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Product Information
as of July, 1986
0906

ProHIBiT®
HAEMOPHILUS b CONJUGATE VACCINE
(Diphtheria Toxoid-Conjugate)

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

DESCRIPTION

ProHIBiT®, Haemophilus b Conjugate Vaccine (Diphtheria Toxoid-Conjugate), for intramuscular use, is a sterile solution, prepared from the purified capsular polysaccharide, a polymer of ribose, ribitol and phosphate (PRP) of the Eagen *Haemophilus influenzae* type b strain covalently bound to

diphtheria toxoid (D) and dissolved in sodium phosphate buffered isotonic sodium chloride solution. The polysaccharide-protein conjugate molecule is referred to as PRP-D. Thimerosal (mercury derivative) 1:10,000 is added as a preservative. The vaccine is a clear, colorless solution. Each single dose of 0.5 ml is formulated to contain 25 mcg of purified capsular polysaccharide and 18 mcg of diphtheria toxoid protein.

CLINICAL PHARMACOLOGY

Haemophilus influenzae type b (Haemophilus b) is a leading cause of serious systemic bacterial disease in the United States. It is the most common cause of bacterial meningitis, accounting for an estimated 12,000 cases annually, primarily among children under 5 years of age. The mortality rate is 5%, and neurologic sequelae are observed in as many as 25%-35% of survivors.¹ Most cases of *Haemophilus influenzae* meningitis among children are caused by capsular strains of type b, although this capsular type represents only one of the six types known for this species. In addition to bacterial meningitis, Haemophilus b is responsible for other invasive diseases, including epiglottitis, sepsis, cellulitis, septic arthritis, osteomyelitis, pericarditis, and pneumonia.¹ In the United States, approximately one of every 1,000 children under 5 years of age develops systemic Haemophilus b disease each year, and a child's cumulative risk of developing systemic Haemophilus b disease at some time during the first 5 years of life is about one in 200. Attack rates peak between 6 months and 1 year of age and decline thereafter.¹ Approximately 30%-38% of Haemophilus b disease occurs among children 18 months of age or older, and 15%-25% occurs above 24 months of age.^{2,3,4} Incidence rates of Haemophilus b disease are increased in certain high-risk groups, such as Native Americans (both American Indian and Eskimo), blacks, individuals of lower socioeconomic status, and patients with splenia, sickle cell disease, Hodgkin's disease, and antibody deficiency syndromes.^{1,4} Recent studies also have suggested that the risk of acquiring primary Haemophilus b disease for children under 5 years of age appears to be greater for those who attend day-care facilities than for those who do not.^{5,6}

The potential for person-to-person transmission of the organism among susceptible individuals has been recognized. Studies of secondary spread of disease in household contacts of index patients have shown a substantially increased risk among exposed household contacts under 4 years of age.⁷ In addition, numerous clusters of cases in day-care facilities have been reported, and recent studies suggest that secondary attack rates in day-care classroom contacts of a primary case also may be increased.^{8,9} Adults can be colonized with *Haemophilus influenzae* type b from children infected with the organism.¹⁰

In 1974, a randomized controlled trial was conducted in Finland, which allowed the evaluation of clinical efficacy of a non-conjugated Haemophilus type b polysaccharide vaccine in children 3-71 months of age.¹¹ Approximately 98,000 children, half of whom received the Haemophilus b vaccine, were enrolled in the field trial and followed for a 4-year period for the occurrence of Haemophilus b disease. Among children 18-71 months of age, 90% protective efficacy (95% confidence limits, 65%-98%) in prevention of all forms of invasive Haemophilus b disease was demonstrated for the 4-year follow-up period.

Based on evidence from this 1974 Finnish efficacy trial, from passive protection in the infant rat model, and from experience with agammaglobulinemic children, an antibody concentration of ≥ 0.15 mcg/ml has been correlated with protection.^{11,12,13,14} In three-week post-vaccination serum in the 1974 Finnish trial, antibody levels of ≥ 1 mcg/ml were correlated with long-term protection.¹¹

The development of stable humoral immunity requires the recognition of foreign material by at least two separate sets of lymphocytes. These sets are the B-lymphocytes which are precursors of antibody forming cells, and the T-lymphocytes which can modulate the function of B-cells. Some antigens such as polysaccharides are capable of stimulating B-cells

directly to produce antibody (T-independent). The responses to many other antigens are augmented by helper T-lymphocytes (T-dependent).¹⁵ ProHIBiT utilizes a new technology, covalent bonding of the capsular polysaccharide of *Haemophilus influenzae* type b to diphtheria toxoid, to produce an antigen which is postulated to convert the T-independent antigen into a T-dependent antigen.^{16,17} The protein carries both its own antigenic determinants and those of the covalently bound polysaccharide. As a result of the conjugation to protein, the polysaccharide is postulated to be presented as a T-dependent antigen resulting in both an enhanced antibody response and an immunologic memory. In studies for functional activity, anti-capsular antibodies induced by ProHIBiT had bactericidal activity, opsonic activity and were also active in passive protection assays.^{18,19,20} In studies conducted with ProHIBiT in several locations throughout the U.S., the antibody responses of 18-26 month old children were measured. (Table 1)¹⁸ In other studies, the antibody responses to licensed Haemophilus b polysaccharide vaccines were measured in a comparable age group. (Table 1)¹⁸ The data shown in Table 1 were obtained from sera tested in one laboratory using a single radioimmunoassay (RIA). Mean antibody levels induced by ProHIBiT in children 18-20 months of age are 30-fold higher than those induced by polysaccharide vaccines in the same age group.¹⁸ The RIA procedure used by Connaught Laboratories, Inc. to estimate antibody responses to the Haemophilus b vaccines has been shown to correlate with the assay used by the Finland National Public Health Institute.²¹ Antibody levels (≥ 1.0 mcg/ml) estimated by the Finnish assay were correlated with protection.¹¹

[See table below.]

Following immunization of 16-24 month old children with a single dose of ProHIBiT, eighty-nine percent (109/123) had antibody levels ≥ 0.15 mcg/ml 12 months post immunization, compared to 93% 1 month post vaccination.¹⁸ A group of 36 patients with sickle cell disease (SS, SC, S-thalassemia), aged 1.5 to 6.0 years (mean 3.3 years), was immunized with ProHIBiT. All produced titers of ≥ 0.15 mcg/ml and 94% produced titers of ≥ 1.0 mcg/ml.^{18,22}

INDICATIONS AND USAGE

ProHIBiT is indicated for the routine immunization of children 18 months to 5 years of age against invasive diseases caused by *Haemophilus influenzae* type b. As with other vaccines, several days following administration of ProHIBiT are required for protective levels of antibody to be attained. A booster dose of ProHIBiT is not required.

ProHIBiT will not protect against *Haemophilus influenzae* other than type b or other microorganisms that cause meningitis or septic disease.

No impairment of the immune response to the individual antigens was demonstrated when ProHIBiT and Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTP) were given at the same time at separate sites.²³ Because the safety and efficacy of ProHIBiT have not been established in children less than 18 months of age, ProHIBiT is not indicated for use in this age group at this time. Studies to establish the safety and efficacy of ProHIBiT in children less than 18 months of age are ongoing.²⁴

ProHIBiT IS NOT RECOMMENDED FOR USE IN CHILDREN YOUNGER THAN 18 MONTHS OF AGE.

CONTRAINDICATIONS

HYPERSENSITIVITY TO ANY COMPONENT OF THE VACCINE, INCLUDING THIMEROSAL AND DIPHTHERIA TOXOID, IS A CONTRAINDICATION TO USE OF THIS VACCINE.

WARNINGS

If ProHIBiT is used in persons with malignancies or those receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

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

PRECAUTIONS**GENERAL**

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. 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 hypersensitivity to the vaccine or similar vaccines. Any febrile illness or acute infection is reason to delay the use of ProHIBiT.

As reported with Haemophilus b to polysaccharide vaccine,²⁵ cases of Haemophilus b disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccine.

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 individual patient to prevent

TABLE 1
Immunogenicity Studies of ProHIBiT and Polysaccharide Vaccines^{*18}

Vaccine	Age Group	No. of Subjects	Anti-Polysaccharide GMT (mcg/ml)		% Subjects Responding with ≥ 1.0 mcg/ml**
			Pre	Post	
ProHIBiT	18-21 Mo.	173	0.025	2.85	75%
	22-26 Mo.	37	0.021	2.96	73%
POLYSACCHARIDE	18-20 Mo.	51	0.021	0.100	24%
	24-27 Mo.	84	0.035	0.520	43%

* Only subjects whose sera had preimmunization levels ≤ 0.60 mcg/ml were included in this analysis.

** A subset of these data was obtained from a randomized comparison of the two vaccines, in which the percentage of children 18-20 months of age responding with ≥ 1.0 mcg/ml was 75% for ProHIBiT (n = 12) and 27% for the polysaccharide (n = 11).

transmission of hepatitis or other infectious agents from one person to another.

ALTHOUGH SOME IMMUNE RESPONSE TO THE DIPHTHERIA TOXOID COMPONENT MAY OCCUR, IMMUNIZATION WITH ProHIBIT DOES NOT SUBSTITUTE FOR ROUTINE DIPHTHERIA IMMUNIZATION.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

ProHIBIT 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 ProHIBIT. It is also not known whether ProHIBIT can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ProHIBIT is NOT recommended for use in a pregnant woman.

ADVERSE REACTIONS

When ProHIBIT alone was given to over 1,000 adults and children, no serious adverse reactions were observed.^{17,18,20} Thrombocytopenia was seen in one adult but a causative relationship was not established.

When ProHIBIT was given with DTP and Inactivated Poliovirus Vaccine to 30,000 young infants, the rate and extent of serious adverse reactions were not different from those seen when DTP was administered alone. Allergic reactions such as urticaria were infrequently observed.^{15,24}

Selected adverse reactions following vaccination with ProHIBIT (without DTP) in subjects 16-24 months of age are summarized in Table 2.

TABLE 2
Percentage of Subjects 16-24 Months Of Age Developing Local Reactions or Fever to One Dose of Haemophilus b Conjugate Vaccine (Diphtheria Toxoid-Conjugate)¹⁸

	No. of Subjects*	Reaction %		
		6 Hours	24 Hours	48 Hours
Fever > 38.3°C	281	1.1	2.1	1.8
Erythema	285	—	2.5	0.4
Induration	285	—	1.0	0.4
Tenderness	285	—	4.6	0.7

*Not all subjects had measurements at all time periods. Other adverse reactions temporally associated with administration of ProHIBIT including diarrhea, vomiting, and crying were reported at a frequency of $\leq 1.2\%$.²⁶ Adverse reactions in clinical evaluations among 689 children, 7-14 months of age, 24 hours after receiving a single dose of ProHIBIT, were observed and compared to 139 children who received a saline placebo. There were no significant differences in the reaction rates for fever, erythema, induration, and tenderness between the two groups.¹⁸

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, vaccine should not be administered. ProHIBIT is indicated for children 18 months to 5 years of age. The immunizing dose is a single injection of 0.5 ml given intramuscularly in the outer aspect area of the vastus lateralis (mid-thigh) or deltoid.

Each 0.5 ml dose contains 25 mcg of purified capsular polysaccharide and 18 mcg of conjugated diphtheria toxoid 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.

HOW SUPPLIED

Vial, 1 Dose (5 per package) — Product No. 49281-541-01
Vial, 5 Dose — Product No. 49281-541-05
Vial, 10 Dose — Product No. 49281-541-10

STORAGE

Store between 2° - 8°C (35° - 46°F). DO NOT FREEZE.

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Product information as of December, 1987 0685

Products are listed alphabetically in the **PINK SECTION.**

Consolidated Midland Corp.
195 EAST MAIN STREET
BREWSTER, NY 10509

ACTIBINE®

Brand of Yohimbine hydrochloride

DESCRIPTION

Yohimbine is a 3 α -15 α -20 β -17 α -hydroxy Yohimbine-carboxylic acid methyl ester. The alkaloid is found in R case and related trees. Also in Rauwolfia Serpentina Benth. Each compressed tablet contains 5 mg of Yohim Hydrochloride.

ACTION

Yohimbine blocks presynaptic alpha-2 adrenergic receptor action on peripheral blood vessels resembles that of re pine though it is weaker and of short duration. Yohimbi peripheric autonomic nervous system effect is to incre parasympathetic (cholinergic) and decrease sympath (adrenergic) activity. It is to be noted that in male ses performance, erection is linked to cholinergic activity an alpha-2 adrenergic blockade which may theoretically re in increased penile inflow, decreased penile outflow or b Yohimbine exerts a stimulation action on the mod and i increase anxiety. Such actions have not been adequa studied or related to dosage although they appear to req high doses of the drug. Yohimbine has a mild anti-diur action, probably via stimulation of hypothalamic centers, release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence cardiac stimulation and other effects mediated by β -adre gic receptors, its effect on blood pressure, if any, would b lower it; however, no adequate studies are at hand to qua tate this effect in terms of Yohimbine dosage.

INDICATIONS

No claims are made by the manufacturer for effectiveness any indications. At present there is a growing inter among urologists to use Yohimbine HCl experimentally the treatment and for the diagnostic classification of cert types of male erectile impotence. Yohimbine is a sympathi lytic agent.

CONTRAINDICATION

Renal diseases, and patient's sensitive to the drug. In view the limited and inadequate information at hand, no prec tabulation can be offered of additional contra-indication

WARNING

Generally, this drug is not proposed for use in females a certainly must not be used during pregnancy. Neither is tl drug proposed for use in pediatric, geriatric or cardio-rem patients with gastric or duodenal ulcer history. Nor should be used in conjunction with mood-modifying drugs such antidepressants, or in psychiatric patients in general.

ADVERSE REACTIONS

Yohimbine readily penetrates the (CNS) and produces a co plex pattern of responses in lower doses than required produce peripheral α -adrenergic blockade. These includ antidiuresis, a general picture of central excitation includi elevation of blood pressure and heart rate increased mot activity, irritability and tremor. Sweating, nausea and vo iting are common after parenteral administration of tl drug. Also dizziness, headache, skin flushing reported wh used orally.

DOSAGE AND ADMINISTRATION

Experimental dosage reported in treatment of erectile imp tence: 1 tablet (5 mg) 4 times a day, to adult males take orally. Occasional side effects reported with dosage are na sea, dizziness or nervousness. In the event of side effects do age is to be reduced to 1/2 tablet 4 times a day, followed b gradual increases to 1 tablet 4 times a day. Reported therap not more than 10 weeks.

HOW SUPPLIED

Oral tablets of Actibin 5 mg in bottles of 100's, U.D. (Un Dose) 100's, and 1000's.

Products are cross-indexed by generic and chemical names in the **YELLOW SECTION**

23 Pneumococcal Capsular Types Included in PNEUMOVAX 23

Nomenclature	Pneumococcal Types																						
Danish	1	2	3	4	5	6B	7F	8	9N	9V	10A	11A	12F	14	15B	17F	18C	19F	19A	20	22F	23F	33F
U.S.	1	2	3	4	5	26	51	8	9	68	34	43	12	14	54	17	56	19	57	20	22	23	70

for possible revisions

HOW SUPPLIED

No. 3276—Tablets PERIACTIN, containing 4 mg of ciproheptadine hydrochloride each, are white, round, scored, compressed tablets, coded MSD 62. They are supplied as follows: NDC 0006-0062-68 bottles of 100 (8605-00-890)-1884 4 mg (100's)

Shown in Product Identification Section, page 419
No. 3289X—Syrup PERIACTIN, 2 mg per 5 mL is a clear, yellow, syrupy liquid. Contains alcohol 5%, with sorbic acid 0.1% added as preservative and is supplied as follows: NDC 0006-3289-74 bottles of 473 mL.

Storage
Store Tablets PERIACTIN in a well-closed container. Avoid storage at temperatures above 40°C (104°F).
Store Syrup PERIACTIN in a container which is kept tightly closed. Avoid storage at temperatures below -20°C (-4°F) and above 40°C (104°F).

A.H.F.S. Category: 4:00
DC 7398317 Issued May 1986

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PNEUMOVAX® 23
Pneumococcal Vaccine Polyvalent, MSD

DESCRIPTION

PNEUMOVAX® 23 (Pneumococcal Vaccine Polyvalent, MSD), is a sterile, liquid vaccine for intramuscular or subcutaneous injection. It consists of a mixture of highly purified capsular polysaccharides from the 23 most prevalent or invasive pneumococcal types accounting for at least 90% of pneumococcal blood isolates and at least 85% of all pneumococcal isolates from sites which are generally sterile as determined by ongoing surveillance of U.S. data.

PNEUMOVAX 23 is manufactured according to methods developed by the MERCK SHARP & DOHME Research Laboratories. Each 0.5 mL dose of vaccine contains 25 µg of each polysaccharide type dissolved in isotonic saline solution containing 0.25% phenol as preservative.

Type 6B pneumococcal polysaccharide exhibits somewhat greater stability in purified form than does Type 6A. A high degree of cross-reactivity between the two types has been demonstrated in adult volunteers. Therefore, Type 6B has replaced Type 6A, which had been used in the 14-valent vaccine. Although contained in the 14-valent vaccine, Type 25 is not included in PNEUMOVAX 23 because it has recently become a rare isolate in many parts of the world including the United States, Canada and Europe. (See table above).

CLINICAL PHARMACOLOGY

Pneumococcal infection is a leading cause of death throughout the world and a major cause of pneumonia, meningitis, and otitis media. The emergence of strains of pneumococci with increased resistance to one or more of the common antibiotics and recent isolations of pneumococci with multiple antibiotic resistance emphasize the importance of vaccine prophylaxis against pneumococcal disease. Based on projection from limited observations in the United States, it has been estimated that 400,000 to 500,000 cases of pneumococcal pneumonia may occur annually. The overall case fatality rate ranges from 5-10%. Populations at high risk are the elderly; individuals with immune deficiencies; patients with asplenia or splenic deficiencies, including sickle cell anemia and other severe hemoglobinopathies; alcoholics; and patients with the following diseases: Hodgkin's disease, multiple myeloma and nephrotic syndrome. About 25% of all persons with pneumococcal pneumonia develop bacteremia. Death occurs in about 28% of these bacteremic patients over 50 years of age. Of all patients with pneumococcal bacteremia who died despite treatment with penicillin or tetracycline, as many as 60% died within five days of onset of the illness.

The annual incidence of pneumococcal meningitis is approximately 1.5 to 2.5 per 100,000 population. One-half of the cases occur in children, in whom the fatality rate is about 40%. Children with sickle cell disease have been estimated to have a risk of pneumococcal meningitis nearly 600 times greater than normal children. Other illnesses caused by

pneumococci include acute exacerbations of chronic bronchitis, sinusitis, arthritis and conjunctivitis. Invasive pneumococcal disease causes high morbidity and mortality in spite of effective antimicrobial control by antibiotics. These effects of pneumococcal disease appear due to irreversible physiologic damage caused by the bacteria during the first 5 days following onset of illness, and occur irrespective of antimicrobial therapy. Vaccination offers an effective means of further reducing the mortality and morbidity of this disease.

At present, there are 83 known pneumococcal capsular types. However, the preponderance of pneumococcal diseases is caused by only some capsular types. For example, a 10-year (1952-1962) surveillance at a New York medical center, showed that 56% of all deaths due to pneumococcal pneumonia were caused by 6 capsular types and that approximately 78% of all pneumococcal pneumonias were caused by 12 capsular types. Such unequal distribution of pneumococcal capsular types causing disease has been shown throughout the world. It is on the basis of this information that the pneumococcal vaccine is composed of 23 capsular types, designed to provide coverage of approximately 90% of the most frequently reported types.

It has been established that the purified pneumococcal capsular polysaccharides induce antibody production and that such antibody is effective in preventing pneumococcal disease. Studies in humans have demonstrated the immunogenicity (antibody-stimulating capability) of each of the 23 capsular types when tested in polyvalent vaccines. Adults of all ages responded immunologically to the vaccines. Earlier studies with 12- and 14-valent pneumococcal vaccines in children two years of age and older and in adults showed immunogenic responses. Protective capsular type-specific antibody levels develop by the third week following vaccination.

The protective efficacy of pneumococcal vaccines containing 6 and 12 capsular polysaccharides was investigated in controlled studies of gold miners in South Africa, in whom there is a high attack rate for pneumococcal pneumonia. Capsular type-specific attack rates for pneumococcal pneumonia were observed for the period from 2 weeks through about 1 year after vaccination. The rates for pneumonia caused by the same capsular types represented in the vaccines are given in the table. Protective efficacy was 76% and 92%, respectively, in the two studies for the capsular types represented. (See table below).

In similar studies carried out by Dr. R. Austrin and associates using similar pneumococcal vaccines prepared for the National Institute of Allergy and Infectious Diseases, the reduction in pneumonias caused by the capsular types contained in the vaccines was 79%. Reduction in type-specific pneumococcal bacteremia was 82%. A preliminary report suggests that in patients with sickle cell anemia and/or anatomical or functional asplenia, the vaccine was highly effective in persons over two years of age in preventing severe pneumococcal disease and bacteremia.

The duration of protective effect of PNEUMOVAX 23 is presently unknown, but it has been shown in previous studies with other pneumococcal vaccines that antibody induced by the vaccine may persist for as long as 5 years. Type-specific antibody levels induced by PNEUMOVAX (Pneumococcal Vaccine, Polyvalent, MSD) (14-valent) have been observed to decline over a 42-month period of observation, but remain significantly above prevaccination levels in almost all recipients who manifest an initial response.

INDICATIONS AND USAGE

PNEUMOVAX 23 is indicated for immunization against pneumococcal disease caused by those pneumococcal types included in the vaccine. Effectiveness of the vaccine in the prevention of pneumococcal pneumonia and pneumococcal bacteremia has been demonstrated in controlled trials. PNEUMOVAX 23 will not immunize against capsular types of pneumococcus other than those contained in the vaccine.

Use in selected individuals over 2 years of age as follows: (1) patients who have anatomical asplenia or who have splenic dysfunction due to sickle cell disease or other causes; (2) persons with chronic illnesses in which there is an increased risk of pneumococcal disease, such as functional impairment of cardiorespiratory, hepatic and renal systems; (3) persons 50 years of age or older; (4) patients with other chronic illnesses who may be at greater risk of developing pneumococcal infection or experiencing more severe pneumococcal illness as a result of alcohol abuse or coexisting diseases including diabetes mellitus, chronic cerebrospinal fluid leakage, or conditions associated with immunosuppression; (5) patients with Hodgkin's disease if immunization can be given at least 10 days prior to treatment. For maximal antibody response immunization should be given at least 14 days prior to the start of treatment with radiation or chemotherapy. Immunization of patients less than 10 days prior to or during treatment is not recommended. (see CONTRAINDICATIONS.)

Use in communities. Persons over 2 years of age as follows: (1) closed groups such as those in residential schools, nursing homes and other institutions. (To decrease the likelihood of acute outbreaks of pneumococcal disease in closed institutional populations where there is increased risk that the disease may be severe, vaccination of the entire closed population should be considered where there are no other contraindications.); (2) groups epidemiologically at risk in the community when there is a generalized outbreak in the population due to a single pneumococcal type included in the vaccine; (3) patients at high risk of influenza complications, particularly pneumonia.

PNEUMOVAX 23 may not be effective in preventing infection resulting from basilar skull fracture or from external communication with cerebrospinal fluid.

Simultaneous administration of pneumococcal polysaccharide vaccine and whole-virus influenza vaccine gives satisfactory antibody response without increasing the occurrence of adverse reactions. Simultaneous administration of the pneumococcal vaccine and split-virus influenza vaccine may also be expected to yield satisfactory results.

Revaccination

Revaccination of adults is not recommended. Adults previously immunized with any polyvalent pneumococcal vaccine should not receive PNEUMOVAX 23 or PNEUMOVAX (Pneumococcal Vaccine, Polyvalent, MSD) (14-valent) since an increased incidence and severity of adverse reactions among healthy adults receiving such reinjections have been noted, most likely due to sustained high antibody levels.

Certain groups of children at very high risk for pneumococcal disease (e.g., children with sickle cell disease or nephrotic syndrome) may have lower peak levels of antibody response and/or more rapid rates of decline in antibody levels than do healthy adults. However, insufficient data are available at this time to permit formulation of guidelines for reimmunization of high-risk children.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine. Epinephrine in injection (1:1000) must be immediately available should an acute anaphylactoid reaction occur due to any component of the vaccine.

Revaccination of adults is contraindicated. Adults previously immunized with any polyvalent pneumococcal vaccine should not receive PNEUMOVAX 23 or PNEUMOVAX (Pneumococcal Vaccine, Polyvalent, MSD) (14-valent) since an increased incidence and severity of adverse reactions among healthy adults receiving such reinjections have been noted, most likely due to sustained high antibody levels. Patients with Hodgkin's disease immunized less than 7 to 10 days prior to immunosuppressive therapy have in some instances been found to have post-immunization antibody levels below their pre-immunization levels. Because of these results, immunization less than 10 days prior to or during treatment is contraindicated.

Patients with Hodgkin's disease who have received extensive chemotherapy and/or nodal irradiation have been shown to have an impaired antibody response to a 12-valent pneumococcal vaccine. Because, in some intensively treated patients, administration of that vaccine depressed pre-existing levels of antibody to some pneumococcal types, PNEUMOVAX 23

Continued on next page

PNEUMOVAX 23

Number of Capsular Types in Pneumococcal Vaccine	Rate/1000 for Pneumonia Caused by Homologous Capsular Types		Protective Efficacy
	Vaccinated Group	Control Group	
6	9.2	38.3	76%
12	1.8	22.0	92%

Information on the Merck Sharp & Dohme products listed on these pages is the full prescribing information from product circulars in use August 31, 1985.

Merck Sharp & Dohme—Cont.

is not recommended at this time for patients who have received these forms of therapy for Hodgkin's disease.

WARNINGS

If the vaccine is used in persons receiving immunosuppressive therapy, the expected serum antibody response may not be obtained. Intradermal administration may cause severe local reactions.

PRECAUTIONS

General

Caution and appropriate care should be exercised in administering PNEUMOVAX 23 to individuals with severely compromised cardiac and/or pulmonary function in whom a systemic reaction would pose a significant risk.

Any febrile respiratory illness or other active infection is reason for delaying use of PNEUMOVAX 23, except when, in the opinion of the physician, withholding the agent entails even greater risk.

In patients who require penicillin (or other antibiotic) prophylaxis against pneumococcal infection, such prophylaxis should not be discontinued after vaccination with PNEUMOVAX 23.

Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with PNEUMOVAX 23. It is also not known whether PNEUMOVAX 23 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PNEUMOVAX 23 should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PNEUMOVAX 23 is administered to a nursing woman.

Pediatric Use

Children less than 2 years of age do not respond satisfactorily to the capsular types of PNEUMOVAX 23 that are most often the cause of pneumococcal disease in this age group. Safety and effectiveness in children below the age of 2 years have not been established. Accordingly, PNEUMOVAX 23 is not recommended in this age group.

ADVERSE REACTIONS

Local erythema and soreness at the injection site, usually of less than 48 hours duration, occurs commonly; local induration occurs less commonly. In a study of PNEUMOVAX 22 (containing 22 capsular types) in 29 adults, 21 (71%) showed local reaction characterized principally by local soreness and/or induration at the injection site within 2 days after vaccination.

Rash, urticaria, arthralgia, serum sickness, and adenitis have been reported rarely.

Low grade fever (less than 100.9°F) occurs occasionally and is usually confined to the 24-hour period following vaccination. Although rare, fever over 102°F has been reported. Malaise, myalgia, and asthenia also have been reported.

Patients with otherwise stabilized idiopathic thrombocytopenic purpura have, on rare occasions, experienced a relapse in their thrombocytopenia, occurring 2 to 14 days after vaccination, and lasting up to 2 weeks.

Reactions of greater severity, duration, or extent are unusual. Neurological disorders such as paresthesias and acute radiculoneuropathy including Guillain-Barré syndrome have been rarely reported in temporal association with administration of pneumococcal vaccine. No cause and effect relationship has been established. Rarely, anaphylactoid reactions have been reported.

Tissue or Fluid	N	Imipenem Level mcg/mL or mcg/g	Range
Vitreous Humor	3	3.4 (3.5 hours post dose)	2.88-3.6
Aqueous Humor	5	2.99 (2 hours post dose)	2.4-3.9
Lung Tissue	8	5.6 (median)	3.5-15.5
Sputum	1	2.1	—
Pleural	1	22.0	—
Peritoneal	12	23.9 S.D. ± 5.3 (2 hours post dose)	—
Bile	2	5.3 (2.25 hours post dose)	4.6 to 6.0
CSF (uninflamed)	5	1.0 (4 hours post dose)	0.26-2.0
CSF (inflamed)	7	2.6 (2 hours post dose)	0.5-5.5
Fallopian Tubes	1	13.6	—
Endometrium	1	11.1	—
Myometrium	1	5.0	—
Bone	10	2.6	0.4-5.4
Interstitial Fluid	12	16.4	10.0-22.6
Skin	12	4.4	NA
Fascia	12	4.4	NA

DOSAGE AND ADMINISTRATION

Do not inject intravenously. Intradermal administration should be avoided.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. PNEUMOVAX 23 is a clear, colorless solution.

Administer a single 0.5 mL dose of PNEUMOVAX 23 subcutaneously or intramuscularly (preferably in the deltoid muscle or lateral mid-thigh), with appropriate precautions to avoid intravascular administration.

Single-Dose and 5-Dose Vials

For Syringe Use Only: Withdraw 0.5 mL from the vial using a sterile needle and syringe free of preservatives, antiseptics and detergents.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another. Store unopened and opened vials at 2-8°C (35.6-46.4°F). The vaccine is used directly as supplied. No dilution or reconstitution is necessary. Phenol 0.25% added as preservative. All vaccine must be discarded after the expiration date.

HOW SUPPLIED

No. 4739—PNEUMOVAX 23 contains one 5-dose vial of liquid vaccine, NDC 0006-4739-00. For use with syringe only (6505-01-092-0391).

No. 4741—PNEUMOVAX 23 is supplied as follows: NDC 0006-4741-00. A box of 5 individual cartons, each containing a single-dose vial of vaccine.

A.H.F.S. Category: 80:12

DC 7497404 Issued September 1988

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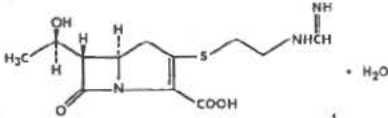
PRIMAXIN®

(Imipenem-Cilastatin Sodium, MSD)

DESCRIPTION

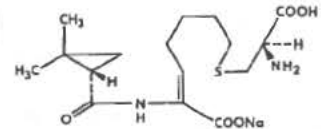
PRIMAXIN® (Imipenem-Cilastatin Sodium, MSD) is a formulation of imipenem, a thienamycin antibiotic, and cilastatin sodium, the inhibitor of the renal dipeptidase, dehydropeptidase I, with sodium bicarbonate added as a buffer. PRIMAXIN is a potent broad spectrum antibacterial agent for intravenous administration.

Imipenem (N-formimidoylthienamycin monohydrate) is a crystalline derivative of thienamycin, which is produced by *Streptomyces cattleya*. Its chemical name is [5R-[5a, 6a (R*)]-6-(1-hydroxyethyl)-3-[[2-[[[iminomethyl]amino] ethyl]thio]-7-oxo-1-azabicyclo [3.2.0] hept-2-ene-2-carboxylic acid monohydrate. It is an off-white, nonhygroscopic crystalline compound with a molecular weight of 317.37. It is sparingly soluble in water, and slightly soluble in methanol. Its empirical formula is C₁₂H₁₇N₃O₄S · H₂O, and its structural formula is:



Cilastatin sodium is the sodium salt of a derivatized heptenoic acid. Its chemical name is [R-[R*,S*(Z)]]-7-[(2-amino-2-carboxyethyl)thio]-2-[[[2, 2-dimethylcyclopropyl] carbonyl]amino]-2-heptenoic acid, monosodium salt. It is an off-white to yellowish-white, hygroscopic, amorphous compound with a molecular weight of 380.43. It is very soluble in water and in methanol. Its empirical formula is

C₁₂H₂₅N₃O₅S Na, and its structural formula is:



PRIMAXIN is buffered to provide solutions in the pH range of 6.5 to 7.5. There is no significant change in pH when solutions are prepared and used as directed. (See COMPATIBILITY AND STABILITY.) PRIMAXIN 250 contains 18.8 mg of sodium (0.8 mEq) and PRIMAXIN 500 contains 37.5 mg of sodium (1.6 mEq). Solutions of PRIMAXIN range from colorless to yellow. Variations of color within this range do not affect the potency of the product.

CLINICAL PHARMACOLOGY

Intravenous Administration

Intravenous infusion of PRIMAXIN over 20 minutes results in peak plasma levels of imipenem antimicrobial activity that range from 14 to 24 mcg/mL for the 250 mg dose, from 21 to 58 mcg/mL for the 500 mg dose and from 41 to 83 mcg/mL for the 1000 mg dose. At these doses, plasma levels of imipenem antimicrobial activity decline to below 1 mcg/mL or less in 4 to 6 hours. Peak plasma levels of cilastatin following a 20-minute intravenous infusion of PRIMAXIN, range from 15 to 25 mcg/mL for the 250 mg dose, from 31 to 49 mcg/mL for the 500 mg dose and from 56 to 88 mcg/mL for the 1000 mg dose.

General

The plasma half-life of each component is approximately 1 hour. The binding of imipenem to human serum proteins is approximately 20% and that of cilastatin is approximately 40%. Approximately 70% of the administered imipenem is recovered in the urine within 10 hours after which no further urinary excretion is detectable. Urine concentrations of imipenem in excess of 10 mcg/mL can be maintained for up to 8 hours with PRIMAXIN at the 500 mg dose. Approximately 70% of the cilastatin sodium dose is recovered in the urine within 10 hours of administration of PRIMAXIN. No accumulation of PRIMAXIN in plasma or urine is observed with regimens administered as frequently as every 6 hours in patients with normal renal function.

Imipenem, when administered alone, is metabolized in the kidneys by dehydropeptidase I resulting in relatively low levels in urine. Cilastatin sodium, an inhibitor of this enzyme, effectively prevents renal metabolism of imipenem so that when imipenem and cilastatin sodium are given concomitantly fully adequate antibacterial levels of imipenem are achieved in the urine.

After a 1 gram dose of PRIMAXIN, the following average levels of imipenem were measured (usually at 1 hour post-dose except where indicated) in the tissues and fluids listed: [See table below].

Microbiology

The bactericidal activity of imipenem results from the inhibition of cell wall synthesis. Its greatest affinity is for penicillin binding proteins (PBP) 1A, 1B, 2, 4, 5, and 6 of *Escherichia coli*, and 1A, 1B, 2, 4 and 5 of *Pseudomonas aeruginosa*. The lethal effect is related to binding to PBP 2 and PBP 1B. Imipenem has *in vitro* activity against a wide range of gram-positive and gram-negative organisms.

Imipenem has a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases produced by gram-negative and gram-positive bacteria. It is a potent inhibitor of beta-lactamases from certain gram-negative bacteria which are inherently resistant to most beta-lactam antibiotics, e.g., *Pseudomonas aeruginosa*, *Serratia* spp., and *Enterobacter* spp.

In vitro, imipenem is active against most strains of clinical isolates of the following microorganisms:

Gram-positive:

Group D streptococci (including enterococci e.g., *Streptococcus faecalis*)

*NOTE: Imipenem is inactive against *Streptococcus faecium*.

Streptococcus pyogenes (Group A streptococci)

Streptococcus agalactiae (Group B streptococci)

Group C streptococci

Group G streptococci

Viridans streptococci

Streptococcus pneumoniae (formerly *Diplococcus pneumoniae*)

Staphylococcus aureus including penicillinase producing strains

Staphylococcus epidermidis including penicillinase producing strains

*NOTE: Many strains of methicillin-resistant staphylococci are resistant to imipenem.

Gram-negative:

Escherichia coli

Proteus mirabilis

Proteus vulgaris