Registration No. 2A 1/59 (NB)
Manufacturer: BioNet-Asia Co., Ltd., Thailand

SUMMARY OF PRODUCT CHARACTERISTICS

Boostagen® $TdaP_{gen}$

1. NAME OF THE MEDICINAL PRODUCT

Boostagen® Combined tetanus toxoid, reduced diphtheria toxoid and recombinant pertussis vaccine (TdaP or $TdaP_{gen}$).

2. QUALITATIVE AND QUANTITATIVE 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 (PT_{gen})*	5 µg
Filamentous Haemagglutinin (FHA)	5 µg

*rPT or PT_{gen} is a genetically-detoxified PT obtained by recombinant DNA technology.

Adsorbed on aluminum hydroxide.

For the full list of excipients, see section 6.1.

Boostagen® meets the World Health Organisation requirements for the manufacture of biological substances, of diphtheria, tetanus, and acellular pertussis combined vaccines.

3. PHARMACEUTICAL FORM

Suspension for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Boostagen® is indicated for active booster immunization against tetanus, diphtheria and pertussis in individuals from the age of 3 years onwards, for pertussis immunization in healthcare providers to prevent nosocomial transmission to infants and for maternal immunization in pregnant women for the prevention of pertussis in infants too young to be vaccinated.

Boostagen® is not indicated for primary immunisation.

4.2 Posology and method of administration

Posology

A single 0.5 mL dose of **Boostagen®** is recommended. **Boostagen®** should be given in accordance with WHO and national recommendations or medical practices for booster vaccination and for maternal immunization:

- in the second or third trimester and preferably at least 15 days before the end of pregnancy. See section 4.6.
- in adolescents and adults with an unknown or incomplete immunization against diphtheria or tetanus as part of vaccination program
- for tetanus prophylaxis in wound management. Tetanus immunoglobulin should be administered in accordance with existing recommendations.

Method of administration

Boostagen® should be administered by deep intramuscular injection, preferably in the deltoid region. The skin over the site of injection should be cleaned before infection. Shake well before use. Do not use if resuspension does not occur after vigorous shaking. Open the needle cap of the prefilled syringe, administer the total volume of 0.5 mL intramuscularly (IM).

4.3 Contraindications

Boostagen® should not be administered to individuals with past experience or signs of:

- hypersensitivity or life-threatening reaction following administration of diphtheria, tetanus or pertussis vaccines or to any component of the vaccine (see section 2 "QUALITATIVE AND QUANTITATIVE COMPOSITION" and section 6.1 "List of excipients");
- any encephalopathy with unknown aetiology such as coma, prolonged seizures, or decreased level of consciousness within 7 days following previous vaccination with any pertussis vaccine;
- progressive or unstable neurological disorders, uncontrolled epilepsy or progressive encephalopathy.

4.4 Special warnings and precautions for use

General

In compliance with local requirements, vaccination should be preceded by a review of the medical history and a clinical examination. 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.

As with other vaccines, administration of **Boostagen®** to subjects suffering from acute severe febrile illness should be postponed. The vaccine 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 pertussis vaccines: high temperature ($\geq 40°C$) 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, 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.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies with other drugs have not been performed. However, since **Boostagen®** is an inactivated vaccine, administration of **Boostagen®** with other vaccines or immunoglobulin at separate site of injections is unlikely to cause any interference with the immune response.

4.6 Pregnancy and lactation

Pregnancy

As per 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 a randomized controlled trial and an active post-marketing surveillance (including a prospective observational study) where 1,069 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 two reproductive and developmental animal toxicity studies.

Lactation

As **Boostagen®** contains toxoids or inactivated antigens, no risk to the breastfed infant should be expected. No study on lactation was performed in humans.

4.7 Effects on ability to drive and use machines

Boostagen® has no effect on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety profile presented below is based on data from 5 clinical trials where **Boostagen®** was administered to children and adolescents (between 3 and 17 years of age) and adults including pregnant women (Table 1). 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). The frequency, severity and duration of adverse events were similar in subjects vaccinated either with **Boostagen®** or with two different $Tdap_{chem}$ or with pediatric

$DTaP_{chem}$ vaccines. These signs and symptoms were mostly mild and moderate in intensity and resolved without sequelae.

Table 1: Safety data of **Boostagen®** in 5 randomized controlled trials

System Organ Class	**Frequency**	**Adverse Reactions**			
		Children aged 3-7 years (*N=100*)	**Adolescents aged 12-17 years** (*N=150*)	**Adults**	
				Adults including non-pregnant Women *(N=70)****	**Pregnant Women** *(N=80)*
General disorders and administration site conditions	Very common (≥1/10)	Pain, fatigue, malaise, fever (≥38ºC)	Pain, redness and induration at injection site, malaise, fatigue	Pain, redness and induration at injection site, fatigue, malaise	Injection site pain, fatigue
Nervous system disorders		Headache	Headache	Headache	Headache
Musculoskeletal and connective tissue disorders		Myalgia	Myalgia, arthralgia	Myalgia, arthralgia	Myalgia, arthralgia
General disorders and administration site conditions	Common (≥1/100 to <1/10)	Redness, swelling, induration and pruritus at injection site, chills	Chills, fever (≥37.5ºC)	Malaise, injection site swelling, chills, fever (≥38ºC)	Redness, induration and pruritus at injection site, malaise, fever (≥38ºC)
Nervous system disorders		Headache		Headache	
Gastrointestinal disorders		Vomiting, nausea	Vomiting	Vomiting, nausea	Vomiting, nausea
Musculoskeletal and connective tissue disorders		Arthralgia	Pain in extremity	Arthralgia	
General disorders and administration site conditions	Uncommon (≥1/1000 to <1/100)		Injection site pruritus	Injection site pruritus	
Nervous system disorders			Dizziness		
Gastrointestinal disorders			Nausea		

* 20 of them received a formulation containing Boostagen® antigens and pertactin

Data from post-marketing experience

Data from active pharmacovigilance confirmed the safety profile of **Boostagen®** in 9,782 individuals aged 11 years to 65 years and older.

4.9 Overdose

No case of overdose was reported with **Boostagen®**.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Immune response

Non-inferiority of the immune response of **Boostagen®** was demonstrated in adolescents one month after vaccination in a comparative randomized controlled trial (Table 2). Seroprotection rates of tetanus and diphtheria toxoids were similar to the $Tdap_{chem}$ comparator. The pertussis antibody booster response and titers were significantly higher after vaccination with $TdaP_{gen}$ than with $Tdap_{chem}$ vaccine. Hence, non-inferiority of **Boostagen®** was met as recommended in WHO TRS 979. In addition, superiority of **Boostagen®** was also demonstrated for pertussis seroresponse rates and GMTs in accordance with EMA guidelines (CPMP/EWP/482).

Boostagen® $TdaP_{gen}$ was also found immunogenic in children aged 3 to 7 years old in a comparative randomized controlled study with a pediatric $DTaP_{chem}$-IPV containing chemically detoxified PT and FHA.

Table 2

Antigen		**Children aged 3-7 years** *Comparative study*		**Adolescents aged 12-17 years** *Non-inferiority study*	
		Boostagen® $TdaP_{gen}$ *(N=20)*	**Comparator** $DTaP_{chem}$ [a] *(N=19)*	**Boostagen®** $TdaP_{gen}$ *(N=149)*	**Comparator** $Tdap_{chem}$ [a] *(N=149)*
Immune response (% vaccinees)					
Tetanus	Seroprotection [b]	100%	100%	100%	100%
Diphtheria		100%	100%	98%	95%
PT	Booster response [c]	100%	100%	97%	55%
FHA		100%	100%	83%	54%
Antibody titers					
PT	GMT (IU/mL) [d]	622	291	343	48
	GMT ratio [e]	2.1 (1.0 – 4.4)		7.1 (5.6 – ∞) [f]	
FHA	GMT (IU/mL) [d]	93	122	550	178
	GMT ratio [e]	1.1 (0.6 – 2.0)		3.1 (2.5 – ∞) [f]	

[a]: 2-component $DTaP_{chem}$ combined to IPV and 5-component $Tdap_{chem}$

[b]: Defined as seroprotective antibody titers against tetanus and diphtheria of > 0.1 IU/mL (ELISA assay)

[c]: Defined as a 4-fold increase of pertussis antibody titers from pre-booster (baseline) antibody concentration

[d]: Geometric Mean Titer (GMT) Change from baseline at Day 28 after vaccination (ELISA assay)

[e]: The ratio of Geometric Mean Change from baseline between Boostagen® and Comparator, reported with 95% confidence interval

[f]: Based on non-inferiority test with GMT Ratio > 0.67

N is the minimum number of subjects with available data for each antigen.

Antibody persistence

There are no well-established antibody levels which correlate absolutely with pertussis protection. However, the rapid decline in antibody levels during the first year observed with $Tdap_{chem}$ vaccines is consistent with the epidemiologic and vaccine effectiveness data in adolescents that indicated its rapid waning of immunity and a short duration of protection (US CDC, 2018). An alternative means suggested to reduce waning is to use pertussis toxin which has been genetically detoxified rather than chemically detoxified in vaccines (IMAC, 2018).

The antibody persistence after one dose of $TdaP_{gen}$ was evaluated against a $Tdap_{chem}$ comparator (Table 3). One year after booster vaccination with **Boostagen®**, 98% of adolescents had anti-PT IgG titers. **Boostagen®** also induced a higher neutralizing antibody response persisting in 85% of adolescents at year 3 as opposed to 43% with $Tdap_{chem}$ vaccine.

Table 3

Antibody Persistence		**Antigen**	**Boostagen® $TdaP_{gen}$**		**Comparator $Tdap_{chem}$ [a]**	
(% vaccinees)	Titers		Year 1	Year 3	Year 1	Year 3
Immune response	(IU/mL)		*N=48*	*N=56*	*N=49*	*N=58*
Seroprotection [b]	> 0.1	Tetanus	100%	100%	100%	100%
	> 0.1	Diphtheria	96%	86%	96%	88%
Seropositivity [b]	> 5	PT	100%	97%	84%	85%
	> 5	FHA	100%	97%	100%	98%
Booster response	(IU/mL)		*N=48*	*N=59*	*N=50*	*N=60*
Total IgG Antibody [b]	≥ 20 [d]	PT	98%	75%	50%	40%
	≥ 20 [d]	FHA	98%	97%	90%	77%
Neutralizing Antibody [c]			*N=48*	*N=20*	*N=50*	*N=21*
	≥ 20 [d]	PT	96%	85%	50%	43%

[a]: Compared to 5-component $Tdap_{chem}$ vaccine
[b]: Total antibody IgG titers measured by ELISA assay
[c]: Neutralizing PT antibody titers measured by PT-neutralization test
[d]: Antibody titers ≥ 20 IU/mL correspond to a 4-fold increase (post-booster) of seropositivity level set at 5 IU/mL
N is the minimum number of adolescents with available data for each antigen.

Protection against Pertussis

Although there is no current correlate of protection to pertussis antigens, induction of anti-PT antibody was shown to induce protection (WHO, 2017). When compared to three different chemically-detoxified pertussis vaccines (2, 3 and 5-component pertussis vaccines) in 5 randomized clinical trials, **Boostagen®** induced significantly higher anti-PT antibody response in children, adolescents and adults (Tables 2 to 5). This response was similar in non-pregnant and pregnant women when **Boostagen®** was given in the 2nd and 3rd trimester of gestation.

Table 4

Pregnant women [a]	**Anti-PT antibodies**	**Boostagen® TdaP$_{gen}$**	**Comparator Tdap$_{chem}$** [d]
Immune response [b] (%)	Total IgG	97%	77%
	Neutralizing	100%	71%
GMT [c] (IU/mL, 95%CI)	Total IgG	126 (101 – 157)	51 (42 – 62)
	Neutralizing	107 (66 – 172)	48 (32 – 72)

[a]: N=80 pregnant women for total IgG assay and 24 for neutralizing assay in randomized controlled study
[b]: Defined as a 4-fold increase of pertussis antibody titers from pre-booster (baseline) antibody concentration
c: Geometric Mean Titers (GMT) at Day 28 after vaccination (Total IgG measured by ELISA assay and PT-neutralizing titers measured by CHO cell assay)
[d]: 3-component Tdap$_{chem}$ vaccine

In one observational study evaluating the pertussis maternal immunization, anti-PT antibodies in cord sera were higher in 200 mothers immunized with **Boostagen®** TdaP$_{gen}$ than in the mothers who received Td vaccine with the respective titers, 153 IU/mL (129 – 181) vs 6 IU/mL (4.8 – 8.7) demonstrating the maternal anti-PT antibodies transfer to the newborn.

In adolescents, **Boostagen®** induces 3 to 7-fold higher anti-PT titers that persist after 3 years, which may confer higher immunity and longer duration of protection in adolescents (Table 5).

Table 5

Adolescents	**Boostagen® / Tdap$_{chem}$ comparator GMC ratios** [a]			
	Month 1	**Year 1**	**Year 2**	**Year 3**
Total antibody	*N=149*	*N=48*	*N=59*	*N=59*
PT	7.0	6.0	3.2	3.1
Functional antibody	*N=49*	*N=48*	*N=17*	*N=20*
PT-neutralizing	6.6	6.1	3.2	3.9

[a]: Geometric Mean Titer Change (from baseline at specified time after vaccination) ratio between Boostagen® and the 5-component Tdap$_{chem}$ vaccine
N is the minimum number of vaccinees with available data for each vaccine and each antigen.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety and toxicity including reproductive and developmental animal toxicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, water for injection.
Formaldehyde and thiomersal may be present in trace amounts as manufacturing process residuals.

6.2 Incompatibilities

Boostagen® should not be mixed with other vaccines in the same syringe.

6.3 Shelf life

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

6.4 Special precautions for storage

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.

6.5 Nature and contents of container

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

6.6 Special precautions for use, handling and disposal

The vaccine should be well shaken to obtain a uniform, cloudy and white suspension.
Do not use if you notice presence of foreign particles or discoloration.
Do not inject intravascularly.
Do not use after expiration date. See expiration on carton and inner label.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BioNet-Asia Co., Ltd., Thailand

8. MARKETING AUTHORISATION NUMBER(S)

2A 1/59 (NB)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07 October 2016

10. DATE OF REVISION OF THE TEXT

10 June 2021

Boostagen® is BioNet-Asia's trademark.