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

SUMMARY OF PRODUCT CHARACTERISTICS

Pertagen® aP_{gen}

1. NAME OF THE MEDICINAL PRODUCT

Pertagen® Recombinant pertussis vaccine (aP or aP_{gen}).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single dose (0.5 mL) contains:

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.

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

Formaldehyde may be present as in trace amounts as a manufacturing process residual.

3. PHARMACEUTICAL FORM

Suspension for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pertagen® is indicated for active booster immunization against pertussis in individuals from the age of 3 years onwards.

Pertagen® is indicated for passive protection against pertussis in early infancy following maternal immunization during pregnancy.

Pertagen® should be used in accordance with official recommendations for booster and catch up vaccination and maternal immunization against pertussis only.

4.2 Posology and method of administration

Posology

A single 0.5 mL dose of **Pertagen®** is recommended.

Pertagen® may be given in individuals aged 3 years and onwards requiring protection against pertussis only as booster, catch-up or maternal immunization in accordance with national, WHO, US or EU official recommendations or medical practices, including:

- pregnant women in the second or third trimester and preferably at least 15 days before the end of pregnancy to prevent pertussis in mothers and in infants too young to be vaccinated
- multiparous women with closely spaced pregnancies to avoid "over-vaccination" and hypersensitivity reactions due to repeated injections of Tdap-IPV or Tdap vaccines
- adolescents, adults, household contacts, childcare providers to maintain herd immunity and to protect the youngest infants
- healthcare providers to prevent nosocomial transmission to infants

Pertagen® may be considered as an alternative to acellular pertussis combinations (DTaP or Tdap-based vaccines) for pertussis booster immunization in subjects with known hypersensitivity to tetanus (Arthus-type hypersensitivity reaction) or diphtheria vaccines and in individuals who have received multiple and frequent tetanus or diphtheria vaccine doses.

Method of administration

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

4.3 Contraindications

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

- severe allergic reaction or any encephalopathy with unknown origin following administration of pertussis vaccines or to any components of the vaccine;
- neurological disorders, uncontrolled epilepsy or progressive encephalopathy.

Hypersensitivity, thrombocytopenia or neurological complications following an earlier immunization against diphtheria and/or tetanus are not contraindication to the use of **Pertagen®**.

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. As with all injectable vaccines, appropriate medical care should be readily available in case of a rare anaphylactic reaction after vaccination.

In the case of acute severe febrile illness, immunosuppressive treatment or immunodeficiency, vaccination should be postponed. Nevertheless, vaccination should be considered in HIV-infected persons or those with chronic immunodeficiency disorder.

As with any vaccines, **Pertagen®** should be administered with caution to subjects who had high body temperature (≥ 40°C) without any identifiable causes within 48 hours after a previous immunization with any pertussis vaccines. **Pertagen®** should be given with caution in individuals receiving anticoagulant therapy or those with

thrombocytopenia or any coagulation disorder because bleeding at injection site may occur after intramuscular injection.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

Pregnancy

Because of the potential benefits of maternal pertussis immunization and the lack of monovalent acellular pertussis vaccine in the USA, pregnant women should receive Tdap boosters during each pregnancy even though moderate to severe local reactions have been associated with high levels of tetanus and diphtheria antitoxin (WHO, 2014).

In a randomized controlled trial where 80 pregnant women were exposed to Boostagen® $TdaP_{gen}$ (Td vaccine combined to **Pertagen®** aP_{gen} components) have shown a safety profile in mothers and foetus/newborns similar to the chemically-detoxified pertussis toxoid ($Tdap_{chem}$) comparator vaccine. In addition, safety data from active post-marketing surveillance (including a prospective observational study) where 1,778 pregnant women were exposed to **Pertagen®** or 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 in two reproductive and developmental animal toxicity studies evaluating **Pertagen®** antigens combined to tetanus and diphtheria toxoids.

Lactation

No study on lactation was performed in humans. However, as **Pertagen®** contains inactivated antigens, no risk to the breastfed infant should be expected.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

As there is no other monovalent pertussis vaccine available, **Pertagen®** monovalent 2-component aP_{gen} and vaccines containing **Pertagen®** components ($TdaP_{gen}$ and $DTaP_{gen}$) were compared to 2, 3 or 5-components acellular pertussis-based vaccines ($Tdap_{chem}$ and $DTaP_{chem}$).

The safety profile of **Pertagen®** or vaccines containing **Pertagen®** components (in quantity not less than in **Pertagen®**) is based on the data from six randomized controlled trials in children, adolescents and adults including pregnant women (Table 1). Within 7 days after vaccination, the most common events occurring were local injection site pain (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 aP_{gen}-based vaccines or aP_{chem}-based comparator vaccines. These signs and symptoms were mostly mild and moderate in intensity and resolved without sequelae within a few days.

Table 1: Safety data of **Pertagen®** or **Pertagen®** vaccine-containing components in children, adolescents and adults including pregnant women

System Organ Class	**Frequency**	**Adverse Reactions**			
		Children aged 3-7 years *(N=126)*[a]	**Adolescents aged 12-17 years** *(N=331)*[b]	**Adults**	
				Men and non-pregnant women *(N=90)*[c]	**Pregnant women** *(N=80)*[d]
General disorders and administration site conditions	Very common (≥ 1/10)	Injection site 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		

[a]: 102 vaccinated with $TdaP_{gen}$ and 24 vaccinated with $DTaP_{gen}$ (using pediatric DT) compared to 2-component $DTaP_{chem}$-IPV

[b]: 181 vaccinated with **Pertagen®** aP_{gen} and 150 vaccinated with Boostagen® $TdaP_{gen}$ compared to 3-component $dTpa_{chem}$ or 5-component $Tdap_{chem}$

[c]: 50 vaccinated with $TdaP_{gen}$ (Boostagen®), 20 vaccinated with $TdaP_{gen}$+Pertactin and 20 vaccinated with aP_{gen}+Pertactin compared to 3- or 5-component $Tdap_{chem}$

[d]: 80 vaccinated with $TdaP_{gen}$ (Boostagen®) compared to 3-component $Tdap_{chem}$

Data from post-marketing experience

Data from active pharmacovigilance of **Pertagen®** (aP_{gen}) and Boostagen® ($TdaP_{gen}$) also confirmed the safety profile of **Pertagen®** in 11,429 individuals aged 11 years and above including 437 adolescents, 10,960 adults (including 1,778 pregnant women) and 32 elderly aged 65 years and above.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Immune response

As there is no other monovalent aP vaccine, **Pertagen®** immunogenicity (Table 2) was evaluated in adolescents in a pivotal non-inferiority trial comparing aP_{gen} and $TdaP_{gen}$ to a combined $Tdap_{chem}$: the pertussis antibody booster response was found significantly higher after one single dose of recombinant pertussis vaccines than after the comparator, demonstrating the non-inferiority and the superiority of the immune response induced by **Pertagen®**, as per WHO TRS 979 and EMA CPMP/EWP/482 guidelines.

In a comparative trial in children (Table 2), Boostagen® $TdaP_{gen}$ containing the same 5 µg PT_{gen} and FHA as in **Pertagen®** induced a higher anti-PT and similar anti-FHA immune response based on GMC ratio to a pediatric $DTaP_{chem}$-IPV containing 25 µg PT_{chem} and FHA.

Table 2: Antibody response of aP_{gen} (**Pertagen®**) and $TdaP_{gen}$ (Boostagen®) in children and adolescents

Antibody response		Children aged 3-7 years		Adolescents aged 12-17 years	
		$TdaP_{gen}$ *(N=20)*	Comparator[a] *(N=19)*	**Pertagen®** aP_{gen} *(N=148)*	Comparator[b] *(N=149)*
Immune response (% vaccinees)					
PT	Booster response[c]	100%	100%	96%	55%
FHA		100%	100%	93%	54%
PT	Booster response difference			*40.9% (32.2 – 49.5)*[d]	
FHA				*38.9% (29.9 – 47.8)*[d]	
Antibody concentration					
PT	GMC (IU/mL)[e]	622	291	562	63
	GMFC[f]	54.5	25.4	41.2	4.1
	GMFC ratio[g]	2.1 (1.1 – 4.4)		*10.1 (7.6 − 13.6)*	
	GMC ratio			*11.0 (8.4 − ∞)*[h]	
FHA	GMC (IU/mL)[e]	93	122	924	242
	GMFC[f]	30.5	27.9	23.7	5.3
	GMFC ratio[g]	1.1 (0.6 – 2.0)		*4.5 (3.2 – 6.4)*	
	GMC ratio			*4.7 (3.9 − ∞)*[h]	

[a]: 2-component $DTaP_{chem}$ combined to IPV
[b]: 5-component $Tdap_{chem}$
[c]: Defined as a 4-fold increase of pertussis antibody concentrations from pre-booster (baseline) antibody concentration
[d]: Pertagen® was non-inferior to comparator based on the lower limit of 95% CI of the difference in booster response rate (-10% different margin). It is also above zero different margin and hence, was considered superior.
[e]: Geometric Mean Concentration (GMC) at Day 28 after vaccination (ELISA assay)
[f]: Geometric Mean of Fold Change (GMFC) from baseline at Day 28 after vaccination
[g]: The ratio of GMFC from baseline between Pertagen® and comparator, reported with 95% confidence interval
[h]: Pertagen® was non-inferior to comparator based on the lower limit of 95% CI of GMC ratio of Pertagen®/comparator (> 0.67 different margin). It is also above 1 different margin and hence, was considered superior.
N is the minimum number of subjects with available data for each antigen.

Antibody persistence

Immunogenicity studies demonstrated that for pertussis antibodies after an initial $Tdap_{chem}$ dose, there is a rapid decline during the first year with a gradual decline afterwards (US CDC, 2018).

In a randomized trial (Table 3), **Pertagen®** induced a booster response which persisted during the first year in 90% of vaccinees. The persistence of high neutralizing antibody titers was also shown in 85% adolescents three years after a single booster dose of **Pertagen®** as opposed to 50% vaccinees with $Tdap_{chem}$ after the first year.

Table 3: Antibody persistence of aP_{gen} (**Pertagen®**) and comparator $Tdap_{chem}$ vaccine in adolescents

Antibody persistence		**Antigen**	**Pertagen® aP_{gen}**		**Comparator $Tdap_{chem}$ [a]**	
			Year 1	Year 3	Year 1	Year 3
Immune response			*N=50*	*N=62*	*N=50*	*N=60*
			(% of vaccinees)			
Seropositivity[b]	> 5 IU/mL	PT	98	95	84	85
		FHA	100	98	100	98
Booster response			*N=50*	*N=62*	*N=50*	*N=60*
			(% of vaccinees)			
Total IgG Antibody[b]	≥ 20 IU/mL[d]	PT	92	81	50	40
		FHA	100	98	90	77
Neutralizing Antibody[c]	≥ 20 IU/mL[d]	PT	*N=50*	*N=20*	*N=50*	*N=21*
			(% of vaccinees)			
			90	85	50	43

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

Protection against Pertussis

For pertussis, antibody contributes to protection, but there are no well-established antibody levels which correlate absolutely with protection. However, the rapid decline in antibody levels (after one Tdap dose) is consistent with the vaccine effectiveness data that indicated rapid waning of immunity and a short duration of protection conferred by Tdap containing the chemically inactivated PT (US CDC, 2018).

In a pivotal trial in adolescents (Table 2 and Table 3), pertussis antibody concentrations declined during the first year but the anti-PT antibody levels one and three years after administration of **Pertagen®** remained significantly higher than after $Tdap_{chem}$ vaccine which shows that **Pertagen®** may confer higher immunity and longer duration of protection. In a controlled trial in children (Table 2), Boostagen® containing the **Pertagen®** aP_{gen} antigens was also compared to a DTaP-IPV containing the same aP_{chem} antigens as a DTaP vaccine of which efficacy was documented in a trial.

Maternal vaccination is effective in protecting infants against pertussis infection through both transfer of maternal antibodies and reduced infant exposure to pertussis (ECDC, 2018). Although there is no current correlate of protection to pertussis antigens, induction of anti-PT antibody was shown to induce protection (WHO, 2017).

In a prospective observational study (Table 4), pregnant women were exposed to aP_{gen}-only, $TdaP_{gen}$ or Td-only vaccines: pertussis neutralizing antibody titers at delivery were higher in **Pertagen®** and Boostagen® groups than in Td vaccinated women. **Pertagen®** induced a higher anti-PT response than Boostagen®. Vaccination with

Pertagen® in the 2nd trimester of pregnancy also induced higher anti-PT concentration than when given in the 3rd trimester.

Boostagen® was also compared to $Tdap_{chem}$ in two randomized trials in women: no difference in pertussis immune response was found after one Boostagen® dose between women of child-bearing age and pregnant women nor when vaccine was given in pregnant women either during the 2nd or 3rd trimester of gestation. The pooled data in pregnant and non-pregnant women shows that Boostagen® induced a higher anti-PT response at Day 28 after vaccination based on the adjusted GMC ratio of Boostagen® to comparator (2.6 (98.75% CI 2.0-3.5)). Boostagen® was non-inferior to comparator based on the lower limit of the 98.75% CI of the adjusted GMC ratio (> 0.5 different margin). It is also above 1 different margin and hence, was considered superior.

These results indicate more effective maternal immune response and antibody transfer from mother to infant after maternal vaccination with **Pertagen**® and Boostagen® than with chemically inactivated PT (PT_{chem}) containing vaccine.

Table 4: Summary of immune response in pregnant and non-pregnant women from observational and randomized controlled trials

Antibody response	**Pregnant women vaccinated in 2nd or 3rd trimester Observational study**			**Pregnant and non-pregnant women Randomized controlled trials[a]**	
Anti-PT Antibody Geometric Mean Concentration/ Titer (IU/mL, 95%CI)[b]	At delivery (in cord blood sera)			1 month after 1 dose	
	Pertagen® aP_{gen}	$TdaP_{gen}$[c]	Td[c]	$TdaP_{gen}$[c]	$Tdap_{chem}$[c]
	N=199	N=200	N=54	N=128 (24)[d]	N=128 (24)[d]
Total IgG Antibody	206 (164-259)	153 (129-182)	7 (5–9)	134 (111-161)	56 (48-65)
Neutralizing Antibody	105 (82-136)	81 (66-100)	4 (3–5)	107 (66-172)	48 (32-72)

[a]: One trial with evaluable 50 non-pregnant women data per group and another one with evaluable 78 pregnant women data per group

[b]: GMC of total IgG and GMT of neutralizing antibodies measured by ELISA and CHO cell assay, respectively

[c]: $TdaP_{gen}$ (Pertagen® antigens-containing Boostagen®), Td and 3-component $Tdap_{chem}$ comparator vaccines

[d]: Neutralizing antibody titers tested in 24 out of 80 pregnant women

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 may be present in trace amounts as a manufacturing process residual.

6.2 Incompatibilities

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

6.3 Shelf life

Five years. The expiry date is indicated on the label and packaging.

6.4 Special precautions for storage

Pertagen® should be stored at 2°C to 8°C in the original package. Do not freeze. Discard if vaccine has been frozen. 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 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 2/59 (NB)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 September 2016

10. DATE OF REVISION OF THE TEXT

4 January 2024

Pertagen® is a trademark of BioNet-Asia.