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PHYSICIANS CIRCULAR

Injection

PNEUMOVAX® 23

(pneumococcal vaccine, polyvalent, MSD)

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 of *Streptococcus pneumoniae*, including the six serotypes that most frequently cause invasive drug-resistant pneumococcal infections among children and adults in the United States (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 United States data.

PNEUMOVAX 23 is manufactured according to methods developed by the MERCK RESEARCH LABORATORIES. Each 0.5 mL dose of vaccine contains 25 mcg of each polysaccharide type dissolved in isotonic saline solution containing 0.25% phenol as a preservative.

Table 1

23 Pneumococcal Capsular Types Included in PNEUMOVAX 23

Danish Nomenclature																					
Pneumococcal Types																					
1	2	3	4	5	6B**	7F	8	9N	9V**	10A	11A	12F	14**	15B	17F	18C	19A**	19F**	20	22F	23F**	33F

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

CLINICAL PHARMACOLOGY

Pneumococcal infection is a leading cause of death throughout the world 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, 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. 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.

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 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 adults, 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.

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.

Invasive pneumococcal disease (e.g., bacteremia or meningitis) and pneumonia cause 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.

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.

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.

Patients at the highest risk of pneumococcal infection are those with functional or anatomic asplenia (e.g., sickle cell disease 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.

Immunogenicity

It has been established that the purified pneumococcal capsular polysaccharides induce antibody production and that such antibody is effective in preventing pneumococcal disease. 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.

Protective capsular type-specific antibody levels generally develop by the third week following vaccination.

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.

Immunogenicity following concomitant administration

In a double-blind, controlled clinical trial, 473 adults, 60 years of age or older, were randomized to receive ZOSTAVAX and PNEUMOVAX 23 concomitantly (N=237), or PNEUMOVAX 23 alone followed 4 weeks later by ZOSTAVAX alone (N=236). At four weeks postvaccination, the VZV antibody levels following concomitant use were significantly lower than the VZV antibody levels following nonconcomitant administration (GMTs of 338 vs. 484 gpELISA units/mL, respectively; GMT ratio = 0.70 (95% CI: [0.61,

0.80])). VZV antibody levels 4 weeks postvaccination were increased 1.9-fold (95% CI: [1.7, 2.1]; meeting the pre-specified acceptance criterion) in the concomitant group vs. 3.1-fold (95% CI: [2.8, 3.5]) in the nonconcomitant group. The GMTs for PNEUMOVAX 23 antigens were comparable between the two groups. Concomitant use of ZOSTAVAX and PNEUMOVAX 23 demonstrated a safety profile that was generally similar to that of the two vaccines administered nonconcomitantly.

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 is a high attack rate for pneumococcal pneumonia and bacteremia. 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 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 prospective study in France found pneumococcal vaccine to be 77% effective in reducing the incidence of pneumonia among nursing home residents.

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. 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.

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. 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 acute otitis media and common upper respiratory diseases (e.g., sinusitis) in children.

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.

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. 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.

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

Duration of Immunity

Following pneumococcal vaccination, serotype-specific antibody levels decline after 5-10 years. A more rapid decline in antibody levels may occur in some groups (e.g., children). Limited published data suggest that antibody levels may decline more rapidly in the elderly > 60 years of age. These findings indicate that revaccination may be needed to provide continued protection† . (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. Decreasing estimates of effectiveness with increasing interval since vaccination, particularly among the very elderly (persons aged ≥ 85 years) have been reported.

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-controlled studies.

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

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† The Advisory Committee on Immunization Practices (ACIP)

If it is known that a person has not received any pneumococcal vaccine or if earlier pneumococcal vaccination status is unknown, then persons in the categories listed below should be administered pneumococcal vaccine; however, if a person has received a primary dose of pneumococcal vaccine, before administering an additional dose of vaccine, please refer to the Revaccination section.

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

Immunocompetent persons:

- routine vaccination for persons 50 years of age or older
- persons aged ≥ 2 years with chronic cardiovascular disease (including congestive heart failure and cardiomyopathies), chronic pulmonary disease (including chronic obstructive pulmonary disease and emphysema), or diabetes mellitus
- persons aged ≥ 2 years with alcoholism, chronic liver disease (including cirrhosis) or cerebrospinal fluid leaks
- persons aged ≥ 2 years with functional or anatomic asplenia (including sickle cell disease and splenectomy)
- persons aged ≥ 2 years living in special environments or social settings (including Alaskan Natives and certain American Indian populations)

Immunocompromised persons:

- persons aged ≥ 2 years, including those with HIV infection, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chronic renal failure or nephrotic syndrome; those receiving immunosuppressive chemotherapy (including corticosteroids); and those who have received an organ or bone marrow transplant (for selected groups, see INDICATIONS AND USAGE, Timing of Vaccination).

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

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), the interval between vaccination and initiation of immunosuppressive therapy should be at least two weeks. Vaccination during chemotherapy or radiation therapy should be avoided. Pneumococcal vaccine may be given several months following completion of chemotherapy or radiation therapy for neoplastic disease. In Hodgkin's disease, immune response to vaccination may be suboptimal for two years or longer after intensive chemotherapy (with or

without radiation). For some patients, during the two years following the completion of chemotherapy or other immunosuppressive therapy (with or without radiation), significant improvement in antibody response has been observed, particularly as the interval between the end of treatment and pneumococcal vaccination increased.
Persons with asymptomatic or symptomatic HIV infection should be vaccinated as soon as possible after their diagnosis is confirmed.

Use With Other Vaccines

It is recommended 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[†]. In contrast to pneumococcal vaccine, influenza vaccine is recommended annually, for appropriate populations.

PNEUMOVAX 23 and ZOSTAVAX should not be given concurrently because concomitant use in a clinical trial resulted in reduced immunogenicity of ZOSTAVAX. In this trial, the immunogenicity of PNEUMOVAX 23 was not affected by ZOSTAVAX. Consider administration of the two vaccines separated by at least 4 weeks.

Revaccination

Revaccination of immunocompetent persons previously vaccinated with 23-valent polysaccharide vaccine is not routinely recommended.
However, revaccination once is recommended for persons ≥ 2 years of age who are at highest risk of serious pneumococcal infection and those likely to have a rapid decline in pneumococcal antibody levels, provided that at least five years have passed since receipt of a first dose of pneumococcal vaccine.
The highest risk group includes persons with functional or anatomic asplenia (e.g., sickle cell disease or splenectomy), HIV infection, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome, or other conditions associated with immunosuppression (e.g., organ or bone marrow transplantation), and those receiving immunosuppressive chemotherapy (including long-term systemic corticosteroids). (See INDICATIONS AND USAGE, Timing of Vaccination.)
For children ≤ 10 years of age at revaccination and at highest risk of severe pneumococcal infection (e.g., children with functional or anatomic asplenia, including sickle cell disease or splenectomy or conditions associated with rapid antibody decline after initial vaccination including nephrotic syndrome, renal failure or

[†] The Advisory Committee on Immunization Practices (ACIP)

renal transplantation), it is recommended that revaccination may be considered three years after the previous dose† .

If prior vaccination status is unknown for patients in the high risk group, patients should be given pneumococcal vaccine.

All persons ≥ 65 years of age who have not received vaccine within 5 years (and were < 65 years of age at the time of vaccination) should receive another dose of vaccine.

Because data are insufficient concerning the safety of pneumococcal vaccine when administered three or more times, revaccination following a second dose is not routinely recommended.

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.

PRECAUTIONS

General

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. (See INDICATIONS AND USAGE, Timing of Vaccination.)

Intradermal administration may cause severe local reactions.

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.

As with any vaccine, vaccination with PNEUMOVAX 23 may not result in complete protection in all recipients.

Pregnancy

It is 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 pregnant women only if clearly needed.

Nursing Mothers

It is not known whether this vaccine is excreted in human milk. Caution should be exercised when PNEUMOVAX 23 is administered to a nursing mother.

Pediatric Use

PNEUMOVAX 23 is not recommended for use 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 vaccine.

Elderly

Persons 65 years of age or older were enrolled in several clinical studies of PNEUMOVAX 23 that were conducted pre- and 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 were ambulatory and had an expected prevalence of age associated chronic diseases. The clinical data did not suggest an increased rate or severity of adverse reactions among subjects ≥ 65 years of age compared to those 50 to 64 years of age. However, 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 frail elderly individuals with multiple co-morbid conditions had severe adverse experiences and a complicated clinical course following vaccination.

SIDE EFFECTS

The following adverse experiences have been reported with PNEUMOVAX 23 in clinical trials and/or post-marketing experience: Injection site reactions, consisting of pain, soreness, erythema, warmth, swelling and local induration, decreased limb mobility and peripheral edema in the injected extremity. Also reported was an increase in the laboratory value for serum C-reactive protein. Rarely, cellulitis-like reactions were reported. These cellulitis-like reactions, reported in post-marketing experience, show short onset time from vaccine administration.

The most common adverse experiences reported in clinical trials were fever (≤ 38.8°C/102°F), injection site reactions including soreness, erythema, warmth, swelling and local induration.

In a clinical trial, an increased rate of self-limited local reactions has been observed with revaccination at 3-5 years following primary vaccination. It was reported that the overall injection-site adverse experiences rate for subjects ≥ 65 years of age was higher following revaccination (79.3%) than following primary vaccination (52.9%). The reported overall injection-site adverse experiences rate for re-vaccinees and primary vaccinees who were 50 to 64 years of age 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 most common systemic adverse experiences were as follows: asthenia/fatigue, myalgia and headache. The observed generally small increase (≤ 13%) in post-vaccination use of analgesics returned to baseline by day 5.

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

Body as a whole
Cellulitis
Asthenia
Fever
Chills
Malaise

Digestive System
Nausea
Vomiting

Hematologic/Lymphatic System
Lymphadenitis
Lymphadenopathy
Thrombocytopenia in patients with stabilized
idiopathic thrombocytopenic purpura
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

Erythema multiforme

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.

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.

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.

Store 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.

Single-Dose Vial

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

Prefilled Syringe

The prefilled syringe is for single use only. Inject the entire contents of the syringe.

AVAILABILITY

PNEUMOVAX 23 is supplied as follows:

- 1 single-dose vial
- 10 single-dose vials
- 1 single-dose prefilled syringe with separate needles

Not all presentations may be available locally.

Product Owner:

Merck Sharp & Dohme LLC

126 East Lincoln Ave.

P.O. Box 2000

Rahway, New Jersey 07065

USA

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MSD