PACKAGE INSERT

(ENGLISH)

Boostagen®

(Tetanus toxoid, reduced diphtheria toxoid, Recombinant acellular pertussis vaccine)

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Boostagen®

DESCRIPTION

Boostagen® is a combined tetanus toxoid, reduced diphtheria toxoid and recombinant acellular pertussis vaccine. **Boostagen®** is a sterile, whitish, cloudy and uniform suspension. This vaccine contains purified tetanus toxoid, diphtheria toxoid and purified *Bordetella pertussis* antigens (rPT and FHA) which are adsorbed on aluminum hydroxide. rPT (Recombinant Pertussis Toxin) is a genetically-detoxified PT obtained by recombinant DNA technology. **Boostagen®** meets the World Health Organisation requirements for the manufacture of biological substances, of diphtheria, tetanus, and acellular pertussis combined vaccines.

COMPOSITION

Each single dose (0.5 mL) contains:

Tetanus Toxoid	7.5 Lf
Diphtheria Toxoid	2.0 Lf
Purified *Bordetella pertussis* antigens	
Recombinant Pertussis Toxin (rPT)	5 µg
Filamentous Haemagglutinin (FHA)	5 µg

Excipients: aluminum hydroxide, sodium chloride, water for injection.

Hydrochloric Acid and/or sodium hydroxide are added for pH adjustment. Their amounts are negligible with respect to the amount of the other excipients.

Formaldehyde and thiomersal may be present in trace amounts as manufacturing process residuals.

INDICATION

Boostagen® is indicated for active booster immunization against tetanus, diphtheria and pertussis in individuals from the age of 11 years onwards.

Boostagen® should be given in accordance with the current local recommendations and medical practices for booster vaccination against diphtheria, tetanus and pertussis.

POSOLOGY

A single 0.5 mL dose of **Boostagen®** is recommended. Booster injections for diphtheria and tetanus must be given at intervals consistent with existing recommendations.

Boostagen® can be used for tetanus prophylaxis in wound management. Tetanus immunoglobulin should be administered in accordance with existing recommendations.

In accordance with 2019 WHO recommendations for routine immunization of pertussis-containing vaccine, the use of **Boostagen®** may be considered in the second or third trimester

and preferably at least 15 days before the end of pregnancy. See **PREGNANCY AND LACTATION** section.

MODE OF ADMINISTRATION

Shake the syringe well to obtain a uniform, cloudy and white suspension. Do not use if resuspension does not occur after vigorous shaking.

Boostagen® should be administered by deep intramuscular injection, preferably in the deltoid region. Before injection, the skin over the site of injection should be cleaned with a suitable germicide. Open the needle cap of the pre-filled syringe, administer the total volume of 0.5 mL intramuscularly (IM).

CONTRAINDICATION

Boostagen® should not be administered to individuals having shown signs of hypersensitivity or life-threatening reaction following administration of diphtheria, tetanus or pertussis vaccines or to any components of the vaccine.

Boostagen® should not be administered to individuals having experienced any encephalopathy with unknown aetiology such as coma, prolonged seizures, or decreased level of consciousness within 7 days following previous vaccination with any whooping cough vaccine.

Boostagen® should not be administered to individuals with progressive or unstable neurological disorders, uncontrolled epilepsy or progressive encephalopathy.

WARNING AND PRECAUTION

It is good clinical practice that vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination in compliance with local requirements. The frequency and severity of adverse events in recipients of tetanus and diphtheria toxoids are influenced by the number of prior doses and level of pre-existing antitoxin antibody. As with all injectable vaccines, appropriate medical care should be readily available in case of a rare anaphylactic reaction after vaccination.

- The vaccine should not be administered intravascularly.
- Fractional doses (< 0.5 mL) should not be given.

As with other vaccines, administration of **Boostagen®** to subjects suffering from acute severe febrile illness should be postponed. **Boostagen®** should be administered with precautionary measures to subjects who had any of the following adverse events within 48 hours after a previous immunization with any whooping cough vaccines: high temperature (≥ 40°C) without any identifiable cause, convulsions and collapse or shock-like state.

Boostagen® should be administered with caution to the recipient with any bleeding disorders, thrombocytopenia or anticoagulant therapy because bleeding at injection site may occur after intramuscular injection.

In the case of immunosuppressive treatment or immunodeficiency, the immune response to the vaccine may be diminished. Vaccination should be postponed until the end of treatment or resolution of disease. Nevertheless, in the case of chronic immunodeficiency, including HIV-infected persons, vaccination is recommended even if the response may be limited.

Thiomersal (an organomercuric compound) has been used in the manufacturing process of this medicinal product and residues of it are present in the final product. Therefore, sensitisation reactions may occur.

INTERACTIONS WITH OTHER DRUGS

Interaction studies with other medicinal products or vaccines have not been performed. However, since **Boostagen®** is an inactivated vaccine, administration of **Boostagen®** concomitantly with other inactivated vaccines or immunoglobulins is unlikely to cause any interference with the immune response.

When considered necessary, **Boostagen®** can be administered simultaneously with other inactivated vaccines or immunoglobulins at separate site of injections.

Immunosuppressive treatment may interfere the development of expected immune response.

PREGNANCY AND LACTATION

Pregnancy

In accordance with 2019 WHO recommendations for routine immunization of pertussis-containing vaccine, the use of **Boostagen®** may be considered in the second or third trimester and preferably at least 15 days before the end of pregnancy.

Safety data from active post-marketing surveillance (including a prospective observational study) where 848 pregnant women were exposed to **Boostagen®** in the second or third trimester of pregnancy have shown no vaccine related adverse effect on pregnancy or the health of newborns.

No adverse effects on pregnancy, parturition, lactation or prenatal and postnatal development were observed after administration of **Boostagen®** in one animal toxicity study. Data in humans from randomized controlled trials on the use of **Boostagen®** during the second or third trimester of pregnancy are not yet available. While vaccination with **Boostagen®** is not expected to be associated with any increased risk to the foetus as the vaccine is inactivated, **Boostagen®** should only be used during pregnancy when the possible advantages outweigh the possible risks for the foetus.

Lactation

The effect of **Boostagen®** during lactation has not been assessed in humans. While no risk to the breastfed infant should be expected as the vaccine is inactivated. **Boostagen®** should only be used during breastfeeding when the possible advantages of vaccination outweigh the potential risks.

UNDESIRABLE EFFECTS

Summary of the safety profile

The safety profile presented below is based on data from a clinical trial where **Boostagen®** was administered to 150 adolescents between 12 and 17 years of age. Within 7 days after vaccination, the most common events occurring were local injection site reactions (pain, redness and induration) and systemic reactions (headache, fatigue, myalgia, malaise and arthralgia). Higher frequency of induration was observed in subjects vaccinated with **Boostagen®**; however, all cases were mild or moderate in intensity and resolved in a few days without sequelae. For the other adverse events, the frequency, severity and duration were

similar in subjects vaccinated either with **Boostagen®** or with a licensed Tdap vaccine. These signs and symptoms were mostly mild and moderate in intensity and resolved without sequelae.

Tabulated summary of adverse reactions

Adverse reactions are listed according to the following frequency:

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Adolescents 12 – 17 years of age, Adverse Reactions Reported

Frequency	Adverse Reaction/Event	System Organ Class
Very common: ≥1/10	Pain, redness and induration at injection site, malaise, fatigue	General disorders and administration site conditions
	Headache	Nervous system disorders
	Myalgia, arthralgia	Musculoskeletal and connective tissue disorders
Common: ≥1/100 to <1/10	Chills, fever (≥ 37.5ºC)	General disorders and administration site conditions
	Vomiting	Gastrointestinal disorders
	Pain in extremity	Musculoskeletal and connective tissue disorders
Uncommon: ≥1/1000 to <1/100	Injection site pruritus	General disorders and administration site conditions
	Dizziness	Nervous system disorders
	Nausea	Gastrointestinal disorders

In another clinical trial, a formulation of combined tetanus, diphtheria (reduced dose) and recombinant acellular pertussis vaccine containing PRN (Pertactin antigen) in addition to **Boostagen®** acellular pertussis antigens (rPT and FHA) was tested in 20 healthy adult subjects aged 18 – 35 years. Subjects vaccinated with this vaccine had similar frequency of adverse events following 7 days after vaccination to subjects vaccinated with a licensed Tdap vaccine.

Adults 18 – 35 years of age, Adverse Reactions Reported

Frequency	Adverse Reaction/Event	System Organ Class
Very common: ≥1/10	Pain, redness and induration at injection site, arthralgia, fatigue	General disorders and administration site conditions
	Myalgia	Musculoskeletal and connective tissue disorders
Common: ≥1/100 to <1/10	Malaise	General disorders and administration site conditions
	Headache	Nervous system disorders

Data from post-marketing experience

The suspected adverse reactions after authorization of the medicinal product will be monitored and reported according to pharmacovigilance practice and local regulations.

OVERDOSE

Overdose is considered highly unlikely due to the presentation of **Boostagen®** in monodose pre-filled syringe.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmaco-therapeutic group: Bacterial vaccines combined, ATC code: J07AJ52

Immunogenicity of **Boostagen®** was evaluated in 150 adolescents aged 12 – 17 years old and compared with a licensed Tdap vaccine to show non-inferiority (Committee for Medicinal Products for Human Use (CHMP) (2005) Guideline on the choice of the non-inferiority margin: EMEA/CPMP/EWP/2158/99).

At 28 days after vaccination, ELISA anti-PT and anti-FHA antibody titers and seroconversion rates were statistically significant higher in subjects vaccinated with **Boostagen®** than in subjects vaccinated with the licensed Tdap vaccine. Non-inferiority of **Boostagen®** was met. In addition, superiority of ELISA anti-PT and anti-FHA seroconversion rates and GMTs was demonstrated according to EMEA guidelines (Committee for Proprietary Medicinal Products (CPMP) (2000) Points to consider on switching between superiority and non-inferiority: CPMP/EWP/482/99). Immunogenicity of tetanus and diphtheria toxoids was similar to the licensed Tdap vaccine.

Non-inferiority test for seroconversion rates of anti-PT and anti-FHA antibody titers as assessed by ELISA in Boostagen® *vs* a licensed Tdap vaccine in 12 – 17 years old adolescents

Seroconversion rates [a]	Boostagen® (N=149)	Licensed Tdap (N=149)	Difference [b]
	n (%)	n (%)	% (95% CI)
PT	144 (96.64)	82 (55.03)	41.61 (33.12 – 50.11)
FHA	123 (82.55)	81 (54.36)	28.19 (18.13 – 38.24)

a: Seroconversion defined as ≥ 4-fold increase at 28 days after vaccination as compared to baseline titers
b: Based on non-inferiority test with different margin of 10%

Non-inferiority test for anti-PT and anti-FHA GMTs as assessed by ELISA in Boostagen® *vs* a licensed Tdap vaccine in 12 – 17 years old adolescents

Geometric Mean	Boostagen® GMT [a] (IU/mL) (95% CI)	Licensed Tdap GMT [a] (IU/mL) (95% CI)	GMT Ratio [b] (95% CI)
PT	343.08 (294.46 – 399.73)	48.09 (36.99 – 62.50)	7.13 (5.57 – ∞)
FHA	549.67 (471.95 – 640.18)	178.19 (148.94 – 213.19)	3.08 (2.54 – ∞)

a: Geometric Mean Change from baseline at Day 28 after vaccination
b: Based on non-inferiority test with GMT Ratio > 0.67

Protective efficacy of pertussis

No established correlates of protection to pertussis antigens are currently available. WHO recommends that for licensure of new acellular pertussis vaccines (WHO TRS) non-inferior immunogenicity of each of the individual antigenic components has to be demonstrated as compared to a licensed acellular pertussis vaccine. Therefore, **Boostagen®** was compared to a licensed Tdap vaccine in a well powered clinical study in adolescents aged 12 – 17 years of age. Non-inferiority to a TdaP licensed vaccine was demonstrated and according to EMEA guidelines, superiority can be claimed.

STORAGE CONDITIONS

Boostagen® should be stored at 2°C to 8°C. Do not freeze. Discard if vaccine has been frozen. Store in the original package in order to protect from light.
Keep out of the sight and reach of children.

SHELF-LIFE

3 years.

EXPIRY DATE

The expiry date of **Boostagen®** is indicated on the label and packaging.

PRESENTATION

Single-dose (0.5 mL) pre-filled syringe which is made of a type I glass, conforming to European Pharmacopoeia requirements. The container closure system of **Boostagen®** is free of latex.

BioNet

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Marketing Authorization Number: SIN16493P

Date of Revision of Package Insert: 08 March 2022