ie, 46% and 58% from baseline (Table) occurred, but these were of short duration and were not associated with oliguria or neurologic manifestations. The hypertension improved such that by the eighth postnatal month the systolic BP was approximately 100 mm Hg and the captopril dose was reduced. The infant was neurologically normal at 8 months of age. He remains oxygen dependent at home.

Case 4

This was a 940-g, 28-week infant who was delivered at home. No Apgar scores were assigned. The clinical course was complicated by severe hyaline membrane disease which progressed to bronchopulmonary dysplasia, cor pulmonale, and reactive airway disease. The medical arrangement included the use of digoxin, diuretics, theophylline, and aerosol therapy (eg, metaproterenol). The initial cranial ultrasound scans, performed during the first week, demonstrated bilateral subependymal hemorrhages which resolved within several weeks.

Hypertension was documented during the second postnatal month. Because of a persistent systolic BP >130 mm Hg, antihypertensive therapy was begun. The infant failed to respond to apresoline and because of elevated renin levels (mean 85 ng/mL/h), captopril was initiated. A beneficial response to this medication, ie, a 20% increase in systolic BP, was noted following each dose.

During approximately the sixth postnatal month, ie, almost 2 months of therapy, after receiving the usual maintenance dose of captopril, the infant had a marked decrease in systolic BP, ie, 58%, from a mean of 132 to 55 mm Hg. This decrease persisted for approximately two hours. Concurrent with the decrease in systolic BP, the infant became lethargic, ashen, and apneic; rhythmic clonic movements of all extremities were noted. The infant was placed in a Trendelenburg position and the BP gradually increased during the following hour to 80 mm Hg. There was an improvement in the neurologic status concurrent with the increase in systolic BP; thus, the infant resumed spontaneous breathing and the color improved. Accompanying this episode and persisting for a total of 12 hours was a prominent decrease in urine output (from 6 to 1.2 mL/kg/h). The infant had no further decreases in BP, and the neurologic status remained normal. The infant died during the sixth postnatal month of a cardiorespiratory arrest.

DISCUSSION

The data in this report demonstrate altered neurologic function in chronically hypertensive premature infants following marked and prolonged reductions in systolic BP, despite the fact that the decreased BP values were often within the normal range for corrected age. Moreover, the episodes of neurologic dysfunction consistently were preceded by oliguria.

Hypertension has been reported with increasing frequency in the sick newborn infant.[1-3] The hypertension is often refractory to standard antihypertensive medications such as apresoline, or methyldopa. More recently, however, captopril, an inhibitor of angiotensin-converting enzyme, has been shown to be effective in lowering BP in those hypertensive infants with elevated renin levels.[8,9] The infants described in this report had markedly elevated renin levels and following an inadequate response to standard antihypertensive therapy were treated with captopril. Captopril was immediately effective in decreasing systemic BP by an average of 20% per dose. Each episode that resulted in neurologic compromise followed a prolonged and marked decrease in systemic BP, ie, the systolic BP decreased by 57% ± 10% and the decrease persisted for 18 ± 6 hours. Furthermore, although the systolic BP had been significantly lowered, the lower values were often within normal limits for corrected age.

The most frequent neurologic manifestation was the occurrence of seizures. One infant exhibited lethargy, apnea, and a full anterior fontanel, and concurrent with the clinical deterioration and the decrease in systolic BP a significant decrease in cerebral blood flow velocity was noted. The serial sonographic changes in this infant were consistent with the evolution of a hemorrhagic infarct.

The data suggest that the persistent reduction in BP was the initiating factor in the genesis of the neurologic disturbances. Thus, although all of the infants were chronically ill and required multiple medications, at the time of seizure activity the only definable change in clinical condition was the sustained lowering in systolic BP. Furthermore, all seven of these neurologic episodes were preceded by oliguria. Although the systolic BP was markedly reduced in the remaining 11 episodes, the duration of the reductions was significantly less and was not associated with obvious alterations in renal or neurologic function.

There are both experimental and human data to suggest that chronic hypertension alters the autoregulation of cerebral blood flow.[4,5,12] Autoregulation refers to the maintenance of a constant cerebral blood flow throughout a wide range of perfusion pressure.[13] With chronic hypertension in an experimental rat model,[4,12] a shift of this autoregulatory curve has been demonstrated such that the threshold for onset of decreasing cerebral blood flow with decreasing BP is higher; this shift increases the vulnerability of the animal to neuronal injury with BPs that, however, are within the normal range.[4] Clinical observations of adult patients suggest a similar phenomenon. Thus, in two reports[6,7] the use of antihypertensive therapy that resulted in reductions in BP to levels often still within the normal range was associated with both neurologic compromise and the development of cerebral infarction. The data in this report suggest a similar phenomenon in the sick newborn infant.

Is there a relationship between the observed oliguria and the neurologic compromise? In the adult, renovascular autoregulatory mechanisms maintain constant renal perfusion despite wide changes in arterial pressure.[14] Thus, renal blood flow is maintained within the normal range within a range of mean arterial pressures from 70 to 200 mm Hg.[14] This renal autoregulatory response can be altered by chronic hypertension.[15] Although the renal autoregulatory curve has not been determined in the newborn infant, our data suggest that, in the presence of chronic hypertension as well as renovascular disease, the latter documented in three of the four infants in this report, renal autoregulatory responses are altered and such alterations increase the vulnerability of the kidney to lowered BP.

In conclusion, these data suggest that both cerebral and renal blood flow responses are altered by chronic hypertension in the sick premature infant, and the alterations cause these organs to be vulnerable to decreases in systemic BP to levels that would otherwise be considered within the normal range. In infants who exhibit marked decreases in systolic BP, rapid correction is required to avoid neurologic injury.

ACKNOWLEDGMENT

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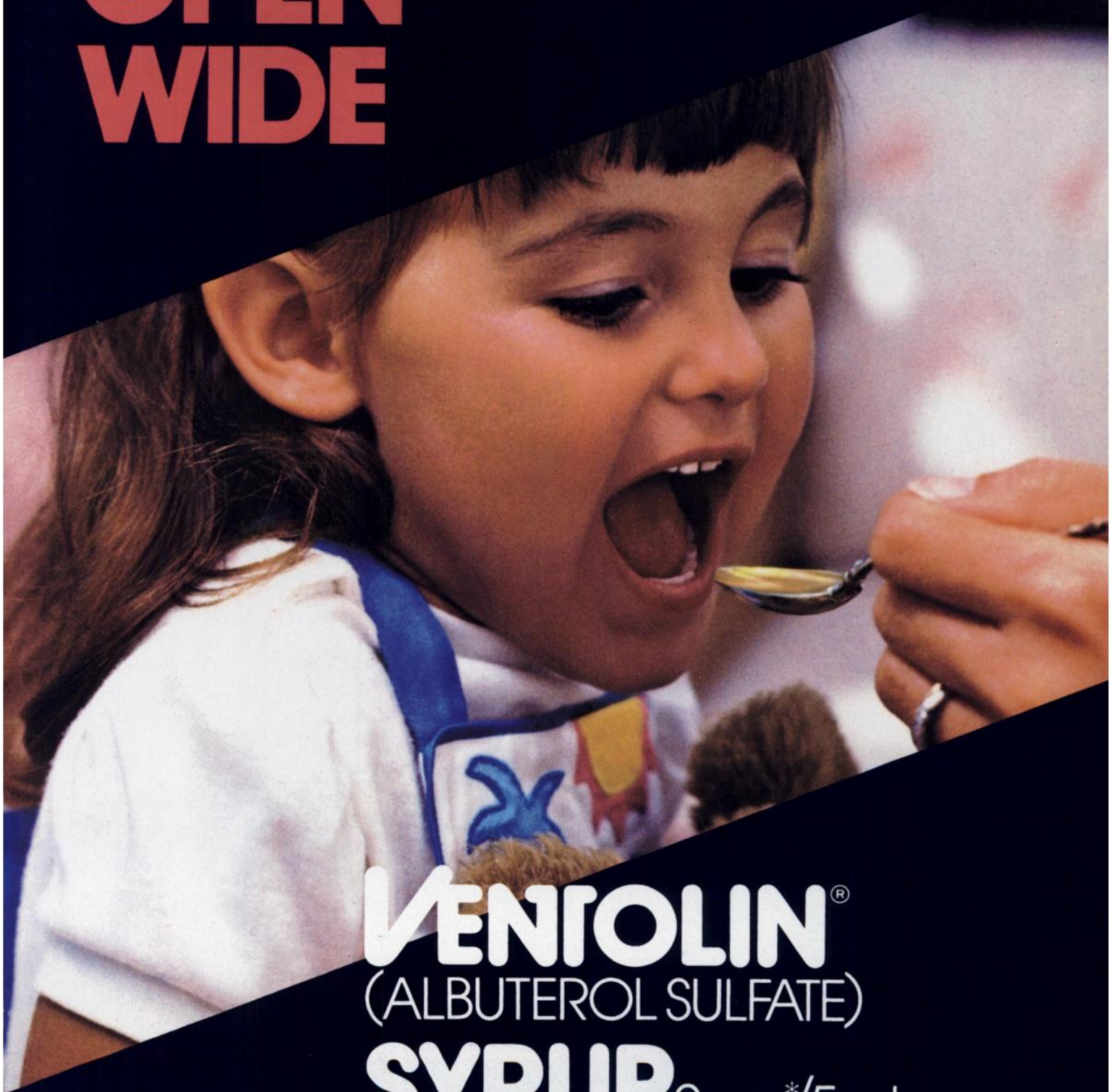

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Indications and Usage:
Temporary relief of coughs and/or upper respiratory symptoms associated with allergy or the common cold.

Contraindications:
Contraindicated in patients with hypersensitivity to any component. Promethazine is contraindicated in individuals hypersensitive or who have had an idiosyncratic reaction to it or to other phenothiazines.
Phenylephrine is contraindicated in patients with hypertension or with peripheral vascular insufficiency (ischemia may result with risk of gangrene or thrombosis of compromised vascular beds).
Avoid phenylephrine in patients hypersensitive to it or on a monoamine oxidase inhibitor (MAOI).
Antihistamines and codeine are both contraindicated in those with lower respiratory tract symptoms, including asthma.
Withhold dextromethorphan from patients on a MAOI.

Warnings
CODEINE: Dosage SHOULD NOT BE INCREASED if cough fails to respond; reevalutate unresponsive cough in 5 days or sooner for possible underlying pathology, e.g., foreign body or lower respiratory tract disease.
Codeine may cause or aggravate constipation.
Respiratory depression leading to arrest, coma, and death occurred with codeine antitussives in young children, particularly in the under-one-year infants whose ability to deactivate the drug is not fully developed.
Codeine may be accompanied by histamine release; use with caution in atopic children.
Head Injury and Increased Intracranial Pressure—The respiratory-depressant effects of narcotic analgesics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, intracranial lesions, or preexisting increase in intracranial pressure. Narcotics may produce adverse reactions which may obscure the clinical course of patients with head injuries.
Asthma and Other Respiratory Conditions—Narcotic analgesics or cough suppressants, including codeine, should not be used in asthmatic patients (see "Contraindications"), nor in acute febrile illness with productive cough or in chronic respiratory disease where interference with ability to clear the tracheobronchial tree of secretions would have a deleterious effect on respiratory function.
Hypotensive Effect—Codeine may produce orthostatic hypotension in ambulatory patients.
PROMETHAZINE: May cause marked drowiness. Caution ambulatory patients against driving or operating machinery until it is known that they do not become drowsy or dizzy from promethazine therapy.
The sedative action of promethazine is additive to the sedative effects of CNS depressants; therefore, agents such as alcohol, narcotic analgesics, sedatives, hypnotics, and tranquilizers should either be eliminated or given in reduced dosage in presence of promethazine. When given concomitantly with promethazine, reduce dose of barbiturates by at least ½, and the dose of analgesic depressants, e.g. morphine or meperidine, by ¼ to ½.
Promethazine may lower seizure threshold. Consider this when giving to persons with known seizure disorders or in combination with narcotics or local anesthetics which may also affect seizure threshold.
Avoid sedative drugs or CNS depressants in patients with history of sleep apnea.Use antihistamines with caution in patients with narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, and urinary bladder obstruction due to symptomatic prostatic hypertrophy and narrowing of bladder neck.
Promethazine has been associated with cholestatic jaundice.
PHENYLEPHRINE: Because phenylephrine is adrenergic, give with caution to patients with thyroid diseases, diabetes mellitus, and heart diseases or those on tricyclic antidepressants.
Men with symptomatic, benign prostatic hypertrophy can experience urinary retention when given oral nasal decongestants.
Phenylephrine can decrease cardiac output. Use extreme caution when giving the drug, parenterally or orally, to patients with arteriosclerosis, to elderly individuals, and/or to patients with initially poor cerebral or coronary circulation.
Use with caution in patients on diet preparations, such as amphetamines or phenylpropanolamine, because synergistic adrenergic effects could result in serious hypertensive response and possible stroke.
DEXTROMETHORPHAN: May be accompanied by histamine release; use with caution in atopic children.

Precautions
Animal reproduction studies have not been conducted with these drug combinations. It is not known if they can cause fetal harm when given to pregnant women, or affect reproduction capacity. Give to pregnant women only if clearly needed.
GENERAL
Give narcotic analgesics, e.g. codeine, with caution and reduce initial dose in patients with acute abdominal conditions, convulsive disorders, significant hepatic or renal impairment, fever, hypothyroidism, Addison's disease, ulcerative colitis, prostatic hypertrophy, in patients with recent gastrointestinal or urinary tract surgery, and in the very young or elderly or debilitated.
Use promethazine cautiously in persons with cardiovascular disease or with impairment of liver function.
Use phenylephrine with caution in patients with cardiovascular disease, particularly hypertension.
Use dextromethorphan with caution in sedated patients, in the debilitated, and in patients confined to supine position.
INFORMATION FOR PATIENTS
All Phenergan Syrups may cause marked drowsiness or impair mental and/or physical abilities required for hazardous tasks, e.g. driving or operating machinery. Tell ambulatory patients to avoid such activities until it is known that they do not become drowsy or dizzy from Phenergan. Supervise children to avoid harm in bike riding or other hazardous activities. Concomitant use of alcohol or other CNS depressants, including narcotic analgesics, sedatives, hypnotics, and tranquilizers, may have an additive effect and should be avoided or their dosage reduced.
Advise patients to report any involuntary muscle movements or unusual sensitivity to sunlight.
Codeine may produce orthostatic hypotension in ambulatory patients; caution patients.
DRUG INTERACTIONS
CODEINE: In patients receiving MAOIs, an initial small test dose is advisable to allow observation of any excessive narcotic effects or MAOI interaction.
PROMETHAZINE: The sedative action is additive to sedative effects of other CNS depressants, e.g. alcohol, narcotic analgesics, sedatives, hypnotics, tricyclic antidepressants, and tranquilizers; therefore, these agents should be avoided or given in reduced dosage.
PHENYLEPHRINE

Drug	Effect
Phenylephrine with prior administration of MAOIs.	Cardiac pressor response potentiated. May cause acute hypertensive crisis.
Phenylephrine with tricyclic antidepressants.	Pressor response increased.
Phenylephrine with ergot alkaloids.	Excessive rise in blood pressure.
Phenylephrine with bronchodilator sympathomimetic agents and with epinephrine or other sympathomimetics.	Tachycardia or other arrhythmias may occur.
Phenylephrine with prior administration of propranolol or other β-adrenergic blockers.	Cardiostimulating effects blocked.
Phenylephrine with atropine sulfate.	Reflex bradycardia blocked; pressor response enhanced.
Phenylephrine with prior administration of phentolamine or other α-adrenergic blockers.	Pressor response decreased.
Phenylephrine with diet preparations, e.g. amphetamines or phenylpropanolamine.	Synergistic adrenergic response.

DRUG/LABORATORY TEST INTERACTIONS
Because narcotic analgesics may increase biliary tract pressure, with resultant increases in plasma amylase or lipase levels, determination of these enzyme levels may be unreliable for 24 hours after a narcotic analgesic has been given. These tests may be affected in patients on promethazine:
Pregnancy Tests
Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.
Glucose Tolerance Test
Increase in blood glucose has been reported in patients on promethazine.
CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
CODEINE, PROMETHAZINE, AND DEXTROMETHORPHAN
Long-term animal studies have not been performed to assess carcinogenic potential of codeine or of promethazine or of dextromethorphan, nor are there other animal or human data concerning carcinogenicity, mutagenicity, or impairment of fertility with these agents. Codeine has been reported to show no evidence of carcinogenicity or mutagenicity in a variety of test systems, including the micronucleus and sperm abnormality assays and the *Salmonella* assay. Promethazine was nonmutagenic in the *Salmonella* test system of Ames.
PHENYLEPHRINE
A study which followed the development of cancer in 143,574 patients over a 4-year period indicated that in 11,981 patients who received phenylephrine (systemic or topical), there was no statistically significant association between the drug and cancer at any or all sites.
Long-term animal studies have not been performed to assess carcinogenic potential of phenylephrine, nor are there other animal or human data on mutagenicity.
A study of the effects of adrenergic drugs on ovum transport in rabbits indicated that treatment with phenylephrine did not alter incidence of pregnancy; the number of implantations was significantly reduced when high doses were used.
PREGNANCY
Teratogenic Effects—Pregnancy Category C
CODEINE: A study in rats and rabbits reported no teratogenic effect of codeine given in the period of organogenesis in doses ranging from 5 to 120 mg/kg. In the rat, doses at the 120-mg/kg level, in the toxic range for the adult animal, were associated with increase in embryo resorption at implantation. In another study a single 100-mg/kg dose in pregnant mice resulted in delayed ossification in offspring. There are no studies in humans; significance of these findings to humans, if any, is not known.
PROMETHAZINE: Teratogenic effects have not been demonstrated in rat-feeding studies at doses of 6.25 and 12.5 mg/kg of promethazine. These doses are 6 and 16.7 times the maximum recommended total daily dose of promethazine for a 50-kg subject depending on the indication for which the drug is prescribed. Specific studies to test the action of the drug on parturition, lactation, and development of the animal neonate were not done, but a general preliminary study in rats indicated no effect on these parameters. Although antihistamines, including promethazine, have been found to produce fetal mortality in rodents, the pharmacological effects of histamine in the rodent do not parallel those in man. There are no adequate and well-controlled studies of promethazine in pregnant women.
PHENYLEPHRINE: A study in rabbits indicated continued moderate overexposure to phenylephrine (3 mg/day) during the second half of pregnancy (22nd day of gestation to delivery) may contribute to perinatal wastage, prematurity, premature labor, and possibly fetal anomalies; when phenylephrine (3 mg/day) was given to rabbits during first half of pregnancy (3rd day after mating for 7 days), a significant number gave birth to litters of low birth weight. Another study showed that phenylephrine was associated with anomalies of aortic arch and with ventricular septal defect in the chick embryo.
Phenergan® (promethazine HCl) Svrups should be used during pregnancy only if potential benefit justifies potential risk to the fetus.
Nonteratogenic Effects
Dependence has been reported in newborns whose mothers took opiates regularly during pregnancy. Withdrawal signs include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting, and diarrhea. Signs usually appear during the first few days of life.
Promethazine taken within 2 weeks of delivery may inhibit platelet aggregation in newborn.
LABOR AND DELIVERY
Narcotic analgesics cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Narcotic analgesics should be avoided during labor if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see "Overdosage"). The effect of codeine, if any, on the later growth, development, and functional maturation of the child is unknown. Administration of phenylephrine to patients in late pregnancy or labor may cause fetal anoxia or bradycardia by increasing contractility of the uterus and decreasing uterine blood flow.
NURSING MOTHERS
Some studies, but not others, have reported detectable amounts of codeine in breast milk. The levels are probably not clinically significant after usual therapeutic dosage. The possibility of clinically important amounts being excreted in breast milk in individuals abusing codeine should be considered.
It is not known whether phenylephrine, promethazine or dextromethorphan is excreted in human milk. Caution should be exercised when any Phenergan Syrup is administered to a nursing woman.
PEDIATRIC USE
These products should not be used in children under 2 years of age because safety for such use has not been established.

Adverse Reactions
CODEINE
CNS—CNS depression, particularly respiratory depression, and to a lesser extent circulatory depression; light-headedness, dizziness, sedation, euphoria, dysphoria, headache, transient hallucination, disorientation, visual disturbances, and convulsions.
CV—Tachycardia, bradycardia, palpitation, faintness, syncope, orthostatic hypotension (common to narcotic analgesics).
GI—Nausea, vomiting, constipation, and biliary tract spasm. Patients with chronic ulcerative colitis may experience increased colonic motility; in patients with acute ulcerative colitis, toxic dilation has been reported.
GU—Oliguria, urinary retention, antidiuretic effect has been reported (common to narcotic analgesics).
Allergic—Infrequent pruritus, giant urticaria, angioneurotic edema, and laryngeal edema.
Other—Flushing of the face, sweating and pruritus (due to opiate-induced histamine release); weakness.
PROMETHAZINE
CNS—Sedation, sleepiness, occasional blurred vision, dryness of mouth, dizziness; rarely confusion, disorientation, and extrapyramidal symptoms such as oculogyric crisis, torticollis, and tongue protrusion (usually in association with parenteral injection or excessive dosage).
CV—Increased or decreased blood pressure.
Dermatologic—Rash, rarely photosensitivity.
Hematologic—Rarely leukopenia, thrombocytopenia, agranulocytosis (1 case).
GI—Nausea and vomiting.
PHENYLEPHRINE
CNS—Restlessness, anxiety, nervousness, and dizziness.
CV—Hypertension (see "Warnings").
Other—Precordial pain, respiratory distress, tremor, and weakness.
DEXTROMETHORPHAN
Occasionally causes slight drowsiness, dizziness, and GI disturbances.

Drug Abuse and Dependence
CONTROLLED SUBSTANCE
Phenergan with codeine and Phenergan VC with codeine are Schedule V Controlled Substances.
ABUSE
Codeine is known to be subject to abuse; however, abuse potential of oral codeine appears to be quite low. Even parenteral codeine does not appear to offer psychic effects sought by addicts to the same degree as heroin or morphine. However, codeine must be administered only under close supervision to patients with history of drug abuse or dependence.
DEPENDENCE
Psychological dependence, physical dependence, and tolerance are known to occur.
According to WHO Expert Committee on Drug Dependence, dextromethorphan could produce very slight psychic but no physical dependence.

Overdosage
CODEINE: Serious overdosage with codeine is characterized by respiratory depression (decrease in respiratory rate and/or tidal volume. Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. The triad of coma, pinpoint pupils, and respiratory depression is strongly suggestive of opiate poisoning. In severe overdosage, particularly by the IV route, apnea, circulatory collapse, cardiac arrest, and death may occur. Promethazine is additive to depressant effects of codeine.
It is difficult to determine what constitutes a standard toxic or lethal dose. However, lethal oral dose of codeine in adults is reported to be in range of 0.5 to 1.0 gram. Infants and children are believed to be relatively more sensitive to opiates on body-weight basis. Elderly patients are also comparatively intolerant to opiates.
PROMETHAZINE: Signs and symptoms of overdose range from mild CNS and cardiovascular depression to profound hypotension, respiratory depression, and unconsciousness.
Stimulation may be evident, especially in children and geriatric patients. Convulsions may rarely occur. A paradoxical reaction has been reported in children receiving single doses of 75 mg to 125 mg orally, characterized by hyperexcitability and nightmares.
Atropine-like signs and symptoms—dry mouth, fixed, dilated pupils, flushing, as well as GI symptoms, may occur.
PHENYLEPHRINE: Signs and symptoms of overdose include hypertension, headache, convulsions, cerebral hemorrhage, and vomiting. Ventricular premature beats and short paroxysms of ventricular tachycardia may also occur. Headache may be a symptom of hypertension. Bradycardia may also be seen early in phenylephrine overdosage through stimulation of baroreceptors.
DEXTROMETHORPHAN
May produce central excitement and mental confusion. Very high doses may produce respiratory depression. One case of toxic psychosis (hyperactivity, marked visual and auditory hallucinations) after single dose of 20 tablets (300 mg) of dextromethorphan was reported.
TREATMENT
Treatment of overdosage with Phenergan Syrups is essentially symptomatic and supportive. Only in cases of extreme overdosage or individual sensitivity do vital signs including respiration, pulse, blood pressure, temperature, and EKG need to be monitored. Activated charcoal orally or by lavage may be given, or sodium or magnesium sulfate orally as a cathartic. Attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation.
The narcotic antagonist, naloxone HCl, may be given when significant respiratory depression occurs with the codeine syrups; any depressant effects of promethazine are not reversed by naloxone. Diazepam may be used to control convulsions.
The antidotal efficacy of narcotic antagonists to dextromethorphan has not been established.
Avoid analeptics, which may cause convulsions. Acidosis and electrolyte losses should be corrected. A rise in temperature or pulmonary complications may signal the need for institution of antibiotic therapy.
Severe hypotension usually responds to norepinephrine or phenylephrine. EPINEPHRINE SHOULD NOT BE USED, since in a patient with partial adrenergic blockade it may further lower blood pressure. Limited experience with dialysis indicates that it is not helpful.

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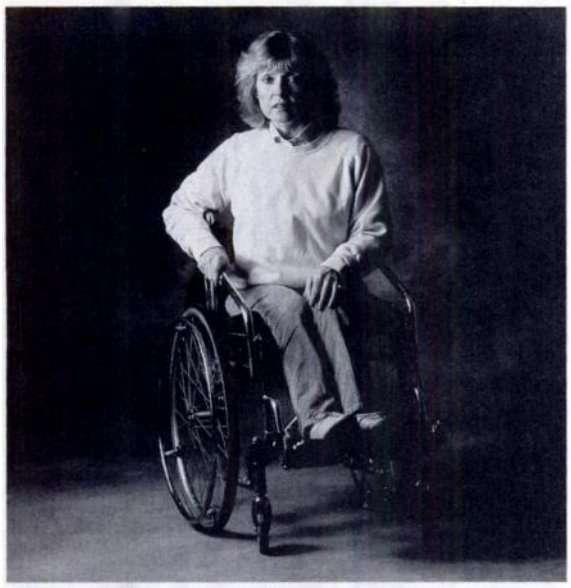

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CONTRAINDICATIONS: *Under no circumstances should this vaccine be administered parenterally.*

Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.

ORIMUNE *must not* be administered to patients with immune deficiency diseases such as combined immunodeficiency, hypogammaglobulinemia, and agammaglobulinemia. It would also be prudent to withhold ORIMUNE from siblings of a child known to have an immunodeficiency syndrome or from children in a family which has a history of immunodeficiency until immune status of all members is determined. Further, ORIMUNE *must not* be administered to patients with altered immune states, such as those occurring in thymic abnormalities, leukemia, lymphoma, or generalized malignancy or by lowered resistance from therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation. All persons with altered immune status should avoid close household-type contact with recipients of the vaccine for at least six to eight weeks. Inactivated poliovirus vaccine (IPV) is preferred for immunizing all persons in the above described circumstances.

WARNINGS: *Under no circumstances should this vaccine be administered parenterally.*

Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.

Other viruses (including poliovirus and other enteroviruses) may interfere with the desired response to this vaccine, since their presence in the intestinal tract may interfere with the replication of the attenuated strains of poliovirus in the vaccine.

PRECAUTIONS: It would seem prudent not to administer trivalent oral poliovaccine (OPV) shortly after Immune Globulin (IG) unless such a procedure is unavoidable, for example, with unexpected travel to or contact with epidemic areas or endemic areas. If OPV is given with or shortly after IG, the dose probably should be repeated after three months if immunization is still indicated.

The vaccine is not effective in modifying or preventing cases of existing and/or incubating poliomyelitis.

Use in Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Poliovirus vaccine live oral trivalent. It is also not known whether OPV can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Although there is no convincing evidence documenting adverse effects of either OPV or IPV on the developing fetus or pregnant woman, it is prudent on theoretical grounds to avoid vaccinating pregnant women. However, if immediate protection against poliomyelitis is needed, OPV is recommended. (See CONTRAINDICATIONS and ADVERSE REACTIONS.)

ADVERSE REACTIONS: Paralytic disease following the ingestion of live poliovirus vaccines has been, on rare occasion, reported in individuals receiving the vaccine (see, for example, CONTRAINDICATIONS), and in persons who were in close contact with vaccinees. The vaccine viruses are shed in the vaccinee's stools for at least six to eight weeks as well as via the pharyngeal route. Most reports of paralytic disease following ingestion of the vaccine or contact with a recent vaccinee are based on epidemiological analysis and temporal association between vaccination or contact and the onset of symptoms. Most authorities believe that a causal relationship exists. Prior to administration of the vaccine, the attending physician should warn or specifically direct personnel acting under his authority to convey the warnings to the vaccinee, parent, guardian, or other responsible person of the possibility of vaccine-associated paralysis, particularly to susceptible family members and other close personal contacts. The Centers for Disease Control report that during 1972 to 1983, approximately 278.8 million OPV doses were distributed in the United States. During this same period, 87 vaccine-associated cases in apparently immunologically normal individuals were reported. Thirty-two occurred among vaccine recipients (one case per 8.7 million OPV doses distributed), and 55 cases occurred among household and nonhousehold contacts of vaccinees (1 case per 5.1 million doses distributed). Sixteen other vaccine-associated cases have been reported in persons (recipients or contacts) with immune deficiency conditions.

Because the number of susceptible vaccine recipients or contacts of recipients is not known, the true risk of vaccine-associated poliomyelitis is impossible to determine precisely.

When the attenuated vaccine strains are to be introduced into a household with adults who have not been adequately vaccinated or whose immune status cannot be determined, the risk of vaccine-associated paralysis can be reduced by giving these adults one dose of IPV per month for three months before the children receive *Poliovirus vaccine live oral trivalent* ORIMUNE. The children may receive the first dose of ORIMUNE at the same visit that the adult receives the third dose of IPV. The CDC reports that no paralytic reactions to IPV are known to have occurred since the 1955 cluster of poliomyelitis cases caused by vaccine that contained live polioviruses that had escaped inactivation.

The ACIP states: "Because of the overriding importance of ensuring prompt and complete immunization of the child and the extreme rarity of OPV-associated disease in contacts, the Committee recommends the administration of OPV to a child regardless of the poliovirus-vaccine status of adult household contacts. This is the usual practice in the United States. The responsible adult should be informed of the small risk involved. An acceptable alternative, if there is a strong assurance that ultimate, full immunization of the child will not be jeopardized or unduly delayed, is to immunize adults according to the schedule outlined above before giving OPV to the child."

The ACIP has concluded that "Oral polio vaccine remains the vaccine of choice for primary immunization of children."

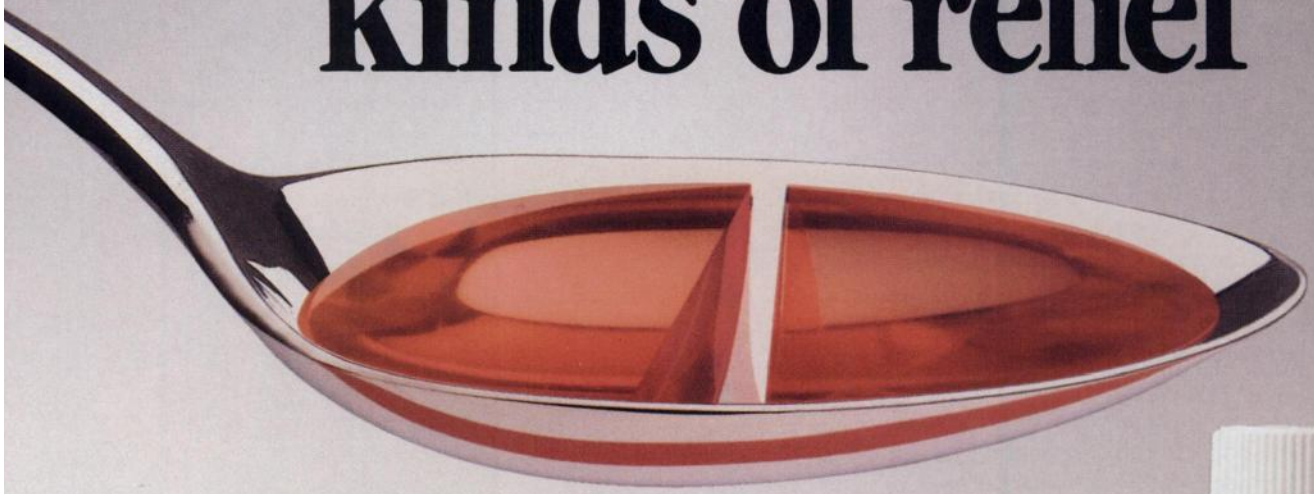
Rev. 8/86

Lederle Biologicals
Protecting Families Through Immunization®

Lederle Laboratories, A Division of American Cyanamid Company, Wayne, New Jersey 07470

603-8

Think of it as two kinds of relief



One for colds

Like all Triaminic® products, Triaminicol® starts with a proven decongestant to reduce nasal and sinus congestion.

In addition, Triaminicol contains an effective antihistamine to dry runny noses and itchy, watery eyes.

And one for coughs

To stop coughs cold, Triaminicol contains dextromethorphan, a centrally acting antitussive that is non-narcotic, but equally as effective as codeine.[1-3†]

And Triaminicol does it all *without analgesics or alcohol.*

#1 PEDIATRICIAN RECOMMENDED

Triaminicol®
MULTI-SYMPTOM COLD SYRUP

†Except in severe cough

For the cold with a cough

REFERENCES

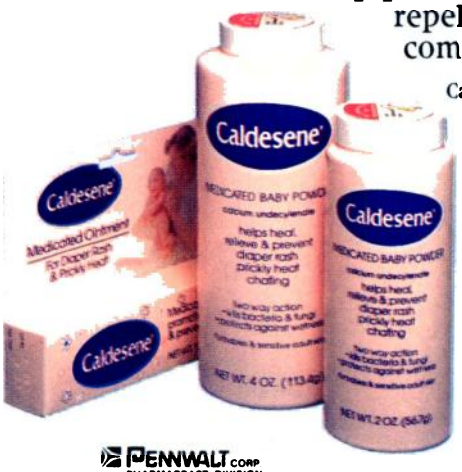
1. Decongestant, Cough and Cold Preparations in *Drug Evaluations*, ed 6. Chicago, American Medical Association, 1986; pp 374 and 384.
2. Geller RJ, Fisher JG: The role of symptomatic therapy for the common cold. *J Respir Dis* 1987;8(1):20-34.
3. Medon PJ, Holshouser MH: Self Medication: Antitussives. *Pharm Times* 1985;51(1):80-90.

SANDOZ PHARMACEUTICALS CORPORATION
Pediatric Division

Meet a happy Caldesene® baby.

Diaper rash isn't something this baby and mother have to expect. They use Caldesene® Medicated Baby Powder.

Caldesene, along with fresh air (leaving the diapers off whenever possible) and frequent diaper changes, fights fungi and bacteria to help prevent chafing and prickly heat. Caldesene repels wetness to protect babies. It soothes and comforts sensitive skin.



Caldesene is also available in a medicated ointment with zinc oxide.

PHARMACRAFT DIVISION, Pennwalt Corporation
P.O. Box 1212, Rochester, NY 14603

Please send me the following:

☐ Caldesene® Medicated Baby Powder Samples
☐ Patient Information Booklets

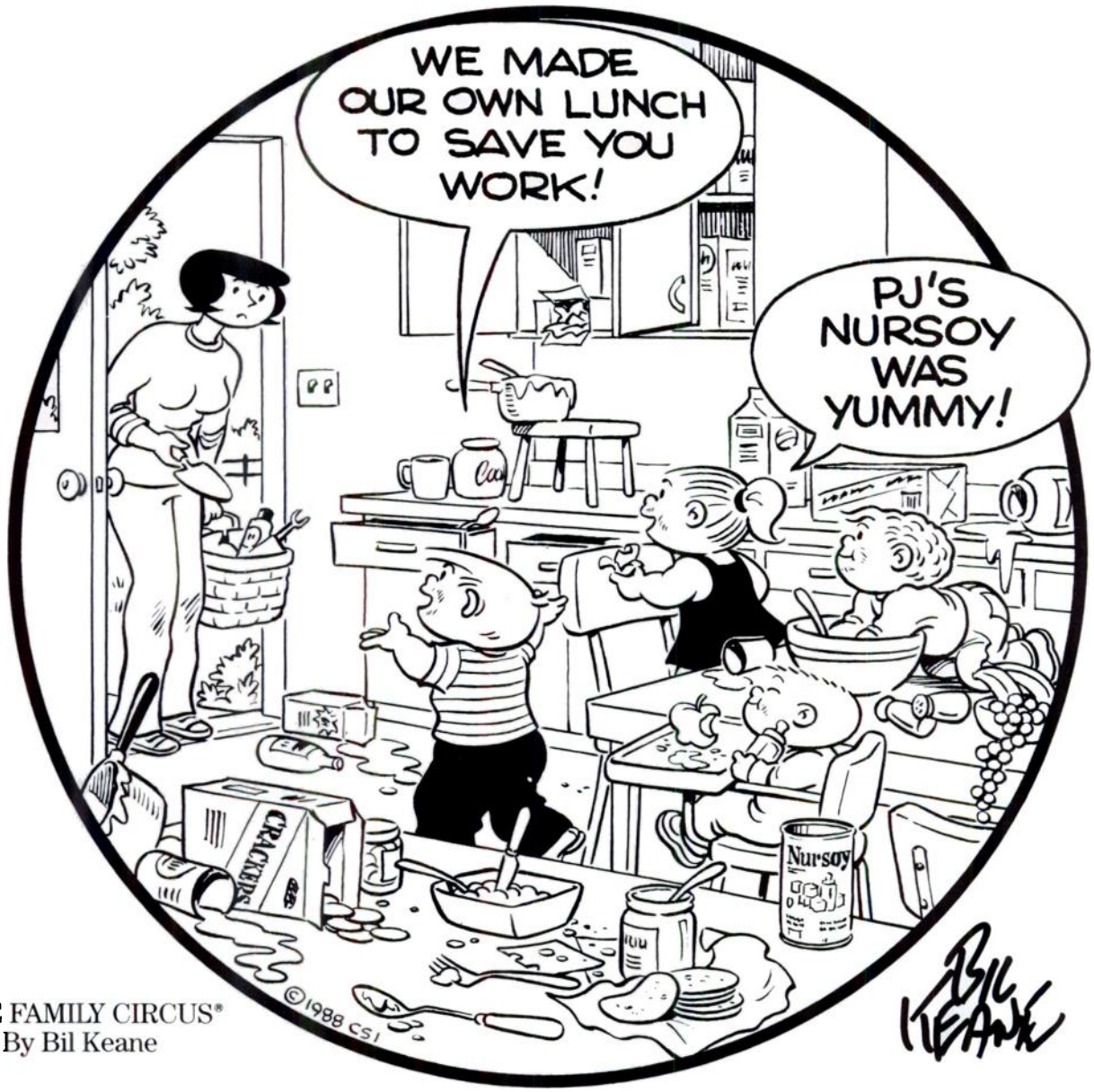
Name _____ M.D.

Address _____

City _____ State _____ Zip _____

PENNWALT CORP
PHARMACRAFT DIVISION
ROCHESTER, NY 14623

The tastiest soy formula in test after test!



THE FAMILY CIRCUS®
By Bil Keane

- With the taste preferred by infants[1]...and by their doctors and nurses[2]
- Closest of all soy formulas to breast milk in its fatty acid profile and sodium content*
- Latest clinical testing again confirms that soy formulas provide growth and bone status similar to that provided by breast milk[3]

Nursoy®
soy protein formula

Taste-tested, time-tested

*Based on ingredients statements from product labels, PDR® or analyses compared to average values of mature breast milk determined in 11 recent studies.

Breast milk is best for babies. Nursoy® milk-free formula is intended to meet the nutritional needs of infants and children who are allergic to cow-milk proteins or intolerant to lactose. It should not be used in infants and children allergic to soybean protein. Nursoy® powder contains corn syrup solids. Professional advice should be followed.

References: 1. Fomon SJ, Ziegler EE, Nelson SE, et al: Sweetness of diet and food consumption by infants. *Proc Soc Exp Biol Med 173*:190-193, 1983. 2. Data on file, Wyeth-Ayerst Laboratories. 3. Chan GM, Gill G, McInnes R: The effects of soy formula on growth and mineral metabolism in term infants. Specialty Platform Presentation. APS-SPR Annual Meeting, Washington DC, May 2-5, 1988.

Wyeth Pediatrics
WYETH-AYERST LABORATORIES
Philadelphia, PA 19101

Serious medicine for head and chest congestion

Triaminic® Expectorant is the congestion medicine for colds and allergies.

It clears congestion. In the head. And in the chest. Because it contains both a decongestant and an expectorant.

The decongestant shrinks swollen nasal and sinus membranes. Relieves the pressure. Promotes nasal drainage.

The expectorant loosens phlegm and clears bronchial passageways.

Triaminic Expectorant. No wonder it's the pediatrician's choice for head and chest congestion.

PEDIATRICIAN #1 RECOMMENDED

Triaminic®
EXPECTORANT

The congestion medicine

SANDOZ PHARMACEUTICALS CORPORATION
Pediatric Division

In steroid-responsive dermatoses

A firm but gentle touch

UNIQUE, NONFLUORINATED

ACLOVATE®

(alclometasone dipropionate)

CREAM, 0.05% OINTMENT, 0.05%

For kids of all sizes

Significantly outperforms Hytone,1.0%[1]

Some dermatoses need a firm hand. ACLOVATE Cream, 0.05% proved significantly more effective than Hytone®* (hydrocortisone) Cream, 1.0% in atopic dermatitis.[1] Multipurpose ACLOVATE is effective and well tolerated in a broad range of steroid-responsive dermatoses,[1-4] including diaper dermatitis.[2†] Furthermore, in psoriasis, ACLOVATE Ointment, 0.05% compares favorably with Tridesilon®‡ (desonide) Creme, 0.05% and Ointment, 0.05%.[1]

Safety comparable to hydrocortisone,1.0%

ACLOVATE provides patients with the gentleness of a low-potency steroid and a safety profile comparable to hydrocortisone, 1.0%.[1] In a study of 39 children, aged 3 months to 12 years, there were no reports of local or systemic adverse effects with ACLOVATE.[2]

Not available over the counter

Multipurpose ACLOVATE is a unique, nonfluorinated steroid molecule and is not available over the counter. ACLOVATE is available in 15 g and 45 g tubes.

*Registered trademark of Dermik Laboratories, Inc.
†As with all topical corticosteroids, caution should be exercised when prescribing ACLOVATE for pediatric use because of a greater susceptibility to HPA axis suppression in children than in mature patients.
‡Registered trademark of Miles Inc., Pharmaceutical Division.

REFERENCES: 1. Data available on request, Glaxo Inc. **2.** Crespi HG: Topical corticosteroid therapy for children: alclometasone dipropionate cream 0.05%. *Clin Ther* 1986;8(2):203-210. **3.** Lassus A: Clinical comparison of alclometasone dipropionate cream 0.05% with hydrocortisone butyrate cream 0.1% in the treatment of atopic dermatitis in children. *J Int Med Res* 1983;11:315-319. **4.** Kint A: Treatment of atopic dermatitis in children: alclometasone dipropionate cream 0.05% versus hydrocortisone butyrate cream 0.1%. *Acta Ther* 1987;13:455-466.

Please see Brief Summary of Prescribing Information on following page.

Glaxo Dermatology Products
Division of Glaxo Inc.
Research Triangle Park, NC 27709
Unique compounds advancing dermatology

ACL056 Printed in USA August 1988

Aclovate®
(aclometasone dipropionate)

CREAM, 0.05% OINTMENT, 0.05%

BRIEF SUMMARY

For Dermatologic Use Only — Not for Ophthalmic Use.

The following is a brief summary only. Before prescribing, see complete prescribing information in ACLOVATE® Cream and Ointment product labeling.

CONTRAINDICATIONS: ACLOVATE® Cream and Ointment are contraindicated in patients who are hypersensitive to aclometasone dipropionate, to other corticosteroids, or to any ingredient in these preparations.

PRECAUTIONS: General: Systemic absorption of topical corticosteroids has resulted in reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions that augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see PRECAUTIONS, Pediatric Use).

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatologic infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for Patients: Patients using ACLOVATE® should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. Patients should be advised not to use this medication for any disorder other than that for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions, especially under occlusive dressing.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Laboratory Tests: Although ACLOVATE® Cream and Ointment were shown not to produce HPA axis suppression, the following tests may be helpful in evaluating if HPA axis suppression does occur:

Urinary free cortisol test

ACTH stimulation test

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.

Studies to determine mutagenicity with prednisolone have revealed negative results.

Pregnancy: *Teratogenic Effects: Pregnancy Category C:* Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic in animals after dermal application.

There are no adequate and well-controlled studies of the teratogenic effects of topically applied corticosteroids in pregnant women. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients in large amounts or for prolonged periods of time.

Nursing Mothers: It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are prescribed for a nursing woman.

Pediatric Use: Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.

HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS: The following local adverse reactions have been reported with ACLOVATE® Cream: itching occurred in about 2 per 100 patients, burning, erythema, dryness, irritation, and papular rashes occurred in about 1 per 100 patients.

The following local adverse reactions have been reported with ACLOVATE® Ointment: itching or burning, 1 per 200 patients, and erythema, 2 per 1 000 patients.

The following local adverse reactions have been reported with topical dermatologic corticosteroids, especially under occlusive dressings: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infections, skin atrophy, striae, and miliaria.

OVERDOSAGE: Topically applied ACLOVATE® can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).

Glaxo

April 1988

Glaxo Dermatology Products
Glaxo Inc
Research Triangle Park, NC 27709

Manufactured for Glaxo Inc., Research Triangle Park, NC 27709
by Schering Corporation, Kenilworth, NJ 07033

CONTROL COUGHS AT 2 SITES

AT THE COUGH CENTER
Control with your choice of antitussives:
- dextromethorphan
- codeine

AT THE ORIGIN
Moisturize with a mucolytic-expectorant for cough caused by:
- mucus or
- irritation

TUSSI-ORGANIDIN® C contains Codeine

LIQUID Each teaspoonful (5 ml) contains: ORGANIDIN® (iodinated glycerol containing 15 mg organically bound iodine), 30 mg; codeine phosphate (WARNING: May be habit-forming), 10 mg

TUSSI-ORGANIDIN® DM

LIQUID Each teaspoonful (5 ml) contains: ORGANIDIN® (iodinated glycerol containing 15 mg organically bound iodine), 30 mg; dextromethorphan hydrobromide, 10 mg

Dual-Action Cough Control

Please see the following page for a brief summary of prescribing information.

WALLACE LABORATORIES
Division of Carter-Wallace, Inc.
Cranbury, New Jersey 08512

TUSSI-ORGANIDIN®/
TUSSI-ORGANIDIN® DM
Combined Brief Summary

Based on INS ORF08-4/84

Before prescribing, please consult complete product information, a brief summary of which follows:

INDICATIONS AND USAGE: For the symptomatic relief of irritating, nonproductive cough associated with respiratory tract conditions such as chronic bronchitis, bronchial asthma, tracheobronchitis, and the common cold; also for the symptomatic relief of cough accompanying other respiratory tract conditions such as laryngitis, pharyngitis, croup, pertussis and emphysema. Appropriate therapy should be provided for the primary disease.

CONTRAINDICATIONS: History of marked sensitivity to inorganic iodides; hypersensitivity to any of the ingredients or related compounds; pregnancy; newborns; and nursing mothers.

WARNINGS: Discontinue use if rash or other evidence of hypersensitivity appears. Use with caution or avoid use in patients with history or evidence of thyroid disease.

PRECAUTIONS: *General*—Iodides have been reported to cause a flare-up of adolescent acne. Children with cystic fibrosis appear to have an exaggerated susceptibility to the goitrogenic effects of iodides.

Dermatitis and other reversible manifestations of iodism have been reported with chronic use of inorganic iodides. Keep these in mind in patients receiving these preparations for prolonged periods.

Drug Interactions—Iodides may potentiate the hypothyroid effect of lithium and other antithyroid drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No long-term animal studies have been performed.

Pregnancy—Teratogenic effects: Pregnancy Category X (see CONTRAINDICATIONS).

Nursing Mothers—Do not administer to a nursing woman.

ADVERSE REACTIONS: Side effects have been rare, including those which may occur with the individual ingredients and which may be modified as a result of their combination. *Organidin*—Gastrointestinal irritation, rash, hypersensitivity, thyroid gland enlargement, and acute parotitis. *Codeine*—(Tussi-Organidin only): Nausea, vomiting, constipation, drowsiness, dizziness and miosis. *Dextromethorphan*—(Tussi-Organidin DM only): Drowsiness or gastrointestinal disturbances.

DRUG ABUSE AND DEPENDENCE (Tussi-Organidin only):
Controlled substance—Schedule V.
Dependence—Codeine may be habit-forming.

The following sections are optional:
OVERDOSAGE: No reports of any serious problems.

DOSAGE AND ADMINISTRATION
Adults: 1 to 2 teaspoonfuls every 4 hours.
Children: ½ to 1 teaspoonful every 4 hours.

HOW SUPPLIED: *Tussi-Organidin Liquid*—clear red liquid, in bottles of one pint (NDC 0037-4812-10) and one gallon (NDC 0037-4812-20).

Tussi-Organidin DM Liquid—clear yellow liquid, in bottles of one pint (NDC 0037-4712-10) and one gallon (NDC 0037-4712-20).

Storage: Store at room temperature; avoid excessive heat. Keep bottle tightly closed.

Distributed by
WALLACE LABORATORIES
Division of
CARTER-WALLACE, INC.
Cranbury, New Jersey 08512

Manufactured by Denver Chemical (Puerto Rico) Inc.
Humacao, Puerto Rico 00661

WALLACE LABORATORIES
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Cranbury, New Jersey 08512

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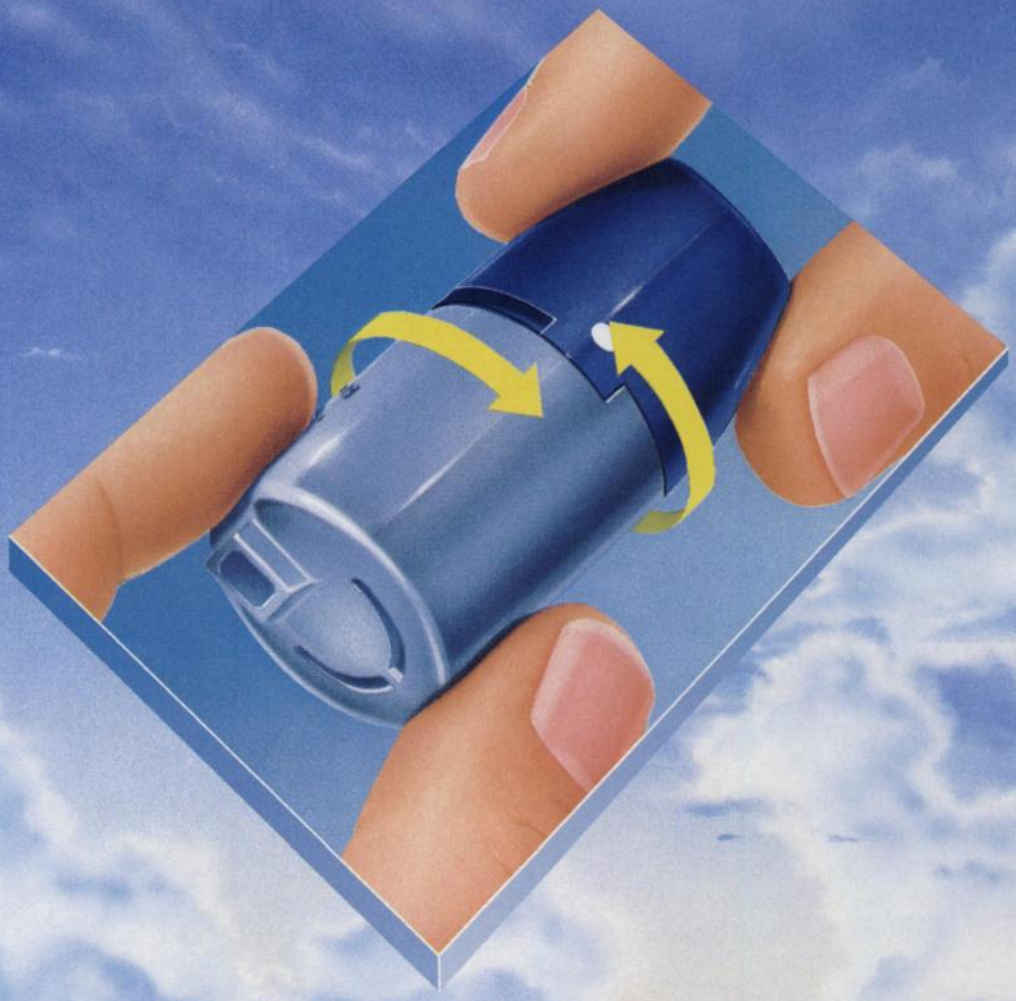

NEW **VENTOLIN ROTACAPS®** FOR INHALATION
(ALBUTEROL SULFATE)
AND
ROTAHALER® INHALATION DEVICE

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

Printed in USA
VIN 362

September 1988

Why send an antitussive to do a bronchodilator's job?

- ☐ Asthma is the most common cause of persistent episodic cough in children.[1,2]
- ☐ PROVENTIL Syrup has been proven to reduce nighttime cough symptoms due to asthma as much as 50%.[3]
- ☐ Starts within 30 minutes—lasts up to 6 hours.
- ☐ Safe enough for 2 year olds.
- ☐ Completely free of sugar, alcohol, tartrazine (yellow dye No. 5), and bisulfites.
- ☐ Pleasant tasting and easy to take.

References: 1. Cloutier MM: The coughing child: Etiology and treatment of a common symptom. *Postgrad Med* 1983;73:169-175. **2.** Miser WF: Variant forms of asthma. *Am Fam Physician* 1987;35(6):89-96. **3.** Rachelefsky GS, Katz RM, Siegel SC: Albuterol syrup in the treatment of the young asthmatic child. *Ann Allergy* 1981;47:143-146.

Proven

Proventil®

(albuterol sulfate) Syrup

2 mg albuterol per 5 ml

Stops coughs asthma starts.

Please see next page for brief summary of prescribing information.

Schering

Helping America breathe easier.

PS-045/14568409

Proven Proventil® (albuterol sulfate) Syrup

2 mg albuterol per 5 ml

INDICATIONS AND USAGE PROVENTIL Syrup is indicated for the relief of bronchospasm in adults and in children 2 years of age and older with reversible obstructive airway disease.

In controlled clinical trials in patients with asthma, the onset of improvement in pulmonary function, as measured by maximal midexpiratory flow rate (MMEF) and forced expiratory volume in one second (FEV_1), was within 30 minutes after a dose of PROVENTIL Syrup. Peak improvement of pulmonary function occurred between 2 to 3 hours. In a controlled clinical trial involving 55 children, clinically significant improvement (defined as maintenance of mean values over baseline of 15% or 20% or more in the FEV_1 and MMEF respectively) continued to be recorded up to 6 hours. No decrease in the effectiveness was reported in one uncontrolled study of 32 children who took PROVENTIL Syrup for a 3-month period.

CONTRAINDICATIONS PROVENTIL Syrup is contraindicated in patients with a history of hypersensitivity to any of its components.

PRECAUTIONS General: Although albuterol usually has minimal effects on the $beta_1$-adrenoceptors of the cardiovascular system at the recommended dosage, occasionally the usual cardiovascular and CNS stimulatory effects common to all sympathomimetic agents have been seen with patients treated with albuterol necessitating discontinuation. Therefore, albuterol should be used with caution in patients with cardiovascular disorders, including coronary insufficiency and hypertension, in patients with hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.

Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Additionally, albuterol and other beta-agonists, when given intravenously, may cause a decrease in serum potassium, possibly through intracellular shunting. The decrease is usually transient, not requiring supplementation. The relevance of these observations to the use of PROVENTIL Syrup is unknown.

Information for Patients: The action of PROVENTIL Syrup may last up to six hours and therefore it should not be taken more frequently than recommended. Do not increase the dose or frequency of medication without medical consultation. If symptoms get worse, medical consultation should be sought promptly.

Drug Interactions: The concomitant use of PROVENTIL Syrup and other oral sympathomimetic agents is not recommended since such combined use may lead to deleterious cardiovascular effects. This recommendation does not preclude the judicious use of an aerosol bronchodilator of the adrenergic stimulant type in patients receiving PROVENTIL Syrup. Such concomitant use, however, should be individualized and not given on a routine basis. If regular coadministration is required, then alternative therapy should be considered.

Albuterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of albuterol on the vascular system may be potentiated.

Beta-receptor blocking agents and albuterol inhibit the effect of each other.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Albuterol sulfate, like other agents in its class, caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium in a 2-year study in the rat, at doses corresponding to 2, 9, and 46 times the maximum human (child weighing 21 kg) oral dose. In another study this effect was blocked by the coadministration of propranolol. The relevance of these findings to humans is not known. An 18-month study in mice and a lifetime study in hamsters revealed no evidence of tumorigenicity. Studies with albuterol revealed no evidence of mutagenesis. Reproduction studies in rats revealed no evidence of impaired fertility.

Teratogenic Effects—Pregnancy Category C: Albuterol has been shown to be teratogenic in mice when given subcutaneously in doses corresponding to 0.2 times the maximum human (child weighing 21 kg) oral dose. There are no adequate and well-controlled studies in pregnant women. Albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A reproduction study in CD-1 mice with albuterol showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg; none was observed at 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5%) fetuses treated with 2.5 mg/kg isoproterenol (positive control). A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses at 50 mg/kg, corresponding to 46 times the maximum human (child weighing 21 kg) oral dose of albuterol sulfate.

Labor and Delivery: Oral albuterol has been shown to delay preterm labor in some reports. There are presently no well-controlled studies which demonstrate that it will stop preterm labor or prevent labor at term. Therefore, cautious use of PROVENTIL Syrup is required in pregnant patients when given for relief of bronchospasm so as to avoid interference with uterine contractibility. Use in such patients should be restricted to those patients in whom the benefits clearly outweigh the risks.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in animal studies, 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.

Pediatric Use: Safety and effectiveness in children below the age of 2 years have not yet been adequately demonstrated.

ADVERSE REACTIONS The adverse reactions to albuterol are similar in nature to those of other sympathomimetic agents. The most frequent adverse reactions to PROVENTIL Syrup in adults and older children were tremor, 10 of 100 patients; nervousness and shakiness, each 9 of 100 patients. Other reported adverse reactions were headache, 4 of 100 patients; dizziness and increased appetite, each 3 of 100 patients; hyperactivity and excitement, each 2 of 100 patients; tachycardia, epistaxis, irritable behavior, and sleeplessness, each 1 of 100 patients. The following adverse effects occurred in less than 1 of 100 patients each: muscle spasm; disturbed sleep, epigastric pain; cough; palpitations; stomach ache; irritable behavior; dilated pupils; sweating; chest pain; weakness.

In young children 2 to 6 years of age, some adverse reactions were noted more frequently than in adults and older children. Excitement was noted in approximately 20% of patients and nervousness in 15%. Hyperkinesia occurred in 4% of patients; insomnia, tachycardia, and gastrointestinal symptoms in 2% each. Anorexia, emotional lability, pallor, fatigue, and conjunctivitis were seen in 1%.

In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vomiting, vertigo, central nervous system stimulation, unusual taste, and drying or irritation of the oropharynx.

The reactions are generally transient in nature, and it is usually not necessary to discontinue treatment with PROVENTIL Syrup. In selected cases, however, dosage may be reduced temporarily; after the reaction has subsided, dosage should be increased in small increments to the optimal dosage.

OVERDOSAGE Manifestations of overdosage include anginal pain, hypertension, hypokalemia, and exaggeration of the effects listed in **ADVERSE REACTIONS**.

The oral LD_{50} in rats and mice was greater than 2,000 mg/kg. Dialysis is not appropriate treatment for overdosage of PROVENTIL Syrup. The judicious use of a cardioselective beta-receptor blocker, such as metoprolol tartrate, is suggested, bearing in mind the danger of inducing an asthmatic attack.

For more complete details, consult package insert or Schering literature available from your Schering representative or Professional Services Department, Schering Corporation, Kenilworth, NJ 07033.

Schering Corporation
Kenilworth, NJ 07033 USA

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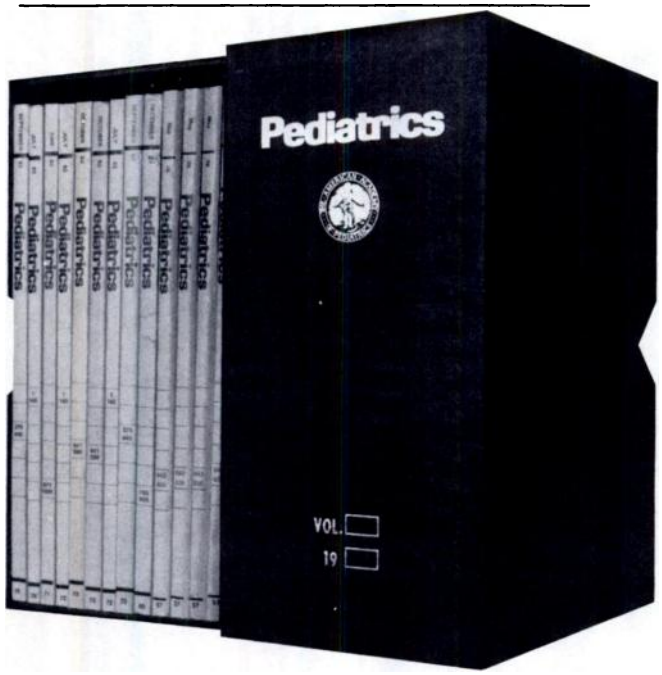

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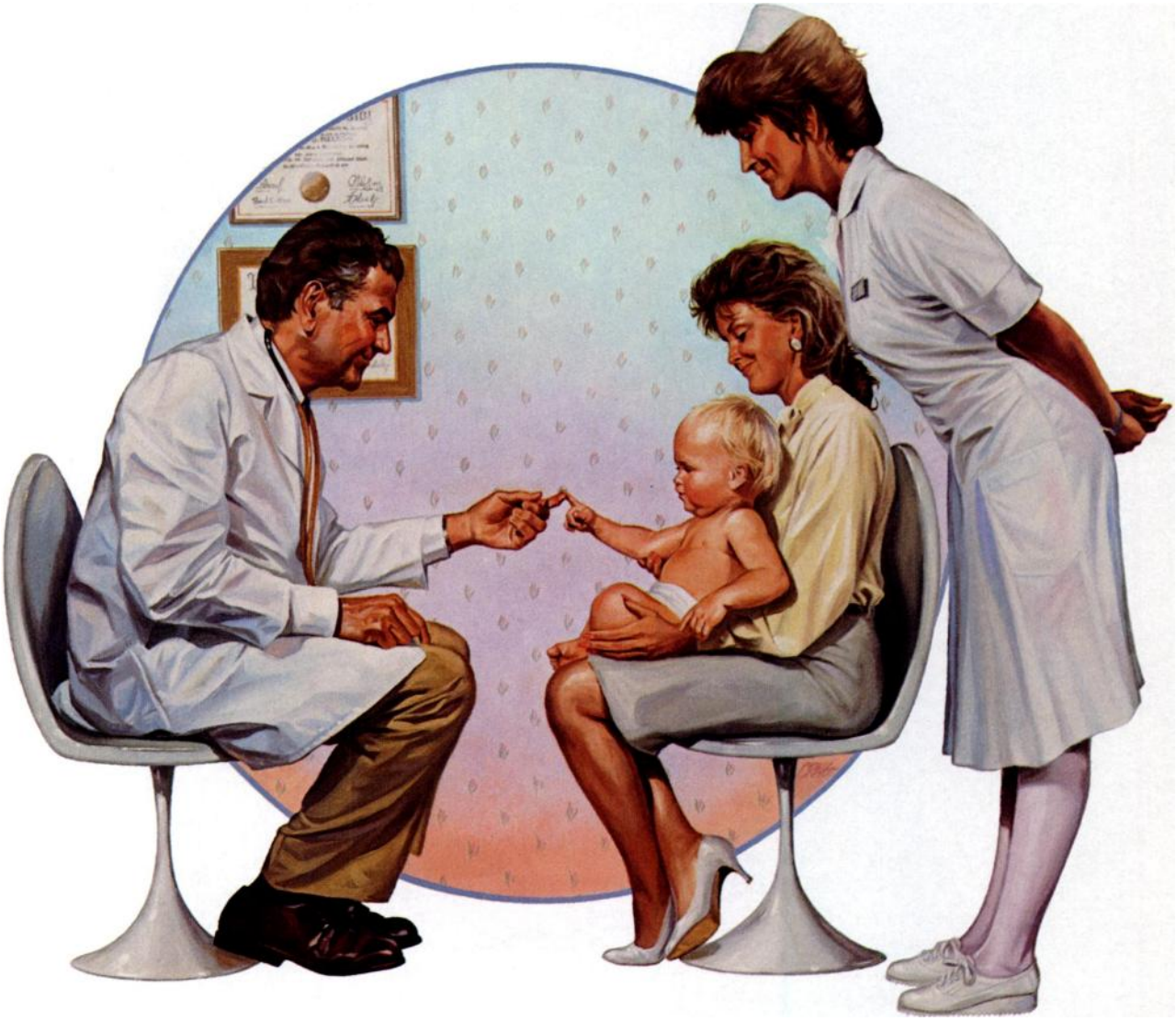

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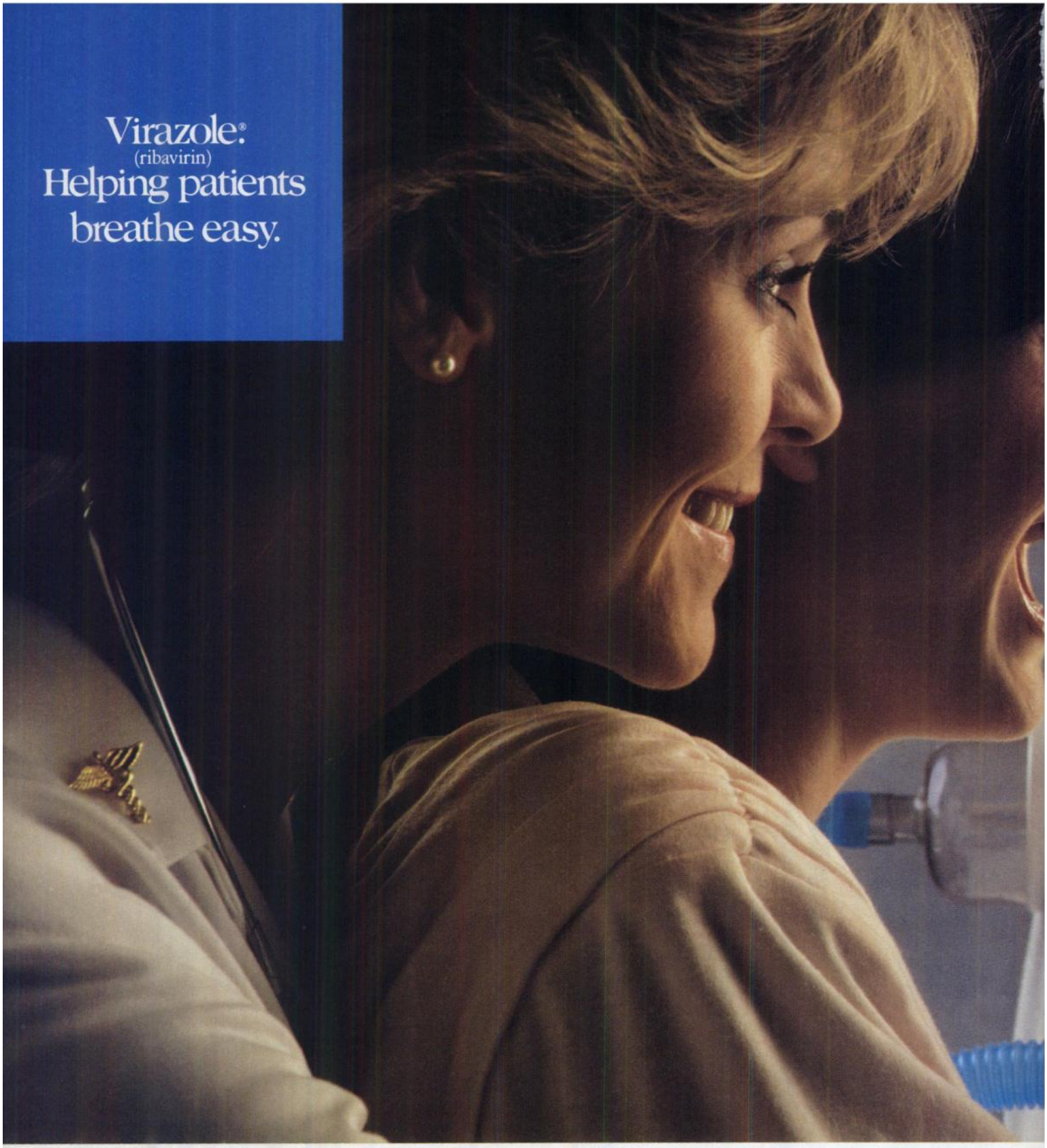
Virazole®
(ribavirin)
Helping patients breathe easy.



Breathe Easy, Virazole on the job.

Virazole® (ribavirin) therapy has been used to treat over 35,000 severely ill infants hospitalized with respiratory syncytial virus (RSV) since its introduction. Ribavirin aerosol has been studied in humans for ten years, and reported side effects have been minimal.[1] Virazole on the job, plus supportive care, means more rapid recovery and easier breathing for babies—and that means "easier breathing" for caregivers and parents.

Early diagnosis, early treatment for fast recovery.

Early diagnosis and treatment with Virazole can reduce the severity and duration of RSV infections in infants.[2-4] New rapid testing procedures have been developed for RSV that

1. Data on file, ICN Pharmaceuticals, Inc.

2. Hall CB, et al: Ribavirin treatment of respiratory syncytial viral infection in infants with underlying cardiopulmonary disease. *JAMA* 1985;254:3047-3051.

3. Taber LH, et al: Ribavirin aerosol treatment of bronchiolitis associated with respiratory syncytial virus infection in infants. *Pediatrics* 1983;72:613-618.

4. Hall CB, et al: Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection. *N Engl J Med* 1983;308:1443-1447.

make positive diagnosis possible in less than 30 minutes. And clinical evidence and experience continue to confirm that early initiation of Virazole therapy provides more rapid clinical improvement and may shorten hospitalization.[2-5]

For complete prescribing information, please see next page.

Breathe Easy

Virazole®
(ribavirin)
lyophilized for aerosol administration

5. McMillan JA, et al: Prediction of the duration of hospitalization in patients with respiratory syncytial virus infection: Use of clinical parameters. *Pediatrics* 1988;81:22-26.

 SPI-47

VIRAZOLE® (ribavirin) aerosol is indicated for treatment of severe lower respiratory tract infections due to RSV in carefully selected, hospitalized infants and young children.

Breathe Easy

Virazole®
(ribavirin)

lyophilized for aerosol administration

PRESCRIBING INFORMATION

WARNING: RIBAVIRIN AEROSOL SHOULD NOT BE USED FOR INFANTS REQUIRING ASSISTED VENTILATION BECAUSE PRECIPITATION OF THE DRUG IN THE RESPIRATORY EQUIPMENT MAY INTERFERE WITH SAFE AND EFFECTIVE VENTILATION OF THE PATIENT. Conditions for safe use with a ventilator are still in development.

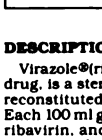
Deterioration of respiratory function has been associated with ribavirin use in infants, and in adults with chronic obstructive lung disease or asthma. Respiratory function should be carefully monitored during treatment. If initiation of ribavirin aerosol treatment appears to produce sudden deterioration of respiratory function, treatment should be stopped and re-instituted only with extreme caution and continuous monitoring.

Although ribavirin is not indicated in adults, the physician should be aware that it is teratogenic in animals (see CONTRAINDICATIONS).

DESCRIPTION:

Virazole®(ribavirin) Aerosol, an antiviral drug, is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100 ml glass vial contains 6 grams of ribavirin, and when reconstituted to the recommended volume of 300 ml with sterile water for injection or sterile water for inhalation (no preservatives added), will contain 20 mg/ml ribavirin, pH approximately 5.5. Aerosolization is to be carried out in a SPAG-2 nebulizer only.

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



Ribavirin, a synthetic nucleoside, is a stable, white, crystalline compound with a maximum solubility in water of 142 mg/ml at 25°C and with only a slight solubility in ethanol. The empirical formula is $C_8H_{12}N_4O_5$ and the molecular weight is 244.2 Daltons.

CLINICAL PHARMACOLOGY:

Antiviral effects:

Ribavirin has antiviral inhibitory activity *in vitro* against respiratory syncytial virus,[1] influenza virus, and herpes simplex virus. Ribavirin is also active against respiratory syncytial virus (RSV) in experimentally infected cotton rats.[2]

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

Immunologic effects:

Neutralizing antibody responses to RSV were decreased in ribavirin treated compared to placebo treated infants.[3] The clinical significance of this observation is unknown. In rats, ribavirin resulted in lymphoid atrophy of thymus, spleen, and lymph nodes. Humoral immunity was reduced in guinea pigs and ferrets. Cellular immunity was also mildly depressed in animal studies.

Microbiology:

Several clinical isolates of RSV were evaluated for ribavirin susceptibility by plaque reduction in tissue culture. Plaques were reduced 85-98% by 16μg/ml; however, plaque reduction varies with the test system. The clinical significance of these data is unknown.

Pharmacokinetics:

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

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

It is likely that the concentration of ribavirin in respiratory tract secretions is much higher than plasma concentrations in view of the route of administration.

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

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

INDICATIONS AND USAGE:

Ribavirin aerosol is indicated in the treatment of carefully selected hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus (RSV). In two placebo controlled trials in infants hospitalized with RSV lower respiratory tract infection, ribavirin aerosol treatment had a therapeutic effect, as judged by the reduction by treatment day 3 of severity of clinical manifestations of disease.[3,4] Virus titers in respiratory secretions were also significantly reduced with ribavirin in one of these studies.[4]

Only severe RSV lower respiratory tract infection is to be treated with ribavirin aerosol. The vast majority of infants and children with RSV infection have no lower respiratory tract disease or have disease that is mild, self-limited, and does not require hospitalization or antiviral treatment. Many children with mild lower respiratory tract involvement will require shorter hospitalization than would be required for a full course of ribavirin aerosol (3 to 7 days) and should not be treated with the drug. Thus the decision to treat with ribavirin aerosol should be based on the severity of the RSV infection.

The presence of an underlying condition such as prematurity or cardiopulmonary disease may increase the severity of the infection and its risk to the patient. High risk infants and young children with these underlying conditions may benefit from ribavirin treatment, although efficacy has been evaluated in only a small number of such patients.

Ribavirin aerosol treatment must be accompanied by and does not replace standard supportive respiratory and fluid management for infants and children with severe respiratory tract infection.

Diagnosis:

RSV infection should be documented by a rapid diagnostic method such as demonstration of viral antigen in respiratory tract secretions by immunofluorescence[3,4] or ELISA[5] before or during the first 24 hours of treatment. Ribavirin aerosol is indicated only for lower respiratory tract infection due to RSV. Treatment may be initiated while awaiting rapid diagnostic test results. However, treatment should not be continued without documentation of RSV infection.

CONTRAINDICATIONS:

Ribavirin is contraindicated in women or girls who are or may become pregnant during exposure to the drug. Ribavirin may cause fetal harm and respiratory syncytial virus infection is self-limited in this population. Ribavirin is not completely cleared from human blood even four weeks after administration. Although there are no pertinent human data, ribavirin has been found to be teratogenic and/or embryolethal in nearly all species in which it has been tested. Teratogenicity was evident after a single oral dose of 2.5 mg/kg in the hamster and after daily oral doses of 10 mg/kg in the rat. Malformations of skull, palate, eye, jaw, skeleton, and gastrointestinal tract were noted in animal studies. Survival of fetuses and offspring was reduced. The drug causes embryolethality in the rabbit at daily oral dose levels as low as 1 mg/kg.

WARNINGS:

Ribavirin administered by aerosol produced cardiac lesions in mice and rats after 30 and 36 mg/kg, respectively, for 4 weeks, and after oral administration in monkeys at 120 and rats at 154 to 200 mg/kg for 1 to 6 months. Ribavirin aerosol administered to developing ferrets at 60 mg/kg for 10 or 30 days resulted in inflammatory and possibly emphysematous changes in the lungs. Proliferative changes were seen at 131 mg/kg for 30 days. The significance of these findings to human administration is unknown.

Ribavirin lyophilized in 6 gram vials is intended for use as an aerosol only.

PRECAUTIONS:

General:

Patients with lower respiratory tract infection due to respiratory syncytial virus require optimum monitoring and attention to respiratory and fluid status.

Drug Interactions:

Interactions of ribavirin with other drugs such as digoxin, bronchodilators, other antiviral agents, antibiotics, or antimetabolites has not been evaluated. Interference by ribavirin with laboratory tests has not been evaluated.

Carcinogenesis, mutagenesis, impairment of fertility:

Ribavirin induces cell transformation in an *in vitro* mammalian system (Balb/C 3T3 cell line). However, *in vivo* carcinogenicity studies are incomplete. Results thus far, though inconclusive, suggest that chronic feeding of ribavirin to rats at dose levels in the range of 16-60 mg/kg body weight can induce benign mammary, pancreatic, pituitary and adrenal tumors.

Ribavirin is mutagenic to mammalian (L5178Y) cells in culture. Results of microbial mutagenicity assays and a dominant lethal assay (mouse) were negative.

Ribavirin causes testicular lesions (tubular atrophy) in adult rats at oral dose levels as low as 16 mg/kg/day (lower doses not tested), but fertility of ribavirin-treated animals (male or female) has not been adequately investigated.

Pregnancy:

Teratogenic Effects: Pregnancy Category X. See "Contraindications" section.

Nursing Mothers: Use of ribavirin aerosol in nursing mothers is not indicated because RSV infection is self-limited in this population. Ribavirin is toxic to lactating animals and their offspring. It is not known whether the drug is excreted in human milk.

ADVERSE REACTIONS:

Approximately 200 patients have been treated with ribavirin aerosol in controlled or uncontrolled clinical studies.

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

Several serious adverse events occurred in severely ill infants with life-threatening underlying diseases, many of whom required assisted ventilation. The role of ribavirin aerosol in these events is indeterminate. The following events were associated with ribavirin use:

Pulmonary: Worsening of respiratory status, bacterial pneumonia, pneumothorax, apnea, and ventilator dependence.

Cardiovascular: Cardiac arrest, hypotension, and digitalis toxicity.

There were 7 deaths during or shortly after treatment with ribavirin aerosol. No death was attributed to ribavirin aerosol by the investigators.

Some subjects requiring assisted ventilation have experienced serious difficulties, which may jeopardize adequate ventilation and gas exchange. Precipitation of drug within the ventilatory apparatus, including the endotracheal tube, has resulted in increased positive end expiratory pressure and increased positive inspiratory pressure. Accumulation of fluid in tubing ("rain out") has also been noted.

Although anemia has not been reported with use of the aerosol, it occurs frequently with oral and intravenous ribavirin, and most infants treated with the aerosol have not been evaluated 1 to 2 weeks post-treatment when anemia is likely to occur. Reticulocytosis has been reported with aerosol use.

Rash and conjunctivitis have been associated with the use of ribavirin aerosol.

Overdosage:

No overdosage with ribavirin by aerosol administration has been reported in the human. The LD_{50} in mice is 2 gm orally. Hypoactivity and gastrointestinal symptoms occurred. In man, ribavirin is sequestered in red blood cells for weeks after dosing.

DOSAGE AND ADMINISTRATION:

Before use, read thoroughly the Viratek Small Particle Aerosol Generator (SPAG) Model SPAG-2 Operator's Manual for small particle aerosol generator operating instructions.

Treatment was effective when instituted within the first 3 days of respiratory syncytial virus lower respiratory tract infection.[3] Treatment early in the course of severe lower respiratory tract infection may be necessary to achieve efficacy.

Treatment is carried out for 12-18 hours per day for at least 3 and no more than 7 days, and is part of a total treatment program. The aerosol is delivered to an infant oxygen hood from the SPAG-2 aerosol generator. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed (see SPAG-2 manual). However, the volume of distribution and condensation area are larger in a tent and efficacy of this method of administering the drug has been evaluated in only a small number of patients. Ribavirin aerosol is not to be administered with any other aerosol generating device or together with other aerosolized medications. Ribavirin aerosol should not be used for patients requiring simultaneous assisted ventilation (see Boxed Warnings).

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

Using the recommended drug concentration of 20 mg/ml ribavirin as the starting solution in the drug reservoir of the SPAG unit, the average aerosol concentration for a 12 hour period would be 190 micrograms/liter (0.19 mg/l) of air.

HOW SUPPLIED:

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

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3. Taber LH, Knight V, Gilbert BE, McClung HW et al. Ribavirin aerosol treatment of bronchiolitis associated with respiratory tract infection in infants. *Pediatrics* 72:613-618, 1983.
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5. Hendry RM, McIntosh K, Fahnestock ML, and Pierik LT. Enzyme-linked immunosorbent assay for detection of respiratory syncytial virus infection. *J Clin Microbiol* 16:329-33, 1982.

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