

**FDA PROPOSED TEXT OF 20-JAN 2011 SHOWING REVISIONS AGREED
UPON AT MERCK/FDA TELECONFERENCE OF 21-JAN-2011**

COMMENTS / SUPPORT

Merck Sharp & Dohme Corp., a subsidiary of
 **MERCK & CO., INC.**
Whitehouse Station, NJ 08889, USA

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**PNEUMOVAX® 23
(PNEUMOCOCCAL VACCINE POLYVALENT)**

DESCRIPTION

PNEUMOVAX* 23 (Pneumococcal Vaccine Polyvalent) 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 of *Streptococcus pneumoniae*, including the six serotypes that most frequently cause invasive drug-resistant pneumococcal infections among children and adults in the United States.¹ (See Table 1.) The 23-valent vaccine accounts 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.²

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

Table 1
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
** These serotypes most frequently cause drug-resistant pneumococcal infections ¹	

CLINICAL PHARMACOLOGY

Pneumococcal infection is a leading cause of death throughout the world³ and a major cause of pneumonia, bacteremia, meningitis, and otitis media.

Strains of drug-resistant *S. pneumoniae* have become increasingly common in the United States and in other parts of the world. In some areas as many as 35% of pneumococcal isolates have been reported to be resistant to penicillin. Many penicillin-resistant pneumococci are also resistant to other antimicrobial drugs (e.g., erythromycin,

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NOTE: This draft incorporates the approved company signature change as approved by FDA on 06-Dec-2010.

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trimethoprim-sulfamethoxazole and extended-spectrum cephalosporins), therefore emphasizing the importance of vaccine prophylaxis against pneumococcal disease.

Epidemiology

Pneumococcal infection causes approximately 40,000 deaths annually in the United States.¹

At least 500,000 cases of pneumococcal pneumonia are estimated to occur annually in the United States; *S. pneumoniae* accounts for approximately 25-35% of cases of community-acquired bacterial pneumonia in persons who require hospitalization.¹

Pneumococcal disease accounts for an estimated 50,000 cases of pneumococcal bacteremia annually in the United States. Some studies suggest the overall annual incidence of bacteremia to be approximately 15 to 30 cases/100,000 population with 50 to 83 cases/100,000 for persons 65 years of age and older and 160 cases/100,000 for children less than two years of age.

The incidence of pneumococcal bacteremia is as high as 1% (940 cases/100,000 population) among persons with acquired immunodeficiency syndrome (AIDS).

In the United States, the risk of acquiring bacteremia is lower among whites than among persons in some other racial/ethnic groups (i.e., blacks, Alaskan Natives, and American Indians).

Despite appropriate antimicrobial therapy and intensive medical care, the overall case-fatality rate for pneumococcal bacteremia is 15-20% among adults⁴, and among elderly patients this rate is approximately 30-40%. An overall case-fatality rate of 36% was documented for adult inner-city residents who were hospitalized for pneumococcal bacteremia.¹

In the United States, pneumococcal disease accounts for an estimated 3,000 cases of meningitis annually. The estimated overall annual incidence of pneumococcal meningitis is approximately 1 to 2 cases per 100,000 population. The incidence of pneumococcal meningitis is highest among children six to 24 months and persons aged ≥ 65 years; rates for blacks are twice as high as those for whites or Hispanics. Recurrent pneumococcal meningitis may occur in patients who have chronic cerebrospinal fluid leakage resulting from congenital lesions, skull fractures, or neurosurgical procedures.¹

Invasive pneumococcal disease (e.g., bacteremia or meningitis) and pneumonia cause high morbidity and mortality in spite of effective antimicrobial control by antibiotics.⁴ These effects of pneumococcal disease appear due to irreversible physiologic damage caused by the bacteria during the first 5 days following onset of illness,^{5,6} and occur regardless of antimicrobial therapy.^{5,7} Vaccination offers an effective means of further reducing the mortality and morbidity of this disease.

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Risk Factors

In addition to the very young and persons 65 years of age or older, patients with certain chronic conditions are at increased risk of developing pneumococcal infection and severe pneumococcal illness.

Patients with chronic cardiovascular diseases (e.g., congestive heart failure or cardiomyopathy), chronic pulmonary diseases (e.g., chronic obstructive pulmonary disease or emphysema), or chronic liver diseases (e.g., cirrhosis), diabetes mellitus, alcoholism or asthma (when it occurs with chronic bronchitis, emphysema, or long-term use of systemic corticosteroids) have an increased risk of pneumococcal disease. In adults, this population is generally immunocompetent.¹

Patients at high risk are those who have a decreased responsiveness to polysaccharide antigen or an increased rate of decline in serum antibody concentrations as a result of: immunosuppressive conditions (congenital immunodeficiency, human immunodeficiency virus [HIV] infection, leukemia, lymphoma, multiple myeloma, Hodgkin's disease, or generalized malignancy); organ or bone marrow transplantation; therapy with alkylating agents, antimetabolites, or systemic corticosteroids; chronic renal failure or nephrotic syndrome.^{1,8}

Patients at the highest risk of pneumococcal infection are those with functional or anatomic asplenia (e.g., sickle cell disease⁹ or splenectomy), because this condition leads to reduced clearance of encapsulated bacteria from the bloodstream. Children who have sickle cell disease or have had a splenectomy are at increased risk for fulminant pneumococcal sepsis associated with high mortality.¹

Immunogenicity

It has been established that the purified pneumococcal capsular polysaccharides induce antibody production and that such antibody is effective in preventing pneumococcal disease.^{6,10} Clinical studies have demonstrated the immunogenicity of each of the 23 capsular types when tested in polyvalent vaccines.

Studies with 12-, 14-, and 23-valent pneumococcal vaccines in children two years of age and older and in adults of all ages showed immunogenic responses.^{10,11-14} Protective capsular type-specific antibody levels generally develop by the third week following vaccination.¹³

Bacterial capsular polysaccharides induce antibodies primarily by T-cell-independent mechanisms. Therefore, antibody response to most pneumococcal capsular types is generally poor or inconsistent in children aged < 2 years whose immune systems are immature.¹

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Efficacy

The protective efficacy of pneumococcal vaccines containing 6 or 12 capsular polysaccharides was investigated in two controlled studies of young, healthy gold miners in South Africa, in whom there was a high attack rate for pneumococcal pneumonia and bacteremia.¹³ Capsular type-specific attack rates for pneumococcal pneumonia were observed for the period from 2 weeks through about 1 year after vaccination. Protective efficacy was 76% and 92%, respectively, in the two studies for the capsular types represented.

In similar studies carried out by Dr. R. Austrian and associates,¹⁵ using similar pneumococcal vaccines prepared for the National Institute of Allergy and Infectious Diseases, the reduction in pneumonia caused by the capsular types contained in the vaccines was 79%. Reduction in type-specific pneumococcal bacteremia was 82%.

A prospective study in France found pneumococcal vaccine to be 77% effective in reducing the incidence of pneumonia among nursing home residents.¹⁶

In the United States, two postlicensure randomized controlled trials, in the elderly or patients with chronic medical conditions who received a multivalent polysaccharide vaccine, did not support the efficacy of the vaccine for nonbacteremic pneumonia.^{17,18} However, these studies may have lacked sufficient statistical power to detect a difference in the incidence of laboratory-confirmed, nonbacteremic pneumococcal pneumonia between the vaccinated and nonvaccinated study groups.^{1,19}

A meta-analysis of nine randomized controlled trials of pneumococcal vaccine concluded that pneumococcal vaccine is efficacious in reducing the frequency of nonbacteremic pneumococcal pneumonia among adults in low-risk groups but not in high-risk groups.²⁰ These studies may have been limited because of the lack of specific and sensitive diagnostic tests for nonbacteremic pneumococcal pneumonia. The pneumococcal polysaccharide vaccine is not effective for the prevention of common upper respiratory disease in children.¹

More recently, multiple case-control studies have shown pneumococcal vaccine is effective in the prevention of serious pneumococcal disease, with point estimates of efficacy ranging from 56% to 81% in immunocompetent persons.^{1,21-26}

Only one case-control study did not document effectiveness against bacteremic disease possibly due to study limitations, including small sample size and incomplete ascertainment of vaccination status in patients.²⁷ In addition, case-patients and persons who served as controls may not have been comparable regarding the severity of their underlying medical conditions, potentially creating a biased underestimate of vaccine effectiveness.^{1,19}

A serotype prevalence study, based on the Centers for Disease Control pneumococcal surveillance system, demonstrated 57% overall protective effectiveness against invasive

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infections caused by serotypes included in the vaccine in persons ≥ 6 years of age, 65-84% effectiveness among specific patient groups (e.g., persons with diabetes mellitus, coronary vascular disease, congestive heart failure, chronic pulmonary disease, and anatomic asplenia) and 75% effectiveness in immunocompetent persons aged ≥ 65 years of age. Vaccine effectiveness could not be confirmed for certain groups of immunocompromised patients; however, the study could not recruit sufficient numbers of unvaccinated patients from each disease group.

In an earlier study, vaccinated children and young adults aged 2 to 25 years who had sickle cell disease, congenital asplenia, or undergone a splenectomy experienced significantly less bacteremic pneumococcal disease than patients who were not vaccinated.^{1,28}

Duration of Immunity

Following pneumococcal vaccination, serotype-specific antibody levels decline after 5-10 years.¹ A more rapid decline in antibody levels may occur in some groups (e.g., children).¹ Limited published data suggest that antibody levels may decline in the elderly > 60 years of age.^{29,30}

The Advisory Committee on Immunization Practices (ACIP) states that these findings indicate that revaccination may be needed to provide continued protection.¹ (See INDICATIONS AND USAGE, *Revaccination*.)

The results from one epidemiologic study suggest that vaccination may provide protection for at least nine years after receipt of the initial dose.²² Decreasing estimates of effectiveness with increasing interval since vaccination, particularly among the very elderly (persons aged ≥ 85 years) have been reported.²³

INDICATIONS AND USAGE

PNEUMOVAX 23 is indicated for vaccination 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 in South Africa, France and in case-control studies.

PNEUMOVAX 23 will not prevent disease caused by capsular types of pneumococcus other than those contained in the vaccine.

Vaccination with PNEUMOVAX 23 is recommended for selected individuals as follows:

- routine vaccination for persons 50 years of age or older†

† NOTE: The ACIP recommends routine vaccination for immunocompetent persons 65 years of age and older.

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- persons aged ≥ 2 years with certain chronic conditions or in special environments or social settings.^{1,31}

The ACIP has vaccine specific recommendations for the prevention of pneumococcal disease. Available from: <http://www.cdc.gov/mmwr/PDF/rr/rr4608.pdf>¹ and <http://www.cdc.gov/vaccines/recs/provisional/downloads/pneumo-Oct-2008-508.pdf>³¹

Timing of Vaccination

Pneumococcal vaccine should be given at least two weeks before elective splenectomy, if possible.

For planning cancer chemotherapy or other immunosuppressive therapy (e.g., for patients with Hodgkin's disease or those who undergo organ or bone marrow transplantation), pneumococcal vaccination should be administered at least two weeks prior to the initiation of immunosuppressive therapy. Vaccination during chemotherapy or radiation therapy should be avoided. Based on literature reports, pneumococcal vaccine may be given as early as several months following completion of chemotherapy or radiation therapy for neoplastic disease.^{32,33} In Hodgkin's disease, immune response to vaccination may be impaired for two years or longer after intensive chemotherapy (with or without radiation). During the two years following the completion of chemotherapy or other immunosuppressive therapy, antibody responses improve in some patients as the interval between the end of treatment and pneumococcal vaccination increases.³²

Persons with asymptomatic or symptomatic HIV infection should be vaccinated as soon as possible after their diagnosis is confirmed.

Use With Other Vaccines

The ACIP states that pneumococcal vaccine may be administered at the same time as influenza vaccine (by separate injection in the other arm) without an increase in side effects or decreased antibody response to either vaccine.¹ In contrast to pneumococcal vaccine, influenza vaccine is recommended annually, for appropriate populations.³⁴

Revaccination

The ACIP has recommendations for revaccination against pneumococcal disease in persons at high risk who were previously vaccinated with PNEUMOVAX 23 or the pneumococcal conjugate vaccine.^{1,31,35}

If PNEUMOVAX 23 is used for revaccination, a single 0.5 mL dose is administered subcutaneously or intramuscularly.

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CONTRAINDICATIONS

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

WARNINGS

For planning cancer chemotherapy or other immunosuppressive therapy (e.g., for patients with Hodgkin's disease or those who undergo organ or bone marrow transplantation), the timing of the vaccination is critical. (See INDICATIONS AND USAGE, *Timing of Vaccination.*)

If the vaccine is used in persons receiving immunosuppressive therapy, the expected serum antibody response may not be obtained and potential impairment of future immune responses to pneumococcal antigens may occur.³⁶ (See INDICATIONS AND USAGE, *Timing of Vaccination.*)

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 cardiovascular 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.

PNEUMOVAX 23 may not be effective in preventing pneumococcal meningitis in patients who have chronic cerebrospinal fluid (CSF) leakage resulting from congenital lesions, skull fractures, or neurosurgical procedures.

Routine revaccination of immunocompetent persons previously vaccinated with a 23-valent vaccine is not recommended. However, revaccination once is recommended for persons aged ≥ 2 years who are at highest risk for serious pneumococcal infections and those likely to have a rapid decline in pneumococcal antibody levels. (See INDICATIONS AND USAGE, *Revaccination.*)

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Instructions to Health Care Provider

The health care provider should determine the current health status and previous vaccination history of the vaccinee. (See INDICATIONS AND USAGE, *Revaccination*.)

The health care provider should question the patient, parent or guardian about reactions to a previous dose of PNEUMOVAX 23 or other pneumococcal vaccine.

Information for Patients

The health care provider should inform the patient, parent or guardian of the benefits and risks associated with vaccination. For risks associated with vaccination, see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS. Patients, parents, or guardians should be told that vaccination with PNEUMOVAX 23 may not offer 100% protection from pneumococcal infection.

Patients, parents and guardians should be instructed to report any serious adverse reactions to their health care provider who in turn should report such events to the vaccine manufacturer or the U.S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7967.³⁷

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

PNEUMOVAX 23 is not indicated in children less than 2 years of age. Safety and effectiveness in children below the age of 2 years have not been established. Children in this age group respond poorly to the capsular types contained in this polysaccharide vaccine. (See CLINICAL PHARMACOLOGY, *Immunogenicity*.)

Geriatric Use

Persons 65 years of age or older were enrolled in several clinical studies of PNEUMOVAX 23 that were conducted post-licensure. In the largest of these studies, the safety of PNEUMOVAX 23 in adults 65 years of age and older (N=629) was compared to the safety of PNEUMOVAX 23 in adults 50 to 64 years of age (N=379). The subjects in this study had underlying chronic illness but were in stable condition; at least 1 medical condition at enrollment was reported by 86.3% of subjects who were 50 to 64 years old, and by 96.7% of subjects who were 65 to 91 years old. The rate of vaccine-related systemic adverse

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experiences was higher following revaccination (33.1%) than following primary vaccination (21.7%) in subjects ≥65 years of age, and was similar following revaccination (37.5%) and primary vaccination (35.5%) in subjects 50 to- -64 years of age.

Since elderly individuals may not tolerate medical interventions as well as younger individuals, a higher frequency and/or a greater severity of reactions in some older individuals cannot be ruled out.

Post-marketing reports have been received in which some elderly individuals had severe adverse experiences and a complicated clinical course following vaccination. For example, some individuals with underlying medical conditions of varying severity experienced local reactions and fever associated with clinical deterioration requiring hospital care.

ADVERSE REACTIONS

The most common adverse experiences reported with PNEUMOVAX 23 in clinical trials were:

Local reaction at injection site including soreness, erythema, warmth, swelling and induration

Fever ≤102°F

Other adverse experiences reported in clinical trials and/or in post-marketing experience with PNEUMOVAX 23 include:

General disorders and administration site conditions

Cellulitis

Asthenia

Malaise

Fever (> 102°F)

Chills

Pain

Decreased limb mobility

Peripheral edema in the injected extremity

Digestive System

Nausea

Vomiting

Hematologic/Lymphatic

Lymphadenitis

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Lymphadenopathy

Thrombocytopenia in patients with stabilized idiopathic thrombocytopenic purpura³⁸

Hemolytic anemia in patients who have had other hematologic disorders

Leukocytosis

Hypersensitivity reactions including

Anaphylactoid reactions

Serum Sickness

Angioneurotic edema

Musculoskeletal System

Arthralgia

Arthritis

Myalgia

Nervous System

Headache

Paresthesia

Radiculoneuropathy

Guillain-Barré syndrome

Febrile convulsion

Skin

Rash

Urticaria

Investigations

Increased serum C-reactive protein

In post-marketing experience, injection site cellulitis-like reactions were reported rarely; between 1989 and 2002, when approximately 43 million doses were distributed, the annual reporting rate was <2/100,000 doses. These cellulitis-like reactions occurred with initial and repeat vaccination at a median onset time of 2 days after vaccine administration.

Systemic signs and symptoms including fever, leukocytosis and an increase in the laboratory value for serum C-reactive protein may be associated with local reactions. Post-marketing reports have been received in which some elderly individuals had severe adverse experiences and a complicated clinical course following vaccination. For example, some individuals, with underlying medical conditions of varying severity experienced local reactions and fever associated with clinical deterioration requiring hospital care. (See PRECAUTIONS, *Geriatric Use*)

In a clinical trial, an increased rate of local reactions has been observed with revaccination at 3-5 years following primary vaccination.

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For subjects aged ≥ 65 years, it was reported that the overall injection-site adverse experiences rate was higher following revaccination (79.3%) than following primary vaccination (52.9%). For subjects aged 50-64 years, the reported overall injection-site adverse experiences rate for re-vaccinees and primary vaccinees were similar (79.6% and 72.8% respectively).

In both age groups, re-vaccinees reported a higher rate of a composite endpoint (any of the following: moderate pain, severe pain, and/or large induration at the injection site) than primary vaccinees. Among subjects ≥ 65 years of age, the composite endpoint was reported by 30.6% and 10.4% of revaccination and primary vaccination subjects, respectively, while among subjects 50-64 years of age, the endpoint was reported by 35.5% and 18.9% respectively. The injection site reactions occurred within the 3 day monitoring period and typically resolved by day 5.

The rate of overall systemic adverse experiences was similar among both primary vaccinees and re-vaccinees within each age group. The rate of vaccine-related systemic adverse experiences was higher following revaccination (33.1%) than following primary vaccination (21.7%) in subjects ≥ 65 years of age, and was similar following revaccination (37.5%) and primary vaccination (35.5%) in subjects 50-64 years of age. The most common systemic adverse experiences reported after PNEUMOVAX 23 were as follows: asthenia/fatigue, myalgia and headache.

Regardless of age, the observed increase in post vaccination use of analgesics ($\leq 13\%$ in the re-vaccinees and $\leq 4\%$ in the primary vaccinees) returned to baseline by day 5.

DOSAGE AND ADMINISTRATION

Do not inject intravenously or intradermally.

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. The vaccine is used directly as supplied. No dilution or reconstitution is necessary. Phenol 0.25% has been added as a preservative.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of infectious agents from one person to another.

Withdraw 0.5 mL from the vial using a sterile needle and syringe free of preservatives, antiseptics, and detergents.

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.

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Store unopened and opened vials at 2-8°C (36-46°F). All vaccine must be discarded after the expiration date.

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HOW SUPPLIED

No. 4739 — PNEUMOVAX 23 is supplied as one 5-dose vial of liquid vaccine, color coded with a purple cap and stripe on the vial labels and cartons, **NDC 0006-4739-00**.

No. 4943 — PNEUMOVAX 23 is supplied as a single-dose vial of liquid vaccine, in a box of 10 single-dose vials, color coded with a purple cap and stripe on the vial labels and cartons, **NDC 0006-4943-00**.

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