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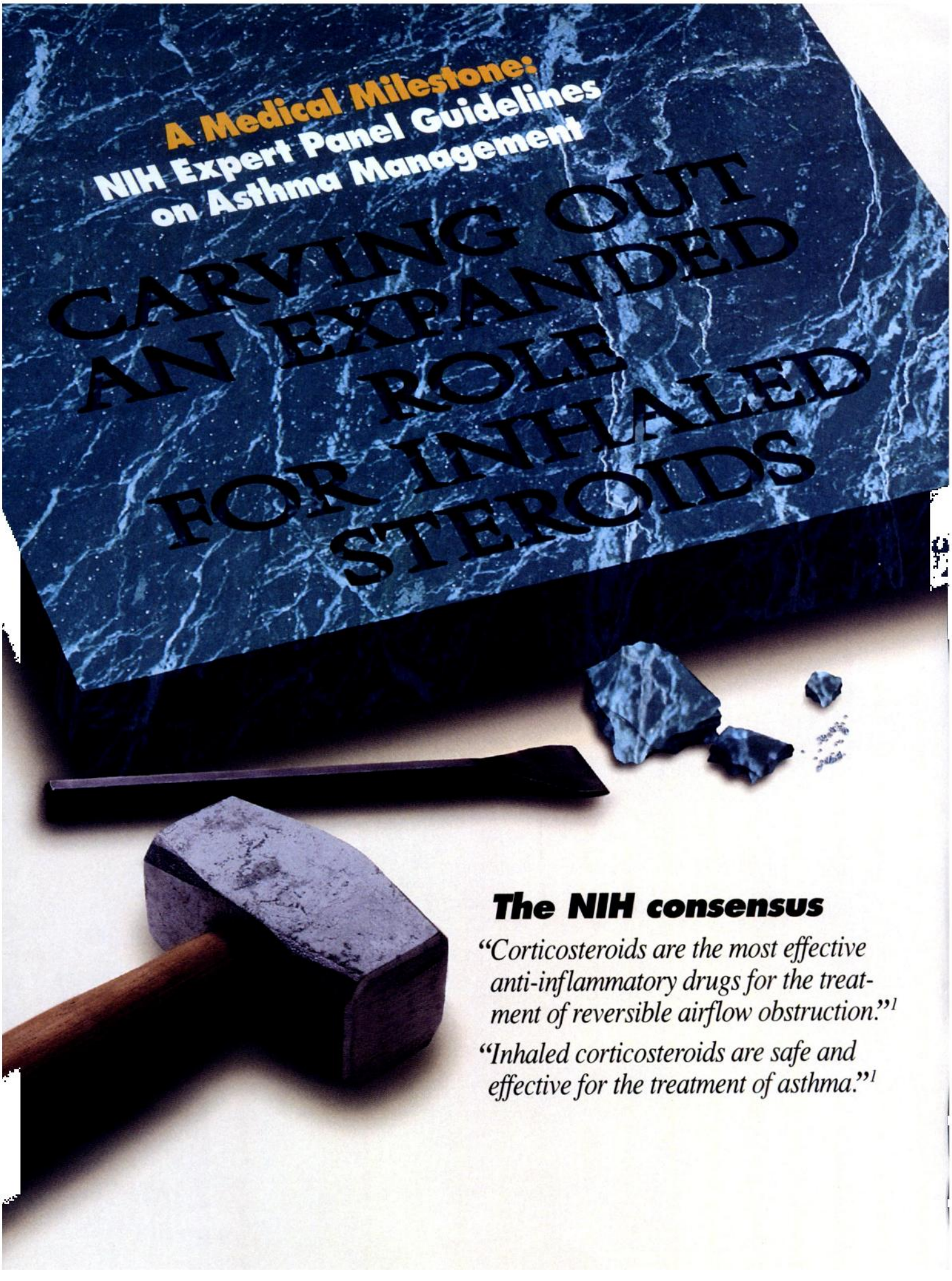

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Manuscripts—including tables, illustrations, and references—should be prepared according to "Uniform requirements for manuscripts submitted to biomedical journals."[1,2] Only information not included in the uniform requirements will be included in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

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

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

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

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References

1. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J.* 1991; 302:338–341
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6. Système International conversion factors for frequently used laboratory components. *JAMA.* 1991;266:45–47

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References:
1. Walson PD et al. Ibuprofen, acetaminophen and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17. 2. Temple A. Review of comparative antipyretic activity in children. *Am J Med.* 1983;38-46. 3. Aspirin or paracetamol? *Lancet.* 1981;11:287-289. 4. Data on file, McNeil Consumer Products Company. 5. Settipane GA. *Am J Med.* 1983;74(6A):102-109.

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Schedule of Continuing Education Courses

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Pediatrics Update II
Williamsburg, Virginia
December 10–12

1993

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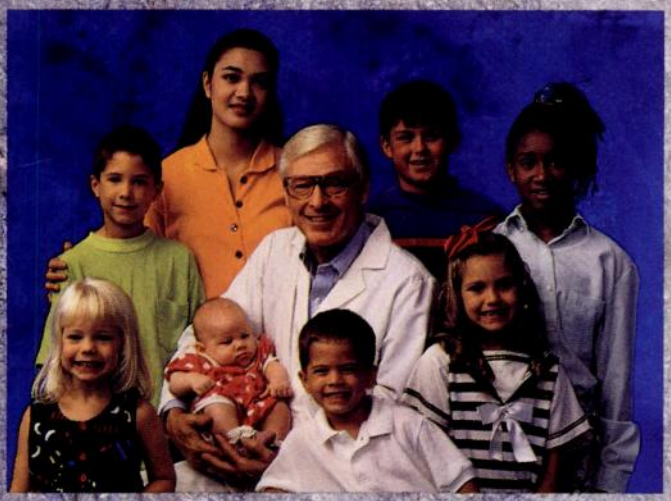

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Brief Summary
Poliovirus Vaccine
Live Oral Trivalent
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Please see package insert for full description, directions for use, and references.

INDICATIONS

For prevention of poliomyelitis caused by Poliovirus Types 1, 2, and 3.

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. Further, ORIMUNE *must not* be administered to patients with altered immune states, such as those occurring in human immunodeficiency virus (HIV) infection, thymic abnormalities, leukemia, lymphoma, generalized malignancy or advanced debilitating conditions, or by lowered resistance from therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation. ORIMUNE should also not be given to members of a household in which there is a family history of immunodeficiency until the immune status of all members is determined to be normal. 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 febrile illness or acute infection and in those with any advanced debilitated condition or persistent vomiting or diarrhea, or suspected gastroenteritis infection.

Other viruses (including poliovirus and other enteroviruses) may compromise 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

The vaccine is not effective in modifying or preventing cases of existing and/or incubating poliomyelitis. **Records Required by the National Childhood Vaccine Injury Act:** Manufacturer and lot number of vaccine administered must be recorded by health care provider in vaccine recipient's permanent record, along with date of administration and name, address, and title of person administering vaccine.

Health care provider must report to a health department or to the FDA the occurrence following immunization of any event set forth in the Vaccine Injury Table including: paralytic poliomyelitis–in a nonimmunodeficient recipient within 30 days of vaccination–in an immunodeficient recipient within 6 months of vaccination; any vaccine-associated community case of paralytic poliomyelitis; or any acute complication or sequela (including death) of above events.

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. A large retrospective study suggests that OPV may be temporally associated with Guillain-Barré syndrome. A causal relationship has not been established. 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 the years 1973 through 1984 approximately 274.1 million OPV doses were distributed in the US. During this same period, 105 vaccine-associated cases were reported (1 case per 2.6 million doses distributed). Of these 105 cases, 35 occurred in vaccine recipients (1 case per 7.8 million doses distributed), 50 occurred in household and nonhousehold contacts of vaccinees (1 case per 5.5 million doses distributed), 14 occurred in immunodeficient recipients or contacts, and 6 occurred in persons with no history of vaccine exposure, from whom vaccine-like viruses were isolated.

Thirty-three (94%) of the recipient cases, 41 (82%) of the contact cases, and 5 (36%) of the immune deficient cases were associated with the recipient's first dose of OPV. Because most cases of vaccine-associated paralysis have occurred in association with the first dose, the CDC has estimated the likelihood of paralysis in association with first *v* subsequent doses of OPV, using the number of births during 1973-1984 to estimate the number of first doses distributed, and subtracting this from the total distribution to estimate the number of subsequent doses distributed. This method estimates a frequency of paralysis for recipients of 1 case per 1.2 million first doses *v* one case per 116.5 million subsequent doses; for contacts, one case per 1 million first doses *v* one case per 25.9 million subsequent doses; with an overall frequency of 1 case per 520,000 first doses *v* 1 case per 12.3 million subsequent doses.

Other methods of estimating the likelihood of paralysis in association with OPV have been described. 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 2 doses of enhanced potency IPV a month apart before the children receive ORIMUNE. The children may receive the first dose of ORIMUNE at the same visit that the adult receives the second dose of enhanced potency IPV. A booster dose of enhanced potency IPV can be given to partially immunized adults at the same visit that the first dose of OPV is given to the child. The adult should be informed of precautions, such as handwashing after changing diapers.

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...[with IPV]... before giving OPV to the child."

The American Academy of Pediatrics and the American College of Physicians have made similar recommendations.

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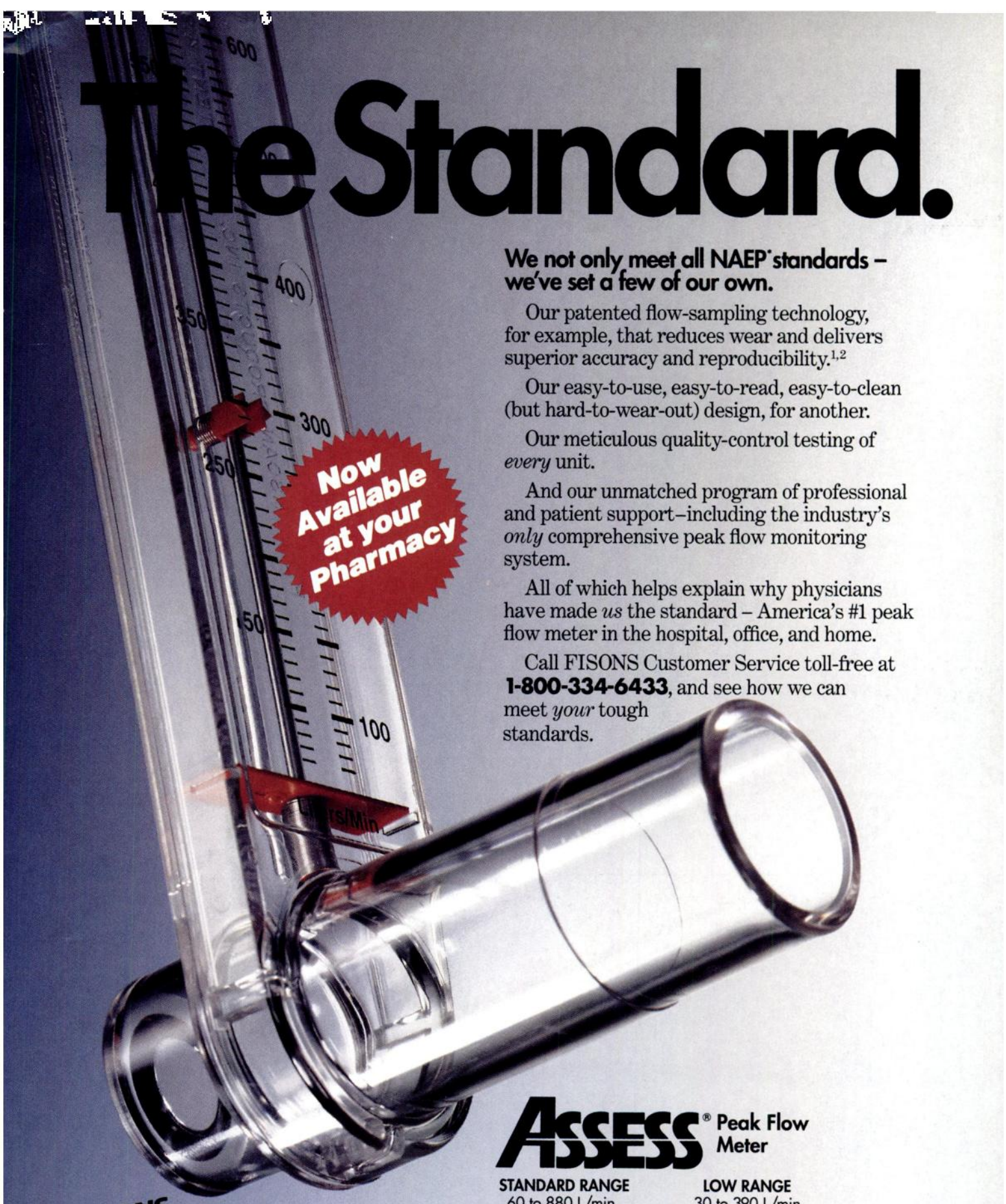

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References: 1. Data on file, HealthScan Products Inc. 2. Shapiro S, Hendler J, Ogirala R, et al.: An evaluation of the accuracy of Assess and MiniWright peak flowmeters. *Chest* 99:358-362, 1991.

*ASSESS Standard and Low Range meters meet ***National Asthma Education Program Technical Standards for Peak Flow Meters*****, January, 1991.** FA710002-0 5/92

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Books Received

Chromosome Anomalies and Prenatal Development: An Atlas. D. Warburton, J. Byrne, and N. Canki. New York, NY: Oxford University Press; 1991, $85.00 (hardcover), 104 pp.

Essential Medical Genetics. 3rd ed. J. Connor and M. Ferguson-Smith. Cambridge, MA: Blackwell Scientific Publications Ltd., 1991, $29.95 (paperback), 259 pp.

Mental Retardation: Developing Pharmacotherapies. J. Ratey, ed. Washington, DC: American Psychiatric Press, Inc., 1991, $29.50 (hardcover), 162 pp.

An Overview of Childhood Fitness: Theoretical Perspectives and Scientific Bases. J. Humphrey. Springfield, IL: Charles C. Thomas, Publisher, 1991, $29.75 (hardcover), 147 pp.

Physicians's Guide to Sunscreens. N. Lowe, ed. New York, NY: Marcel Dekker, Inc.; 1991, $59.75 (hardcover), 219 pp.

Schaffer & Avery's Diseases of the Newborn. H. Taeusch, R. Ballard, and M. Avery. Philadelphia, PA: W. B. Saunders Co., 1991, $125.00 (hardcover), 1115 pp.

Tracheal Reconstruction in Infancy. T. Lobe. Philadelphia, PA: W. B. Saunders: 1991, $80.00 (hardcover), 218 pp.

Adolescent Medicine: A Practical Guide. V. Strasburger and R. Brown. Boston, MA: Little, Brown and Company, 1991 $45.00 (paperback), 569 pp.

Body Composition in Biological Anthropology. R. Shephard. New York, NY: Cambridge University Press, 1991, $69.50 (hardcover), 345 pp.

Concepts in Pediatric Neurosurgery. Vol. 11. A. Marlin, ed. Basel, Switzerland: S. Karger AG; 1991, $172.00 (hardcover), 163 pp.

Pediatrics in Review: December 1992 Contents

Child Sexual Abuse—Berkowitz
Bacterial Meningitis—Smith
Failure to Thrive/Growth Deficiency—Bithoney, Dubowitz, and Egan
Index of Suspicion

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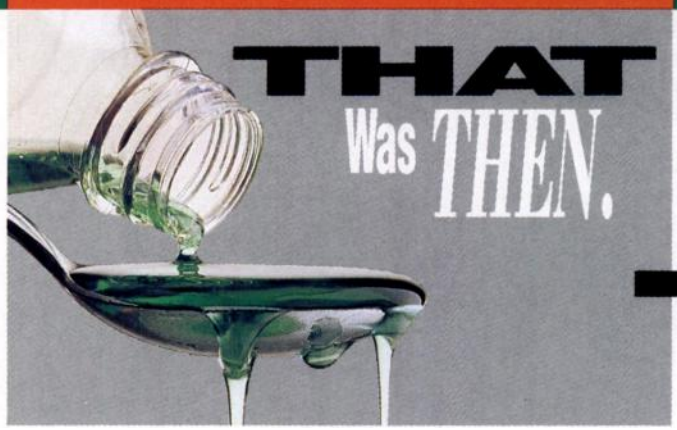

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Each teaspoonful (5 mL) contains: ORGANIDIN®
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Rx ONLY
TUSSI-ORGANIDIN®-S* V LIQUID

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.

Please see following page for prescribing information.

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March 1992

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ORGANIDIN®
Tablets, Elixir, Solution
TUSSI-ORGANIDIN® Liquid G
TUSSI-ORGANIDIN®-S* Liquid G
TUSSI-ORGANIDIN® DM Liquid
TUSSI-ORGANIDIN® DM-S* Liquid

DESCRIPTION

Organidin® (iodinated glycerol), a mucolytic-expectorant, contains a mixture of several iodinated compounds formed by the reaction of iodine and glycerin. The major iodinated compounds are 3-iodo-1,2-propanediol and a mixture of diastereomers of 1,5,6-trihydroxy-2-iodomethyl-3-oxahexane. Iodinated glycerol is an amber liquid which contains virtually no free iodine and is stable in an acid medium.

Organidin is available for oral administration as:

Tablets — each containing 30 mg Organidin (15 mg organically bound iodine).

Other ingredients: corn starch, dibasic calcium phosphate, FD&C Red #40, magnesium stearate, microcrystalline cellulose, tribasic calcium phosphate.

Elixir — containing 60 mg Organidin (30 mg organically bound iodine) per 5 mL (teaspoonful); and alcohol, 21.75% by volume.

Other ingredients: flavors (natural and artificial), liquid glucose, purified water, saccharin sodium.

Solution — containing 50 mg Organidin (25 mg organically bound iodine) per mL.

Other ingredients: caramel, glycerin, purified water.

Tussi-Organidin® and Tussi-Organidin® DM are antitussive/mucolytic-expectorant combinations available for oral administration as **liquids**.

Tussi-Organidin — each 5 mL (teaspoonful) contains Organidin® (iodinated glycerol) 30 mg (15 mg organically bound iodine) and codeine phosphate (**Warning:** May be habit-forming), 10 mg.

Other ingredients: citric acid, FD&C Red #40, flavor (artificial), glycerin, propylene glycol, purified water, saccharin sodium, sodium benzoate, sorbitol solution.

Tussi-Organidin DM — as for Tussi-Organidin; codeine phosphate is replaced by dextromethorphan hydrobromide, 10 mg per 5 mL.

Other ingredients: citric acid, D&C Yellow #10, FD&C Red #40, flavor (artificial), glycerin, propylene glycol, purified water, saccharin sodium, sodium benzoate, sorbitol solution.

CLINICAL PHARMACOLOGY

Organidin increases the output of thin respiratory tract fluid and helps liquefy tenacious mucus in the bronchial tree. Iodides are readily absorbed from the gastrointestinal tract and concentrated primarily in the secretions of the respiratory tract, but their mechanism of action as mucolytic-expectorants is not clear.

Tussi-Organidin combines the antitussive action of codeine with the mucolytic-expectorant action of Organidin.

Tussi-Organidin DM combines the non-narcotic antitussive action of dextromethorphan with the mucolytic-expectorant action of Organidin.

INDICATIONS AND USAGE

Organidin is indicated for adjunctive treatment as a mucolytic-expectorant in respiratory tract conditions such as bronchitis and asthma.

Tussi-Organidin and *Tussi-Organidin DM* are indicated for the symptomatic relief of irritating, nonproductive cough associated with respiratory tract conditions such as bronchitis and asthma. Appropriate therapy should be provided for the primary disease.

DURATION OF TREATMENT

The antitussive therapy is directed at the symptomatic relief of the irritating cough. The effects of mucolytic therapy may be seen early after the initiation of therapy; however, at least three to four weeks may be needed to demonstrate maximum effects for those patients responding. Patients not responding within four weeks should not be continued on this therapy. Continuation of therapy beyond eight weeks cannot currently be recommended unless in the experience and/or opinion of the physician, the ongoing condition or clinical status of the patient warrants such continuation. It should be recognized that chronic pulmonary diseases are intermittently marked by exacerbations and that the adjunctive use of Organidin during these exacerbations is the most appropriate form of therapy as opposed to long term, continuous use.

CONTRAINDICATIONS

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

The human fetal thyroid begins to concentrate iodine in the 12th to 14th week of gestation and the use of inorganic iodides in pregnant women during this period and thereafter has rarely been reported to induce fetal goiter (with or without hypothyroidism) with the potential for airway obstruction. If the patient becomes pregnant while taking any of these products, the drug should be discontinued and the patient should be apprised of the potential risk to the fetus.

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 effect of iodides.

Dermatitis and other reversible manifestations of iodism have been reported with chronic use of inorganic iodides. Although these have not been a problem clinically with Organidin formulations, they should be kept in mind in patients receiving these preparations for prolonged periods.

Laboratory Tests — Chronic administration of pharmacologic doses of iodide does not affect the normal thyroid; the excess iodide is excreted by the kidneys. Reversible, mild to moderately elevated TSH (thyrotropin) levels with or without depressed serum T4 and T3 levels have been noted sporadically in patients (usually elderly) receiving iodide therapy for prolonged periods; in most such cases, no pretreatment thyroid function tests were available. Iodide-induced 'biochemical hypothyroidism' (i.e., subclinical hypothyroidism manifested only by depressed serum T4 or T3 levels and/or elevated TSH) may be noted in patients with underlying thyroid dysfunction (where the thyroid homeostatic mechanism does not function normally). Iodide-induced 'biochemical hypothyroidism' typically reverses to pretreatment levels (in weeks or months) usually spontaneously. Patients with 'functional' hypothyroidism may receive iodotherapy, provided thyroid hormone (e.g., Synthroid-levothyroxine) is administered concomitantly in replacement doses. Radioactive iodine (I^{131}) and iodide transport tests are depressed during iodide therapy; these tests could be expected to return to basal levels two or three days after stopping treatment with Organidin, Tussi-Organidin or Tussi-Organidin DM.

Pediatric Use — Due to the developmental nature of many organ systems in this age group, the physician must weigh the perceived benefit against any potential risk in using iodide in children.

Drug Interactions — Iodides may potentiate the hypothyroid effect of lithium and other antithyroid drugs. Tussi-Organidin DM — potential for a drug interaction exists between dextromethorphan and monoamine oxidase inhibitors (MAOIs).

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: **Twenty-four (24) month carcinogenicity studies were conducted by the National Toxicology Program (NTP) in rats and mice using doses of iodinated glycerol that ranged between 13 and 52 times the recommended human dose. The conclusions of the NTP under the conditions of these gavage studies were species and sex specific and included the following: (1) no evidence of carcinogenicity in female F344/N rats; some evidence in male F344/N rats, based on increased incidences of a) mononuclear cell leukemia and b) follicular cell carcinomas of the thyroid gland. (There were no other chemical related nonneoplastic lesions of the thyroid gland in male or female rats.) (2) No evidence of carcinogenicity in male B6C3F1 mice; some evidence in female B6C3F1 mice, based on increased incidences of a) adenomas of the pituitary gland and b) neoplasms of the Harderian gland. The latter tumors were not found in the male mouse or in male or female rats. (There are no known human equivalents to mononuclear cell leukemia in the rat and Harderian gland neoplasms in the mouse.) The relevance of these findings to humans is not known. Both positive and negative results were found with iodinated glycerol in a standard battery of in vitro mutagenicity assays that were conducted with or without microsomal activation. In the only in vivo mutagenicity study that was conducted, the results were negative for genotoxic effects, in that no increase in micronucleated polychromatic erythrocytes was observed in the bone marrow of B6C3F1 mice after administration of either iodinated glycerol or 3-iodo-1,2-propanediol. The relevance of these findings to humans is not known. No long-term animal studies on impairment of fertility have been performed with these products.**

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

Nursing Mothers — These products should not be administered to a nursing woman.

ADVERSE REACTIONS

Side effects with Organidin formulations have been rare, including those which may occur with the individual ingredients and which may be modified as a result of their combination.

Organidin — Rare side effects include gastrointestinal irritation, rash, hypersensitivity, thyroid gland enlargement, and acute parotitis.

Codeine — (Tussi-Organidin only): Nausea, vomiting, constipation, drowsiness, dizziness, and miosis have been reported.

Dextromethorphan — (Tussi-Organidin DM only): Rarely produces drowsiness or gastrointestinal disturbances.

DRUG ABUSE AND DEPENDENCE (Tussi-Organidin only)

Controlled Substance — Schedule V.
Dependence — Codeine may be habit-forming.

OVERDOSAGE

Acute overdosage experience with Organidin formulations has been rare and there have been no reports of any serious problems.

DOSAGE AND ADMINISTRATION

Organidin: Note — Add *Solution* to fruit juice or other liquid. One drop *Solution* equals approximately 3 mg 'Organidin.'

Adults — Tablets: 2 tablets 4 times a day, with liquid.
Elixir: 1 teaspoonful (5 mL) 4 times a day.
Solution: 20 drops 4 times a day.

Children — Up to one-half the adult dosage, based on the child's weight.

Tussi-Organidin and *Tussi-Organidin DM:*

Adults — 1 to 2 teaspoonfuls (5-10 mL) every 4 hours.
Children — ½ to 1 teaspoonful (2½-5 mL) every 4 hours.

HOW SUPPLIED

Organidin: Tablets — round, flat-faced, bevel-edged, one side scored, other side imprinted 37-WALLACE 4224, mottled, rose-colored tablets, each containing 30 mg Organidin (15 mg organically bound iodine), in bottles of 100 (NDC 0037-4224-40) and 500 (NDC 0037-4224-03).

Elixir — clear amber liquid, each teaspoonful (5 mL) containing 60 mg Organidin (30 mg organically bound iodine), in bottles of one pint (NDC 0037-4213-30) and one gallon (NDC 0037-4213-40).

Solution — clear amber liquid, containing 50 mg Organidin (25 mg organically bound iodine) per mL, in 30 mL dropper bottles (NDC 0037-4211-10).

Tussi-Organidin Liquid — clear red liquid, each 5 mL (teaspoonful) contains Organidin® (iodinated glycerol) 30 mg (15 mg organically bound iodine) and codeine phosphate 10 mg (Warning: May be habit-forming), in 4 fl. oz. bottles (NDC 0037-4812-01, labeled Tussi-Organidin* and NDC 0037-4812-50, labeled Tussi-Organidin®-S*) and in bottles of one pint (NDC 0037-4812-10) and one gallon (NDC 0037-4812-20).

Tussi-Organidin DM Liquid — clear yellow liquid, each 5 mL (teaspoonful) contains Organidin* (iodinated glycerol) 30 mg (15 mg organically bound iodine) and dextromethorphan 10 mg, in 4 fl. oz. bottles (NDC 0037-4712-01, labeled Tussi-Organidin® DM and NDC 0037-4712-50, labeled Tussi-Organidin® DM-S*) and in bottles of one pint (NDC 0037-4712-10) and one gallon (NDC 0037-4712-20).

Storage: (Organidin Tablets) Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

(Organidin Elixir and Solution, Tussi-Organidin Liquid and Tussi-Organidin DM Liquid) Store at controlled room temperature 15°-30°C (59°-86°F).

*Patent Pending
Tussi-Organidin®-S and Tussi-Organidin* DM-S are Tussi-Organidin* and Tussi-Organidin* DM Liquids, respectively, either in 4 fl. oz. unit of use containers with a 10 mL graduated, oral syringe (patent pending) or in 30 mL sample containers.

Organidin Tablets are manufactured by:
Wallace Laboratories, Division of Carter-Wallace, Inc.
Cranbury, New Jersey 08512

Organidin Elixir and Solution, Tussi-Organidin Liquid and Tussi-Organidin DM Liquid are distributed by:
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Cranbury, New Jersey 08512

Manufactured by: Denver Chemical (Puerto Rico), Inc.
Subsidiary of Carter-Wallace, Inc.
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SURVANTA®

beractant
intratracheal suspension
bovine pulmonary surfactant

From Ross Laboratories—
Helping Premature Babies Survive™

Please see adjacent column for Brief Summary of prescribing information.

B401/2980
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ROSS LABORATORIES
COLUMBUS, OHIO 43216
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LITHO IN USA

BRIEF SUMMARY: Please see package insert for full prescribing information.

SURVANTA® (1040)

beractant

intratracheal suspension

Sterile Suspension/For Intratracheal Use Only

INDICATIONS AND USAGE

SURVANTA is indicated for prevention and treatment ("rescue") of Respiratory Distress Syndrome (RDS) (hyaline membrane disease) in premature infants. SURVANTA significantly reduces the incidence of RDS, mortality due to RDS and air leak complications.

Prevention

In premature infants less than 1250 g birth weight or with evidence of surfactant deficiency, give SURVANTA as soon as possible, preferably within 15 minutes of birth.

Rescue

To treat infants with RDS confirmed by x-ray and requiring mechanical ventilation, give SURVANTA as soon as possible, preferably by 8 hours of age.

CONTRAINDICATIONS

None known.

WARNINGS

SURVANTA is intended for intratracheal use only.

SURVANTA CAN RAPIDLY AFFECT OXYGENATION AND LUNG COMPLIANCE. Therefore, its use should be restricted to a highly supervised clinical setting with immediate availability of clinicians experienced with intubation, ventilator management, and general care of premature infants. Infants receiving SURVANTA should be frequently monitored with arterial or transcutaneous measurement of systemic oxygen and carbon dioxide.

DURING THE DOSING PROCEDURE, TRANSIENT EPISODES OF BRADYCARDIA AND DECREASED OXYGEN SATURATION HAVE BEEN REPORTED. If these occur, stop the dosing procedure and initiate appropriate measures to alleviate the condition. After stabilization, resume the dosing procedure.

PRECAUTIONS

General

Rales and moist breath sounds can occur transiently after administration. Endotracheal suctioning or other remedial action is not necessary unless clear-cut signs of airway obstruction are present.

Increased probability of post-treatment nosocomial sepsis in SURVANTA-treated infants was observed in the controlled clinical trials (Table 3). The increased risk for sepsis among SURVANTA-treated infants was not associated with increased mortality among these infants. The causative organisms were similar in treated and control infants. There was no significant difference between groups in the rate of post-treatment infections other than sepsis.

Use of SURVANTA in infants less than 600 g birth weight or greater than 1750 g birth weight has not been evaluated in controlled trials. There is no controlled experience with use of SURVANTA in conjunction with experimental therapies for RDS (eg, high-frequency ventilation or extracorporeal membrane oxygenation).

No information is available on the effects of doses other than 100 mg phospholipids/kg, more than four doses, dosing more frequently than every 6 hours, or administration after 48 hours of age.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Reproduction studies in animals have not been completed. Mutagenicity studies were negative. Carcinogenicity studies have not been performed with SURVANTA.

ADVERSE REACTIONS

The most commonly reported adverse experiences were associated with the dosing procedure. In the multiple-dose controlled clinical trials, transient bradycardia occurred with 11.9% of doses. Oxygen desaturation occurred with 9.8% of doses.

Other reactions during the dosing procedure occurred with fewer than 1% of doses and included endotracheal tube reflux, pallor, vasoconstriction, hypotension, endotracheal tube blockage, hypertension, hypocarbia, hypercarbia, and apnea. No deaths occurred during the dosing procedure, and all reactions resolved with symptomatic treatment.

The occurrence of concurrent illnesses common in premature infants was evaluated in the controlled trials. The rates in all controlled studies are in Table 3.

TABLE 3

	All Controlled Studies		
Concurrent Event	SURVANTA (%)	Control (%)	P-Value[a]
Patent ductus arteriosus	46.9	47.1	0.814
Intracranial hemorrhage	48.1	45.2	0.241
Severe intracranial hemorrhage	24.1	23.3	0.693
Pulmonary air leaks	10.9	24.7	<0.001
Pulmonary interstitial emphysema	20.2	38.4	<0.001
Necrotizing enterocolitis	6.1	5.3	0.427
Apnea	65.4	59.6	0.283
Severe apnea	46.1	42.5	0.114
Post-treatment sepsis	20.7	16.1	0.019
Post-treatment infection	10.2	9.1	0.345
Pulmonary hemorrhage	7.2	5.3	0.166

[a]P-value comparing groups in controlled studies

When all controlled studies were pooled, there was no difference in intracranial hemorrhage. However, in one of the single-dose rescue studies and one of the multiple-dose prevention studies, the rate of intracranial hemorrhage was significantly higher in SURVANTA patients than control patients (63.3% *v* 30.8%, $P=0.001$; and 48.8% *v* 34.2%, $P=0.047$, respectively). The rate in a Treatment IND involving approximately 4400 infants was lower than in the controlled trials.

In the controlled clinical trials, there was no effect of SURVANTA on results of common laboratory tests: white blood cell count and serum sodium, potassium, bilirubin, creatinine.

More than 3700 pretreatment and post-treatment serum samples were tested by Western Blot immunoassay for antibodies to surfactant-associated proteins SP-B and SP-C. No IgG or IgM antibodies were detected.

Several other complications are known to occur in premature infants. The following conditions were reported in the controlled clinical studies. The rates of the complications were not different in treated and control infants, and none of the complications were attributed to SURVANTA.

Respiratory: lung consolidation, blood from the endotracheal tube, deterioration after weaning, respiratory decompensation, subglottic stenosis, paralyzed diaphragm, respiratory failure.

Cardiovascular: hypotension, hypertension, tachycardia, ventricular tachycardia, aortic thrombosis, cardiac failure, cardiorespiratory arrest, increased apical pulse, persistent fetal circulation, air embolism, total anomalous pulmonary venous return.

Gastrointestinal: abdominal distention, hemorrhage, intestinal perforations, volvulus, bowel infarct, feeding intolerance, hepatic failure, stress ulcer.

Renal: renal failure, hematuria.

Hematologic: coagulopathy, thrombocytopenia, disseminated intravascular coagulation.

Central Nervous System: seizures.

Endocrine/Metabolic: adrenal hemorrhage, inappropriate ADH secretion, hyperphosphatemia.

Musculoskeletal: inguinal hernia.

Systemic: fever, deterioration.

Follow-Up Evaluations

To date, no long-term complications or sequelae of SURVANTA therapy have been found.

Single-Dose Studies

Six-month adjusted-age follow-up evaluations of 232 infants (115 treated) demonstrated no clinically important differences between treatment groups in pulmonary and neurologic sequelae, incidence or severity of retinopathy of prematurity, rehospitalizations, growth, or allergic manifestations.

Multiple-Dose Studies

Six-month adjusted age follow-up evaluations have not been completed. Preliminarily, in 605 (333 treated) of 916 surviving infants, there are trends for decreased cerebral palsy and need for supplemental oxygen in SURVANTA infants. Wheezing at the time of examination tended to be more frequent among SURVANTA infants, although there was no difference in bronchodilator therapy.

Twelve-month follow-up data from the multiple-dose studies have been completed in 328 (171 treated) of 909 surviving infants. To date no significant differences between treatments have been found, although there is a trend toward less wheezing in SURVANTA infants in contrast to the six month results.

OVERDOSAGE

Overdosage with SURVANTA has not been reported. Based on animal data, overdosage might result in acute airway obstruction. Treatment should be symptomatic and supportive.

Rales and moist breath sounds can transiently occur after SURVANTA is given, and do not indicate overdosage. Endotracheal suctioning or other remedial action is not required unless clear-cut signs of airway obstruction are present.

HOW SUPPLIED

SURVANTA (beractant) Intratracheal Suspension is supplied in single-use glass vials containing 8 mL of SURVANTA (NDC 0074-1040-08). Each milliliter contains 25 mg of phospholipids (200 mg phospholipids/8 mL) suspended in 0.9% sodium chloride solution. The color is off-white to light brown.

Store unopened vials at refrigeration temperature (2-8°C). Protect from light. Store vials in carton until ready for use. Vials are for single use only. Upon opening, discard unused drug.

June, 1991

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Announcing:
Pediatric Cryptococcal Meningitis Study

Pfizer Central Research is seeking investigators to recruit pediatric patients for a funded, open, non-comparative research clinical trial with an investigational triazole antifungal in patients with acute Cryptococcal Meningitis.

Major eligibility criteria include:

- Culture positive CSF infection (tentative diagnosis is acceptable).
- Prior systemic antifungal therapy is limited to ≤1.5 mg/kg of amphotericin B for this episode of acute infection.

or

limited to ≤1 mg/kg/week of amphotericin B over the past 4 weeks for patients who have relapsed.

- Patients must be between 6 months and 13 years of age.
- Other criteria will be discussed by Pfizer clinical monitor.
- Enrollment will be prompt for patients and sites meeting all eligibility criteria.

To inquire about this study, call: **203 441 4814**

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340

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PEDIATRIC SCIENTIST DEVELOPMENT PROGRAM

Special Fellowship Program for Residents
Academic Pediatric Careers

The Association of Medical School Pediatric Department Chairmen, Inc. (AMSPDC) invites applications for support of basic research training for young pediatricians interested in academic careers. THE PEDIATRIC SCIENTIST DEVELOPMENT PROGRAM is funded by a consortium of the National Institute for Child Health and Human Development, St. Jude Children's Research Hospital, The March of Dimes Birth Defects Foundation, The Cystic Fibrosis Foundation, The William T. Grant Foundation, The American Academy of Pediatrics, and The Johnson & Johnson Institute for Pediatric Service.

Physicians in the second, third, or chief residency years of pediatric residency training who wish to spend at least two years in basic science departments acquiring strong research skills are encouraged to apply. Candidates with PhD degrees do not qualify for this program. Applicants must be US citizens, permanent residents of the US, or Canadian citizens. Candidates must be nominated by the chairperson of the medical school pediatric department in which residency takes place.

Fellows receive a stipend and research support for two years of full-time research training in outstanding research environments in any field of pediatrics or developmental medicine.

February 1, 1993 is the application deadline for research training to begin July 1, 1993. For application forms, information, and direction in selection of a training site, contact:

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We were going to talk about fat content.

We came up with nothing.

And that's good news for your patients. Kellogg's *Frosted Flakes*® has long been one of America's favorite cereals, but it can also be a part of a complete breakfast of cereal, toast, fruit or juice and skim milk that gives kids a healthy start to their day. Leading health experts recommend that everyone over age two should watch their fat intake. So when you're recommending a healthy breakfast, remember Kellogg's® fat-free cereals—with their great taste, kids will look forward to breakfast.

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Clinical clues may indicate severe bronchiolitis:[1,2,3]

"Ill" or "toxic" appearance

O_2 saturation < 95%*

PaO_2 < 65 mmHg

Acidosis without respiratory compensation

Atelectasis on chest x-ray

Age < 3 months

Gestational age < 34 weeks

$PaCO_2$ rising level

Respiratory rate ≥ 70/minute

$AaDO_2$ ≥ 100 mmHg

*As determined by pulse oximetry.

Identify Patients with Severe Infections

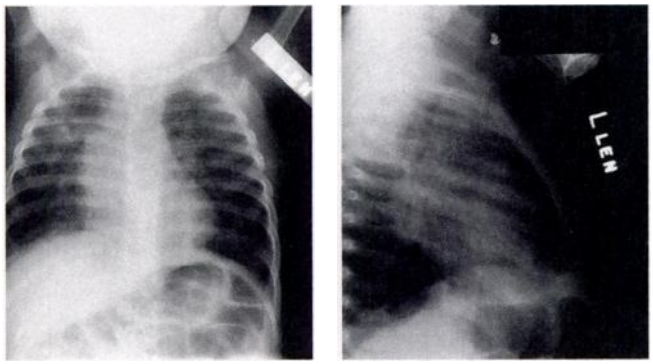
Smaller, Younger Patients–Higher Risk

How can you tell whether a patient with bronchiolitis has a severe infection and is at risk for clinical deterioration?

A recent study[1] was conducted during an RSV epidemic in Philadelphia. Two hundred thirteen infants with bronchiolitis were prospectively followed at the time of initial presentation to identify clues that would help predict disease severity.

The study identified six independent clinical and laboratory findings that were strongly associated with more severe illness: "ill" or "toxic" appearance; oxygen saturation less than 95% as determined by pulse oximetry; gestational age younger the 34 weeks; respiratory rate of 70/minute or greater; atelectasis on chest x-ray; and age younger than 3 months.

Radiographic Images of Severe RSV Infection



RSV-infected infant with bilateral infiltrates (A-P view and lateral view).

RSV–Induced Hypoxia

Hypoxemia resulting from severe bronchiolitis is caused by extensive airway obstruction. There are at least 3 major potential mechanisms for RSV-induced airway obstruction.

First, RSV infections are associated with increased edema of the airway walls causing luminal narrowing.

Second, airway obstruction can result from mucus accumulation and cell debris sloughed into the airways.

Third, irritation of inflamed airways caused by the RSV infections can induce airway smooth muscle contraction.

Treat the Infection–Not Just the Symptoms

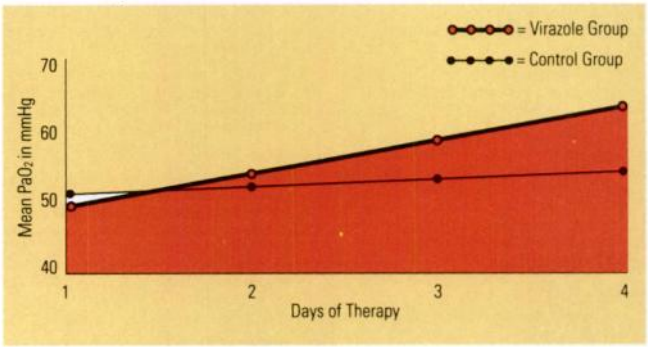
Until recently, physicians could only treat the symptoms of RSV-bronchiolitis. Supplemental oxygen and bronchodilators help control hypoxia, but they do not touch the underlying cause. Neither inhibit viral replication.

Now you can treat the infection–not just the symptoms.

Infants with lower respiratory tract RSV infection, who received Virazole, showed significant improvement in lower respiratory tract signs over untreated controls. Improvement was associated with better levels of arterial oxygen saturation and decreased viral shedding.[4]

"Five placebo-controlled, double-blind studies, each including approximately 30 subjects, have addressed the question of the effect of aerosolized ribavirin [Virazole] on the course of RSV lower respiratory infection. The fact that each was able to establish a beneficial effect despite the small number of subjects is convincing evidence that effect exists."[5]

Resolution of Hypoxia



Virazole significantly raised mean PaO_2.[4]

Accelerate Recovery with Virazole

Since 1986, Virazole has been helping infants with severe bronchiolitis due to RSV breath a little easier.

Studies have shown that Virazole significantly improves oxygen saturation. Early aggressive management of severe infections due to RSV in high-risk children is warranted because of the substantial morbidity in this patient population and the established safety pro-file of this drug.[4,5]

You can start treatment while awaiting rapid diagnostic test results.[6*]

Severe bronchiolitis can lead to serious complications. Treat severely-ill patients early with Virazole.

Virazole®
(ribavirin)

ICN®
ICN Pharmaceuticals Inc.

1. Shaw, KN et al. Outpatient assessment of infants with bronchiolitis. AJDC. February 1991;145:151-154.
2. Lebel, MH et al. Respiratory failure and mechanical ventilation in severe bronchiolitis. Archives of Diseases in Childhood. 1989;64:1431-1437.
3. Report of the Committee on Infectious Diseases, 22nd Ed. American Academy of Pediatrics. 1991;581.
4. Hall C. et al. Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection: A randomized double-blind study. New Eng J Med. 1983;308:1443-1447.
5. McBride, J. Study design considerations for ribavirin: efficacy studies. Ped. Infec. Disease. 1990;Vol. 9. No. 9 Suppl:S74-S78.
6. Virazole prescribing information, ICN Pharmaceuticals.
*Treatment should not be continued without documentation of RSV infection.

Virazole®
(ribavirin)
lyophilized for aerosol administration

Rapid Response. Rapid Recovery.

PRESCRIBING INFORMATION

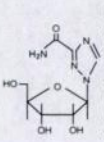
WARNING:
RIBAVIRIN AEROSOL SHOULD NOT BE USED FOR INFANTS REQUIRING ASSISTED VENTILATION BECAUSE PRECIPITATION OF THE DRUG IN THE RESPIRATORY EQUIPMENT MAY INTERFERE WITH SAFE AND EFFECTIVE VENTILATION OF THE PATIENT. Conditions for safe use with a ventilator are still in development.

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 appeares to produce sudden deterioration of respiratory function, treatment should be stopped and re-instituted only with extreme caution and continuous monitoring.

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 16 ug/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 1.55μM, with a mean concentration of 0.76μM. 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 14.3μM, with a mean concentration of 6.8μM.

It is likely that the concentration of ribavirin in respiratory tract secretions in 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 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 in 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 in 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 anti-metabolites 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 or 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 and 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 with 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 an 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 wide-mouth 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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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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Too soft for soap

Baby's skin needs superior mildness

Soaps are alkaline by nature. And alkaline cleansing can dry and irritate baby's delicate skin. This can contribute to diaper rash discomfort and exacerbate existing eczema or cradle cap. What baby needs is the mildness of Dove® Bar.

The non-soap Dove formula provides mildness superior to soap

Dove is unique. It has a non-soap surfactant that replaces soap's alkaline end group with a milder isethionyl radical. This results in a pH-neutral formulation with superior mildness. Dove also contains 1/4 moisturizing cream so baby's skin is softer and smoother than skin washed with soap.

Recommend Dove – because baby's skin is too soft for soap.

Dove is also available in a new liquid – Dove® Beauty Wash.

Beauty Bar and Beauty Wash
Available in original and Unscented.

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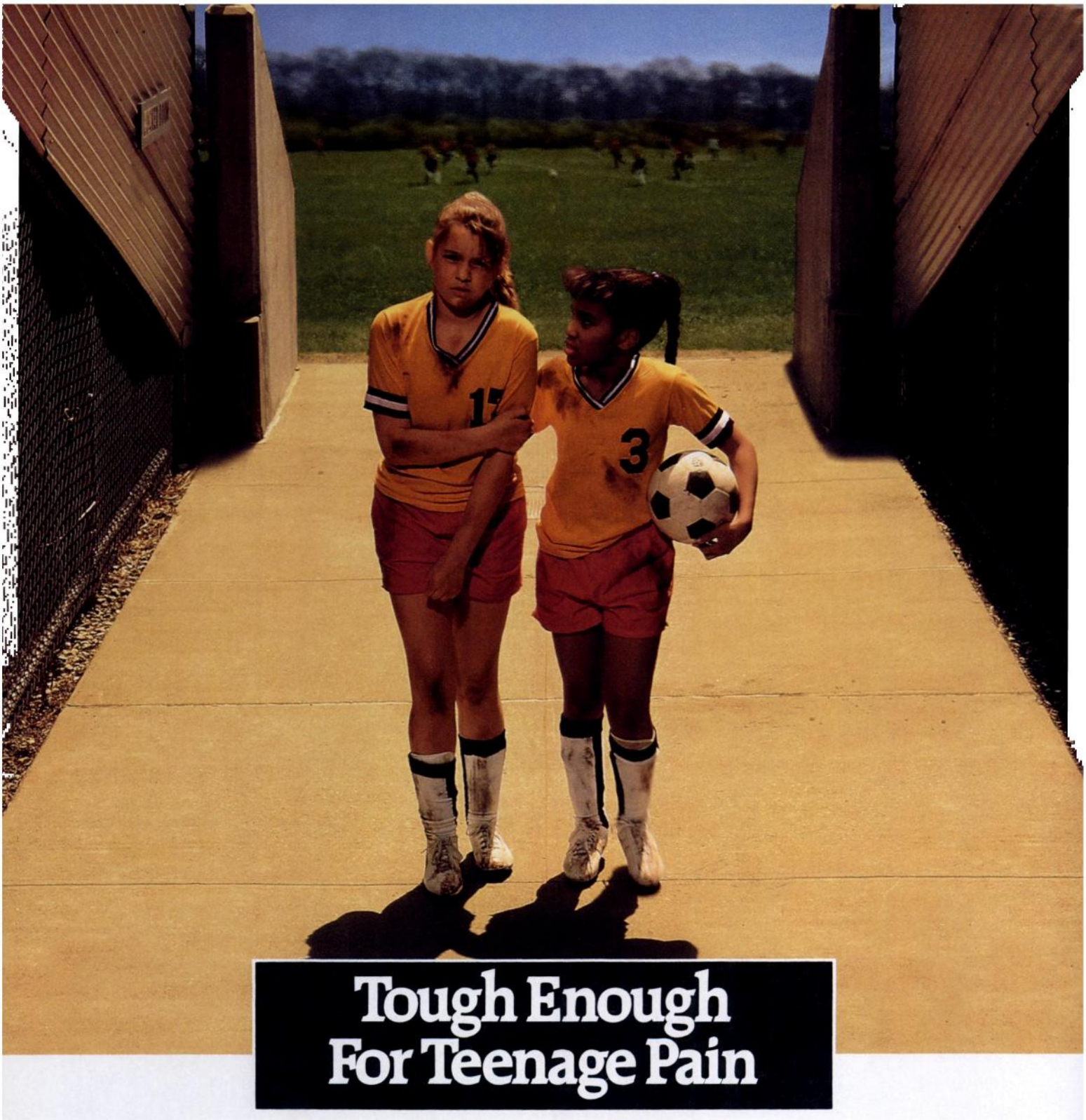
MILDER TO SKIN THAN SOAP



Pain from physical activity can be tough on teens. But 1000 mg of Extra Strength TYLENOL® is tough on mild-to-moderate pain.

1000 mg of Extra Strength TYLENOL® is as effective as 400 mg of ibuprofen for mild-to-moderate pain. It has a superior GI safety profile to OTC ibuprofen with no effect on hemostasis.[1] What's more, it's available in convenient, easy to swallow 500 mg Gelcaps and Caplets.

EXTRA STRENGTH
TYLENOL®
acetaminophen
500 mg GELCAPS

Tough On Pain, Not On The Patient

Reference: 1. Mielke CH Jr, et al. *JAMA*. 1976;235(6):613-616.

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McNEIL

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

Do not exceed eight Gelcaps or Caplets per 24-hour period. Acetaminophen in large overdoses can cause serious adverse effects. In the event of accidental overdose, contact a poison control center immediately. Consumer labeling states: Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a physician.

Pediatric Hematology—Oncology Fellowships At NIH.

The National Cancer Institute is one of fifteen institutes on the campus of the National Institutes of Health in Bethesda, Maryland. NIH provides the opportunity to work side-by-side with some of the most cited physicians and scientists in the world.

The NCI's Pediatric Hematology-Oncology Training Program is considering applications for three-year fellowships beginning in July 1994. Positions are available to physicians who have completed three years of training in Pediatrics.

This unique program consists of one year of primary clinical responsibility on the Pediatric Service of the National Cancer Institute, headed by Dr. Philip Pizzo. Rotations in pediatric hematology are coordinated with the NIH Clinical Center and affiliated area hospitals. The second and third years consist of an individualized program of laboratory research and clinical investigations.

Emphasis is placed on continuity of patient care, principles of patient management, and design and conduct of clinical trials. Seminars, lectures and conferences deal with a variety of related subjects including biostatistics, immunology, epidemiology, cell biology, cell kinetics, molecular biology, virology, genetics, clinical pharmacology, diagnostic pathology and radiobiology.

The laboratory aspects of the program are directed at training Fellows to become independent investigators. Topics under study include the cellular and molecular biology of pediatric tumors, clinical pharmacology, immunology, and the study of host defenses against infection. In addition, the Pediatric Branch has a program related to the treatment of children with symptomatic HIV infection. Fellows may also seek laboratory opportunities throughout the Division of Cancer Treatment. There are also ample opportunities for participation in clinical research topics.

Incoming Fellows may join the Commissioned Corps of the Public Health Service as Clinical Associates. The compensation package is evaluated on an individual basis and is comparable to an annual salary of approximately $38,500. Benefits include health care, life insurance options, vacation and sick leave. In addition, moving and travel expenses are available.

For further information and application procedures, please contact: Philip A. Pizzo, MD, Chief of Pediatrics, Head, Infectious Disease Section, National Cancer Institute. The deadline for applications is March 1, 1993.

National Cancer Institute

National Institutes of Health, Building 10, Room 13N240, Bethesda, Maryland 20892 · 301-496-4256

Equal Opportunity Employer

PITTSBURGH PROFESSOR SUES SCHOOL, NIH, TO BLOCK INQUIRY INTO LEAD-POISON STUDY

A University of Pittsburgh professor has sued the school and the National Institutes of Health, seeking to block an investigation of possible scientific misconduct in his landmark studies on lead poisoning.

The outcome of the legal challenge, brought in U.S. District Court in Pittsburgh by Herbert Needleman, could affect the future of environmental regulation and legislation concerning lead.

More broadly, attorneys say Dr. Needleman's lawsuit represents a new kind of threat to the government's expanding efforts to police scientific fraud. Dr. Needleman asked that the court treat his suit as a class action on behalf of all scientists under NIH investigation.

Scientists' Allegations

Acting at the request of NIH, Pitt is readying an investigation of Dr. Needleman's work in 1979 and 1990 studies of lead's effects on children's intelligence. The NIH and Pitt acted after two scientists familiar with the studies alleged that Dr. Needleman misrepresented data to support his conclusions. Dr. Needleman denies any misconduct and contends he is a victim of a lead industry campaign to discredit him.

Putka G. Pittsburgh professor sues School, NIH, to block inquiry into lead-poison study. *The Wall Street Journal*. April 2, 1992.

Noted by J.F.L., MD

ANNOUNCING
A NEW ORAL CEPHALOSPORIN

VANTIN™

Oral Suspension and Tablets

cefpodoxime proxetil

PREDICTABILITY

IN MILD TO MODERATE RESPIRATORY INFECTIONS

BROAD SPECTRUM

GRAM-POSITIVE AND GRAM-NEGATIVE COVERAGE

SAFETY

Please see brief summary of prescribing information on last page of this advertisement.

VANTIN™ = PR

Oral Suspension and Tablets

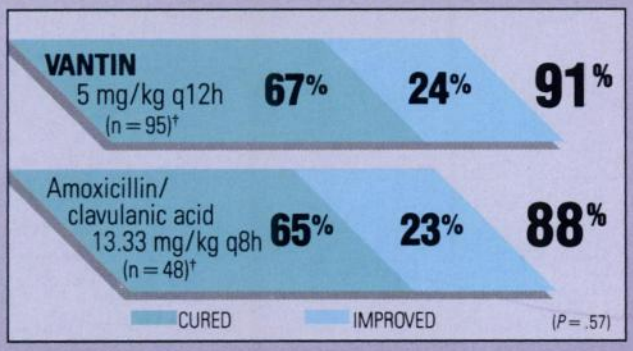
cefpodoxime proxetil

PREDICTABLE SUCCESS IN MILD TO

Proven clinical efficacy in acute otitis media

in children (aged 6 months through 12 years) caused by *Streptococcus pneumoniae, Haemophilus influenzae* (including ß-lactamase–producing strains), or *Moraxella (Branhamella) catarrhalis.*

END-OF-TREATMENT* CLINICAL SUCCESS RATE



*0 to 4 days after completing therapy.
†Evaluable patients.

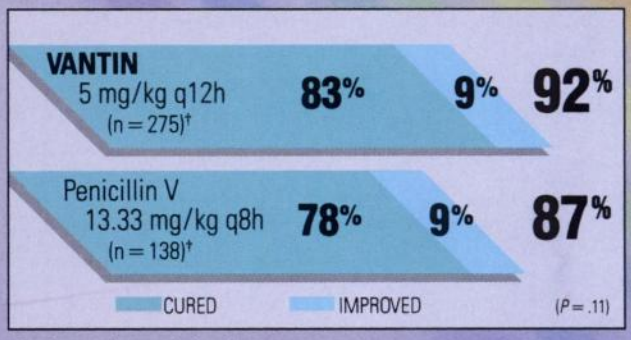
US investigator-blinded controlled trial[1]; clinical success defined as complete resolution or substantial improvement in signs and symptoms; treatment recommended for 10 days.

Proven clinical efficacy in pharyngitis/tonsillitis

in adults and children caused by *Streptococcus pyogenes.*

Note: Only penicillin by the intramuscular route of administration has been shown to be effective in the prophylaxis of rheumatic fever. Cefpodoxime proxetil is generally effective in the eradication of streptococci from the oropharynx. However, data establishing the efficacy of cefpodoxime proxetil for the prophylaxis of subsequent rheumatic fever are not available.

END-OF-TREATMENT* CLINICAL SUCCESS RATE



*3 to 8 days after completing therapy.
†Evaluable pediatric patients.

Two US multicenter investigator-blinded studies[1]; clinical success defined as complete resolution or substantial improvement in signs and symptoms; treatment recommended for 10 days.

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EDICTABILITY

MODERATE RESPIRATORY INFECTIONS

Safety documented in over 9,300 patients worldwide[1]

Diarrhea, the most frequent drug-related adverse reaction during clinical trials, was reported by approximately 7% of patients following multiple doses of tablets or oral suspension. *Clostridium difficile* organisms or toxin was reported in up to 10% of adult patients treated with **VANTIN** who had diarrhea; however, no specific diagnosis of pseudomembranous colitis was made in these patients. Other gastrointestinal complaints (nausea, abdominal pain, vomiting) were also reported. Less than 3% of patients treated with multiple doses of **VANTIN** Tablets discontinued treatment because of drug-related side effects.[1]

As with other cephalosporins, **VANTIN** should be used with caution in penicillin-sensitive patients because cross-hypersensitivity among β-lactam antibiotics may occur in up to 10% of penicillin-allergic patients.

Simple bid dosing schedule with two dosage forms

VANTIN has a simple bid dosing schedule and is available in both tablets (100 mg and 200 mg) and oral suspension (50 mg/5 mL and 100 mg/5 mL, in 100-mL bottles), which should be taken with food to enhance absorption. Recommended dosages, duration of therapy, and applicable patient populations vary among infections.

Available in a pleasant lemon creme–flavored oral suspension

IN OTITIS MEDIA • PHARYNGITIS/ TONSILLITIS*

NEW Vantin™ *Oral Suspension and Tablets*

*Caused by susceptible strains of designated microorganisms.

Please see brief summary of prescribing information on last page of this advertisement.

VANTIN™ = BR

Oral Suspension and Tablets

cefpodoxime proxetil

AN ORAL CEPHALOSPORIN WITH BROAD-SPECTRUM GRAM-POSITIVE AND GRAM-NEGATIVE COVERAGE

VANTIN combines gram-positive in vitro coverage against *Staphylococcus aureus* (including penicillinase-producing strains), *Staphylococcus saprophyticus, Streptococcus pneumoniae,* and *Streptococcus pyogenes...*

...with gram-negative in vitro activity against *Haemophilus influenzae* (including β-lactamase–producing strains), *Moraxella catarrhalis, Klebsiella pneumoniae, Escherichia coli, Proteus mirabilis,* and *Neisseria gonorrhoeae.*[1]

ROAD SPECTRUM

Broad in vitro activity against* ...gram-positive pathogens†

VANTIN MIC_{90} (μg/mL)

0.012	**0.05**	**3.13**
Streptococcus pyogenes (n = 33)	*Streptococcus pneumoniae* (n = 39)	*Staphylococcus aureus* (n = 68)

*In vitro activity may be used as a guide to initiate treatment; however, once bacteriologic results are available, antibiotic treatment should be adjusted accordingly.
†VANTIN is inactive against methicillin-resistant staphylococci and most strains of enterococcus.

...gram-negative pathogens*

VANTIN MIC_{90} (μg/mL)

≤0.06	**≤0.06**	**1.0**
Haemophilus influenzae (β-lactamase negative) (n = 24)	*Haemophilus influenzae* (β-lactamase positive) (n = 24)	*Moraxella catarrhalis* (n = 20)
0.25	**1.0**	**≤0.06**
Klebsiella spp† (n = 25)	*Escherichia coli* (n = 24)	*Proteus mirabilis* (n = 25)

*VANTIN is inactive against most strains of *Pseudomonas* and *Enterobacter.*
†Includes *Klebsiella oxytoca* (four strains; clinical effectiveness against this organism has not been established) and *K pneumoniae* (21 strains).

Highly stable in the presence of β-lactamase enzymes

To date, clinical effectiveness has been established in only a limited number of indications.

NEW Vantin™ *Oral Suspension and Tablets*

Please see brief summary of prescribing information on last page of this advertisement.

NEW Vantin™ Oral Suspension and Tablets

cefpodoxime proxetil

INDICATIONS AND USAGE
Mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below. **Recommended dosages, therapy durations, and applicable patient populations vary among these infections. See DOSAGE AND ADMINISTRATION for specific recommendations.**
LOWER RESPIRATORY TRACT
Acute, community-acquired pneumonia caused by *Streptococcus pneumoniae* or *Haemophilus influenzae* (non-β-lactamase-producing strains only). Data are insufficient at this time to establish efficacy in patients with pneumonia caused by β-lactamase-producing strains of *H influenzae*.
SEXUALLY TRANSMITTED DISEASES
Acute, uncomplicated urethral and cervical gonorrhea (men and women) caused by *Neisseria gonorrhoeae* (including penicillinase-producing strains).
Acute, uncomplicated anorectal infections in women caused by *N gonorrhoeae* (including penicillinase-producing strains). **Note:** The efficacy of VANTIN in treating male patients with rectal infections caused by *N gonorrhoeae* has not been established. Data do not support the use of VANTIN in the treatment of pharyngeal infections caused by *N gonorrhoeae* in men or women.
SKIN AND SKIN STRUCTURES
Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (including penicillinase-producing strains) or *Streptococcus pyogenes*. Abscesses should be surgically drained as clinically indicated. **Note:** In clinical trials, successful treatment of uncomplicated skin and skin structure infections was dose related. The effective therapeutic dose for skin infections was higher than that used in other recommended indications (see DOSAGE AND ADMINISTRATION).
UPPER RESPIRATORY TRACT
Acute otitis media caused by *S pneumoniae, H influenzae* (including β-lactamase-producing strains), or *Moraxella (Branhamella) catarrhalis*.
Pharyngitis and/or tonsillitis caused by *S pyogenes*. **Note:** Only penicillin by the intramuscular route of administration has been shown to be effective in the prophylaxis of rheumatic fever. VANTIN is generally effective in the eradication of streptococci from the oropharynx. However, data establishing the efficacy of VANTIN for the prophylaxis of subsequent rheumatic fever are not available.
URINARY TRACT
Uncomplicated urinary tract infections (cystitis) caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis*, or *Staphylococcus saprophyticus*. **Note:** In considering the use of VANTIN in the treatment of cystitis, the lower bacterial eradication rates of VANTIN should be weighed against the increased eradication rates and different safety profiles of some other classes of approved agents.
Adjust antimicrobial therapy accordingly once causative organism identification and susceptibility information becomes available.

CONTRAINDICATIONS
Known allergy to cefpodoxime or to cephalosporins.

WARNINGS
BEFORE STARTING THERAPY WITH *VANTIN*, CAREFULLY INQUIRE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFPODOXIME, OTHER CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. CROSS HYPERSENSITIVITY AMONG β-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO *VANTIN* OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINE, AND AIRWAY MANAGEMENT, IF INDICATED.
PSEUDOMEMBRANOUS COLITIS HAS BEEN REPORTED WITH NEARLY ALL ANTIBIOTICS, INCLUDING CEFPODOXIME, AND MAY RANGE FROM MILD TO LIFE THREATENING. THIS DIAGNOSIS MUST BE CONSIDERED IN PATIENTS WHO PRESENT WITH DIARRHEA SUBSEQUENT TO USE OF ANTIBACTERIAL AGENTS.
Observe extreme caution when using this product in patients at increased risk for antibiotic-induced pseudomembranous colitis because of exposure to institutional settings, such as nursing homes or hospitals with endemic *Clostridium difficile*.
VANTIN can alter normal colonic flora and may permit overgrowth of clostridia; a toxin produced by *C difficile* is the primary cause of "antibiotic-associated colitis." Initiate therapeutic measures once the diagnosis of pseudomembranous colitis has been established. Mild cases usually respond to drug discontinuation alone. Moderate to severe cases may require management with fluids and electrolytes, protein supplementation, and treatment with an oral antibiotic effective against *C difficile*.
C difficile organisms or toxin was reported in 10% of adult patients treated with VANTIN who had diarrhea; however, no specific diagnosis of pseudomembranous colitis was made. Postmarketing experience outside the United States includes reports of pseudomembranous colitis associated with use of VANTIN.

PRECAUTIONS
General Reduce total daily doses of VANTIN in patients with transient or persistent reduction in urinary output due to renal insufficiency because high and prolonged serum levels can occur following usual doses. Administer with caution to patients taking potent diuretics. Prolonged use may cause overgrowth of nonsusceptible organisms. Take appropriate measures if superinfection occurs during therapy.
Drug Interactions High doses of antacids or H_2 blockers reduce peak blood levels and extent of cefpodoxime absorption; rate of absorption is not altered. Oral anticholinergics delay peak blood levels but do not affect extent of absorption. Probenecid inhibits renal excretion of cefpodoxime, resulting in increased absorption and peak plasma levels of cefpodoxime. Closely monitor renal function when VANTIN is administered concomitantly with known nephrotoxic compounds.
Drug/Laboratory Test Interactions A positive direct Coombs' test may be induced.
Carcinogenesis, Mutagenesis, Fertility Impairment Long-term carcinogenesis studies have not been done. Mutagenesis studies were negative. No untoward effects on fertility or reproduction in rats.
Pregnancy-Teratogenic Effects: Pregnancy Category B Cefpodoxime proxetil was not teratogenic or embryocidal in rats or rabbits. However, no adequate and well-controlled studies have been done in pregnant women. Use VANTIN during pregnancy only if clearly needed.
Labor and Delivery Has not been studied; use only if clearly needed.
Nursing Mothers Cefpodoxime is excreted in human milk. Because of the potential for serious reactions in nursing infants, decide whether to discontinue nursing or discontinue drug, taking into account the importance of the drug to the mother.
Pediatric Use Safety and efficacy in infants less than 6 months old have not been established.
Geriatric Use There were no overall differences in effectiveness or safety between the elderly and younger patients. Plasma half-life was prolonged and urinary recovery reduced in healthy geriatric volunteers with normal renal function when compared with healthy young adults; other pharmacokinetic parameters were unchanged. Dosage adjustment in elderly patients with normal renal function is not necessary.

ADVERSE REACTIONS
Clinical Trials: The following adverse reactions were considered possibly or probably related to VANTIN:
Film-coated tablets (multiple dose): 3,144 patients. Incidence >1%: Diarrhea, 7.1% (diarrhea or loose stools were dose related, decreasing from 10.6% of patients who received 800 mg per day to 5.9% of those who received 200 mg per day; of patients with diarrhea, 10% had *C difficile* organism or toxin in the stool–see WARNINGS); nausea, 3.8%; vaginal fungal infections, 3.3%; abdominal pain, 1.6%; rash, 1.4%; headache, 1.1%; and vomiting, 1.1%. Incidence <1%: *Cardiovascular:* Chest pain, hypotension; *Dermatologic:* Fungal skin infection, skin scaling/peeling; *Endocrine:* Menstrual irregularity; *Genital:* Pruritus; *GI:* Flatulence, decreased salivation, candidiasis, pseudomembranous colitis; *Hypersensitivity:* Anaphylactic shock; *Metabolic:* Decreased appetite; *Miscellaneous:* Malaise, fever; *CNS:* Dizziness, fatigue, anxiety, insomnia, flushing, nightmares, weakness; *Respiratory:* Cough, epistaxis; and *Special senses:* Taste alteration, eye itching. Seventy-eight patients (2.4%) discontinued medication due to adverse events thought possibly or probably related to drug toxicity. Sixty-six (68%) of the 95 patients who discontinued therapy (regardless of relationship to therapy) did so because of GI disturbances, usually diarrhea. Significantly more patients discontinued drug because of adverse events at a dose of 800 mg daily than at a dose of 400 mg daily or at a dose of 200 mg daily.
Oral suspension (multiple dose): 758 patients (90% were less than 12 years old). Incidence >1%: Diarrhea, 7.0% (incidence ranged from 17.8% in infants and toddlers to 4.1% in 2- to 12-year-olds to 6.0% in adolescents); diaper rash, 3.5%; other skin rashes, 1.8%; and vomiting, 1.7%. Incidence <1%: *CNS:* Headache; *Dermatologic:* Exacerbation of acne; *Genital:* Pruritus or vaginitis; *GI:* Nausea, abdominal pain, candidiasis; *Metabolic:* Decreased appetite; and *Miscellaneous:* Fever. Seven patients (<1%) discontinued medication because of adverse events thought possibly or probably related to drug toxicity, primarily, for GI disturbances, usually diarrhea or diaper rashes.
Film-coated tablets (single dose): 509 patients. Incidence >1%: Nausea, 1.4%, and diarrhea, 1.2%. Incidence <1%: *CNS:* Dizziness, headache, syncope; *Dermatologic:* Rash; *Genital:* Vaginitis; *GI:* Abdominal pain; and *Psychiatric:* Anxiety.
Laboratory Changes The following significant laboratory changes were reported, without regard to drug relationship. Most were transient and not clinically significant.
Adults: *Hepatic:* Transient increases in AST (SGOT), ALT (SGPT), GGT, alkaline phosphatase, bilirubin, and LDH. *Hematologic:* Eosinophilia, leukocytosis, lymphocytosis, granulocytosis, basophilia, monocytosis, thrombocytosis, decreased hemoglobin, leukopenia, neutropenia, lymphocytopenia, thrombocytopenia, positive Coombs' test, and prolonged PT and PTT. *Serum Chemistry:* Increases in glucose; decreases in glucose, serum albumin, and serum total protein. *Renal:* Increases in BUN and creatinine.
Children: *Hematologic:* Agranulocytosis, pancytopenia, eosinophilia, decreased hemoglobin, and decreased hematocrit. *Hepatic:* Transient increases in ALT (SGPT).
Postmarketing Experience Serious adverse events outside the United States were pseudomembranous colitis, bloody diarrhea with abdominal pain, ulcerative colitis, rectorrhagia with hypotension, anaphylactic shock, acute liver injury, in utero exposure with miscarriage, purpuric nephritis, pulmonary infiltrate with eosinophilia, and eyelid dermatitis. One death was attributed to pseudomembranous colitis and disseminated intravascular coagulation.
Cephalosporin Class Labeling Other adverse reactions reported for cephalosporin class antibiotics are allergic reactions including Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, and hemorrhage. Several cephalosporins have triggered seizures, particularly in patients with renal impairment when dosage was not reduced (see DOSAGE AND ADMINISTRATION and OVERDOSAGE). If seizures associated with drug therapy occur, discontinue the drug; anticonvulsants may be indicated.

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

DOSAGE AND ADMINISTRATION
VANTIN should be given with food to enhance absorption.
Adults (aged 13 years and older), tablets or oral suspension
Acute community-acquired pneumonia: 200 mg q12h for 14 days.
Uncomplicated gonorrhea (men and women) and rectal gonococcal infections (women): single 200-mg dose.
Skin and skin structure: 400 mg q12h for 7 to 14 days.
Pharyngitis and/or tonsillitis: 100 mg q12h for 10 days.
Uncomplicated urinary tract infection: 100 mg q12h for 7 days.
Children (aged 6 months through 12 years)
Acute otitis media: 10 mg/kg/day divided q12h (maximum 400 mg/day) for 10 days.
Pharyngitis and/or tonsillitis: 10 mg/kg/day divided q12h (maximum 200 mg/day) for 10 days.
Patients with renal dysfunction See full prescribing information for dosing adjustments recommended for patients with severe renal impairment (<30 mL/min creatinine clearance) or maintained on hemodialysis.
Patients with cirrhosis Dosage adjustment is not necessary in cirrhotic patients, with or without ascites.

HOW SUPPLIED
VANTIN is available as 100-mg and 200-mg film-coated tablets and as flavored granules for oral suspension in 50 mg/5 mL and 100 mg/5 mL strengths in 100-mL bottles. Store tablets and unsuspended granules between 15°C and 30°C (59°F and 86°F). After mixing, store the suspension in a refrigerator, 2°C to 8°C (36°F to 46°F); discard unused portion after 14 days. For tablets and reconstituted suspension, keep container tightly closed. Protect unit-dose packs from excessive moisture.
Caution: Federal law prohibits dispensing without a prescription.
Licensed from Sankyo Company, Ltd, Japan, and manufactured by
Upjohn S.A., Puurs, Belgium, for The Upjohn Company
Kalamazoo, MI 49001, USA SB-1-S

Reference:
1. Data on file, The Upjohn Company, Kalamazoo, MI.

Upjohn USJ 7713.00
Printed in USA December 1992

ANNOUNCING
A NEW ORAL CEPHALOSPORIN

VANTIN™

Oral Suspension and Tablets

cefpodoxime proxetil

PREDICTABILITY

IN MILD TO MODERATE RESPIRATORY INFECTIONS

BROAD SPECTRUM

GRAM-POSITIVE AND GRAM-NEGATIVE COVERAGE

SAFETY

Please see brief summary of prescribing information on adjacent page.

PREDICTABLE SUCCESS IN MILD TO MODERATE RESPIRATORY INFECTIONS

Proven clinical efficacy[1] in

- **Acute community-acquired pneumonia** in adults (aged 13 years and older) caused by *Streptococcus pneumoniae* or *Haemophilus influenzae* (non–β-lactamase–producing strains only).

  Data are insufficient at this time to establish efficacy in patients with pneumonia caused by β-lactamase–producing strains of *H influenzae.*

- **Acute otitis media** in children (aged 6 months through 12 years) caused by *Streptococcus pneumoniae, Haemophilus influenzae* (including β-lactamase–producing strains), or *Moraxella (Branhamella) catarrhalis.*

- **Pharyngitis and/or tonsillitis** in adults and children caused by *Streptococcus pyogenes.*

  Note: Only penicillin by the intramuscular route of administration has been shown to be effective in the prophylaxis of rheumatic fever. Cefpodoxime proxetil is generally effective in the eradication of streptococci from the oropharynx. However, data establishing the efficacy of cefpodoxime proxetil for the prophylaxis of subsequent rheumatic fever are not available.

Safety documented in over 9,300 patients worldwide[1]

Diarrhea, the most frequent drug-related adverse reaction was reported by approximately 7% of patients following multiple doses of tablets or suspension. *Clostridium difficile* organisms or toxin was reported in up to 10% of adults who had diarrhea (patients were not diagnosed with pseudomembranous colitis).

Simple bid dosing schedule with two dosage forms

Available as tablets and a pleasant lemon creme–flavored oral suspension

NEW Vantin™ *Oral Suspension and Tablets*

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Please see brief summary of prescribing information on last page of this advertisement.

NEW Vantin™ Oral Suspension and Tablets

cefpodoxime proxetil

INDICATIONS AND USAGE

Mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below. **Recommended dosages, therapy durations, and applicable patient populations vary among these infections. See DOSAGE AND ADMINISTRATION for specific recommendations.**

LOWER RESPIRATORY TRACT

Acute, community-acquired pneumonia caused by *Streptococcus pneumoniae* or *Haemophilus influenzae* (non-β-lactamase-producing strains only). Data are insufficient at this time to establish efficacy in patients with pneumonia caused by β-lactamase-producing strains of *H influenzae*.

SEXUALLY TRANSMITTED DISEASES

Acute, uncomplicated urethral and cervical gonorrhea (men and women) caused by *Neisseria gonorrhoeae* (including penicillinase-producing strains).

Acute, uncomplicated anorectal infections in women caused by *N gonorrhoeae* (including penicillinase-producing strains). **Note:** The efficacy of VANTIN in treating male patients with rectal infections caused by *N gonorrhoeae* has not been established. Data do not support the use of VANTIN in the treatment of pharyngeal infections caused by *N gonorrhoeae* in men or women.

SKIN AND SKIN STRUCTURES

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (including penicillinase-producing strains) or *Streptococcus pyogenes*. Abscesses should be surgically drained as clinically indicated. **Note:** In clinical trials, successful treatment of uncomplicated skin and skin structure infections was dose related. The effective therapeutic dose for skin infections was higher than that used in other recommended indications (see DOSAGE AND ADMINISTRATION).

UPPER RESPIRATORY TRACT

Acute otitis media caused by *S pneumoniae*, *H influenzae* (including β-lactamase-producing strains), or *Moraxella (Branhamella) catarrhalis*.

Pharyngitis and/or tonsillitis caused by *S pyogenes*. **Note:** Only penicillin by the intramuscular route of administration has been shown to be effective in the prophylaxis of rheumatic fever. VANTIN is generally effective in the eradication of streptococci from the oropharynx. However, data establishing the efficacy of VANTIN for the prophylaxis of subsequent rheumatic fever are not available.

URINARY TRACT

Uncomplicated urinary tract infections (cystitis) caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, or *Staphylococcus saprophyticus*. **Note:** In considering the use of VANTIN in the treatment of cystitis, the lower bacterial eradication rates of VANTIN should be weighed against the increased eradication rates and different safety profiles of some other classes of approved agents.

Adjust antimicrobial therapy accordingly once causative organism identification and susceptibility information becomes available.

CONTRAINDICATIONS

Known allergy to cefpodoxime or to cephalosporins.

WARNINGS

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

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

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

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

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

PRECAUTIONS

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

Drug Interactions High doses of antacids or H_2 blockers reduce peak blood levels and extent of cefpodoxime absorption; rate of absorption is not altered. Oral anticholinergics delay peak blood levels but do not affect extent of absorption. Probenecid inhibits renal excretion of cefpodoxime, resulting in increased absorption and peak plasma levels of cefpodoxime. Closely monitor renal function when VANTIN is administered concomitantly with known nephrotoxic compounds.

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

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

Pregnancy-Teratogenic Effects: Pregnancy Category B Cefpodoxime proxetil was not teratogenic or embryocidal in rats or rabbits. However, no adequate and well-controlled studies have been done in pregnant women. Use VANTIN during pregnancy only if clearly needed.

Labor and Delivery Has not been studied; use only if clearly needed.

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

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

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

ADVERSE REACTIONS

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

Film-coated tablets (multiple dose): 3,144 patients. Incidence >1%: Diarrhea, 7.1% (diarrhea or loose stools were dose related, decreasing from 10.6% of patients who received 800 mg per day to 5.9% of those who received 200 mg per day; of patients with diarrhea, 10% had *C difficile* organism or toxin in the stool - see WARNINGS); nausea, 3.8%; vaginal fungal infections, 3.3%; abdominal pain, 1.6%; rash, 1.4%; headache, 1.1%; and vomiting, 1.1%. Incidence <1%: *Cardiovascular:* Chest pain, hypotension; *Dermatologic:* Fungal skin infection, skin scaling/peeling; *Endocrine:* Menstrual irregularity; *Genital:* Pruritus; *GI:* Flatulence, decreased salivation, candidiasis, pseudomembranous colitis; *Hypersensitivity:* Anaphylactic shock; *Metabolic:* Decreased appetite; *Miscellaneous:* Malaise, fever; *CNS:* Dizziness, fatigue, anxiety, insomnia, flushing, nightmares, weakness; *Respiratory:* Cough, epistaxis, and *Special senses:* Taste alteration, eye itching. Seventy-eight patients (2.4%) discontinued medication due to adverse events thought possibly or probably related to drug toxicity. Sixty-six (68%) of the 95 patients who discontinued therapy (regardless of relationship to therapy) did so because of GI disturbances, usually diarrhea. Significantly more patients discontinued drug because of adverse events at a dose of 800 mg daily than at a dose of 400 mg daily or at a dose of 200 mg daily.

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

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

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

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

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

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

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OVERDOSAGE

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DOSAGE AND ADMINISTRATION

VANTIN should be given with food to enhance absorption.

Adults (aged 13 years and older), tablets or oral suspension

Acute community-acquired pneumonia: 200 mg q12h for 14 days.

Uncomplicated gonorrhea (men and women) and rectal gonococcal infections (women): single 200-mg dose.

Skin and skin structure: 400 mg q12h for 7 to 14 days.

Pharyngitis and/or tonsillitis: 100 mg q12h for 10 days.

Uncomplicated urinary tract infection: 100 mg q12h for 7 days.

Children (aged 6 months through 12 years)

Acute otitis media: 10 mg/kg/day divided q12h (maximum 400 mg/day) for 10 days.

Pharyngitis and/or tonsillitis: 10 mg/kg/day divided q12h (maximum 200 mg/day) for 10 days.

Patients with renal dysfunction See full prescribing information for dosing adjustments recommended for patients with severe renal impairment (<30 mL/min creatinine clearance) or maintained on hemodialysis.

Patients with cirrhosis Dosage adjustment is not necessary in cirrhotic patients, with or without ascites.

HOW SUPPLIED

VANTIN is available as 100-mg and 200-mg film-coated tablets and as flavored granules for oral suspension in 50 mg/5 mL and 100 mg/5 mL strengths in 100-mL bottles. Store tablets and unsuspended granules between 15°C and 30°C (59°F and 86°F). After mixing, store the suspension in a refrigerator, 2°C to 8°C (36°F to 46°F); discard unused portion after 14 days. For tablets and reconstituted suspension, keep container tightly closed. Protect unit-dose packs from excessive moisture.

Caution: Federal law prohibits dispensing without a prescription.

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Upjohn S.A., Puurs, Belgium, for The Upjohn Company
Kalamazoo, MI 49001, USA

SB-1-S

Reference:

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

Upjohn
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Printed in USA

December 1992

Get *IN2IT!*

Quantities are limited. If you haven't already signed up to receive the American Academy of Pediatrics' new magazine for teens, now is your chance!

This magazine will be free to Academy members for distribution through your offices. We are currently planning a publication schedule of three times per year (spring/summer, fall and winter) with the premiere issue appearing in April 1993.

We are excited and enthusiastic about this project. *IN2IT* will cover a variety of topics that interest teens such as nutrition, sports, and developmental issues. It will also encourage teens to view the pediatrician as a resource for information on these vital issues.

If you are interested in distributing copies of this magazine, please fill out the order form below as soon as possible. You will be eligible to receive a maximum of 75 free copies three times per year, however, you can also subscribe in smaller quantities.

IN2IT will offer teens a chance to learn something about themselves and offers you an opportunity to make them aware of the pediatrician as their health care provider.

In order to receive your free copies of *IN2IT*, the AAP's new teen magazine, please complete this order form. Thanks for your support and interest in this project!

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Please send me _____ copies of *IN2IT* every four months.

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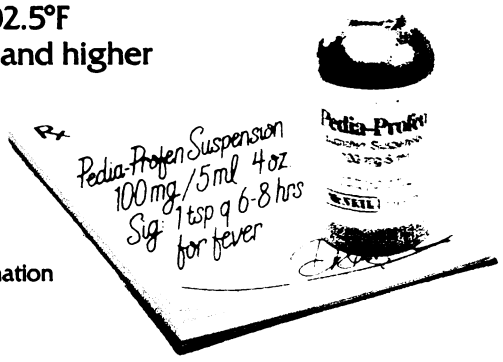
EXTENDED
FEVER RELIEF

Prescribe

Rx **Pedia-Profen®**
Ibuprofen Suspension
100 mg/5 ml

Provides 6 to 8 hours of fever relief[1]

- **Effective fever relief is achieved with 2 levels of dosing:**
  - — 5 mg/kg for fevers under 102.5°F
  - — 10 mg/kg for fevers 102.5°F and higher
- **Pleasant tasting and easy to swallow**



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

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

© McN, 1991

Reference: 1. Walson PD et al. Ibuprofen, acetaminophen and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17

Pedia-Profen®

Ibuprofen Suspension **100 mg/5 ml**

The following is a brief summary only. Before prescribing, see complete prescribing information in **Pedia-Profen** labeling.

INDICATIONS AND USAGE: Pedia-Profen is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

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

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

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

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

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

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

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

Patients on **Pedia-Profen** should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

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

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

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

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

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

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

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

Safety and efficacy of **Pedia-Profen** in children below the age of 6 months has not been established.

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

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

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

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

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

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

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

HOW SUPPLIED: Pedia-Profen Ibuprofen Suspension 100 mg/5 ml (teaspoon)—orange, berry-vanilla flavored

Bottles of 4 oz (120 ml) ..... NDC 0045-0469-04

Bottles of 16 oz (480 ml) ..... NDC 0045-0469-16

SHAKE WELL BEFORE USING. Store at room temperature.

Caution: Federal law prohibits dispensing without prescription.

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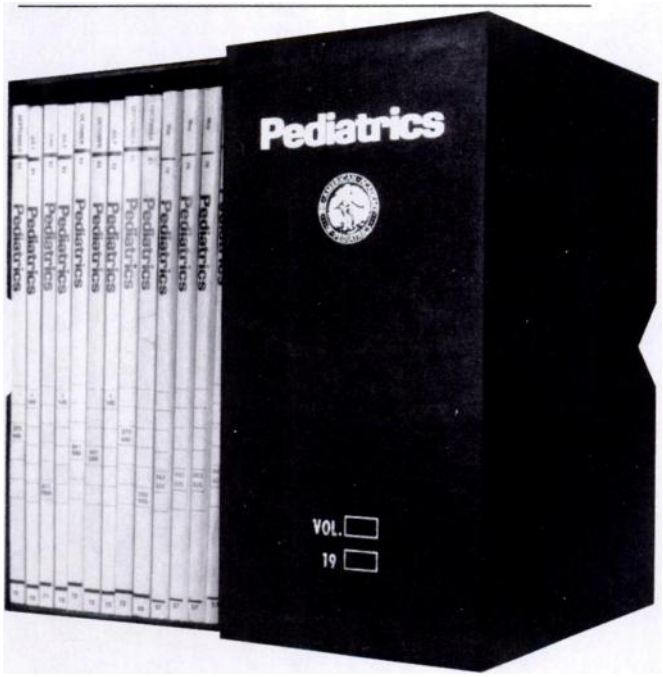

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NOTICE REGARDING THE AMERICAN ACADEMY OF PEDIATRICS (AAP) PRACTITIONER RESEARCH AWARD 1993

The Practitioner Research Award was established to provide suitable recognition to a full-time practitioner responsible for a major advance in pediatrics.

With this notice we are inviting the nominations of candidates for the Practitioner Research Award. We will present this award at the October 1993 annual meeting of the AAP.

The Practitioner Research Award provides an honorarium of $1,500. The award also includes round trip tourist class airfare, two days lodging, plus all actual expenses incidental to attending the meeting.

Criteria for receipt of the award are as follows:

- The candidate should have spent at least 80% of his/her time in patient care in a nonacademic practice at the time of research.
- Research must be done in an office setting and priority will be given to general pediatricians.
- The research initiated and conducted by the awardee must have been published in peer-reviewed publications.
- The candidate should be a fellow of the Academy and living when selected.

The award is not intended for a group or a practice but for an individual fellow.

Nominations for the AAP Practitioner Research Award will be solicited up to January 29, 1993. Separate letters should be written for each nomination. The letter should briefly state the work for which the award might be granted and should include the candidate's curriculum vitae as well as one copy of at least one but no more than *five* different reprints representing the candidate's work. The emphasis of the award is on quality, not quantity. If a critical paper is in press, a copy of the manuscript should be included. Sponsoring letters are encouraged but not required. These letters should be sent to the person making the nomination, who will then forward them to this office.

Address all nominations to Donna Worthington, Administrative Assistant, Department of Research, American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois 60007, who will in turn submit them to the Council on Pediatric Research Selection Committee.

Please share this announcement with any pediatric department heads and other fellows of the Academy who you feel are in a good position to identify candidates for this award.

For further information contact Donna Worthington at 1-800-433-9016.

A Balance of Protection and Purity

Artist's interpretation of the shapes of filamentous hemagglutinin (the rod) and pertussis toxoid (the sphere), as shown on an electron micrograph.

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Manufactured by:

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LABORATORIES, INC.
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NEW

Tripedia™

(Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed)

FOR CHILDREN 15 MONTHS TO THE SEVENTH BIRTHDAY

Protection and Purity

A unique balance of purified pertussis antigens

Fully dedicated to immunotechnology, Connaught Laboratories, Inc. combines quality vaccine protection with purity in new acellular Tripedia™. The pertussis component is composed of two highly purified pertussis antigens, pertussis toxoid* and filamentous hemagglutinin (FHA).[1] In addition, Tripedia is the only licensed acellular DTP vaccine to provide these antigens in a 1:1 ratio.[1]

Protection and Purity

A significantly reduced risk of adverse reactions

Tripedia substantially reduces the risk of certain adverse reactions as shown in controlled clinical trials comparing acellular Tripedia with whole-cell DTP vaccine when given as the fourth dose to children at 15-20 months and as a fifth dose at 4-6 years of age. The results of these studies demonstrated that Tripedia was associated with two to three times fewer local reactions (including tenderness, erythema and swelling) and three to five times fewer systemic reactions.[1†‡]

Protection and Purity

A high level of immunogenicity

In the same clinical trials described above, new acellular Tripedia provided high levels of antibodies to pertussis toxin and filamentous hemagglutinin, as well as to diphtheria and tetanus, when given as the fourth dose to children at 15-20 months and as a fifth dose at 4-6 years of age.[1†‡]

Tripedia...

Enhancing vaccine purity through acellular technology

*Pertussis Toxoid = Inactivated Lymphocytosis Promoting Factor (LPF).

†All children in the 15-20 month group received whole-cell DTP vaccine for their first three doses.

‡All children in the 4-6 year group received whole-cell DTP vaccine for their four doses.

Reference: 1. Data on file, Connaught Laboratories, Inc.

Tripedia is indicated for the fourth-dose immunization in children at 15 months and for fifth-dose immunization in children at 4-6 years of age (up to the seventh birthday).
Before administering Tripedia, please read the Contraindications, Warnings, Precautions and Adverse Reactions sections of the summary of Prescribing Information.

DIPHTHERIA AND TETANUS TOXOIDS AND ACELLULAR PERTUSSIS VACCINE ADSORBED

Tripedia™

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

DESCRIPTION

Tripedia™, Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, for intramuscular use, is a sterile solution of diphtheria and tetanus toxoids adsorbed, with acellular pertussis vaccine in an isotonic sodium chloride solution containing thimerosal as a preservative and sodium phosphate to control pH. After shaking, the vaccine is a homogeneous white suspension. The acellular pertussis vaccine components are isolated from culture fluids of Phase 1 *Bordetella pertussis* grown in a modified Stainer-Scholte medium.[1] After purification by salt precipitation, ultracentrifugation, and ultrafiltration, pertussis toxin (PT) and filamentous hemagglutinin (FHA) are combined to obtain a 1:1 ratio and treated with formaldehyde to inactivate PT. Thimerosal (mercury derivative) 1:10,000 is added as a preservative.

Corynebacterium diphtheriae cultures are grown in a modified Mueller and Miller medium. *Clostridium tetani* cultures are grown in a peptone based medium. Both toxins are detoxified with formaldehyde. The detoxified materials are then separately purified by serial ammonium sulfate fractionation and diafiltration.

The toxoids are adsorbed using aluminum potassium sulfate (alum). The adsorbed diphtheria and tetanus toxoids are combined with acellular pertussis concentrate, and diluted to a final volume using sterile phosphate-buffered physiological saline. Thimerosal (mercury derivative) 1:10,000 is added as a preservative. Each 0.5 mL dose contains, by assay, not more than 0.170 mg of aluminum and not more than 100 µg (0.02%) of residual formaldehyde. The vaccine contains gelatin and polysorbate 80 (Tween-80) which are used in the production of the pertussis concentrate.

Each 0.5 mL dose is formulated to contain 6.7 Lf units of diphtheria toxoid and 5 Lf units of tetanus toxoid (both toxoids induce at least 2 units of antitoxin per mL in the guinea pig potency test), and 46.8 µg of pertussis antigens. This is represented in the final vaccine as 23.4 µg of inactivated pertussis toxin (PT - also referred to as lymphocytosis promoting factor or LPF) and 23.4 µg of filamentous hemagglutinin antigen (FHA).

The potency of the pertussis component is evaluated by measurement, using an ELISA system, of the antibody response to PT and FHA in immunized mice.

Acellular Pertussis Vaccine Concentrate (For Further Manufacturing Use) is produced by The Research Foundation for Microbial Diseases of Osaka University ("BIKEN®"), Osaka, Japan under U.S. license, and is combined with diphtheria and tetanus toxoids manufactured by Connaught Laboratories, Inc. The bulk vaccine is prepared by Connaught Laboratories, Inc. Tripedia is filled, labeled, packaged, and released by Connaught Laboratories, Inc. (CLI).

CLINICAL PHARMACOLOGY

Simultaneous immunization against diphtheria, tetanus, and pertussis, using a conventional "whole-cell" pertussis DTP vaccine (Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed - For Pediatric Use), has been a routine practice during infancy and childhood in the United States since the late 1940s. This practice has played a major role in markedly reducing the incidence rates of cases and deaths from each of these diseases.[2]

Tripedia (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) combines Connaught Laboratories, Inc. diphtheria and tetanus toxoids with purified pertussis antigens (inactivated PT and FHA). These pertussis antigens, produced by The Research Foundation for Microbial Diseases of Osaka University ("BIKEN®"), have been used routinely in Japan for approximately ten years[3,4,5,6] and have been under investigational use in Sweden,[1,7,8,9,10] as well as in the United States.[11,12,13,14]

DIPHTHERIA

Corynebacterium diphtheriae may cause both localized and generalized disease. The systemic intoxication is caused by diphtheria exotoxin, an extracellular protein metabolite of toxigenic strains of *C. diphtheriae*. Protection against disease is due to the development of antibody to diphtheria toxin.

At one time, diphtheria was common in the United States. More than 200,000 cases, primarily among children, were reported in 1921. Approximately 5% to 10% of cases were fatal; the highest case-fatality rates were in the very young and the elderly. Reported cases of diphtheria of all types declined from 306 in 1975 to 59 in 1979; most were cutaneous diphtheria reported from a single state. After 1979, cutaneous diphtheria was no longer reportable.[2] From 1980 to 1986, only 18 cases of respiratory diphtheria were reported in the United States; 14 occurred among persons 15 years of age or older.[15,16]

Diphtheria is currently a rare disease in the United States primarily because of the high level of appropriate vaccination among children (97% of children entering school have received ≥three doses of diphtheria and tetanus toxoids and pertussis vaccine adsorbed [DTP]) and because of an apparent reduction in the circulation of toxigenic strains of *Corynebacterium diphtheriae*.[2] Most cases occur among unvaccinated or inadequately vaccinated persons.[2]

Both toxigenic and nontoxigenic strains of *C. diphtheriae* can cause disease, but only strains that produce diphtheria toxin cause severe manifestations, such as myocarditis and neuritis. Diphtheria remains a serious disease, with the highest case-fatality rates among infants and the elderly.[2]

Complete immunization significantly reduces the risk of developing diphtheria, and immunized persons who develop disease have milder illness. Protection is thought to last at least 10 years. Immunization does not, however, eliminate carriage of *C. diphtheriae* in the pharynx or nose or on the skin.[2]

The efficacy of the CLI's diphtheria toxoid used in Tripedia was determined on the basis of immunogenicity studies, with a comparison to a serological correlate of protection (0.01 antitoxin units/mL) established by the Panel on Review of Bacterial Vaccines & Toxoids.[17]

TETANUS

Tetanus is an intoxication manifested primarily by neuromuscular dysfunction caused by a potent exotoxin elaborated by *Clostridium tetani*.

The occurrence of tetanus in the United States has decreased dramatically from 560 reported cases in 1947 to a record low of 48 reported cases in 1987. Tetanus in the United States is primarily a disease of older adults. Of 99 tetanus patients with complete information reported to the Centers for Disease Control (CDC) during 1987 and 1988, 68% were ≥50 years of age, while only six were <20 years of age. Overall, the case-fatality rate was 21%. The disease continues to occur almost exclusively among persons who are unvaccinated or inadequately vaccinated or whose vaccination histories are unknown or uncertain.[2]

In 4% of tetanus cases reported during 1987 and 1988, no wound or other condition was implicated. Non-acute skin lesions, such as ulcers, or medical conditions, such as abscesses, were reported in 14% of cases.[2]

Spores of *C. tetani* are ubiquitous. Serological tests indicate that naturally acquired immunity to tetanus toxin does not occur in the United States. Thus, universal primary immunization, with subsequent maintenance of adequate antitoxin levels by means of appropriately timed boosters, is necessary to protect all age groups. Tetanus toxoid is a highly effective antigen, and a completed primary series generally induces protective levels of serum antitoxin that persist for 10 or more years.[2]

The efficacy of the CLI's tetanus toxoid used in Tripedia was determined on the basis of immunogenicity studies with a comparison to a serological correlate of protection (0.01 antitoxin units/mL) established by the Panel on Review of Bacterial Vaccines & Toxoids.[17]

PERTUSSIS

Pertussis (whooping cough) is a disease of the respiratory tract caused by *Bordetella pertussis*. This gram-negative coccobacillus produces a variety of biologically active components. One of these components, pertussis toxin (PT), has been associated with a number of effects such as lymphocytosis, leukocytosis, sensitivity to histamine, changes in glucose and/or insulin levels, neurological effects, and adjuvant activity.[18] The role of the different components produced by *B. pertussis* in either the pathogenesis of, or the immunity to, pertussis is not well understood. Immunization with vaccines containing inactivated PT and filamentous hemagglutinin (FHA), have been associated with protection in clinical studies. The pertussis component in Tripedia induces immunity against pertussis.[8] The acellular pertussis component, in Tripedia, contains not more than 50 endotoxin units/mL.

Pertussis is highly communicable (attack rates of >90% have been reported among unvaccinated household contacts)[19] and can cause severe disease, particularly among very young children. Of 10,749 patients <1 year of age reported nationally as having pertussis during the period 1980 to 1989, 69% were hospitalized, 22% had pneumonia, 3.0% had ≥one seizure, 0.9% had encephalopathy, and 0.6% died.[20] Because of the substantial risks of complications of the disease, completion of a primary series of DTP vaccine early in life is essential.[2]

In older children and adults, including in some instances those previously immunized, infection may result in nonspecific symptoms of bronchitis or an upper respiratory tract infection, and pertussis may not be diagnosed because classic signs, especially the inspiratory whoop, may be absent. Older preschool-aged children and school-aged siblings who are not fully immunized and develop pertussis can be important sources of infection for young infants, the group at highest risk of disease and disease severity.[2] The infected adult is important in the overall transmission of pertussis.[21,22]

General use of whole-cell pertussis DTP vaccines has resulted in a substantial reduction in cases and deaths from pertussis disease.[23,24] The use of Tripedia as the fourth or fifth dose evokes an antibody response at least as great as Connaught's whole-cell pertussis DTP vaccine following a primary series with commercially available U.S. whole-cell pertussis DTP with respect to PT and FHA antibodies.[11,12]

Acellular pertussis vaccines have been used in Japan since 1981, mostly in 2-year-old children. Evidence for the efficacy of these vaccines, as a group, is demonstrated by the decline in pertussis disease with their routine use in that country.[3,25] In addition, a review of epidemiological studies of the Japanese acellular pertussis vaccines estimated that these vaccines, as a group, were 88% efficacious in protecting against clinical pertussis on household exposure, with a 95% confidence interval of 79% to 93%.[25]

A large placebo-controlled efficacy trial of two BIKEN acellular pertussis vaccines was carried out in Sweden in 1986-1987. One of the vaccines contained a BIKEN two-component acellular pertussis vaccine comparable to that contained in Tripedia. In its first phase, the trial in Sweden was a randomized, blinded prospective trial using a standardized case definition and active case ascertainment. In this phase, 1,389 children, 5 to 11 months of age, received two doses of the BIKEN inactivated PT/FHA acellular pertussis vaccine 7 to 13 weeks apart and 954 received a placebo control. During the 15 months of follow-up from 30 days after the second dose, culture-confirmed whooping cough (cough and a positive culture of *Bordetella pertussis*) occurred in 40 placebo and 18 acellular pertussis vaccine recipients. The point estimate of protective efficacy for the vaccine was 69% (95% confidence interval; 47% to 82%) for all cases of culture-confirmed pertussis and 80% (95% confidence interval; 59% to 91%) for culture confirmed cases with cough of over 30 days duration.[9]

A three-year unblinded passive follow-up of vaccine and placebo recipients from the above Swedish study has shown a post-trial efficacy of 77% (95% confidence interval; 65% to 85%) for all culture-proven cases of pertussis, and an efficacy of 92% (95% confidence interval; 84% to 96%) for culture-proven cases with a cough of over 30 days duration.[26]

Anti-PT and anti-FHA antibody responses in children enrolled in the trial in Sweden were subsequently compared to responses observed in clinical trials of Tripedia conducted in the U.S. In the U.S. trials, children 15 to 20 months of age who had previously received three doses of licensed whole-cell pertussis DTP and children 4 to 6 years of age who had previously received four doses of licensed whole-cell pertussis DTP were immunized with a single dose of Tripedia. The anti-PT and anti-FHA antibody responses to Tripedia in the U.S. trials were found to be similar to the responses observed in children enrolled in the trial in Sweden.[1] Although in the Swedish efficacy trial immunization with an inactivated PT/FHA vaccine was shown to protect against pertussis, no specific serological correlate or measure of protective immune response was found.[1,9] The role in clinical protection of specific serum antibodies is, therefore, not known at this time.

Additionally, the antibody responses in children immunized with Tripedia were compared to those in children immunized with CLI's licensed whole-cell pertussis DTP vaccine. Immunogenicity data from the clinical trials in the U.S. are summarized in Table 1. Anti-PT and anti-FHA responses to Tripedia were significantly higher than those to CLI's whole-cell pertussis DTP vaccine. Serological responses to diphtheria and tetanus antigens, not shown in Table 1, were equal to or greater than those produced by CLI's whole-cell pertussis DTP vaccine.[11,12]

Clinical experience (immunogenicity) in the United States is summarized in TABLE 1.[11,12]

TABLE 1.[11,12] COMPARISON OF IgG ANTIBODY TO PT AND FHA IN ELISA UNITS (EU) AND CHO-CELL NEUTRALIZATION TITERS (CHO) INDUCED BY A SINGLE DOSE OF EITHER TRIPEDIA OR CLI'S WHOLE-CELL PERTUSSIS DTP VACCINE IN CHILDREN 15 TO 20 MONTHS OF AGE* AND 4 TO 6 YEARS OF AGE

	AGE GROUP (n=)	PT/GMT† (EU)		FHA/GMT† (EU)		CHO	
		Pre-Vaccination	Post-Vaccination‡	Pre-Vaccination	Post-Vaccination‡	Pre-Vaccination	Post-Vaccination‡
Tripedia	15-20 Months (354)	14.5	443.0§	7.0	65.0§	25.3	300§
CLI's Whole-Cell DTP	15-20 Months (175)	14.5	67.0	6.0	19.0	24.8	119
Tripedia	4-6 Years (211)	14.5	408.0§	18.9	362.0§	23.6	210¶
CLI's Whole-Cell DTP	4-6 Years (65)	15.2	81.0	19.2	104.0	27.9	107

* All children in the 15- to 20-month group received U.S. licensed whole-cell pertussis DTP vaccine for the first three doses of their primary series.

** All children in the 4- to 6-year group received U.S. licensed whole-cell pertussis DTP vaccine for the first four doses in their primary series.

† Geometric mean titer.

‡ Post-vaccination 4 to 6 weeks.

¶ Post-vaccination GMT for the Tripedia group, (4 to 6 year olds), is significantly higher than that of the whole-cell pertussis DTP vaccine group (P<0.05).

§ Post-vaccination GMT's for the Tripedia group, at 15 to 20 months and at 4 to 6 years, are significantly higher than those of the matching whole-cell DTP group, (P<0.001 in each case).

A total of 3,700 doses of Tripedia have been administered in U.S. clinical trials, in children 15-20 months of age and 4-6 years of age. When compared to CLI's whole-cell pertussis DTP vaccine, Tripedia produced fewer and milder local reactions such as erythema, swelling, and tenderness at the injection site; as well as fewer and milder systemic reactions such as fever, irritability, drowsiness, vomiting, anorexia and high-pitched unusual cry.[1] Rates of more serious and infrequent adverse experiences for Tripedia are not known at this time.

INDICATIONS AND USAGE

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Tripedia, is indicated as a fourth and/or fifth dose for immunization of children 15 months to 7 years of age (prior to seventh birthday) who have previously been immunized against diphtheria, tetanus and pertussis with three or four doses of whole-cell pertussis DTP vaccine. However, in instances where the pertussis vaccine component is contraindicated, Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) (DT) should be used for each of the remaining doses.

If passive immunization is required, Tetanus Immune Globulin (Human) (TIG) and/or equine Diphtheria Antitoxin should be used.

Persons recovering from confirmed pertussis do not need additional doses of DTP but should receive additional doses of DT to complete the series.

Tripedia is not to be used for treatment of actual infection.

As with any vaccine, vaccination with Tripedia may not protect 100% of susceptible individuals.

THIS VACCINE IS NOT RECOMMENDED FOR USE IN CHILDREN BELOW THE AGE OF 15 MONTHS. THIS VACCINE IS NOT RECOMMENDED FOR USE AS A PRIMARY SERIES IN CHILDREN OF ANY AGE.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including thimerosal, a mercury derivative, is a contraindication.

Immunization should be deferred during the course of any febrile illness or acute infection. A minor afebrile illness such as a mild upper respiratory infection is not usually reason to defer immunization.

Elective immunization procedures should be deferred during an outbreak of poliomyelitis.[27]

Data on the use of Tripedia in children for whom whole-cell pertussis DTP vaccine is contraindicated are not available. Until such data are available, it would be prudent to consider the Immunization Practices Advisory Committee (ACIP) and American Academy of Pediatrics (AAP) contraindications to whole-cell pertussis DTP vaccine to be contraindications to Tripedia.

Immunization with Tripedia is contraindicated if the child has experienced any event following previous immunization with pertussis vaccine (whole-cell DTP or acellular pertussis-containing DTP vaccine), which is considered by the ACIP or AAP to be a contraindication to further doses of pertussis vaccine. The ACIP states that if any of the following events listed in Table 2 occur in temporal relation to receipt of DTP, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered.

It is a contraindication to use this or any other vaccine after a serious adverse reaction temporally associated with a previous dose, including an anaphylactic reaction.[2]

Encephalopathy not due to an identifiable cause, occurring within 7 days of a prior whole-cell pertussis DTP or acellular pertussis DTP immunization and consisting of major alterations of consciousness, unresponsiveness, generalized or focal seizures that persist for more than a few hours and failure to recover within 24 hours should be considered a contraindication to further use; this includes severe alterations in consciousness with generalized or focal neurologic signs. Even though causation cannot be established, no subsequent doses should be given.[2]

WARNINGS

This vaccine is not recommended for use in children below the age of 15 months. Efficacy data for Tripedia in infants is not available. Although antibody responses to diphtheria, tetanus, and pertussis toxin, and FHA in infants immunized with Tripedia were at least equivalent to those for CLI's whole-cell pertussis DTP vaccine, the role of serum antibodies in protection against pertussis is unknown.

Tripedia is not recommended for immunization on or after the seventh birthday.

If any of the following events occur in temporal relation to receipt of DTP, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered. There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks, particularly since these events are not associated with permanent sequelae.[2]

THE FOLLOWING EVENTS WERE PREVIOUSLY CONSIDERED CONTRAINDICATIONS AND ARE NOW CONSIDERED PRECAUTIONS BY THE ACIP:[2]

Temperature of ≥40.5°C (105°F) within 48 hours not due to another identifiable cause. Such a temperature is considered a precaution because of the likelihood that fever following a subsequent dose of DTP vaccine also will be high. Because such febrile reactions are usually attributed to the pertussis component, vaccination with DT should not be discontinued.[2]

Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours. Although these uncommon events have not been recognized to cause death nor to induce permanent neurological sequelae, it is prudent to continue vaccination with DT, omitting the pertussis component.[2]

Persistent, inconsolable crying lasting ≥3 hours, occurring within 48 hours of vaccination. Follow-up of infants who have cried inconsolably following DTP vaccination has indicated that this reaction, though unpleasant, is without long-term sequelae and not associated with other reactions of greater significance. Inconsolable crying occurs most frequently following the first dose and is less frequently reported following subsequent doses of DTP vaccine.[2]

Convulsions with or without fever occurring within three days. Short-lived convulsions, with or without fever, have not been shown to cause permanent sequelae. Furthermore, the occurrence of prolonged febrile seizures (i.e., status epilepticus - any seizure lasting >30 minutes or recurrent seizures lasting a total of 30 minutes without the child fully regaining consciousness), irrespective of their cause, involving an otherwise normal child does not substantially increase the risk for subsequent febrile (brief or prolonged) or afebrile seizures. The risk is significantly increased only among those children who are neurologically abnormal before their episode of status epilepticus.[2]

Tripedia should not be given to children with any coagulation disorder, including thrombocytopenia, that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.

In the opinion of the manufacturer, use of this vaccine is also contraindicated if the child, siblings, or parents have a history of a seizure disorder. Recent studies suggest that infants and children with a history of convulsions in first-degree family members (i.e., siblings and parents) have a 3.2-fold increased risk for neurologic events compared with those without such histories.[28,29]

However, the ACIP has concluded that a family history of convulsions in parents and siblings is not a contraindication to pertussis vaccination and that children with such family histories should receive pertussis vaccine according to the recommended schedule.[2,23,28]

Acetaminophen should be given at the time of DTP vaccination and every four hours for 24 hours to reduce the possibility of post-vaccination fever.[2]

Studies have failed to provide evidence to support a causal relation between DTP vaccination and either serious acute neurologic illness or permanent neurologic injury.[2]

Infants and children with recognized possible or potential underlying neurologic conditions seem to be at enhanced risk for the appearance of manifestations of the underlying neurologic disorder within two or three days following vaccination. Whether to administer DTP (or Tripedia) to children with proven or suspected underlying neurologic disorders must be decided on an individual basis. Important considerations include the current local incidence of pertussis, the near absence of diphtheria in the United States and the low risk of infection with *C. tetani*.[2]

Only full doses (0.5 mL) of DTP (or Tripedia) vaccine should be given; if a specific contraindication to DTP exists, the vaccine should not be given.[2]

Controversy regarding the safety of pertussis vaccine during the 1970s led to several studies of the benefits and risks of this vaccination during the 1980s. These epidemiologic analyses clearly indicate that the benefits of the pertussis immunization program outweigh the risks.[2,30]

PRECAUTIONS

GENERAL

Care is to be taken by the health-care provider for the safe and effective use of this vaccine.

EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ACUTE ANAPHYLACTIC REACTION OCCUR DUE TO ANY COMPONENT OF THE VACCINE.

Previous immunization history should be ascertained to confirm that at least three doses of whole-cell pertussis DTP vaccine have been given.

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible sensitivity and any previous adverse reactions to the vaccine or similar vaccines, previous immunization history, current health status (see **CONTRAINDICATIONS** section), and a current knowledge of the literature concerning the use of the vaccine under consideration. Immunosuppressed patients may not respond. Tripedia is not contraindicated

based on the presence of HIV infection.[7]

TABLE 2.[1] Contraindications and Precautions to Further DTP (or acellular pertussis) Vaccination

Contraindications
An immediate anaphylactic reaction.
Encephalopathy occurring within 7 days following DTP (or acellular pertussis) vaccination.

Precautions
Temperature ≥40.5°C (105°F) within 48 hours not due to another identifiable cause.
Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
Persistent, inconsolable crying lasting ≥3 hours, occurring within 48 hours.
Convulsions with or without fever occurring within 3 days.

Special care should be taken to ensure that the injection does not enter a blood vessel.
A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of hepatitis or other infectious agents from person to person. Needles should not be recapped and should be disposed of properly.

INFORMATION FOR PATIENT
Parents should be fully informed of the benefits and risks of immunization with Tripedia. The health-care provider should provide the Vaccine Information Pamphlets (VIPs) which are required to be given with each immunization.
The physician should inform the parents or guardians about the potential for adverse reactions that have been temporally associated with whole-cell pertussis DTP vaccine and Tripedia administration and obtain informed consent. Parents or guardians should be instructed to report any serious adverse reactions to their health-care provider.

IT IS EXTREMELY IMPORTANT WHEN A CHILD IS RETURNED FOR THE NEXT DOSE IN THE SERIES, THAT THE PARENT SHOULD BE QUESTIONED CONCERNING OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE REACTION AFTER THE PREVIOUS DOSE (SEE CONTRAINDICATIONS; ADVERSE REACTIONS).

The health-care provider should inform the parent or guardian the importance of completing the immunization series, unless a contraindication to further immunization exists.
The U.S. Department of Health and Human Services has established a new Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986.[31] The toll-free number for VAERS forms and information is 800-822-7967.
The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer vaccines to maintain permanent vaccination records and to report occurrences of certain adverse events to the U.S. Department of Health and Human Services. Reportable events include those listed in the Act for each vaccine and events specified in the package insert as contraindications to further doses of the vaccine.[32,33]

DRUG INTERACTIONS
As with other IM injections use with caution in patients on anticoagulant therapy.
Influenza Virus Vaccine should not be given within three days of the administration of Tripedia.[30]
Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Although no specific studies with pertussis vaccine are available, if immunosuppressive therapy will be discontinued shortly, it would be reasonable to defer immunization until the patient has been off therapy for one month; otherwise, the patient should be vaccinated while still on therapy.[7]
If Tripedia has been administered to persons receiving immunosuppressive therapy, a recent injection of immune globulin or having an immunodeficiency disorder, an adequate immunologic response may not be obtained.
Tetanus Immune Globulin, or Diphtheria Antitoxin, if used, should be given in a separate site, with a separate needle and syringe.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
Tripedia has not been evaluated for its carcinogenic, mutagenic potentials or impairment of fertility.

THIS VACCINE IS NOT RECOMMENDED FOR PERSONS 7 YEARS OF AGE AND OLDER.

PEDIATRIC USE
Efficacy data for Tripedia in infants is not available. Although antibody responses to diphtheria, tetanus, and pertussis toxin and FHA in infants immunized with Tripedia were at least equivalent to those for CLI's whole-cell pertussis DTP vaccine, the role of serum antibodies in protection against pertussis is unknown at this time.
Tripedia is not recommended for use in children below 15 months of age. This vaccine is not recommended for use as a primary series in children of any age.
Tripedia is not recommended for individuals over 7 years of age. Tetanus and Diphtheria Toxoids Adsorbed For Adult Use (Td) is to be used in individuals 7 years of age or older. Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, should not be used to immunize children less than 15 months of age.

ADVERSE REACTIONS
Local adverse reactions which include pain, erythema, heat, edema, and induration, and systemic reactions such as fever, drowsiness, fretfulness, and anorexia may occur following vaccination. Table 3 lists the frequency of adverse reactions in 372 children who received Tripedia at 15 to 20 months and 239 children who received Tripedia at 4 to 6 years of age. These children had previously received three or four doses of whole-cell pertussis DTP vaccine at approximately 2, 4, 6 and 18 months of age.[1]
Rarely, an anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) has been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.[7]
Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2 to 8 hours after an injection), may follow receipt of tetanus toxoid. A few cases of peripheral neuropathy have been reported following tetanus toxoid administration, although a causal relationship has not been established.[7]
In the National Childhood Encephalopathy Study, (NCES), a large, case-control study in England, children 2 to 35 months of age with serious, acute neurologic disorders such as encephalopathy or complicated convulsion(s), were more likely to have received DTP in the 7 days preceding onset than their age-, sex-, and neighborhood-matched controls. Among children known to be neurologically normal before entering the study, the relative risk (estimated by odds ratio) of a neurologic illness occurring within the 7-day period following receipt of DTP dose, compared to children not receiving DTP vaccine in the 7-day period before onset of their illness, was 3.3 ($p < 0.001$).[7]
Within this 7-day period, the risk was significantly increased for immunized children only within 3 days of vaccination (relative risk 4.2, $p < 0.001$). The relative risk for illnesses occurring 4 to 7 days after vaccination was 2.1 ($.05 < p < 0.1$). Serious neurologic illnesses requiring hospitalization attributable to pertussis vaccine are rare. Final analysis of a comprehensive case-control study has estimated that the risk of such illnesses is 1 in 140,000 doses administered. An earlier analysis had estimated this risk at 1/110,000 doses. In contrast, final analysis of the case control study found that the risk of serious neurologic illness following pertussis disease was 1/11,000 pertussis cases.[34] Repeated evaluations have shown that the benefits of vaccination outweigh the risks; therefore, both the ACIP and the American Academy of Pediatrics continue to recommend the use of DTP vaccine.[7,35]
The methods and results of the NCES have been thoroughly scrutinized since publication of the study. This reassessment by multiple groups has determined that the number of patients was too small and their classification subject to enough uncertainty to preclude drawing valid conclusions about whether a causal relation exists between pertussis vaccine and permanent neurologic damage. Preliminary data from a 10-year follow-up study of some of the children studied in the original NCES study also suggested a relation between symptoms following DTP vaccination and permanent neurologic disability. However, details are not available to evaluate this study adequately, and the same concerns remain about DTP vaccine precipitating initial manifestations of pre-existing neurologic disorders.[7]
Sudden Infant Death Syndrome (SIDS) has occurred in infants following administration of DTP. Large case-control studies of SIDS in the United States have shown that receipt of DTP was not causally related to SIDS.[36,37] It should be recognized that the first three primary immunizing doses of DTP are usually administered to infants 2 to 6 months old and that approximately 85% of SIDS cases occur at ages 1 to 6 months, with the peak incidence occurring at 6 weeks to 4 months of age. By chance alone, some cases of SIDS can be expected to be related to recent receipt of DTP.[36] Recent evidence does not indicate a causal relation between DTP vaccine and SIDS.[38]
Onset of infantile spasms has occurred in infants who have recently received DTP or DT. Analysis of data from the NCES on children with infantile spasms showed that receipt of DT or DTP was not causally related to infantile spasms.[39] The incidence of onset of infantile spasms increases at 3 to 9 months of age, the time period in which the second and third doses of DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of DTP.[7]
A bulging fontanelle associated with increased intracranial pressure which occurred within 24 hours following DTP immunization has been reported, although a causal relationship has not been established.[40,41,42]

TABLE 3.[1] ADVERSE EVENTS OCCURRING 24, 48 AND 72 HOURS FOLLOWING DIPHTHERIA AND TETANUS TOXOIDS AND ACELLULAR PERTUSSIS VACCINE ADSORBED (TRIPEDIA) IMMUNIZATIONS GIVEN AT 15 TO 20 MONTHS AND 4 TO 6 YEARS OF AGE.

EVENT	FREQUENCY					
	15 to 20 Months Reaction % (n = 372)			4 to 6 Years Reaction % (n = 239)		
	24 hr.	48 hr.	72 hr.	24 hr.	48 hr.	72 hr.
Local						
Erythema*	13%	7%	3%	25%	23%	14%
Swelling**	6%	2%	1%	21%	20%	14%
Tenderness	6%	4%	2%	35%	20%	8%
Mild/Moderate Systemic						
Fever >101°F (rectal)	4%	1%	1%	3%	2%	1%
Gastrointestinal						
Diarrhea	3%	3%	2%	0%	0%	0%
Vomiting	2%	1%	0%	1%	1%	0%
Anorexia	6%	4%	3%	5%	3%	1%
Neurological						
Drowsiness	11%	4%	1%	13%	3%	2%
Irritability	15%	9%	5%	10%	7%	5%
High-pitched unusual cry	1%	1%	0%	0%	0%	0%

*Includes all occurrences of erythema.
**Includes all occurrences of swelling.

The following illnesses have been reported as temporally associated with vaccine containing tetanus toxoid: neurological complications[43,44] including cochlear lesion,[45] brachial plexus neuropathies,[46,48] paralysis of the radial nerve,[47] paralysis of the recurrent nerve,[48] accommodation paresis, and EEG disturbances with encephalopathy.[49] In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.[48,50]

Reporting of Adverse Events
Reporting by parents and patients of all adverse events occurring after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by the health-care provider to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS). Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 800-822-7967.[31,32,33]
The health-care provider also should report these events to Director of Medical Affairs, Connaught Laboratories, Inc., Route 611, P.O. Box 187, Swiftwater, PA 18370 or call 1-800-822-2463.

DOSAGE AND ADMINISTRATION
Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, the vaccine should not be administered.

SHAKE VIAL WELL *before withdrawing each dose.* Inject 0.5 mL of Tripedia intramuscularly only. The preferred injection sites are the anterolateral aspect of the thigh and the deltoid muscle of the upper arm. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk. During the course of immunizations, injections should not be made more than once at the same site.
The use of reduced volume (fractional doses) is not recommended. The effect of such practices on the frequency of serious adverse events and on protection against disease has not been determined.
Do NOT administer this product subcutaneously. Special care should be taken to ensure that the injection does not enter a blood vessel.

TRIPEDIA IS INDICATED FOR THE FOURTH DOSE OF THE DIPHTHERIA, TETANUS AND PERTUSSIS IMMUNIZATION SERIES. TRIPEDIA MAY BE GIVEN 6 TO 12 MONTHS AFTER THE THIRD DOSE OF WHOLE-CELL PERTUSSIS DTP TO MAINTAIN ADEQUATE IMMUNITY DURING THE PRESCHOOL YEARS. THIS DOSE IS AN INTEGRAL PART OF THE PRIMARY VACCINATING COURSE.

TRIPEDIA IS INDICATED FOR THE FIFTH DOSE OF THE DIPHTHERIA, TETANUS AND PERTUSSIS IMMUNIZATION SERIES. PRIOR IMMUNIZATIONS MAY CONSIST OF THREE DOSES OF WHOLE-CELL PERTUSSIS DTP AND ONE DOSE OF ACELLULAR PERTUSSIS DTP OR FOUR DOSES OF WHOLE-CELL PERTUSSIS DTP. TRIPEDIA MAY BE GIVEN TO CHILDREN 4 TO 6 YEARS OF AGE, BEFORE ENTERING KINDERGARTEN OR ELEMENTARY SCHOOL (NOT CONSIDERED NECESSARY IF FOURTH PRIMARY VACCINATING DOSE ADMINISTERED AFTER FOURTH BIRTHDAY).

The vial of vaccine should be shaken to ensure a proper suspension of the vaccine prior to use.
The simultaneous administration of DTaP, OPV, and MMR has not been evaluated. However, on the basis of studies using whole-cell DTP, the ACIP does not anticipate any differences in seroconversion rates and rates of side effects from those observed when the vaccines are administered separately. The ACIP recommends the simultaneous administration of all vaccines appropriate to the age and the previous vaccination status of the child, including the special circumstance of simultaneous administration of DTP or DTaP, OPV, HbCV, and MMR at age ≥15 months.[51]

HOW SUPPLIED
Vial 7.5 mL - Product No. 49281-282-15

STORAGE
Store between 2° - 8°C (35° - 46°F). DO NOT FREEZE. Temperature extremes may adversely affect resuspendability of this vaccine.

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Product information
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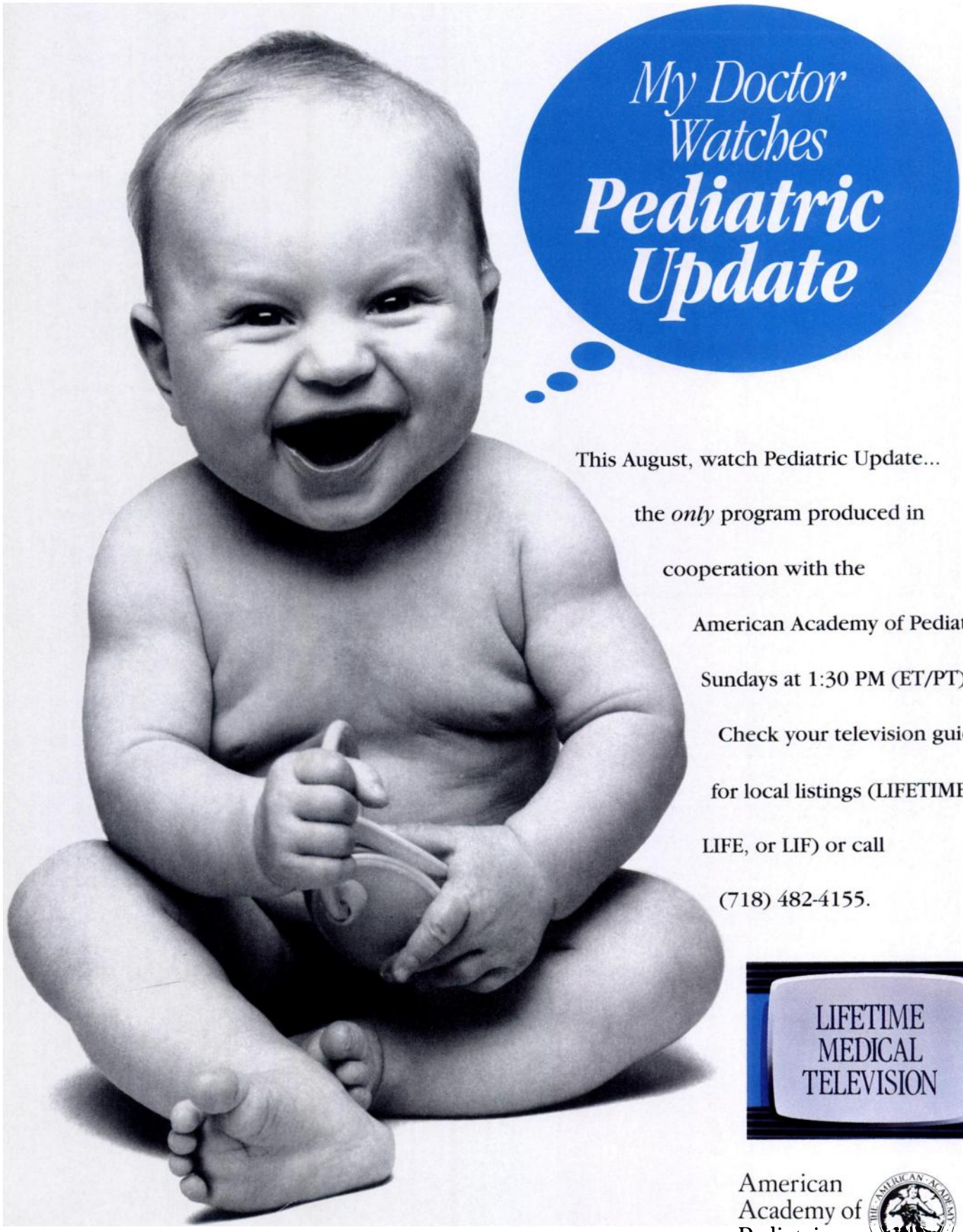

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Pedia-Profen®

Ibuprofen Suspension **100 mg/5 ml**

The following is a brief summary only. Before prescribing, see complete prescribing information in **Pedia-Profen** labeling.

INDICATIONS AND USAGE: Pedia-Profen is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

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

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

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

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

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

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

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

Patients on **Pedia-Profen** should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

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

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

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

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

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

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

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

Safety and efficacy of **Pedia-Profen** in children below the age of 6 months has not been established.

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

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

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

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

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

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

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

HOW SUPPLIED: Pedia-Profen Ibuprofen Suspension 100 mg/5 ml (teaspoon)—orange, berry-vanilla flavored

Bottles of 4 oz (120 ml) ..... NDC 0045-0469-04

Bottles of 16 oz (480 ml) ..... NDC 0045-0469-16

SHAKE WELL BEFORE USING. Store at room temperature

Caution: Federal law prohibits dispensing without prescription.

McNEIL CONSUMER PRODUCTS CO.
DIVISION OF McNEIL-PPC, INC.
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Healthy Start
FOOD TO GROW ON

A Healthy Eating Campaign for Children

Healthy Start...Food To Grow On is an information and education campaign for children that promotes healthful food choices and eating habits as a part of an overall healthful life-style.

Developed as a cooperative effort by the American Academy of Pediatrics, the Food Marketing Institute, and the American Dietetic Association, these four colorful nutrition information brochures target families with young children ages 2 to 6 years old.

The four brochures are listed below:

- ***Right From the Start: ABCs of Good Nutrition for Young Children***
  Setting the stage for healthy eating habits and food choices
- ***What's to Eat? Healthy Foods for Hungry Children***
  Suggestions for meals that are tasty, convenient, and nutritious
- ***Feeding Kids Right Isn't Always Easy: Tips for Preventing Food Hassles***
  Advice for parents and caregivers on children's eating behavior problems
- ***Growing Up Healthy: Fat, Cholesterol and More***
  Health and eating guidelines for children 2 to 6 years old

Order Now –

Please send me:

	Code	Member Price	Non-Member Price	Qty (*Min 100)	Total Price
What's to Eat?	**HE0094**	***$20.00/ 100 copies**	***$25.00/ 100 copies**	_____	_____
Right From the Start	**HE0095**	***$20.00/ 100 copies**	***$25.00/ 100 copies**	_____	_____
Growing Up Healthy	**HE0096**	***$20.00/ 100 copies**	***$25.00/ 100 copies**	_____	_____
Feeding Kids Right	**HE0097**	***$20.00/ 100 copies**	***$25.00/ 100 copies**	_____	_____

Shipping/Handling (see schedule) _____

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Under $25	$3.95	$50 to $75	$7.50
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Enclosed is my check/money order for $ _____
payable to the American Academy of Pediatrics.

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Allow 2 to 3 weeks for UPS delivery. Mail this form to: AAP Publications Department, PO Box 927, Elk Grove Village, IL 60009-0927

American Academy of Pediatrics

NOMINEES SOUGHT FOR THE PEDIATRIC RESIDENT RESEARCH AWARD FOR 1993

This award is for research carried out during pediatric residency training.

Requirements for Nomination

- Candidate must be first author on manuscript or paper reporting research.
- Candidate must be in residency or in first year following residency year at the point of nomination for the award.
- Research may be of clinical, bench, or health services significance.
- Research must have been carried out during PL1–PL3 years.
- One copy of a manuscript reporting research must be submitted, accompanied by a nomination letter from either the pediatric department chairman, the residency program director, or the resident's faculty mentor at the institution where the research was conducted. The letter should include: (1) name, address, and phone number(s) of the candidate; (2) year of residency when research was conducted; (3) name of residency program; (4) name of program director; (5) a description of the exact involvement of the resident in the research project; (6) current employment status or professional activity of the candidate. This letter must be submitted by January 29, 1993 to:

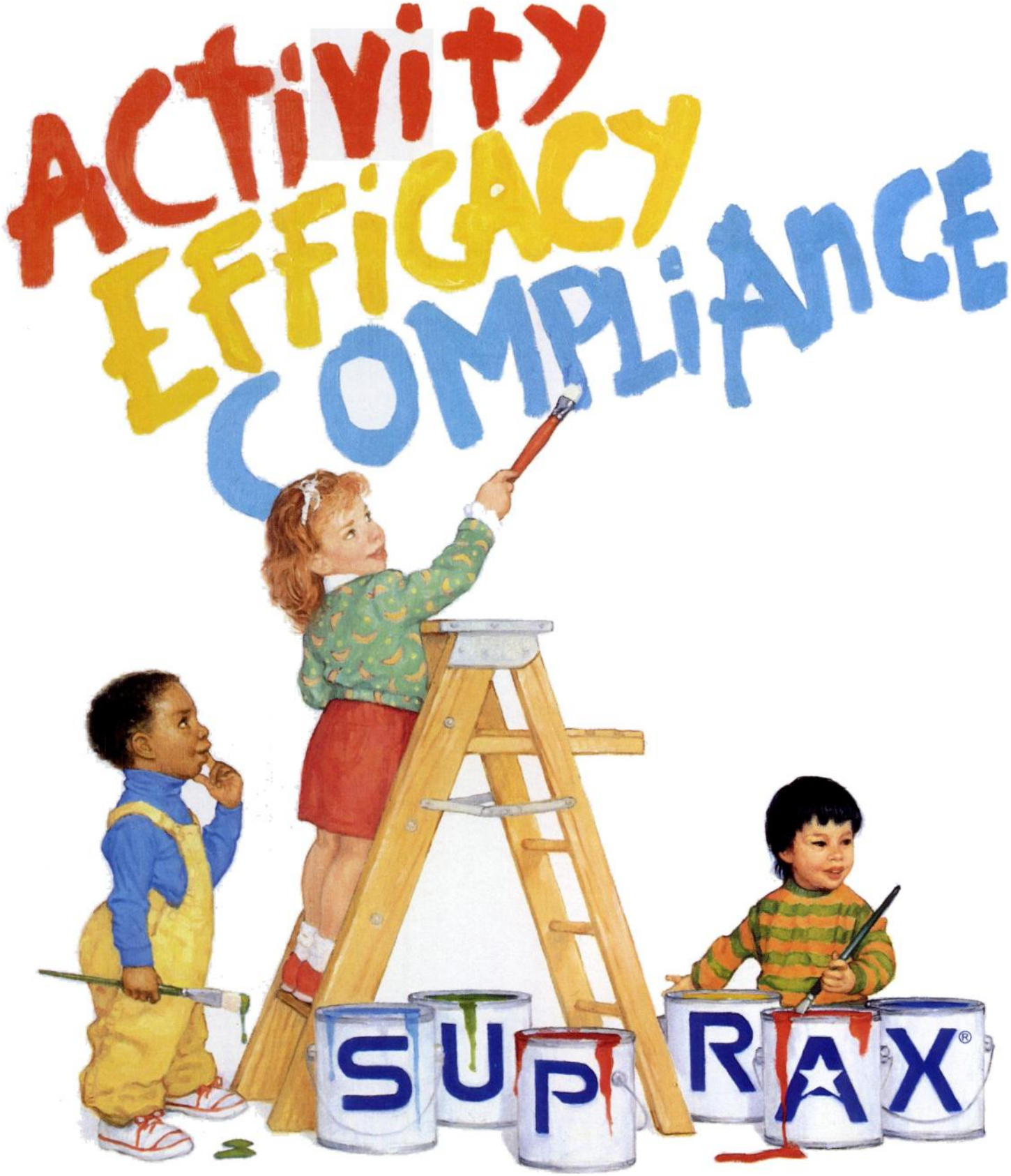
Patricia Rogers
Department of Research
American Academy of Pediatrics
141 Northwest Point Blvd.
P. O. Box 927
Elk Grove Village, IL 60009-0927

A prize of $1,000 will be presented to the awardee during the Academy's annual fall meeting. In addition, reimbursement for travel expenses to the Academy's meeting will be provided.

The awardee will be selected by the Academy's Council on Pediatric Research. Selection will be based on quality of experimental design, execution, and scientific and clinical significance of the research.

For further information contact Patricia Rogers at 1-800-433-9016, extension 7626.

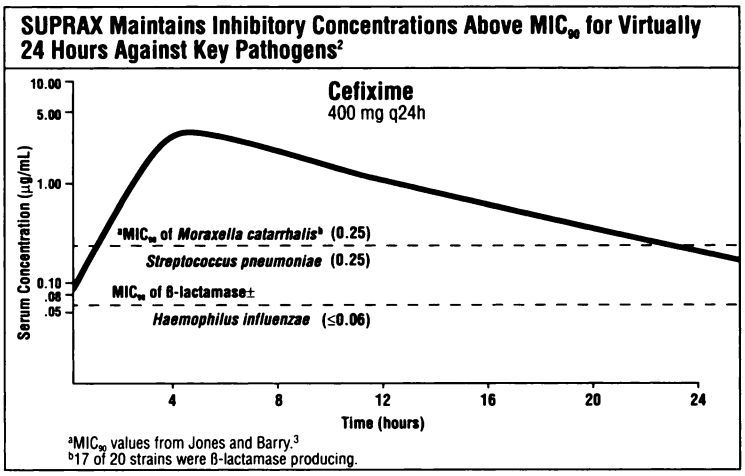
THE RIGHT COMBINATION OF



ADVANTAGES FOR OTITIS MEDIA*

Activity

- Excellent activity against ß-lactamase producing pathogens[1†]



Efficacy

- Outstanding clinical success noted in clinical trials and confirmed in 27,000-patient study[4]

Compliance

- Excellent compliance because of convenient qd dosing[5]
- Great strawberry taste—rated #1 for taste[6]

ONCE-A-DAY

SUPRAX®

cefixime/Lederle

Oral Suspension 100 mg/5 mL

8 mg/kg/day

NOW AVAILABLE IN COST-EFFECTIVE 75 mL BOTTLE

The right combination of advantages in one antibiotic

*Due to indicated susceptible organisms.

†Although a useful guide, *in vitro* activity does not necessarily correlate with clinical response.

Cephalosporin antibiotics should be administered cautiously in penicillin-sensitive patients, as partial cross-allergenicity for these two drug classes has been reported. SUPRAX is contraindicated in patients with known allergy to the cephalosporin group of antibiotics. Please see complete Prescribing Information for WARNINGS, ADVERSE REACTIONS, and CONTRAINDICATIONS. GI side effects are the most frequently reported adverse effects.

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

Please see brief summary of Prescribing Information on adjacent page.

ONCE-A-DAY

SUPRAX®

cefixime/Lederle

Oral Suspension 100 mg/5 mL

8 mg/kg/day

NOW AVAILABLE IN COST-EFFECTIVE 75 mL BOTTLE

References: 1. Nash DR, Flanagan C, Steele LC, et al. Comparison of the activity of cefixime and activities of other oral antibiotics against adult clinical isolates of *Moraxella (Branhamella) catarrhalis* containing BRO-1 and BRO-2 and *Haemophilus influenzae*. *Antimicrob Agents Chemother.* 1991;35:192-194. 2. Schentag JJ. Pharmacokinetic profiles as predictors of therapeutic success. In: *Respiratory Infections: Therapeutic Considerations in a Dynamic Environment.* Lederle Laboratories; 1990. Data on file. Lederle Laboratories, Pearl River, NY. 3. Jones RN, Barry AL. Antimicrobial activity, spectrum, and recommendations for disk diffusion susceptibility testing of ceftibuten (7432-S; SCH 39720), a new orally administered cephalosporin. *Antimicrob Agents Chemother.* 1988; 32(10):1576-1582. 4. Pichichero ME. Cefixime multicenter national otitis media study. In: *The Contemporary Treatment of Otitis Media.* Lederle Laboratories; 1990. Data on file. Lederle Laboratories, Pearl River, NY. 5. Cockburn J, Gibberd RW, Reid AL, et al. Determinants of non-compliance with short term antibiotic regimens. *Br Med J.* 1987;295:814-818. 6. Ruff ME, Schotik DA, Bass JW, et al. Antimicrobial drug suspensions: a blind comparison of taste of fourteen common pediatric drugs. *Pediatr Infect Dis J.* 1991;10:30-33.

Brief Summary

SUPRAX® Cefixime
Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

Otitis Media caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Moraxella (Branhamella) catarrhalis* (most of which are beta-lactamase positive), and *Streptococcus pyogenes.**
Note: For information on otitis media caused by *Streptococcus pneumoniae*, see **CLINICAL STUDIES** section.

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

Perform culture and susceptibility studies to determine causative organism and its susceptibility to SUPRAX. Therapy may begin while waiting for study results and may be adjusted when results are known.

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

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

*Efficacy for this organism was studied in fewer than ten patients with otitis media.

CLINICAL STUDIES

In clinical trials of otitis media in nearly 400 children between the ages of 6 months and 10 years, *S pneumoniae* was isolated from 47% of the patients, *H influenzae* from 34%, *M catarrhalis* from 15%, and *S pyogenes* from 4%.

The overall response rate of *S pneumoniae* to cefixime was approximately 10% lower and that of *H influenzae* or *M catarrhalis* approximately 7% higher (12% when beta-lactamase positive strains of *H influenzae* are included) than the response rates of these organisms to the active control drugs.

In these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg bid or 8 mg/kg qd, or with a standard antibiotic regimen. Sixty-nine to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated 2 to 4 weeks posttreatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had *H influenzae* resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the 2- to 4-week follow-up, a total of 30% to 31% of patients had evidence of either treatment failure or recurrent disease.

Bacteriological Outcome of Otitis Media at 2- to 4-Weeks Posttherapy Based on Repeat Middle Ear Fluid Culture or Extrapolation From Clinical Outcome

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

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

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

CONTRAINDICATIONS

Known allergy to cephalosporins.

WARNINGS

BEFORE THERAPY WITH SUPRAX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO SUPRAX OCCURS, DISCONTINUE THE DRUG. SERIOUS, ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Administer cautiously to allergic patients.

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

Pseudomembranous colitis has been reported with the use of SUPRAX and other broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins). It is important to consider this diagnosis in patients who develop diarrhea in association with antibiotic use. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment and may range in severity from mild to life-threatening. Mild cases usually respond to drug discontinuation alone.

SUPRAX® Cefixime

Moderate-to-severe cases should be managed with fluid, electrolyte, and protein supplementation. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes of colitis should be excluded.

PRECAUTIONS

General: Prolonged use may result in overgrowth of nonsusceptible organisms. If superinfection occurs, take appropriate measures.

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

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

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

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

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

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

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

Usage in Pregnancy: *Pregnancy Category B:* Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of harm to the fetus due to SUPRAX.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

Renal: Transient elevations in BUN or creatinine.

Central Nervous System: Headaches or dizziness.

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

Other: Genital pruritus, vaginitis, candidiasis.

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

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

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

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

OVERDOSAGE

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

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Eucerin provides the gentle cleansing your patients need.

Eucerin's extremely mild, non-drying cleansers are the ideal choice for even the most sensitive skin. And that means smooth sailing for your patients. Eucerin Cleansing Lotion and Cleansing Bar are soap-and-fragrance-free, pH balanced and non-comedogenic.

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Eucerin Cleansers are clinically proven safe as base therapy for atopic dermatitis, a condition which often requires a total ban of washing.* So you can recommend them with confidence.

Patients give Eucerin a high rating, too.

Patients with very sensitive skin rate Eucerin Cleansing Lotion and Bar as good to excellent for both mildness and cosmetic appeal.* Eucerin has the rich lather and silky feel usually missing in therapeutic cleansers.

Eucerin Cleansers, together with your #1 choice, Eucerin Moisturizers, provide a superior skin care system. And that means smooth sailing for even the most sensitive skin.

Eucerin. The New Choice For Cleansing.

*Data on file Eucerin is a registered trademark of Beiersdorf AG

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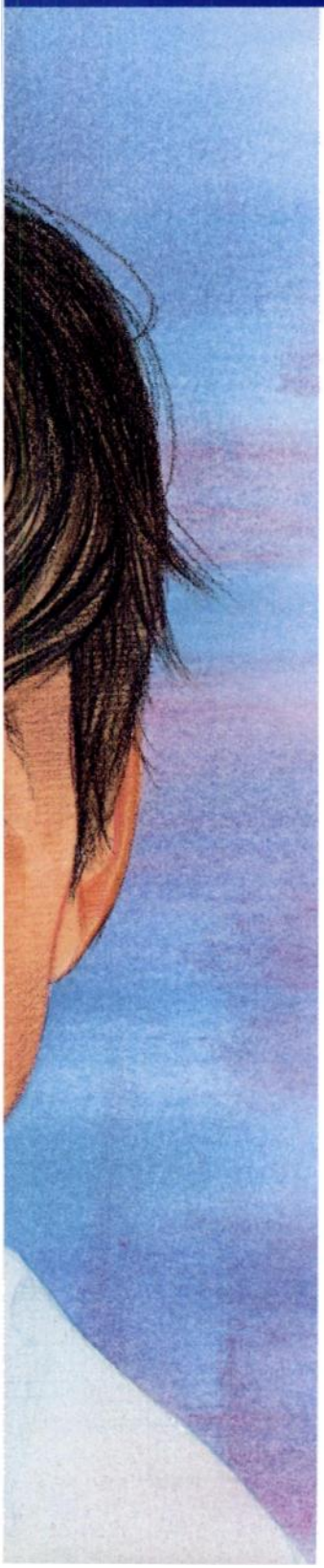
morning after morning



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Works safely

- Well tolerated…an incidence of adverse events comparable to placebo
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- Approximately 20 years of safe use in children with diabetes insipidus[3]

Works effectively, rapidly

- Success rates as high as 82%[4]
- Significant response in as few as 1-3 days[5]

Works to improve children's self-concept

- Children frequently experience feelings of happiness and achievement at becoming dry[6]
- Significantly improves self-concept, restores quality of life[7]

Nighttime fluid intake should be restricted to decrease the potential occurrence of fluid overload; serum electrolytes should be checked at least once when therapy is continued beyond 7 days.

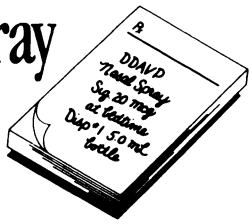
DDAVP® Nasal Spray
(desmopressin acetate) 5mL

Dry Nights For Good Mornings

Please see Brief Summary of prescribing information on following page.

DDAVP® Nasal Spray
(desmopressin acetate) 5mL

Dry Nights For Good Mornings



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

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

OVERDOSAGE: See adverse reactions above. In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for DDAVP Nasal Spray. An oral LD_{50} has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.
HOW SUPPLIED: A 5-mL bottle with spray pump delivering 50 doses of 10 mcg (NDC 0075-2450-02). Also available as 2.5 mL per vial, packaged with two rhinal tube applicators per carton (NDC 0075-2450-01). Keep refrigerated at 2°-8°C (36°-46°F). When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 22°C (72°F).
CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.
Please see full prescribing information in product circular.

References: 1. Roth D: Introduction to *Current Concepts in the Management of Primary Nocturnal Enuresis*. Proceedings from a symposium sponsored by the Baylor College of Medicine: January 1991. 2. Miller K, Goldberg S, Atkin B: Nocturnal enuresis: Experience with long-term use of intranasally administered desmopressin. *J Pediatr* 1989;114(Part 2):723-726. 3. Harris AS: Clinical experience with desmopressin: Efficacy and safety in central diabetes insipidus and other conditions. *J Pediatr* 1989;114(Part 2):711-718. 4. Rittig S, Knudsen UB, Sorenson S, et al: Long-term double-blind cross-over study of desmopressin intranasal spray in the management of nocturnal enuresis. In: Meadow SR, ed. *Desmopressin in Nocturnal Enuresis: Proceedings of an International Symposium*. England: Horus Medical Publications; 1988:43-55. 5. Aladjem M, Wohl R, Boichis H, et al: Desmopressin in nocturnal enuresis. *Arch Dis Child* 1982;57:137-140. 6. Baker BL: Symptom treatment and symptom substitution in enuresis. *J Abnorm Psych* 1969;74:42-49. 7. Moffat MEK: Nocturnal enuresis: Psychologic implications of treatment and nontreatment. *J Pediatr* 1989;114(Part 2):697-704.

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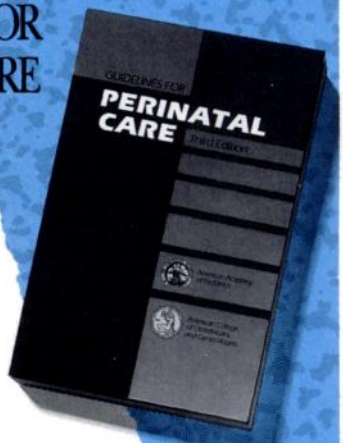
THE NEW GUIDELINES FOR PERINATAL CARE



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When the heat's on...

Children's Advil® (ibuprofen) Suspension

100mg/5mL

- Children's Advil® Suspension (10 mg/kg) provides better temperature reduction and longer duration of action than Tylenol®* (10 mg/kg) in fevers above 102.5°F[1†]
- Comparable to acetaminophen in incidence of side effects[1-3]
- Minimal risk for adverse reactions at recommended doses[1-5‡]
- Demonstrated safety profile in acute antipyretic use[1-3]

* Tylenol (acetaminophen) is a registered trademark of McNeil Consumer Products Company.

† Labeled fever-reducing dose of acetaminophen drops and liquid is approximately 10-15 mg/kg.

‡ Children's Advil Suspension is contraindicated in patients hypersensitive to aspirin or other NSAIDs. As with other NSAIDs, the most frequent complaints relate to the GI tract.

Please see following page for brief summary of prescribing information.

WYETH PEDIATRICS

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BY PRESCRIPTION ONLY

Children's Advil® (ibuprofen) Suspension

AN ALTERNATIVE FOR PEDIATRIC CARE

100 mg/5 mL

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

INDICATIONS: For reduction of fever in patients aged 6 months and older, and relief of mild-to-moderate pain in patients 12 years and older; for relief of the signs/symptoms of juvenile arthritis, rheumatoid arthritis and osteoarthritis; for relief of primary dysmenorrhea.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

C14123-1 5/7/91

References:

1. Walson PD, Galletta G, Braden NJ, et al: Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther* 1989;46:9-17.
2. Kauffman RE, Alexander LA, Scheinbaum ML: Ibuprofen suspension in children. *Pediatr Res* 1989;25:67A. Abstract # 388.
3. Walson PD, Galletta G, Chomilo F, et al: Ibuprofen liquid: multi-dose treatment of febrile children. *Fourth World Congress of Clinical Pharmacology and Therapeutics.* Heidelberg, Germany, July 24-28, 1989.
4. Giannini EH, Brewer EJ, Miller ML, et al: Ibuprofen suspension in the treatment of juvenile rheumatoid arthritis. *J Pediatr* 1990;117:645-652.
5. Steans A, Manners PJ, Robinson IG: A multicentre, long-term evaluation of the safety and efficacy of ibuprofen syrup in children with juvenile chronic arthritis. *Br J Clin Pract* 1990;44:172-175.

WYETH PEDIATRICS

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ANIMALS ALTERED TO MAKE DRUGS IN THEIR MILK

. . .Researchers have genetically engineered animals to produce drugs in their milk potentially worth tens of thousands of dollars a day.

Scientists said the development proves the commercial feasibility of "pharming"—using herds of animals as living pharmaceutical factories. Pharming may give the biotechnology industry a cheaper, better way to make genetically engineered drugs now made in vats by bacteria and other microbes genetically altered to produce human proteins.

Reports by U.S. and British teams said they have developed genetically altered goats and sheep, respectively, that secrete sizable amounts of drugs [albumin, TPA and alpha-1-antitrypsin] in their milk. In a third report, scientists in the Netherlands said they developed the first practical technique to put foreign genes in cattle, which eventually could lead to an even more productive source of drugs in milk. The three teams reported their finds in the September issue of the journal Bio/Technology.

Stipp D. Animals altered to make drugs in their milk. *The Wall Street Journal.* August 27, 1991.

Noted by J.F.L., MD

A $100,000 GRANT CAN COST NIH $174,000 DUE TO INDIRECT COSTS

Extramural researchers this year will find themselves competing for NIH grants on a new playing field and some of them already dislike the new game plan. . .

. . .Extramural scientists seem mostly unsettled by talk that grant applications will no longer by funded solely using percentile scores. The new cost management strategy now calls upon NIH to consider the total cost of a scientist's research in making the final funding decision.

Congress inspired the latter change to address the rapidly rising overhead, or indirect, costs among NIH grantees. Indirect costs rose faster in the past decade than did direct costs—161 vs. 124 percent, respectively, according to NIH figures. . .

. . .In FY 1990, study sections approved 95 percent of grant applications, but NIH funded only 25.4 percent.

More money, more grants, and still not satisfied. *The Journal of NIH Research.* January 1991;3:15–16.

Noted by J.F.L., MD

Interchanging Haemophilus *b conjugate vaccines in infants is not recommended*

Six months of age and she's protected against *Haemophilus* b disease after three doses[1] with...

HibTITER®

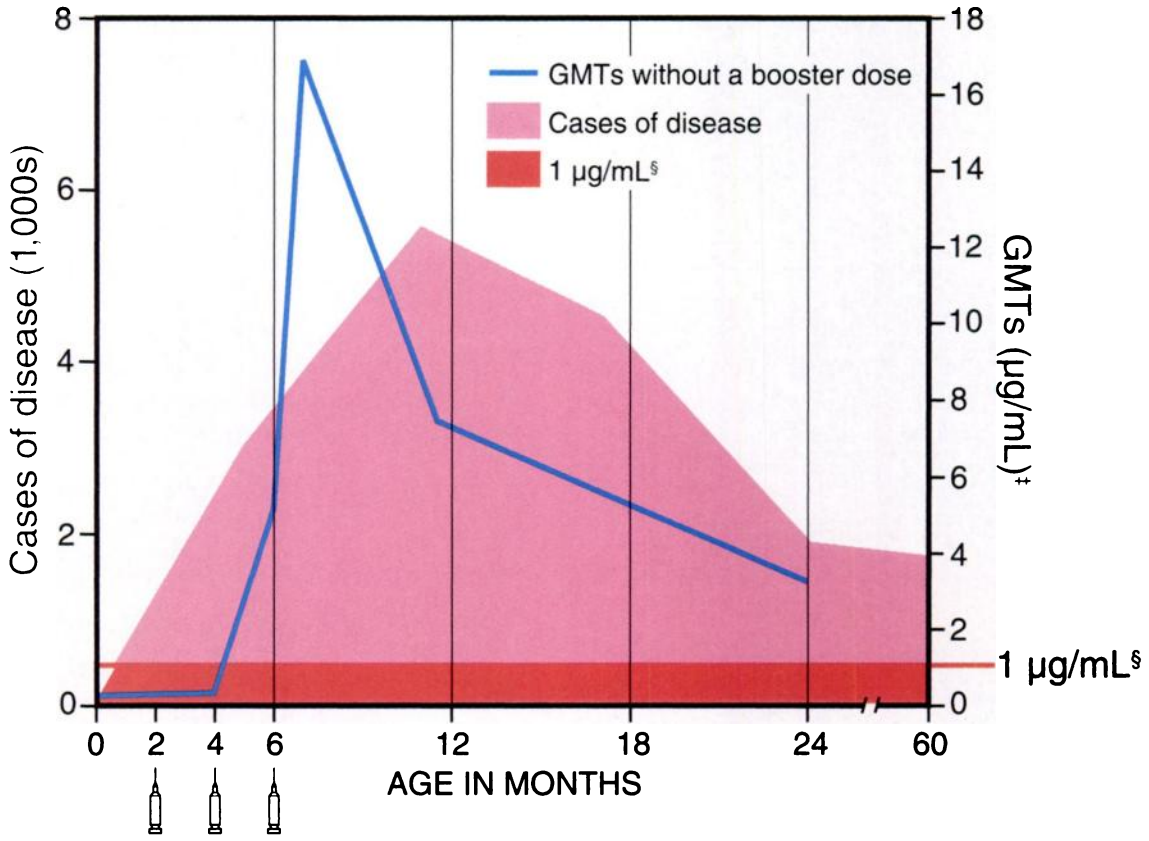
Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate)

Complete Protection With Primary Series Given at 2, 4, and 6 Months of Age[1]

100%* estimated protective efficacy documented in 20,800 infants from a representative US population.[1]

Protection for the Period of Greatest Risk—and Beyond

Immune Response[2] Following HibTITER During Period of Greatest Risk of *Haemophilus* b Disease†



Excellent Immunogenicity and Lasting Antibody Levels

80% retained ≥1 µg/mL§ of anti-HbPs antibodies at 24 months of age in a study when the recommended booster dose was withheld.[2//]

* 95% confidence intervals, two-tailed, 68% to 100%.

† Disease incidence calculated using data from Wenger, age-specific incidence of invasive *Haemophilus influenzae* disease in selected US population-based studies,[3] and combining these data with an annual US birthrate of 4 million.

‡ In infants beginning the three-dose primary series at 1 to 2 months of age, without a booster dose. Antibody activities are from sera drawn immediately before the initial dose of vaccine, 2 months after dose 1 or 2, and 1 month after dose 3.

§ An antibody concentration of ≥1 µg/mL is associated with long-term protection for immunized children 18 months of age after only one dose of *Haemophilus* b polysaccharide vaccine.

// In infants beginning the three-dose primary series at 1 to 2 months of age.

1. Black SB, Shinefield HR, Fireman B, et al. Efficacy in infancy of oligosaccharide conjugate *Haemophilus influenzae* type b (HbOC) vaccine in a United States population of 61 080 children. *Pediatr Infect Dis J*. 1991;10:97-104.
2. Madore DV, Johnson CL, Phipps DC, et al. Safety and immunologic response to *Haemophilus influenzae* type b oligosaccharide-CRM$_{197}$ conjugate vaccine in 1- to 6-month-old infants. *Pediatrics*. 1990;85:331-337.
3. Wenger JD, Ward JI, Broome CV. Prevention of *Haemophilus influenzae* type b disease: vaccines and passive prophylaxis. In: Remington JS, Swartz MN, eds. *Current Clinical Topics in Infectious Diseases*. Boston, Mass: Blackwell Scientific Publications; 1989;10:306-339.

Please see next page for brief summary of full Prescribing Information.

Brief Summary HibTITER® Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate)

For complete Prescribing Information and references, please consult package insert

INDICATIONS AND USAGE: HibTITER is indicated for the immunization of children 2 months to 5 years of age against invasive diseases caused by *Haemophilus influenzae* type b

CONTRAINDICATIONS: Hypersensitivity to any component of the vaccine, including diphtheria toxoid or thimerosal in the multidose presentation, is a contraindication to use of HibTITER

WARNINGS: If used in persons deficient in producing antibody, due to genetic defect or to immunosuppressive therapy, the expected immune response may not be obtained

As with any vaccine, HibTITER may not protect 100% of individuals receiving the vaccine

PRECAUTIONS General: Prior to an injection of any vaccine, all reasonable precautions should be taken to prevent adverse reactions. Any febrile illness or acute infection is reason to delay use of HibTITER. A minor afebrile illness such as a mild upper respiratory infection is not usually reason to defer immunization

As with the injection of any biological material, Epinephrine Injection (1:1000) should be available for immediate use should an anaphylactic or other allergic reaction occur

As reported with Haemophilus b Polysaccharide Vaccine, cases of Haemophilus b disease may occur prior to the onset of the protective effects of the vaccine

Antigenuria has been detected following receipt of Haemophilus b Conjugate Vaccine. Therefore, antigen detection may not have diagnostic value in suspected Haemophilus b disease within 2 weeks of immunization

The vaccine should not be injected intradermally or intravenously, since the safety and immunogenicity of these routes have not been evaluated. The vaccine should be given intramuscularly. Special care should be taken to ensure that the injection does not enter a blood vessel

A separate sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of infectious agents from one person to another

ALTHOUGH SOME ANTIBODY RESPONSE TO DIPHTHERIA TOXIN OCCURS, IMMUNIZATION WITH HibTITER DOES NOT SUBSTITUTE FOR ROUTINE DIPHTHERIA IMMUNIZATION

Carcinogenesis, Mutagenesis, Impairment of Fertility: HibTITER has not been evaluated for its carcinogenic, mutagenic potential or impairment of fertility

Pregnancy Reproductive Studies: *Pregnancy Category C.* Animal reproduction studies have not been conducted with HibTITER. It is also not known whether HibTITER can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HibTITER is NOT recommended for use in a pregnant woman

ADVERSE REACTIONS: Adverse reactions associated with HibTITER have been evaluated in 401 infants vaccinated initially at 1 to 6 months of age given 1,118 doses independent of DTP vaccine. Observations were made during the day of vaccination and days 1 and 2 postvaccination. A temperature >38.3°C was recorded at least once during the observation period following 2% of the vaccinations. Local erythema, warmth, or swelling (≥2 cm) was observed following 3.3% of vaccinations.

The incidence of temperature >38.3°C was greater during the first postvaccination day than during the day of vaccination or the second postvaccination day. The incidence of local erythema, warmth, or swelling was similar during the day of vaccination and the first postvaccination day; it was lower during the second postvaccination day. All side effects have been infrequent, mild, and transient with no serious sequelae (Table 1). No difference in rates of these complaints was reported after doses 1, 2, or 3.

TABLE 1 Number of Subjects (Percent) Manifesting Side Effects Associated with HibTITER Administered Independently from DTP* (Infants Vaccinated Initially at 1-6 Months of Age)

Symptoms	Dose 1 n = 401 Same Day As Vacc	+1 Day	+2 Days	Dose 2 n = 383 Same Day As Vacc	+1 Day	+2 Days	Dose 3 n = 334 Same Day As Vacc	+1 Day	+2 Days
Temp >38.3°C	0 —	2 <1%	2 <1%	2 <1%	3 <1%	2 <1%	2 <1%	6 1.8%	5 1.5%
Redness ≥2 cm	1 <1%	0 —	0 —	1 1%	6 1.6%	0 —	5 1.5%	4 1.2%	0 0
Warmth ≥2 cm	1 <1%	1 <1%	0 —	2 <1%	1 <1%	0 —	1 <1%	6 1.8%	0 —
Swelling ≥2 cm	5 1.2%	1 <1%	0 —	2 <1%	2 <1%	0 —	1 <1%	0 —	0 —

**DTP and HibTITER given 2 weeks apart with DTP having been given first.*

The following complaints were also reported after 1,118 vaccinations with HibTITER: irritability (133), sleepiness (91), prolonged crying [≥4 hours] (38), appetite loss (23), vomiting (9), diarrhea (2), and rash (1).

Additional HibTITER safety data are available from efficacy studies conducted in young infants. 79,483 doses were given to 30,844 infants at 2, 4, and 6 months in California at the same time as DTP (but at a separate injection site) and oral polio vaccine; approximately 100,000 doses have been given to 53,000 infants at 4 and 6 months in Finland at the same time as a combined DTP and inactivated polio vaccine (IPV), but at a separate injection site. The rate and type of reaction associated with the vaccinations were no different from those seen when DTP or DTP-IPV was administered alone. These included fever, local reactions, rash, and one hyporesponsive episode with a single seizure. The safety of HibTITER was also evaluated in the California study by direct phone questioning of the parents or guardians of 6,887 vaccine recipients. The incidence and type of side effects reported within 24 hours of vaccination were similar to those cited in Table 1. In addition, analysis of emergency room (ER) visits within 30 days and hospitalization within 60 days after receipt of 23,800 doses of HibTITER showed no increase in the rates of any type of ER visit or hospitalization.

Table 2 details the side effects associated with a single vaccination of HibTITER given (without DTP) to infants of 15-23 months of age.

Similar results have been observed in the analysis of 2,285 subjects 18-60 months of age, vaccinated as part of a postmarketing safety study of HibTITER. This data was collected by telephone survey 24-48 hours postvaccination. Additional observations included irritability, restless sleep, and GI symptoms (diarrhea, vomiting, and loss of appetite) in the group that received HibTITER alone. A cause and effect relationship between these observations and the vaccinations has not been established.

TABLE 2 Selected Adverse Reactions* in Children of 15-23 Months of Age Following Vaccination with HibTITER Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate)

Adverse Reaction	No. of Subjects	Reaction % Postvaccination Within 24 Hrs	At 48 Hrs
Fever >38.3°C	354	1.4	0.6
Erythema	354	2.0	—
Swelling	354	1.7	—
Tenderness	354	3.7	0.3

**The following complaints were reported after vaccination of these 354 children in the indicated number of children: diarrhea (9), vomiting (5), prolonged crying [>4 hours] (4), and rashes (2).*

Following the use of Haemophilus b Polysaccharide Vaccine and another Haemophilus b Conjugate Vaccine, reports of the following types of associated adverse reactions were recorded by passive reporting and postmarketing surveillance methods: fever >38.3°C, local erythema, swelling, and tenderness.

Rash, hives, convulsions, vomiting/diarrhea, and Guillain-Barre syndrome have been observed. A cause and effect relationship among any of these events and the vaccination has not been established.

DOSAGE AND ADMINISTRATION: HibTITER is for intramuscular use only. Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, HibTITER should not be administered.

HibTITER is indicated for children 2 months to 5 years of age for the prevention of invasive Haemophilus b disease. For infants 2 to 6 months of age, the immunizing dose is three separate injections of 0.5 mL given at approximately 2-month intervals intramuscularly, preferably in the outer aspect of the vastus lateralis (mid-thigh). Previously unvaccinated infants from 7 through 11 months of age should receive two separate intramuscular injections, as described, approximately 2 months apart. Children from 12 through 14 months of age who have not been vaccinated previously receive one intramuscular injection. All vaccinated children receive a single booster dose at 15 months of age or older, but not less than 2 months after the previous dose. Previously unvaccinated children 15 to 60 months of age receive a single intramuscular injection of HibTITER, as described, or in the deltoid muscle.

Age at First Immunization (Mos.)	No. of Doses	Booster
2-6	3	Yes
7-11	2	Yes
12-14	1	Yes
15 and Over	1	No

NO DATA ARE AVAILABLE TO SUPPORT THE INTERCHANGING OF HibTITER OR OTHER HAEMOPHILUS b CONJUGATE VACCINES WITH ONE ANOTHER. IT IS RECOMMENDED THAT THE SAME CONJUGATE VACCINE BE USED THROUGHOUT EACH IMMUNIZATION SCHEDULE, CONSISTENT WITH THE DATA SUPPORTING APPROVAL AND LICENSURE OF THE VACCINE.

The current recommendation of the Immunization Practices Advisory Committee (ACIP) is for routine vaccination of children at 15 months of age. The ACIP has not yet reviewed the new indication for children less than 15 months of age.

Each dose of 0.5 mL is formulated to contain 10 μg of purified Haemophilus b saccharide and approximately 25 μg of CRM_{197} protein.

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

DO NOT INJECT INTRAVENOUSLY.

STORAGE: Stability studies indicate that HibTITER can be shipped at ambient temperatures and stored at 2°-8°C (35°-46°F). DO NOT FREEZE.

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TOPICS

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P2283(10-92)

SCIENCE AND MATH EDUCATION IN U.S. FAILS TO MAKE GRADE

WASHINGTON—Despite a decade of federal and state efforts to improve science and math education, more than half of U.S. public high-school students still don't take chemistry or advanced algebra before graduation.

A report by the Council of Chief State School Officers sketched a dismal portrait of science and math education. About half the high-school teachers didn't major in the subjects they teach, the report said. And some of the states that have made publicized efforts to reform science and math education have undercut those efforts by letting students take simple courses to satisfy additional graduation requirements.

Davis B. Science and math education in U.S. fails to make grade. *The Wall Street Journal.* May 30, 1991.

Noted by J.F.L., MD

KIDS AT THE BOTTOM OF THE PILE

America is losing sight of its children. In decisions made every day we are placing them at the very bottom of our agenda with grave consequences for the future of the nation.

Carnegie Foundation for the Advancement of Teaching. Quoted in: *The New York Times.* December 8, 1991.

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Here Are Two Excellent Plans That Will Protect Your Earning Power Should You Become Disabled

Part II: This is the second part of a two-part feature. Part I appeared in the April 1992 issue.

Jean Gorski, Manager, Pediatrics Insurance Consultants, Inc.

Since publication of the April '92 PEDIATRICS, Lincoln National Life has agreed to increase the maximum limits to $9,000/Month for the Disability Income and $10,000/Month for the Office Overhead Expense Plan.

Are your income and the expenses of running your office adequately protected if you become disabled? Probably not. Many professionals don't have a long-term disability policy because either they haven't thought about it or they think Social Security will provide enough coverage. If you're in this category of the uninsured (or underinsured) you should read this article and Part I, which appeared in the April 1992 issue. You could be taking much more risk than you realize.

What about Social Security benefits? To be eligible for disability income from Social Security a person must be unable to engage in "substantial gainful activity." That is, productive work performed for money. The severity of the disability is the key. According to Social Security, you are considered *disabled* if you are suffering from a physical or mental condition that: 1. Prevents you from doing *any* substantial, gainful work, and 2. Your disability is expected to last (or has lasted) at least 12 months, or is expected to result in your death.

An important point...Social Security doesn't consider you disabled unless you're unable to do *any* substantial gainful work—*not just your current work that suits your training.* These rigid eligibility requirements prevent 70% of those applying for Social Security Disability Income from collecting a cent!

For more information about Government Social Security benefits contact your local Social Security Administration Office or the U.S. Department of Health and Human Services.

As you can see, according to Social Security, you may not be eligible for benefits unless your disability results in your not being able to work at *any gainful work.* And, even if your disability should qualify for these rigid eligibility requirements would the monthly benefits be enough to sustain you? Probably not. Moreover, Social Security does not pay any benefits that would allow you to maintain your office while you're disabled. You would probably be forced to close your office during your disability because of the expense.

You need an insurance benefit plan that will pay you *if you are disabled from performing pediatrics* even if your disability does not prevent you from working at another profession.

As a member of the American Academy of Pediatrics you can apply for group-rated plans that provide the financial security you need should you become disabled First, there's a DISABILITY INCOME plan to replace your monthly paycheck for your personal and family needs. Secondly, to keep your office operating, there's an OFFICE OVERHEAD EXPENSE plan. Information, including rates and enrollment materials are available direct-by-mail. However, if you want assistance or have questions regarding these or any insurance plans offered through the AAP Group Insurance Trust, you can call 1-800-257-3220.

DISABILITY INCOME—UP TO $9,000 A MONTH

Through AAP Group Insurance Trust you can select a monthly benefit that will pay you up to 75% of your gross average monthly earnings...up to a maximum of $9,000 a month. The cost of the plan depends on the monthly benefit you choose, the waiting period, and of course, your age. The waiting period is the time after your total disability starts and the time benefit payments begin. There are three waiting periods to choose from—30, 90 or 180 days. The longer the waiting period the less you pay for insurance. Coverage is guaranteed renewable to age 70. There are a number of physical and non-physical requirements to be met. If accepted your coverage begins on the date your application is approved.

After the initial waiting period, monthly checks will be paid to you as long as you are disabled. Even for a lifetime if your disability occurred prior to age 55. If your covered accident or sickness occurs at age 55 (or after) benefits are payable to age 70 or for 2 years (whichever occurs later). The AAP Disability plan insures you in your specialty. During the first five years of the claim the policy will pay benefits if you are prevented from performing pediatrics but are able to work in another profession.

The AAP Disability Plan also pays for partial disability. Benefits are payable when your restored monthly income is less than 80% and greater than the 25% of pre-disability monthly income. During the first six months of partial disability the benefit check will not exceed 50% of the total monthly benefit.

There are more features, provisions, definitions and exclusions covered in the INFORMATION PACKAGE available through Pediatrics Insurance Consultants, Inc. This direct-by-mail package also includes easy-to-follow guides for determining the monthly benefit amount you may need and a simple formula for calculating the insurance premium. Actual contractural provisions are contained in the Voluntary Group Master Policy (G46536) and the individual Certificate/Booklet of Insurance issued to each insured.

AAP Disability Income insurance is underwritten by The Lincoln National Life Insurance Co. of Fort Wayne, Indiana and is available only to members of The American Academy of Pediatrics.

OFFICE OVERHEAD EXPENSE INSURANCE

In the event you are totally disabled, there's a plan to provide benefits to cover the monthly fixed expenses of your office...rent/mortgage interest, utilities, personnel salaries and other business expenses. This AAP Office Overhead Expense coverage provides the funds to keep your office running smoothly in your absence. Benefits begin on the 31st day of total disability and continue up to 2 years so long as the office remains open.

You determine the amount of financial resources necessary—from $500 to $10,000 a month. You can calculate your office requirements by using an expense checklist (simple worksheet/guide) in the INFORMATION PACKAGE available to members, direct-by-mail. (See coupon on facing page)

These plans are available to all members of AAP under age 65, not in military service and who are actually and fully engaged in performing all the regular duties of their profession. There are a number of physical and non-physical requirements to be met. If accepted your coverage begins on the date your application is approved.

The cost of this valuable protection is considerably less than that of comparable coverage purchased individually. That's because of the AAP's wholesale buying power and the economies of group administration. Premiums for this insurance are tax deductible as a business expense, according to current IRS rulings. (Consult your tax advisor).

More details are spelled out in the INFORMATION PACKAGE available upon request. Use the coupon on the facing page or call the toll-free number. Actual contractural provisions are contained in Voluntary Group Master Policy 46622. Insureds also receive an individual Certificate of Insurance containing all the provisions.

This article highlights the benefits and coverages of both the *Disability Income* and the *Office Overhead Expense* insurance plans provided by the American Academy of Pediatrics Group Insurance Trust Program. More details are spelled out in the INFORMATION PACKAGES available free to AAP members. Use coupon on facing page.

The American Academy of Pediatrics derives no monetary benefit from insurance plans administrated by Pediatrics Insurance Consultants, Inc. Any surplus will accrue only to individual plan participants.

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Pediatrics Insurance Consultants has developed a series of easy-to-understand brochures on all of the benefit plans listed in the coupon below. Check the one(s) you're interested in and receive all of the details (literature, application, rates) direct-by-mail.

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P-1292

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NATIONAL NICU DATABASE SURVEY

Number of **NICU** admissions in **1989**_____ **Total** number of deliveries in **1989** _____
Number of transported **NICU** admissions in 1989 _____
Pediatric residency program ❑ NO ❑ YES Neonatal fellowship program ❑ NO ❑ YES

Type of hospital (check one): ❑ University
❑ University affiliated
❑ Community

Type of neonatal program (check one): ❑ Single hospital program
❑ Lead nursery of multi-hospital program
❑ Member of multi-hospital program

Does your nursery have a database? (check one)
❑ NO, we never had a database and do not plan to have one in the future.
❑ NO, we never had a database but plan to have one in the future.
❑ NO, we had a prior database but no longer use it.
❑ YES, we have one nursery database.
❑ YES, we have multiple nursery databases.

Are you a member of a national or regional neonatal data consortium (network)? (check one)
❑ NO
❑ YES, in addition to a personal database
❑ YES, this is our only database
If **YES** which data consortium? _____

Are you responsible for maintaining a multi-hospital database? ❑ NO ❑ YES

If you do not have a database please return survey now. Thank you for your time.
If you have several databases please base your answers on your primary database.

Which infants are included in your database? (check one)
❑ All newborns (NICU and well baby)
❑ All NICU admissions
❑ Selected NICU admissions (e.g. only inborn)
❑ Only infants in research projects

How many infants were entered into your database in **1989**? (check one)
❑ None
❑ 1-250
❑ 251-1000
❑ 1001-5000
❑ >5000

Are non-infant patients entered into the **same** database your nursery uses? (check ALL that apply)
❑ NO
❑ YES, maternity patients
❑ YES, pediatric patients
❑ YES, other _____

What are the **primary** reasons you started your current nursery database? (check ALL that apply)
❑ To obtain statistical information
❑ To generate patient care forms (e.g. discharge summary, birth certificate)
❑ To conduct a research project
❑ To monitor quality of care
❑ Other _____

How long have you used your **current** database? (check one)

- ❑ <1 year
- ❑ 1-5 years
- ❑ > 5 years

Is this your first nursery database? (check one)

- ❑ YES (please skip next question)
- ❑ NO, we had 1 or 2 prior databases
- ❑ NO, we had 3 or more prior databases

Why did you abandon your prior database? (check ALL that apply)

- ❑ Information was hard to retrieve
- ❑ Information collected was not being used
- ❑ Data collection was too time consuming
- ❑ No one was available to collect data
- ❑ No one was available to process data
- ❑ Research project ended
- ❑ Financial support ended
- ❑ New technology became available
- ❑ Worried about data confidentiality
- ❑ Information was inaccurate
- ❑ Other _____

Who developed your current database? (check one)

- ❑ Our Neonatal division
- ❑ Our Obstetric division
- ❑ Combined effort of our Neonatal and Obstetric divisions
- ❑ Another group within our hospital
- ❑ Another institution
- ❑ We use a commercial database. Which one? _____
- ❑ Other _____

What type of data is in your database? (check ALL that apply)

- ❑ Demographic information (e.g. race)
- ❑ Prenatal information
- ❑ Labor and delivery data
- ❑ Birth weight and gestational age
- ❑ Diagnoses (e.g. meconium aspiration, ROP)
- ❑ Procedures (e.g. umbilical line placement, surgery)
- ❑ Medications
- ❑ Laboratory data (e.g. blood type, hematocrit)
- ❑ Discharge data (including survival)
- ❑ Financial information (e.g. source of pay, billing costs)
- ❑ Other _____

Who was **primarily** responsible for choosing the specific data you collect? (check one)

- ❑ Clinical care provider(s) at our hospital
- ❑ Research group at our hospital
- ❑ Regional or national data network (consortium)
- ❑ Commercial database developer
- ❑ Other _____

Does your database duplicate data found in another hospital database? (check one)

- ❑ NO
- ❑ YES, several items duplicated
- ❑ YES, large blocks of information duplicated

Do you obtain raw information (by print-out or electronically) from **another database**? (check ALL that apply)

- ❑ NO
- ❑ YES, from a separate obstetric database
- ❑ YES, from a referring hospital's database
- ❑ YES, from office practice or clinic databases
- ❑ YES, from another neonatology division's database
- ❑ YES, other _____

How many different data entry items (fields) do you collect? (check one)

- ❑ <10
- ❑ 10-50
- ❑ 51-100
- ❑ 101-250
- ❑ >250

When are data forms (either paper or computer screen) filled out for an infant? (check one)

- ❑ Daily while infant is in the hospital
- ❑ Periodically while infant is in the hospital (e.g. weekly)
- ❑ After the infant is discharged

Who fills out >75% of an individual infant's data forms? (check one)

- ❑ No one person fills out >75%
- ❑ Neonatologist
- ❑ Research assistant or chart abstracter
- ❑ Neonatal fellow or housestaff
- ❑ Nurse clinician or nurse practitioner
- ❑ General Pediatrician
- ❑ Obstetrician
- ❑ Staff nurse
- ❑ Medical records staff
- ❑ Other _____

Who else fills out data forms? (check ALL that apply)

- ❑ No one else assists in filling out forms.
- ❑ Neonatologist
- ❑ Research assistant or chart abstracter
- ❑ Neonatal fellow or housestaff
- ❑ Nurse clinician or nurse practitioner
- ❑ General Pediatrician
- ❑ Obstetrician
- ❑ Staff nurse
- ❑ Medical records staff

In a one year period how many **separate people** fill out data forms? (check one)

- ❑ Only 1
- ❑ 2-5
- ❑ 6-10
- ❑ 11-20
- ❑ 21 or more

How long does it take to fill out the data forms on a **routine** infant? (check one)

- ❑ <1 minute
- ❑ 1-5 minutes
- ❑ 6-15 minutes
- ❑ 16-30 minutes
- ❑ > 30 minutes

How long does it take to fill out the data forms on a **complicated** infant? (check one)

- ❑ <1 minute
- ❑ 1-5 minutes
- ❑ 6-15 minutes
- ❑ 16-30 minutes
- ❑ >30 minutes

Have you **used** your database for statistical information? ❑ **NO** ❑ **YES**

Which ones? Please answer each item:	**NO**	**YES**
Annual statistical data (including survival data)	❑	❑
Data for state or federal agencies	❑	❑
Information for training program accreditation	❑	❑
Data for staff planning purposes	❑	❑
Data for published manuscripts	❑	❑

Have you **used** your database for quality assurance activities? ❑ **NO** ❑ **YES**

Which ones? Please answer each item:	**NO**	**YES**
Diagnosis identification for quality assurance audits	❑	❑
Monitor individual physician practices	❑	❑
Develop educational programs	❑	❑
Comparison of your nursery population to others	❑	❑
Investigate trends in patient care	❑	❑

Do you use your database to generate any patient care forms? ❑ **NO** ❑ **YES**

Which ones? Please answer each item:	**NO**	**YES**
Birth certificate	❑	❑
Admission history and physical	❑	❑
Daily progress notes	❑	❑
Flow sheets (eg weight, caloric intake)	❑	❑
Chart face sheet or problem list	❑	❑
Discharge summary	❑	❑

Have you **used** your database for any of the following reasons?

Please answer each item:	**NO**	**YES**
Designing clinical research projects	❑	❑
To describe case mix or outcome for marketing	❑	❑
Administrative cost allocation or priority setting	❑	❑
Communication with referring physicians / hospitals	❑	❑
Patient billing	❑	❑

Other uses for database _____

How much of the data collected do you feel you actually use? (check one)

- ❑ <10%
- ❑ 10-25%
- ❑ 26-50%
- ❑ 51-75%
- ❑ 76-90%
- ❑ >90%

Who pays for the majority of your database operation? (check one)

- ❑ Neonatal division
- ❑ Other physician based group
- ❑ Hospital
- ❑ Granting agency
- ❑ Other_____

Do you use a computer for your database? (check one)

- ❑ NO (please skip next question)
- ❑ YES, a personal computer
- ❑ YES, a mini-computer or mainframe

Does your database program have built in error codes? ❑ NO ❑ YES ❑ Don't know

What data source is used to verify information in your database? (check ALL that apply)

- ❑ Caretaker recall
- ❑ Comparison with case summary or discharge summary
- ❑ Comparison with hospital ICD-9 coding
- ❑ Comparison with another data source
- ❑ Chart review

Do you use a **routine schedule** to monitor database accuracy? ❑ NO ❑ YES

How is database accuracy monitored? (check one)

- ❑ **All** data items are verified in **all** cases.
- ❑ Select data items are verified in **all** cases.
- ❑ Intermittent quality of data audits are conducted on **all** data items.
- ❑ Intermittent quality of data audits are conducted on select data items.
- ❑ Data are verified only when discrepancies are suspected.
- ❑ Other _____

What is the **overall** accuracy of your database? (check one)

- ❑ The majority (>90%) of items are accurate enough for use in research publication.
- ❑ Most (>70%) items are accurate enough for use in research publication.
- ❑ The majority of items are accurate enough to suggest trends.
- ❑ Most items are accurate enough to suggest trends.
- ❑ The accuracy is too inconsistent for data to be relied on.
- ❑ Overall accuracy has not been established.

Do you like your current nursery database? (check one)

- ❑ NO, and we are giving up on databases.
- ❑ NO, and we are looking for a different database.
- ❑ NO, and we plan to modify our current database.
- ❑ YES, but we plan to modify our current database.
- ❑ YES, we are very satisfied.

What don't you like about your database? (check ALL that apply)

- ❑ We like all features.
- ❑ It does not provide the right information.
- ❑ It does not provide enough information.
- ❑ The information it provides is inaccurate.
- ❑ It takes too long to collect data.
- ❑ It takes too long to enter or process data.
- ❑ There is too much useless information collected.
- ❑ It's not worth all the effort.
- ❑ It costs too much to maintain.
- ❑ Other _____

COMMENTS:

Thank you for your time.