MODULE 1

1.3 - Product Information

1.3.1

SPC, Labelling and Package Leaflet

1.3.1.2

SPC

Pertagen$_{RED}^{™}$ (ap_{gen})

(Reduced Recombinant Pertussis Vaccine)

Registration No. ……
Manufacturer: BioNet-Asia Co., Ltd., Bangkok, Thailand

SUMMARY OF PRODUCT CHARACTERISTICS

Pertagen$_{RED}$™ (ap$_{gen}$)

1. NAME OF THE MEDICINAL PRODUCT

Pertagen$_{RED}$™ (**ap$_{gen}$**) Reduced recombinant pertussis vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single dose *(*0.5 mL*)* contains*:*

Purified *Bordetella pertussis* antigens

Recombinant Pertussis Toxin *(*PT$_{gen}$*)*[*]	2 µg
Filamentous Haemagglutinin *(*FHA*)*	5 µg

[*] 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

ap$_{gen}$ is indicated for active booster immunization against pertussis in individuals from the age of 9 years onwards.

ap$_{gen}$ is indicated for passive protection against pertussis in early infancy following maternal immunization during pregnancy.

ap$_{gen}$ 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 **ap$_{gen}$** is recommended.

ap$_{gen}$ may be given in individuals aged 9 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

ap$_{gen}$ 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

ap$_{gen}$ 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

ap$_{gen}$ 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 **ap$_{gen}$**.

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, **ap$_{gen}$** 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. **ap$_{gen}$** 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 **ap$_{gen}$** is an inactivated vaccine, the simultaneous administration of **ap$_{gen}$** 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

Because of the potential benefits of maternal pertussis immunization and the lack of monovalent acellular pertussis vaccine, 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).

Safety data of **ap$_{gen}$** containing Tdap vaccine (**Td-ap$_{gen}$**) given either in the second or third trimester are available from one randomized controlled trial (80 pregnancies). Additional safety data from **ap$_{gen}$** based vaccines containing with a higher PTgen content (aP$_{gen}$ and TdaP$_{gen}$) obtained from another randomized controlled trial (90 pregnancies), one observational study (399 pregnancy outcomes), active post-marketing surveillance (3,924 pregnant women) and passive surveillance) are supporting the safety profile of **ap$_{gen}$**.

Adverse events following immunization (AEFIs) in pregnant women were mostly injection site pain and muscle pain. Symptoms were mild and resolved within a few days with no complications. It has shown no vaccine-related adverse effect on pregnancy or on the health of the foetus/newborns.

As with other inactivated vaccines, it is not expected that vaccination with **ap$_{gen}$** vaccine harm the foetus at any trimester of pregnancy.

No adverse effects on pregnancy, parturition, lactation or prenatal and postnatal development were observed after administration of **ap$_{gen}$** based vaccines in two reproductive and developmental animal toxicity studies.

Lactation

No study on lactation was performed in humans. However, as **ap$_{gen}$** vaccine contains inactivated antigens, no risk to the breastfed infant should be expected.

4.7 Effects on ability to drive and use machines

ap$_{gen}$ vaccine has no effect on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of **ap$_{gen}$** and Tdap$_{gen}$ was compared to 3 or 5-components Tdap$_{chem}$ vaccines in four randomized controlled trials in adolescents, adults including pregnant women and elderly (Table 1).

Within 7 days after vaccination, the most common events were local injection site pain and systemic reactions (headache, fatigue, myalgia, malaise and arthralgia). Significantly lower pain at injection site was reported in **ap$_{gen}$** compared to Td-containing vaccine. Nevertheless, the frequency, severity and duration of other adverse events were similar in participants vaccinated either with **ap$_{gen}$** containing vaccines or comparator vaccines. Symptoms were mild and moderate in intensity and resolved without sequelae within a few days.

Table 1: Safety data of **ap$_{gen}$** and Td- **ap$_{gen}$** in in adolescents, adults including pregnant women and elderly

System Organ Class	**Frequency**	**Adverse Reactions**			
		Adolescents aged 9-17 years *(N=300)*[a]	**Adults**		**Elderly aged 65-75 years** *(N=60)*[d]
			Men and non-pregnant women *(N=290)*[b]	**Pregnant Women** *(N=80)*[c]	
General disorders and administration site conditions	Very common (≥1/10)	Pain and pruritus at injection site, fatigue	Pain and pruritus injection site, malaise	Injection site pain, fatigue	Injection site pain
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)	Redness, swelling, and induration at injection site, malaise, chills, fever (≥ 38ºC)	Fatigue, chills	Pruritus, redness, bruising and induration at injection site, malaise, chills, fever (≥38ºC)	Injection site pruritus, malaise, fatigue
Nervous system disorders		-	-	-	Headache
Gastrointestinal disorders		Vomiting, nausea	Vomiting, nausea	Vomiting, nausea	Nausea
Musculoskeletal and connective tissue disorders		Arthralgia	Arthralgia	-	Myalgia, Arthralgia
General disorders	Uncommon	-	Redness,	-	-

System Organ Class	Frequency	Adverse Reactions			
		Adolescents	Adults		Elderly
and administration site conditions	(≥ 1/1000 to < 1/100)		swelling and induration at injection site, fever (≥38ºC), axillary pain		
Musculoskeletal and connective tissue disorders		-	Pain in extremity	-	-
Psychiatric disorders		-	Insomnia	-	-

[a]**:** 150 vaccinated with ap_{gen} and 150 vaccinated with Td-ap_{gen}

[b]**:** 120 vaccinated with ap_{gen} and 170 vaccinated with Td-ap_{gen}

[c]**:** 80 vaccinated with Td-ap_{gen}

[d]**:** 30 vaccinated ap_{gen} and 30 vaccinated with Td-ap_{gen}

Data from post-marketing experience

Data from active pharmacovigilance confirmed the safety profile of **ap_{gen}** based vaccines in 16,141 vaccinees including adolescents, adults, elderly and 3,924 pregnant women.

4.9 Overdose

No case of overdose was reported with **ap_{gen}.**

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Immune response

A randomized controlled trial evaluating **ap_{gen}** and $Tdap_{gen}$ to a $Tdap_{chem}$ comparator in adolescents showed that both vaccines induced significantly higher pertussis antibody response and demonstrated the non-inferiority and superiority of **ap_{gen},** as per WHO TRS 979 and EMA CPMP/EWP/482 guidelines, respectively (Table 2). **ap_{gen}** also induced high pertussis antibody titers in adults and elderly (Table 3).

Table 2 Antibody response of **ap$_{gen}$** in adolescents

Immune response (1 month post-vaccination)	Adolescents aged 9-17 years		
	ap$_{gen}$ (N=150)	Tdap$_{chem}$[a] (N = 149)	Comparison
Booster response[b]	% vaccinees	% vaccinees	% difference
PT	92.6%	70.5%	22.2%[c]
FHA	95.3%	83.2%	12.1%[c]
Antibody concentration	GMC (IU/mL)[d]	GMC (IU/mL)[d]	GMC ratio
PT	228.1	32.8	8.1[e]
FHA	279.6	86.0	3.6[e]

[a] 5-component Tdap$_{chem}$
[b.] Defined as a 4-fold increase of pertussis antibody concentrations from baseline.
c. Non-inferior to comparator based on the lower limit of 95% CI of the difference in booster response rate higher than different margin (-10%). Superior (above zero).
d. Geometric Mean Concentration (GMC) measured by ELISA
e. Non-inferior to comparator based on the lower limit of 95% CI around the GMC ratio higher than different margin (0.67). Superior (above one different margin).

Table 3 Antibody response of **ap$_{gen}$** in adults and elderly

Immune response (1 month post-vaccination)	Adults aged 18-64 years		Adults aged 65-75 years	
	ap$_{gen}$ (N=60)	Comparison to Tdap[a] (N = 60, N=59)	**ap$_{gen}$** (N = 15)	Comparison to Tdap[a] (N = 15, N= 15)
Booster response[b]	% vaccinees	% difference	% vaccinees	% difference
PT	96.7%	18.7%[d]	86.7%	26.7%
FHA	95.0%	1.8%	93.3%	0.0%
Antibody concentration	GMC (IU/mL)[c]	GMC ratio	GMC (IU/mL)[c]	GMC ratio
PT	165.3	3.0[d]	94.1	2.7
FHA	305.3	1.5[d]	206.9	1.0

[a] 5-component Tdap$_{chem}$
[b.] Defined as by proportions of participants, ≥ 4-fold from baseline titers of ≥ 5.0 and < 20 IU/mL, ≥ 2-fold increase from baseline titers of ≥ 20 and ≥ 20 IU/mL from seronegative baseline (< 5 IU/mL)
[c.] Geometric Mean Concentration (GMC) measured by ELISA
[d] *p*-value ≤ 0.05 is considered statistically significant

Antibody persistence

The rapid decline in anti-PT antibody levels is consistent with the vaccine effectiveness data 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 **ap$_{gen}$** in adolescents was evaluated against a Tdap$_{chem}$ comparator (Table 4).

Table 4 Antibody persistence

Antibody persistence (1 year post-vaccination)	Adolescents aged 9-17 years		
	ap$_{gen}$ (N=49)	Tdap$_{chem}$[a] (N = 50)	Comparison **ap$_{gen}$**/Tdap$_{chem}$
Booster response[b]	% vaccinees	% vaccinees	% difference
PT	73.5%	16.0%	57.5%[c]
FHA	69.4%	46.0%	23.4%[c]
Antibody concentration	GMC (IU/mL)[d]	GMC (IU/mL)[d]	GMC ratio
PT	59.4	9.3	6.4[c]
FHA	61.9	25.7	2.4[c]

[a] 5-component Tdap$_{chem}$
[b.] Defined as a 4-fold increase of pertussis antibody concentrations from baseline.
[c.] p-value ≤ 0.05 is considered statistically significant
[d.] Geometric Mean Concentration (GMC) measured by ELISA

Protection against Pertussis

There are no well-established antibody levels which correlate absolutely with protection (CDC, 2018). However, present knowledge seems to indicate that PT, particularly if genetically detoxified, represents the main antigen that ensures protection from disease.

ap$_{gen}$ was shown to be superior (Table 2) to a Tdap$_{chem}$ vaccine evaluated in effectiveness studies that indicated pertussis protection in adolescents. However anti-pertussis antibodies declined rapidly after the first year (CDC).

One dose of **ap$_{gen}$** in adolescents, adults and elderly was also shown to induce higher and persisting neutralizing antibody titers which may confer longer duration of protection (Table 5).

Table 5: Pertussis neutralizing antibody persistence

Pertussis Neutralizing Antibody Titers (PTNA)	Adolescents (9-17 years-old)		Adults (18-75 years old)	
	Month 1	Year 1	Month 1	Year 1
ap$_{gen}$	N = 50	N = 49	N =75	N = 70
- GMT (IU/mL) [a]	223.5	61.3	101.1	28.1
- % seroconversion[b]	96.0%	83.7%	94.7%	64.3%
Tdap comparator[c]	N = 50	N = 50	N = 74	N =71
- GMT (IU/mL) [a]	29.1	9.1	29.6	12.6
- % seroconversion[b]	82.0%	26.0%	71.6%	43.7%

[a]: Geometric Mean Titer
[b] defined as proportion of vaccinees with titers ≥ 20IU/mL
[c] 5-component Tdap$_{chem}$ vaccine
N is the number of vaccinees

Maternal Immunization

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).

Randomized controlled trials evaluating maternal pertussis immunization with **ap$_{gen}$** containing vaccine (Tdap$_{gen}$) demonstrated:

- anti-PT antibody titers induced by Td-**ap$_{gen}$** from the pooled data of non-pregnant and pregnant women are non-inferior to a Tdap$_{chem}$ for which effectiveness in protecting infants under 2 months was documented **(**CDC**).**
- there was no difference in response between pregnant women and women of child-bearing age,
- Td-**ap$_{gen}$** 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 Tdapchem comparator**.**
- No difference when vaccine was given in pregnant women either during the second or third trimester of gestation
- These maternal antibodies were transferred to neonates with a GMT ratio above 1 in neonates at birth **(**Table 6**).**

Lower titers were observed later in infancy for both Td-**ap$_{gen}$** and the comparators, Maternal pertussis immunization appears to interfere with the infants' pertussis immune response after primary immunization. However, no evidence suggests the clinical relevance of immunological interference on protection against pertussis.

Table 6: Transfer of maternal antibody

Maternal immunization	**Td-ap$_{gen}$ /Tdap$_{chem}$ comparator GMT ratio [a]**		
	Mother		**Neonate**
Pertussis Antibodies	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 **Td-ap$_{gen}$ (**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 may be present in trace amounts as a manufacturing process residual.

6.2 Incompatibilities

ap$_{gen}$ vaccine should not be mixed with other vaccines in the same syringe.

6.3 Shelf life

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

6.4 Special precautions for storage

ap$_{gen}$ vaccine 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 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)

…….

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date Month Year (approval date)

10. DATE OF REVISION OF THE TEXT

Date Month Year (approval date)

Pertagen$_{RED}$™ is a trademark of BioNet-Asia.