THE MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

PACKAGE LEAFLET

of a Drug Product for Human Use

#### PREVENAR® 13

(a 13-valent pneumococcal polysaccharide conjugate adsorbed vaccine)

**INTERNATIONAL NON-PROPRIETARY OR GENERIC NAME:** vaccine for prevention of pneumococcal infections

**REGISTRATION NUMBER:** LP-000798

**DOSAGE FORM:** suspension for intramuscular injection

Prevenar® 13 contains capsular polysaccharides of 13 Pneumococcus serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) individually conjugated with CRM197 diphtheria protein and adsorbed on aluminum phosphate.

**COMPOSITION**

Ingredients per dose (0.5 mL):

***Active substances:***

Pneumococcal conjugates (polysaccharide-CRM197):

|  |  |
| --- | --- |
| Serotype 1 polysaccharide | 2.2 μg |
| Serotype 3 polysaccharide | 2.2 μg |
| Serotype 4 polysaccharide | 2.2 μg |
| Serotype 5 polysaccharide | 2.2 μg |
| Serotype 6A polysaccharide | 2.2 μg |
| Serotype 6B polysaccharide | 4.4 μg |
| Serotype 7F polysaccharide | 2.2 μg |
| Serotype 9V polysaccharide | 2.2 μg |
| Serotype 14 polysaccharide | 2.2 μg |
| Serotype 18C polysaccharide | 2.2 μg |
| Serotype 19A polysaccharide | 2.2 μg |
| Serotype 19F polysaccharide | 2.2 μg |
| Serotype 23F polysaccharide | 2.2 μg |
| CRM197 carrier protein | ~32 μg |

***Excipients:*** aluminum phosphate — 0.5 mg (0.125 mg calculated based on aluminum), sodium chloride — 4.25 mg, succinic acid — 0.295 mg, polysorbate 80 — 0.1 mg, water for injections — up to 0.5 mL.

**DESCRIPTION**

White homogenous suspension.

**PHARMACOTHERAPEUTIC GROUP:** Medical immunobiological drug vaccine.

**ATC code:** J07AL02

**IMMUNOLOGICAL PROPERTIES**

Injection of Prevenar® 13 vaccine causes production of antibodies to capsular polysaccharides of Streptococcus pneumoniae, thereby providing specific protection against infections caused by 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F pneumococcus serotypes included into the vaccine.

WHO recommendations for new conjugated pneumococcal vaccines determined the equivalence of Prevenar® 13 immune response according to three criteria: percentage of patients attaining the concentration of IgG specific antibodies ≥0.35 μg/mL, geometric mean concentrations (GMC) of immunoglobulins, and the opsonophagocytic activity (OPA) of bactericidal antibodies (OPA titre ≥1:8 and geometric mean titres (GMT)). No protective level of anti-pneumococcal antibodies has been defined for adults, and serotype-specific OPA (GMT) is used.

Prevenar® 13 vaccine includes up to 90% of the serotypes causing invasive pneumococcal infections (IPIs), including antibiotic resistant variants.

***Immune response to three or two doses in a primary vaccination series***

Children under 6 months showed a significant rise in the levels of antibodies to all vaccine serotypes after the injection of **three doses** of Prevenar® 13 in primary vaccination.

Children of this age group also showed a significant rise in the titres of antibodies to all vaccine components following the injection of **two doses** of Prevenar® 13 in primary vaccination during the mass immunization; IgG level ≥0.35 μg/mL for serotypes 6B and 23F was detected in a smaller percentage of children. However, there was a pronounced booster response to revaccination for all serotypes. Immune memory formation has been confirmed for both vaccination schedules mentioned above. The secondary immune response to the booster dose in children of the second year of life is comparable for all 13 serotypes when using **three** or **two** doses in the primary vaccination series.

After the completed vaccination course beginning from the age of two months, the level of specific protective anti-pneumococcal antibodies and their opsonophagocytic antibodies was above the protective values in 87-100% of the preterm infants (born at <37 weeks of gestation, including deep-premature infants born at <28 weeks of gestation) vaccinated against all thirteen serotypes.

***Immunogenicity in children and adolescents aged 5 to 17 years***

After one dose of Prevenar® 13, the children aged 5 to <10 years who previously received at least one dose of a 7-valent pneumococcal conjugated vaccine, as well as previously unvaccinated children and adolescents aged 10 to 17 years, demonstrated an immune response to all 13 serotypes equivalent to that in the children aged 12 to 15 months vaccinated with four doses of Prevenar® 13.

A single injection of Prevenar® 13 to children aged 5 to 17 years may ensure the required immune response to all pathogen serotypes included into the vaccine.

***Efficiency of Prevenar® 13***

***Invasive pneumococcal infections (IPI)***

A 98% (95% CI: 95; 99) decrease in the incidence of IPIs caused by vaccine-specific serotypes was reported four years after the introduction of Prevenar® using the 2+1 scheme (two doses in the first year of life and a single revaccination in the second year of life) with 94% vaccination coverage. Following the transition to Prevenar® 13, a further decrease in the incidence of IPIs caused by vaccine-specific additional serotypes comprised from 76% in children younger than 2 years to 91% in children aged 5 to 14 years.

Serotype-specific efficacy against IPIs for additional Prevenar® 13 serotypes in children aged ≤5 years ranged from 68% to 100% (serotypes 3 and 6A, respectively), and was 91% for serotypes 1, 7F and 19A, with no cases of IPIs caused by serotype 5. After the inclusion of Prevenar® 13 into national immunization programs, the incidence of IPIs caused by serotype 3 in children under 5 years of age decreased by 68% (95% CI 6-89%). A case control study in this age group showed a 79.5% decrease in the incidence of IPIs caused by serotype 3 (95% CI 30.3-94.8).

***Otitis media (OM)***

Following the introduction of Prevenar® vaccination and transition to Prevenar® 13 using the 2+1 scheme, a 95% decrease has been demonstrated in the incidence of OM caused by serotypes 4, 6B, 9V, 14, 18C, 19F, 23F and serotype 6A, as well as an 89% decrease in the incidence of OM caused by serotypes 1, 3, 5, 7F and 19A.

***Pneumonia***

The transition from Prevenar® to Prevenar® 13 was followed by a 16% reduction in the incidence of all community-acquired pneumonia (CAP) cases in children aged from 1 month to 15 years. CAP cases with pleural effusion decreased by 53% (p <0.001), and pneumococcal CAPs decreased by 63% (p <0.001). In the second year following the introduction of Prevenar® 13, there was a 74% decrease in the incidence of CAPs caused by 6 additional Prevenar® 13 serotypes. The introduction of Prevenar® 13 vaccination using the 2+1 scheme was marked by a 68% (95% CI: 73; 61) decrease in outpatient visits and a 32% (95% CI: 39; 22) decrease in hospitalizations for alveolar CAP of any etiology in children under 5 years of age.

***Reduced antimicrobial resistance (AMR)***

Following the introduction of Prevenar® 7 vaccination and later introduction of Prevenar® 13, the decrease in AMR prevalence is the result of reduced circulation of AMR-related serotypes and clones, including 19A, as well as lower morbidity (population effect) and reduced administration of antimicrobial drugs.

The US Centers for Disease Control and Prevention analyzed the usage trends across four classes of antibiotics and found that the annual incidence of IPIs caused by pneumococci resistant to macrolides, cephalosporins, penicillins and tetracycline decreased by 63%, 81%, 83% and 81%, respectively, in children younger than 5 years of age, and by 24%, 49%, 57% and 53%, respectively, in patients aged 65 and over in 2013 compared to 2009 (the last year of the use of a 7-valent pneumococcal conjugated vaccine in the US, after which it was replaced by Prevenar® 13, a 13-valent conjugated pneumococcal vaccine).

***Carriage and population effect***

Prevenar® 13 showed efficacy at reducing the nasopharyngeal carriage of vaccine-specific serotypes, including those common with Prevenar® vaccine (4, 6B, 9V, 14, 18C, 19F, 23F), 6 additional serotypes (1, 3, 5, 6A, 7A, 19A) and related 6C serotype.

The population effect (serotype-specific reduction of morbidity in unvaccinated individuals) has been observed in the countries where Prevenar® 13 has been used in mass immunization for more than 3 years with high vaccination coverage and adherence to the immunization schedule. IPI incidence decreased by 25% among those who have not been vaccinated with Prevenar® 13 and are 65 years and older; IPIs caused by 4, 6B, 9V, 14, 18C, 19F, 23F serotypes decreased by 89%, and IPIs caused by 6 additional serotypes (1, 3, 5, 6A, 7A, 19A) decreased by 64%. The incidence of infections caused by serotype 3 decreased by 44% (by 95% for serotype 6A and by 65% for serotype 19A).

***Efficiency study in adults aged 65 and over***

A randomized double-blind placebo-controlled trial (Clinical Immunization Trial for Community-acquired Pneumococcal Pneumonia in Adults, CAPiTA) conducted in the Netherlands demonstrated clinical efficacy of Prevenar® 13 for community-acquired pneumococcal pneumonia and IPIs caused by vaccine-specific serotypes. Patients aged 65 and older (n = 84,496) received a single Prevenar® 13 or placebo vaccination at 1:1 randomization.

Prevenar® 13 has demonstrated efficacy in preventing the first episodes of IPI caused by vaccine-specific serotypes (CAPiTA VSS), which was the primary endpoint of the study, and two secondary endpoints, as shown in Table 1.

| **Table 1. Vaccine efficacy (VE) by primary and secondary endpoints of the CAPiTA study (per population according to the protocol)** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Primary efficacy endpoint** | **Number of cases** | | | **VE (%)**  **(95.2% CI)** | **p value** |
| **Total** | **Prevenar® 13 group** | **Placebo group** |
| *Primary endpoint* | | | | | |
| First episode of CAPiTA VSS | 139 | 49 | 90 | 45.56  (21.82; 62.49) | 0.0006 |
| *Secondary Endpoints* | | | | | |
| **First episode of confirmed non-invasive CAPiTA VSS** | 93 | 33 | 60 | 45.00  (14.21; 65.31) | 0.0067 |
| **First episode of IPI VSS1** | 35 | 7 | 28 | 75.00  (41.06; 90.87) | 0.0005 |
| 1 **IPI VSS** — Invasive pneumococcal infection caused by a vaccine-specific serotype | | | | | |

The protective efficacy of Prevenar® 13 against the first episodes of CAPiTA VSS, non-invasive CAPiTA VSS and IPI VSS became apparent shortly after vaccination and persisted throughout the study.

In order to assess the impact on public health, a retrospective analysis of the vaccine’s efficacy against clinical cases of community-acquired pneumonia (CAP) diagnosed according to case determination in the CAPiTA study and on the basis of clinical criteria (regardless of the presence of infiltrate on radiograms or etiological confirmation of disease) has been conducted to show reduced CAP incidence and a fewer number of people who need to be vaccinated to prevent one clinical case (see Table 2).

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 2. Public health impact for CAP clinical cases\***  **(a modified sample of patients who received prescribed treatment)** | | | |
|  | **Vaccine efficacy**  **% (95% CI)** | **CAP1 incidence reduction (95% CI)** | **Number of people who need to be vaccinated to prevent one clinical case2** |
| **Analysis of all CAP episodes** | 8.1  (-0.6; 16.1) | 72.2  (-5.3; 149.6) | 277 |
| **Analysis of the first CAP episode** | 7.3  (-0.4; 14.4) | 53.0  (-2.7; 108.7) | 378 |
| \* Patients with at least two of the following symptoms: cough; purulent sputum, body temperature >38°C or <36.1°C; auscultation-detected pneumonia; leukocytosis; C-reactive protein levels 3 times higher of the upper limit; hypoxemia at partial oxygen pressure <60 mmHg when breathing the room air.  1 in 100,000 person-years on follow-up.  2 on the basis of protective action during 5 years. | | | |

Although the CAPiTA study has not been designed to prove serotype-specific vaccine efficacy (VE), CAP clinical cases have been assessed for all serotypes that caused at least 10 outcomes in the placebo group. VE (95% CI) for the five assessed serotypes relative to the first episode of clinical CAP was 20.0% (-83.1% to 65.8%) for serotype 1; 61.5% (17.6% to 83.4%) for serotype 3; 33.3% (-58.6% to 73.2 %) for serotype 6A; 73.3% (40.5% to 89.4%) for serotype 7F; and 45.2% (-2.2% to 71.5%) for serotype 19A.

***Immunogenicity of Prevenar® 13 vaccine in adults***

Prevenar® 13 clinical trials provide immunogenicity data for adults aged 18 and over, including those 65 years of age and over and those who have previously received one or more doses of a 23-valent polysaccharide pneumococcal vaccine (PPV23) five years prior to inclusion in the study. Each study involved healthy adults and immunocompetent patients with chronic diseases in the compensatory stage, including comorbidities forming increased susceptibility to pneumococcal infection (chronic cardiovascular diseases, chronic lung diseases, including asthma; kidney diseases and diabetes mellitus, chronic liver diseases, including alcohol liver damage), as well as adults with social risk factors (smoking and alcohol abuse). Immunogenicity and safety of Prevenar® 13 have been demonstrated for adults of 18 years and older, including the patients previously vaccinated with PPV23. Immunological equivalence has been established for 12 serotypes common with PPV23. In addition, a statistically significant higher immune response to Prevenar® 13 has been demonstrated for 8 serotypes common with PPV23 and serotype 6A unique to Prevenar® 13. In adults aged 18-59, the serotype specific opsonophagocytic activity (OPA GMT) to all 13 Prevenar® 13 serotypes were not lower than that in adults aged 60-64. Moreover, those aged 50-59 gave a statistically higher immune response to 9 out of 13 serotypes compared to people aged 60-64.

***Immune response in adults previously vaccinated with PPV23***

In adults aged 70 and older previously vaccinated with 1 dose of PPV23 ≥5 years ago, Prevenar® 13 administration demonstrated immunological equivalence for 12 general serotypes compared to the response to PPV23. For 10 common serotypes and serotype 6A, the immune response to Prevenar® 13 was statistically significantly higher compared to the response to PPV23. Prevenar® 13 provides a more pronounced immune response compared to PPV23 revaccination.

***Immune response in special patient groups***

Patients with the conditions described below are at increased risk of pneumococcal infection.

*Sickle cell anemia (SCA)*

An open noncomparative study involving 158 children and adolescents aged ≥6 and <18 with sickle cell anemia, previously vaccinated with one or more doses of PPV23 at least 6 months prior to inclusion into the study, showed that administration of the first dose of Prevenar® 13 at double vaccination with a 6-month interval resulted in a statistically significantly high immune response (geometric mean concentrations (GMC) of IgG to each serotype determined by ELISA test and OPA GMT to each serotype). The immune response after the second dose was comparable to that after the first dose of the drug.

*HIV infection*

HIV-infected children and adults with CD4 ≥200 cells/μL (average 717.0 cells/μL), viral load <50,000 copies/mL (average 2,090.0 copies/mL), without any active AIDS-associated diseases and previously unvaccinated with pneumococcal vaccines, received three doses of Prevenar® 13. IgG GMC and OPA values were significantly higher after the first Prevenar® 13 vaccination compared to pre-vaccinal levels. A higher immune response developed after the second and third doses (6 and 12 months later) when compared to the response after the single dose of Prevenar® 13.

*Hematopoietic stem cell transplantation*

Children and adults who have performed allogenic hematopoietic stem cell transplantation (HSCT) at ≥ 2 years of age with complete hematological remission of the underlying disease or with satisfactory partial remission for lymphoma and myeloma, received three doses of Prevenar® 13 with at least 1 month intervals between doses. The first dose of the drug was injected 3-6 months after HSCT. The fourth (booster) dose of Prevenar® 13 was administered 6 months after the third dose. According to general guidelines, a single dose of PPV23 was administered one month after the fourth dose of Prevenar® 13. The titres of functionally active antibodies (OPA GMT) were not determined in this study. The administration of Prevenar® 13 caused an increase in the GMC of serotype-specific antibodies after each dose. The immune response to a booster dose of Prevenar® 13 was significantly higher in comparison with the response to the primary immunization series for all serotypes.

**INDICATIONS:**

- prevention of pneumococcal infections, including invasive (such as meningitis, bacteraemia, sepsis, severe pneumonia) and non-invasive (community acquired pneumonias and otitis media) forms caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F for patients aged 2 months and older without age limits;

- as part of the national preventive vaccination schedule;

- in patients at high risk of pneumococcal infection.

Vaccination is conducted as part of the national preventive vaccination schedule according to approved deadlines, as well as for the individuals being at risk for developing pneumococcal infection, including patients with immunodeficient conditions such as HIV, cancer patients receiving immunosuppressive therapy, patients with anatomical/functional asplenia, premature children, patients with cochlear implants or those planning to undergo this surgery, patients with cerebrospinal fluid leakage, patients with diabetes, bronchial asthma, chronic lung, cardiovascular, liver and kidney conditions, persons in organized groups (orphanages, boarding schools, army formations), convalescents of acute otitis media, meningitis and pneumonia, frequently and chronically ill children, patients infected with Mycobacterium tuberculosis, all persons of 50 years of age and over, as well as tobacco smokers.

**CONTRAINDICATIONS**

* Hypersensitivity to the previous administration of Prevenar® 13 or Prevenar® (including anaphylactic shock, severe generalized allergic reactions);
* hypersensitivity to diphtheria anatoxin and/or excipients;
* acute infectious or non-infectious diseases, exacerbated chronic diseases. Vaccinations are carried out after recovery or during remission.

**ADMINISTRATION DURING PREGNANCY AND BREASTFEEDING PERIOD**

The safety of the vaccine use during pregnancy and breastfeeding has not been confirmed. There are no data on Prevenar® 13 use during pregnancy. There are no data on the release of vaccine antigens or post-vaccinal antibodies with breast milk at lactation.

**POSOLOGY AND METHOD OF ADMINISTRATION**

***Dose Route***

The vaccine is administered intramuscularly at a single dose of 0.5 mL. In children of the first years of life, the vaccine is injected into the upper and outer surface of the middle third of the thigh, and in those older than 2 years old to the deltoid muscle of the shoulder.

Before using the Prevenar® 13 vaccine syringe, it should be shaken well until homogenous suspension is obtained. Do not use if foreign particles are identified when examining the contents of the syringe, or the contents differs from that specified in the “Description” section of this package leaflet.

***Do not inject Prevenar® 13 intravascularly and intramuscularly into the gluteus!***

If Prevenar® 13 vaccination is initiated, it is recommended to complete it with Prevenar® 13 vaccine as well. If there is a need to increase the intervals between injections during any of the above vaccination courses, additional doses of Prevenar® 13 are not required.

***Vaccination Schedule***

|  |  |  |
| --- | --- | --- |
| Vaccination start age | Vaccination schedule | Intervals and dosage |
| **2-6 months** | 3+1  or  2+1 | Individual immunization: 3 doses with an interval of at least 4 weeks between injections. The first dose can be administered at the age of 2 months. Revaccination with a single dose at the age of 11-15 months.  Mass immunization of children: 2 doses with an interval of at least 8 weeks between injections. Revaccination with a single dose at the age of 11-15 months. |
| **7-11 months** | 2+1 | 2 doses with an interval of at least 4 weeks between injections. Revaccination with a single dose during the second year of life |
| **12-23 months** | 1+1 | 2 doses with an interval of at least 8 weeks between injections. |
| **2 years and over** | 1 | Single dose |

***Children previously vaccinated with Prevenar®***

Vaccination against pneumococcal infection initiated using the 7-valent Prevenar® vaccine can be continued with Prevenar® 13 at any stage of the immunization schedule.

***Patients aged 18 or older***

Prevenar® 13 is administered once. The need for revaccination with Prevenar® 13 has not been determined. Decision on the interval between the administration of Prevenar® 13 and PPV23 vaccines should be made in accordance with the official guidelines.

***Special populations***

For patients after hematopoietic stem cell transplantation, an immunization series consisting of four doses of Prevenar® 13 (by 0.5 mL) is recommended. The first immunization series includes three doses of the drug: the first dose is injected from the third to sixth month after the transplantation. The interval between injections should be 1 month. A revaccination dose is recommended to be injected 6 months after administration of the third dose.

Quadruple vaccination is recommended for preterm infants. The first immunization series includes 3 doses. The first dose should be administered at 2 months of age regardless of the child’s body weight with a 1-month interval between doses. The administration of the fourth (booster) dose is recommended at 12-15 months of age.

*Elderly patients*

Immunogenicity and safety of the Prevenar® 13 vaccine for older patients have been confirmed.

**SIDE EFFECTS**

The safety of Prevenar® 13 vaccine has been studied in healthy infants (4,429 children/14,267 vaccine doses) aged 6 weeks to 11-16 months, and in 100 preterm infants (<37 weeks of gestation). In all studies, Prevenar® 13 was used simultaneously with other vaccines recommended for the mentioned age.

In addition, the safety of Prevenar® 13 vaccine has been assessed in 354 children aged 7 months to 5 years having no previous vaccination with any of the pneumococcal conjugated vaccines. The most frequent adverse reactions were local reactions at the injection site, body temperature rise, irritability, reduced appetite, and sleep disturbances. Older children experienced a higher incidence of local reactions compared to infants after the primary vaccination with Prevenar® 13.

In preterm infants (born at ≤37 weeks of gestation, including deeply preterm infants born at less than 28 weeks of gestation and extremely low body weight (≤ 500 g)) vaccinated with Prevenar® 13, the nature, frequency and severity of post-vaccine reactions were not different from those in term infants.

Those aged 18 and older had fewer side effects regardless of prior vaccinations. However, the frequency of reactions was similar to those in younger patients.

In general, the incidence of side effects was the same in patients of 18-49 age group and in patients over 50 (except for vomiting). This side effect was more common in patients aged 18-49 than in patients aged 50 years and older.

Adult HIV-infected patients had the same incidence of side effects as those aged 50 and older, except for fever and vomiting that were observed very frequently, and nausea that was observed frequently.

In patients after hematopoietic stem cell transplantation, the incidence of side effects was the same as in healthy adult patients, except for fever and vomiting, which occurred very frequently in patients after transplantation. Children and adolescents with sickle cell anemia, HIV infection, or those who underwent hematopoietic stem cell transplantation had the same incidence of side effects as healthy patients aged 2 to 17, except for headaches, vomiting, diarrhea, fever, fatigue, arthralgia and myalgia, which were found to be “very common” in such patients.

The adverse reactions listed below are classified according to the frequency of their manifestation across all age groups as follows: very common (≥1/10), common (≥1/100 but <1/10), uncommon (≥1/1000 but <1/100), rare (≥1/10000 but <1/1000), and very rare (≤1/10000).

***Adverse reactions observed in Prevenar® 13 clinical trials***

*Very common:* hyperthermia; irritability; skin redness, pain, induration or swelling of 2.5-7.0 cm at the injection site (after revaccination and/or in children aged 2-5); vomiting (in patients ages 18 to 49), drowsiness, sleep deterioration, impaired appetite, headache, newly diagnosed generalized or exacerbated joint pain and myalgia, chills, fatigue.

*Common*: hyperthermia above 39°C; injection site soreness resulting in short-term limb movement limitation; hyperemia, induration or swelling (2.5–7.0 cm in size) at the site of injection (after a series of primary vaccinations in children under 6 months), vomiting, diarrhea, rash.

*Uncommon*: skin redness, induration or swelling (larger than 7.0 cm in size) at the site of injection; tearfulness, seizures (including febrile convulsions), hypersensitivity reactions at the injection site (urticaria, dermatitis, itching)\*\*, nausea.

*Rare*: hypotonic collapse cases\*, blood flushes to the face\*\*, hypersensitivity reaction including shortness of breath, bronchospasm, variously localized Quincke’s edema, including face edema, anaphylactic/anaphylactoid response including acute anaphylaxis\*\*, lymphadenopathy in the injection site.

*Very rare*: regional lymphadenopathy\*\*, polyform erythema\*\*.

\* observed only in Prevenar® vaccine clinical trials, but are also possible for Prevenar® 13.

\*\* observed in post-marketing studies of Prevenar® vaccine; such effects are considered to be possible for Prevenar® 13 as well.

Adverse events observed in other age groups may also occur in children and adolescents aged 5 to 17. However, they were not observed in clinical studies due to the small number of participants.

There were no significant differences in the incidence of side effects in adults who were previously vaccinated and unvaccinated with PPV23.

**OVERDOSE**

An overdose of Prevenar® 13 is unlikely, as the vaccine is released in a syringe containing a single dose.

**DRUG INTERACTIONS**

There are no data on Prevenar® 13 interchangeability for other pneumococcal conjugated vaccines. At the same time, Prevenar® 13 and other vaccines are injected into different areas of the body.

***Children aged 2 months to 5 years***

Prevenar® 13 is compatible with any other vaccines in the immunization schedule for children, except BCG. Prevenar® 13 does not affect the immunogenicity of both monovalent and combination vaccines when injected simultaneously with any of the following antigens being the part of such vaccines: diphtheria, tetanus, cellular or whole-cell pertussis, Haemophilus influenzae type B, polio, hepatitis A, hepatitis B, measles, parotitis, rubella, chickenpox and rotavirus infection. Due to a higher risk of febrile reactions, symptomatic prescribing of antipyretic agents is recommended for children with convulsive disorders, including patients with a history of febrile convulsions, as well as those receiving Prevenar® 13 simultaneously with whole-cell pertussis vaccines. When Prevenar® 13 and Infanrix hexa were used simultaneously, the frequency of febrile reactions coincided with that for the simultaneous administration of Prevenar® (PCV7) and Infanrix hexa. The increased incidence of convulsions (with and without increased body temperature) and hypotonic-hyporesponsive episodes (HHE) has been observed in case of simultaneous administration of Prevenar® 13 and Infanrix hexa. The use of antipyretic drugs should be initiated in accordance with local guidelines for treating children with convulsive disorders or children with a history of febrile convulsions, and all children who were administered Prevenar® 13 together with the whole-cell pertussis vaccine.

Prevenar® 13 can be used simultaneously with a meningococcal polysaccharide vaccine (serotypes A, C, W and Y) conjugated with tetanus anatoxin in children aged 12 to 23 months.

According to the post-marketing study of the preventive use of antipyretic agents against the immune response to the injection of Prevenar® 13 vaccine, it is assumed that preventive prescribing of acetaminophen (paracetamol) may reduce the immune response to Prevenar® 13 primary vaccination series. The immune response to Prevenar® 13 revaccination at the age of 12 months with preventive use of paracetamol remains unchanged. The clinical significance of these data is unknown.

***Children and adolescents aged 6 to 17 years***

No data are available on the use of Prevenar® 13 simultaneously with the human papillomavirus infection vaccine, meningococcal conjugated vaccine, tetanus, diphtheria and pertussis vaccine, and tick-borne encephalitis vaccine.

***Patients aged 18 to 49 years***

No data are available on the simultaneous use of Prevenar® 13 with other vaccines.

***Patients aged 50 and over***

Prevenar® 13 vaccine can be used simultaneously with a trivalent or quadrivalent inactivated seasonal influenza vaccine (TIV and QIV). When Prevenar® 13 and TIV vaccines were combined, the immune responses to the TIV vaccine matched those received when TIV vaccine alone was administered; the immune responses to Prevenar® 13 vaccine were lower compared to the use of Prevenar® 13 alone. The clinical significance of this fact is unknown. The incidence of local reactions did not increase when Prevenar® 13 was administered with inactivated influenza vaccine, while the incidence of general reactions (headache, chills, rash, impaired appetite, joint and muscle pain) increased in case of simultaneous immunization. Simultaneous use with other vaccines has not been investigated.

**SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

Taking into account the rare cases of anaphylactic reactions occurring when any vaccines are used, the vaccinated patient must be medically monitored for a minimum of 30 minutes after vaccination. Vaccination facilities must be provided with anti-shock therapy medications.

The vaccination of both preterm and term infants should be started at the second month of life (the passport age). When deciding to vaccinate a preterm infant (born at <37 weeks of gestation), especially with a history of respiratory immaturity, one should take into account that the benefit of vaccination against pneumococcal infection in this group of patients is particularly high and the vaccination should not be refused or rescheduled. Due to the potential risk of apnea when using any vaccines, the first vaccination with Prevenar® 13 in preterm infants can be carried out under medical supervision (during at least 48 h) on the second phase of development care in a hospital.

Like other intramuscular injections, Prevenar® 13 vaccination in patients with thrombocytopenia and/or other blood clotting disorders (and/or in patients treated with anticoagulants) should be performed with care to ensure patient stabilization and hemostasis control. Subcutaneous administration of Prevenar® 13 vaccine is possible in this patient group.

Prevenar® 13 cannot prevent diseases caused by pneumococci of other serotypes whose antigens are not part of this vaccine.

The high-risk group children younger than 2 years of age should be given Prevenar® 13 primary vaccination in accordance with their age. In patients with impaired immunoreactivity, vaccination may be accompanied by reduced levels of antibody formation.

*Use of Prevenar® 13 and PPV23*

For immune memory formation, immunization against pneumococcal infection is preferable to be started with Prevenar® 13 vaccine. The need for revaccination has not been determined. Persons in high-risk groups may be advised to introduce PPV23 to expand serotype coverage later. There is evidence from clinical studies of PPV23 vaccination in 1 year, as well as in 3.5 to 4 years after Prevenar® 13 vaccination. At a 3.5–4 year vaccination interval, the immune response to PPV23 was higher without any changes in reactogenicity.

In children vaccinated with Prevenar® 13 and belonging to high risk groups (e. g., patients with sickle cell anemia, asplenia, HIV infection, chronic diseases or immune dysfunction), PPV23 is administered at an interval of at least 8 weeks. At the same time, the patients at high risk for pneumococcal infection (patients with sickle cell anemia or HIV infection), including those previously vaccinated with one or more doses of PPV23 may receive at least one dose of Prevenar® 13.

The interval between PPV23 and Prevenar® 13 injections should be selected in accordance with official guidelines. In a number of countries (such as the US), the recommended interval is at least 8 weeks (up to 12 months). If a patient has previously been vaccinated with PPV23, Prevenar® 13 should be administered no earlier than 1 year later. In the Russian Federation, PCV13 is recommended to all adults who are 50 years old and patients at risk; PCV13 is administered first with possible subsequent revaccination with PPV23 at the intervals less than 8 weeks.

Prevenar® 13 contains less than 1 mmol of sodium (23 mg) per dose, i. e., it is almost sodium free.

Within the specified shelf life, Prevenar® 13 maintains stability for 4 days at the temperatures up to 25°C. At the end of this period, the drug should either be used immediately or returned to the fridge. This data is not an indication of storage and transport conditions, but may be the basis for the decision to use the vaccine in case of any temperature fluctuations during storage and transportation.

***Effects on the ability to drive or use machines***

Prevenar® 13 has either no or negligible impact on the ability to drive and use machines. However, some of the reactions specified in “Side Effect” section may temporarily affect the ability to drive a vehicle and use potentially dangerous mechanisms.

**Presentation**

0.5 mg/dose suspension for intramuscular injection.

0.5 mL per a 1 mL syringe of clear colorless glass (type I).

1 syringe and 1 sterile needle in plastic packaging sealed with plastic film. 1 plastic package with the package leaflet in an optionally tamper-evident cardboard pack.

5 syringes in plastic packaging sealed with plastic film.

2 plastic packages and 10 sterile needles with the package leaflet in an optionally tamper-evident cardboard pack.

**Storage and transportation conditions**

At a temperature of +2°C to +8°C. Do not freeze.

Keep out of the reach of children.

Transport at the temperature from +2 to +25°C. Do not freeze.

Transport at the temperatures above 2-8°C for no more than five days.

**Shelf life**

3 years.

Do not use after the expiry date printed on the package.

**Conditions of release**

1 syringe packaging upon prescription

10 syringes packaging for health care institutions.

**Manufacturer**

Manufactured by:

1) Pfizer Ireland Pharmaceuticals, Ireland

Grange Castle Business Park, Clondalkin, Dublin 22, Ireland

2) NPO Petrovax Pharm LLC, Russian Federation

1 Sosnovaya st., Pokrov village, Podolsk, Moscow region 142143

Packed:

1) NPO Petrovax Pharm LLC, Russian Federation

1 Sosnovaya st., Pokrov village, Podolsk, Moscow region 142143

2) Pfizer Manufacturing Belgium NV, Belgium

12 Rijksweg, 2870 Puurs, Belgium

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