MODULE 1

1.3 - Product Information

1.3.1

SPC, Labelling and Package Leaflet

1.3.1.2

SPC

Boostagen$_{RED}^{TM}$ Tdap$_{gen}$

(Tetanus toxoid, reduced diphtheria toxoid, reduced recombinant pertussis vaccine)

SUMMARY OF PRODUCT CHARACTERISTIC

Boostagen$_{RED}$™ Tdap$_{gen}$

(Tetanus toxoid, reduced diphtheria toxoid, reduced recombinant pertussis vaccine)

SUMMARY OF PRODUCT CHARACTERISTICS

Boostagen$_{RED}$ ™

1. NAME OF THE MEDICINAL PRODUCT

Boostagen$_{RED}$ ™ Combined tetanus toxoid, reduced diphtheria toxoid, reduced recombinant pertussis vaccine (Tdap$_{gen}$)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single dose (0.5 mL) contains:

Tetanus Toxoid	7.5 Lf
Diphtheria Toxoid	2.0 Lf
Bordetella pertussis antigens	
Recombinant Pertussis Toxin (rPT)*	2 µg
Filamentous Haemagglutinin (FHA)	5 µg

* rPT is a genetically-detoxified PT (PTgen) obtained by recombinant DNA technology. Adsorbed on aluminum hydroxide.
For the full list of excipients, see section 6.1

Boostagen$_{RED}$™ (Tdap$_{gen}$ vaccine) meets the World Health Organisation (WHO) requirements for the manufacture of diphtheria, tetanus, and acellular pertussis combined vaccines.

3. PHARMACEUTICAL FORM

Suspension for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Boostagen$_{RED}$ ™ is indicated for active booster immunization against tetanus, diphtheria and whooping cough in individuals from the age of 9 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 (WHO recommendations). **Boostagen$_{RED}$™** is not indicated for primary immunisation.

4.2 Posology and method of administration

Posology

A single 0.5 mL dose of **Boostagen$_{RED}$ ™** is recommended.

Boostagen$_{RED}$ ™ 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.

- 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

$Boostagen_{RED}$ ™ should be administered by deep intramuscular injection, preferably in the deltoid region. The skin over the site of injection should be cleaned with alcohol before injection. Shake well before use. Do not use if resuspension does not occur after vigorous shaking. Open the cap of the pre-filled syringe or vial, administer 0.5 mL intramuscularly (IM). Opened multi-dose vial should be discarded at the end of the immunization or within six hours after opening, whichever comes first.

4.3 Contraindications

$Boostagen_{RED}$ ™ 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;
- 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

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 **$Boostagen_{RED}$ ™** 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 (> 40ºC) without any identifiable cause, convulsions and collapse or shock-like state.

$Boostagen_{RED}$ ™ 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 **$Boostagen_{RED}^{TM}$** is an inactivated vaccine, the simultaneous administration of **$Boostagen_{RED}^{TM}$** with other inactivated vaccines or immunoglobulins 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 **$Boostagen_{RED}$ ™** 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 of one dose of **$Boostagen_{RED}$ ™** administered to pregnant women in the second or third trimester of pregnancy have shown a safety profile in mothers and foetus/newborns similar to the chemically-detoxified pertussis toxin ($Tdap_{chem}$) comparator vaccine. In addition, an active post-marketing surveillance (including a prospective observational study) where 1,069 pregnant women were exposed to Boostagen® (similar to **$Boostagen_{RED}$ ™** but with a higher amount of PT_{gen}) in the second or third trimester of pregnancy have also 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 **$Boostagen_{RED}$ ™** 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

$Boostagen_{RED}$ ™ 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 three clinical trials where **$Boostagen_{RED}$ ™** was administered to adolescents and adults including non- pregnant and pregnant women (Table 1) . Within 7 days after vaccination, the most common events occurring were local injection site reactions (pain, redness and pruritus at injection site) and systemic reactions (headache, fatigue, myalgia, malaise and arthralgia) . The frequency, severity and duration of adverse events were similar in subjects vaccinated

either with **$Boostagen_{RED}$ ™** or with two different $Tdap_{chem}$ vaccines. These signs and symptoms were mostly mild and moderate in intensity and resolved without sequelae.

Table 1: Safety data of **$Boostagen_{RED}$™** in 3 randomized controlled trials

System Organ Class	Frequency	Adverse Reactions		
		Adolescents aged 9-17 years (N=150)	**Adults**	
			Women of Child Bearing Age (N=50)	**Pregnant Women** (N=80)
General disorders and administration site conditions	Very common (≥1/10)	Pain, redness and pruritus at injection site, fatigue	Injection site pain, fatigue, malaise	Injection site pain, fatigue
Nervous system disorders		Headache	Headache	Headache
Musculoskeletal and connective tissue disorders		Myalgia	Myalgia	Myalgia, arthralgia
General disorders and administration site conditions	Common (≥1/100 to <1/10)	Swelling and induration at injection site, malaise, chills, fever (≥38ºC)	Swelling and pruritus at injection site, chills, fever (≥38ºC),	Redness, induration, at injection site, malaise, chills, fever (≥38ºC)
Gastrointestinal disorders		Nausea	Vomiting, nausea	Vomiting, nausea
Musculoskeletal and connective tissue disorders		Arthralgia	Arthralgia, pain in extremity	-
Psychiatric disorders		-	Insomnia	-

In addition, data from active pharmacovigilance confirmed the safety profile of Boostagen® (similar to **$Boostagen_{RED}$ ™** but with a higher amount of PT_{gen}) in 9,782 individuals (adolescents, adults including pregnant women and elderly aged 65 years and above).

Data from post-marketing experience

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

4.9 Overdose

No case of overdose was reported with **$Boostagen_{RED}$ ™**.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Non- inferiority of the immune response o**f Boostagen$_{RED}$ ™** 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 **Boostagen$_{RED}$ ™** $Tdap_{gen}$ than with $Tdap_{chem}$ vaccine. Hence, non-inferiority of **Boostagen$_{RED}$ ™** was met as recommended in WHO TRS 979. In addition, superiority of **Boostagen$_{RED}$ ™** was also demonstrated for pertussis seroresponse rates and GMTs in accordance with EMA guidelines (CPMP/EWP/482/99).

Table 2

	Antigen	**Boostagen$_{RED}$ ™ Tdap$_{gen}$** *(N=150)*	**Comparator Tdap$_{chem}$** [1] *(N=149)*	
Immune response (% vaccinees)				***Difference***[a]
Seroprotection [2]	Tetanus	100%	100%	-
	Diphtheria	100%	100%	-
Booster response [3]	PT	94%	70%	*24%*
	FHA	96%	83%	*13%*
Antibody Titers (IU/mL)				***GMT Ratio*** [4, b]
GMT (95%CI)	PT	90.3 (77.3-105.5)	26.9 (22.6-32.0)	*3.4 (2.8-∞)*
	FHA	136.8 (120.3-155.5)	72.0 (61.6-84.2)	*1.9 (1.6-∞)*

[1]: Compared to 5-component $Tdap_{chem}$ comparator vaccine

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

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

[4]: Geometric Mean Titers (GMT) change from baseline at Day 28 after vaccination (ELISA assay), reported with 95% confidence interval

[a]: Based on non-inferiority test with different margin of 10%

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

N is the minimum number of adolescents 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 rapid waning of immunity and a short duration of protection

conferred by $Tdap_{chem}$ (US CDC, 2018). An alternative means suggested to reduce waning is to use pertussis toxin **(**PT**)** which has been genetically detoxified **(**PT_{gen}**)** rather than chemically detoxified (PT_{chem}) in vaccines **(**IMAC, 2018**).**

The antibody persistence one year after one dose of **$Boostagen_{RED}$** ™ was evaluated against a $Tdap_{chem}$ comparator. **$Boostagen_{RED}$** ™ induced a higher anti-PT booster response persisting in 60% of adolescents as opposed to 20% with $Tdap_{chem}$ vaccine (Table 3).

Table 3

1 Year Antibody Persistence		**Antigen**	**$Boostagen_{RED}$ ™ $Tdap_{gen}$**	**Comparator $Tdap_{chem}$ [a]**
(% vaccinees)	Titers		*N=50*	*N=50*
Immune response	(IU/mL)			
Seroprotection [b]	> 0.1	Tetanus	100%	100%
	> 0.1	Diphtheria	96%	100%
Seropositivity [c]	> 5	PT	94%	76%
	> 5	FHA	96%	96%
Booster response	(IU/mL)			
Total IgG Antibody [b]	≥ 20 [d]	PT	60%	20%
	≥ 20 [d]	FHA	84%	64%
Neutralizing Antibody [c]				
	≥ 20 [d]	PT	66%	26%

[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). Data on the effectiveness of $Boostagen_{RED}$™ against pertussis are not yet available.

In a pivotal study, adolescents who received $Boostagen_{RED}$ ™ $Tdap_{gen}$ induced significantly higher anti-PT antibodies than the ones who received a $Tdap_{chem}$ comparator of which effectiveness was evaluated (Tables 2 and 3). The 2.6-fold higher anti-PT titers persist after 1 year, which may confer higher immunity and longer duration of protection in adolescents (Table 4).

Table 4

Adolescents	**$Boostagen_{RED}$ ™ / $Tdap_{chem}$ comparator GMC ratios [a]**	
	Month 1	**Year 1**
Pertussis Antibodies	*N=150*	*N=50*
PT IgG	2.9	2.8
FHA IgG	1.7	1.6
	N=50	*N=50*
PT-neutralizing	2.6	2.6

[a]: Geometric Mean Titer Change (from baseline at specified time after vaccination) ratio between **$Boostagen_{RED}$ ™** and the 5-component $Tdap_{chem}$ vaccine

N is the minimum number of vaccinees with available data for each vaccine and each antigen**.**

Maternal vaccination during pregnancy confers protection to infant. Transplacental transfer of maternal pertussis antibodies from mother to infant provides some protection against pertussis in early life (US CDC, 2017).

In a randomized controlled trial, **$Boostagen_{RED}$ ™** induced a 4-fold increase in maternal anti-PT neutralizing antibodies in 83% pregnant women vaccinated in the second or third trimester of pregnancy as opposed to 71% with a $Tdap_{chem}$ comparator. These maternal antibodies were transferred to neonates with a GMT ratio when compared to $Tdap_{chem}$ above 1 in neonates at birth (Table 5).

Table 5

Maternal immunization	**$Boostagen_{RED}$ ™ / $Tdap_{chem}$ comparator GMT ratios [a]**		
	Mother		Neonate
	1 month after vaccination	at time of delivery	at birth
PT IgG [b]	1.4	1.4	1.1
PT-neutralizing [c]	1.6	1.7	1.1

[a]: Geometric Mean Titer ratio between **$Boostagen_{RED}$ ™** and the 3-component $Tdap_{chem}$ comparator

[b]: PT IgG measured by ELISA assay in 79 pregnant women vaccinated with **$Boostagen_{RED}$ ™** and 78 with comparator

[c]: PT-neutralizing titers measured by CHO cell assay in 23 pregnant women vaccinated with **$Boostagen_{RED}$ ™** and 24 with comparator

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.

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

$Boostagen_{RED}$ ™ should not be mixed with other vaccines in the same syringe.

6.3 Shelf life

Five years in pre-filled syringe and three years in vial.

The expiry date of **$Boostagen_{RED}$ ™** is indicated on the label and packaging.

6.4 Special precautions for storage

$Boostagen_{RED}$ ™ should be stored at 2°C to 8°C in the original package. Do not freeze. Discard if vaccine has been frozen. For opened multi-dose vial, see section ADMINISTRATION. Keep out of the sight and reach of children.

6.5 Nature and contents of container

Single-dose vial (0.5 mL), mono-dose pre-filled syringe (0.5 mL) and two-dose vial (1.0 mL) are made of a type I glass (Ph. Eur.) with a latex-free container closure system.

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 1/64 (NBC)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 September 2021

10. DATE OF REVISION OF THE TEXT

14 November 2023

$Boostagen_{RED}$ ™ is BioNet-Asia's trademark.