SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PNEUMOCOCCAL POLYSACCHARIDE VACCINE IP
Solution for injection
0.5-mL single dose vials and prefilled syringes
BRAND NAME: PNEUMOVAX® 23

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredients:
Each 0.5 ml Pre-filled Syringe contains:
Pneumococcal serotypes ----- 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, l0A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F-- 25 meg each.

Inactive Ingredients:
Phenol
Sodium chloride
Water for injections

3. PHARMACEUTICAL FORM

Solution for injection in a vial and prefilled syringe
PNEUMOVAX® 23 is a sterile liquid vaccine for intramuscular or subcutaneous injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PNEUMOVAX® 23 is indicated for active immunization against disease caused by the pneumococcal serotypes included in the vaccine.

4.2 Posology and method of 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.

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.

<u>Timing of Vaccination</u>

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.

Revaccination

Revaccination of immunocompetent persons previously vaccinated with 23-valent polysaccharide vaccine is not routinely recommended.

However, revaccination once is recommended for persons $\geq$ 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 Timing of Vaccination).

For children $\leq$ 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 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 $\geq$ 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.

4.3 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.

4.4 Special warnings and precautions for use

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 section 4.2 POSOLOGY AND METHOD OF ADMINISTRATION - 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.

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

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 section 4.2 Posology and Method of Administration - Timing of Vaccination).

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

4.5 Interaction with other medicinal products and other forms of Interaction

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.*

† The Advisory Committee on Immunization Practices (ACIP)

4.6 Pregnancy and lactation

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.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable 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, local induration, decreased limb mobility and peripheral edema in the injected extremity.

Very rarely, cellulitis-like reactions were reported. These cellulitis-like reactions, reported in post marketing experience, show short onset time from vaccine administration. Local reactions may be accompanied by systemic signs and symptoms including fever, leukocytosis and an increase in the laboratory value for serum C-reactive protein.

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:

<u>Body as a whole</u>
Cellulitis
Asthenia
Fever
Chills
Malaise

<u>Digestive System</u>
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

4.9 Overdose
Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: pneumococcal vaccines; ATC code: J07 AL

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® concomitantly (N=237), or PNEUMOVAX® alone followed 4 weeks later by ZOSTAVAX alone (N=236). At four weeks post-vaccination, the VZV antibody levels following concomitant use were significantly lower than the VZV antibody levels following non- concomitant 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 post-vaccination 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 non-concomitant group. The GMTs for PNEUMOVAX® antigens were comparable between the two groups. Concomitant use of ZOSTAVAX and PNEUMOVAX® demonstrated a safety profile that was generally similar to that of the two vaccines administered non-concomitantly.

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 chronicmedical 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 section 4.2 POSOLOGY AND METHOD OF ADMINISTRATION - 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.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

No preclinical safety testing was performed using the vaccine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phenol
Sodium chloride
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at 2-8°C. The vaccine should be 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.

6.5 Nature and contents of container
PNEUMOVAX® 23 is available as:
1 single dose vial of liquid vaccine,
or
1 single-dose, pre-filled syringe with needle.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION/ PREQUALIFICATION HOLDER
MSD Pharmaceuticals Pvt. Ltd.,
Gala No. 1B, Building No. B-3,
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8. MARKETING>AUTHORISATION NUMBER(S)
Import Permission No.: Import-7399/07

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION
Date of first authorization (Form 45): 03 May 2007

Manufactured and packed by	Imported and Marketed by
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