PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

BOOSTRIX

Combined diphtheria, tetanus, acellular pertussis (adsorbed) vaccine for booster vaccination

Not less than 2.5 limit of flocculation ('Lf') or 2 IU ('International Units') of diphtheria toxoid;
8 mcg of pertussis toxoid; 8 mcg of filamentous hemagglutinin;
2.5 mcg of pertactin (69 kDa outer membrane protein); and,
not less than 5 Lf (20 IU) of tetanus toxoid, Suspension for injection, Intramuscular

Active immunizing agent against infection by diphtheria, tetanus and whooping cough

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RECENT MAJOR LABEL CHANGES

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Sections or subsections that are not applicable at the time of authorization are not listed .

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

BOOSTRIX (combined diphtheria, tetanus, acellular pertussis (adsorbed) vaccine) is indicated for:

- Booster vaccination against diphtheria, tetanus and pertussis of individuals from the age of four years onwards.
- Passive protection against pertussis in early infancy following maternal immunisation during pregnancy (see 4 DOSAGE AND ADMINISTRATION, 7 WARNINGS AND PRECAUTIONS, and 14 CLINICAL TRIALS).

BOOSTRIX is not intended for primary immunization.

2 CONTRAINDICATIONS

- BOOSTRIX (combined diphtheria, tetanus, acellular pertussis (adsorbed) vaccine) is contraindicated in individuals who are hypersensitive to any component of the vaccine or individuals having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, or pertussis vaccines (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING ~~**Error! Reference source not found.**~~).
- BOOSTRIX is contraindicated if the individual has experienced an encephalopathy of unknown etiology, occurring within 7 days following previous vaccination with pertussis containing vaccine. In these circumstances, adult-type combined diphtheria tetanus vaccine should be used.
- BOOSTRIX should not be administered to individuals who have experienced transient thrombocytopenia or neurological complications following an earlier immunization against diphtheria and/or tetanus.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Tetanus Prophylaxis in Wound Management

Table 1 summarizes the recommended use of immunizing agents in wound management. It is important to ascertain the number of doses of toxoid previously given and the interval since the last dose. When a tetanus booster dose is required, the combined preparation of tetanus and diphtheria toxoid formulated for adults (Td) is preferred. Appropriate cleansing and debridement of wounds is imperative, and use of antibiotics may be considered.

Some individuals with humoral immune deficiency, including those with HIV infection, may not respond adequately to tetanus toxoid. Therefore, tetanus immune globulin (TIG) should be used in addition to tetanus toxoid if a wound occurs that is not clean, regardless of the time elapsed since the last booster.

Table 1 - Guide to Tetanus Prophylaxis in Wound Management

History of Tetanus Immunization	Clean, minor wounds		All other wounds	
	Td or Tdap*	Tig**	Td or Tdap*	Tig
Uncertain of < 3 doses of an immunization series†	Yes	No	Yes	Yes
≥ 3 doses received in an immunization series†	No‡	No	No§	No¶

*Adult type combined tetanus and diphtheria toxoids or a combined preparation of diphtheria, tetanus and acellular pertussis. If the individual is < 7 years old a tetanus toxoid-containing vaccine is given as part of the routine childhood immunization.
**Tetanus immune globulin, given at a separate site from Td (or Tdap).
† The immunization series for tetanus is described in the text (Schedule and Dosage).
‡Yes, if > 10 years since last booster.
§Yes, if > 5 years since last booster. More frequent boosters not required and can be associated with increased adverse events. The bivalent toxoid, Td, is not considered to be significantly more reactogenic than T alone and is recommended for use in this circumstance. The individual should be informed that Td (or Tdap) has never been given.
¶Yes, if individuals are known to have a significant humoral immune deficiency state (e.g. HIV, agammaglobulinemia) since immune response to tetanus toxoid may be suboptimal.

4.2 Recommended Dose and Dosage Adjustment

A single 0.5 mL dose of the vaccine is recommended.

Repeat vaccination against diphtheria and tetanus should be performed at intervals as per official recommendations (generally 10 years). It is not necessary to recommence primary vaccination, should the officially recommended interbooster interval be exceeded.

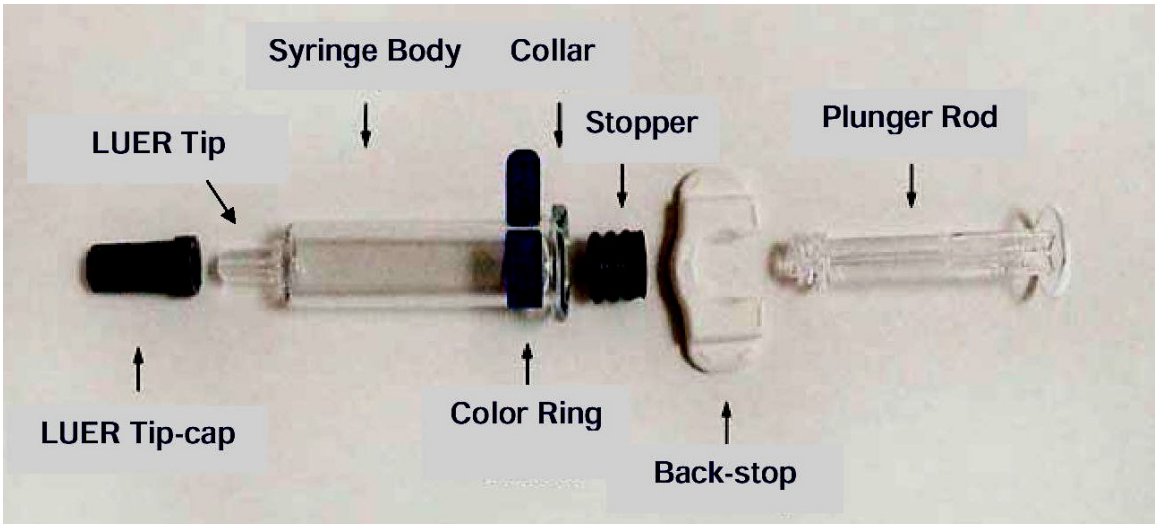
If BOOSTRIX is administered to a pregnant woman, it should ideally be done during the third trimester of pregnancy or according to recommendations from the National Advisory Committee on Immunization (NACI).

BOOSTRIX (combined diphtheria, tetanus, acellular pertussis (adsorbed) vaccine) should not be mixed with other vaccines in the same syringe.

BOOSTRIX is for deep muscular injection.

4.4 Administration

Do not remove the white back-stop from the syringe. Prior to administration, ensure that the plunger rod is firmly attached to the rubber stopper by turning the plunger clockwise until slight resistance is felt. **Do not** over tighten. Remove syringe LUER Tip-cap and needle cap. Attach needle by pressing and twisting in a clockwise rotation until secured to the syringe.



Prior to vaccination, the vaccine should be well shaken in order to obtain a homogeneous turbid white suspension and visually inspected for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either being observed, do not administer the vaccine, and any unused vaccine or waste material should be disposed of in accordance with local requirements.

5 OVERDOSAGE

Cases of overdose have been reported during post-marketing surveillance. Adverse events following overdosage, when reported, were similar to those reported with normal vaccine administration.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 2 Administration Route, Dosage Form, Strength, Non-medicinal Ingredients

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Intramuscular	Suspension for injection/ not less than 2.5 limit of flocculation ('Lf') or 2 IU ('International Units') of diphtheria toxoid; 8 mcg of pertussis toxoid; 8 mcg of filamentous hemagglutinin; 2.5 mcg of pertactin (69 kDa outer membrane protein); and, not less than 5 Lf (20 IU) of tetanus toxoid.	0.5 mg aluminum (as aluminum salts), sodium chloride, water for injection. Residues*: disodium phosphate, formaldehyde, glutaraldehyde, glycine, monopotassium phosphate, polysorbate 80, and potassium chloride.

*From the manufacturing process.

Packaging

BOOSTRIX is presented as a turbid white suspension in a single dose prefilled syringe. Upon storage, a white deposit and clear supernatant can be observed. This is a normal finding. The vaccine is available in prefilled syringes (in packages of 10).

Description

BOOSTRIX (combined diphtheria, tetanus, acellular pertussis (adsorbed) vaccine) is presented as a turbid white suspension in a single dose prefilled syringe. Upon storage, a white deposit and clear supernatant can be observed. This is a normal finding.

BOOSTRIX meets the World Health Organization requirements for manufacture of biological substances and for diphtheria and tetanus vaccines.

7 WARNINGS AND PRECAUTIONS

General

It is good clinical practice that immunization should be preceded by a review of the medical history (especially with regards to previous immunization and possible occurrence of undesirable events).

As with any other vaccine, BOOSTRIX (combined diphtheria, tetanus, acellular pertussis (adsorbed) vaccine) may not protect 100% of individuals receiving the vaccine.

BOOSTRIX should under no circumstances be administered intravenously.

As with other vaccines, the administration of BOOSTRIX should be postponed in individuals suffering from acute severe febrile illness. The presence of a minor infection is not a contraindication.

If any of the following events occur in temporal relation to administration of whole-cell DTP or acellular DTP vaccine, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered. There may be circumstances, such as high incidence of pertussis, in

which the potential benefits outweigh possible risks, particularly since these events have not been proven to cause permanent sequelae.

- Temperature of ≥ 40.0°C within 48 hours of vaccination, not due to another identifiable cause.
- Collapse or shock like state (hypotonic hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination.
- Convulsions with or without fever, occurring within 3 days of vaccination.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Hematologic
BOOSTRIX should be administered with caution to individuals with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these individuals. Firm pressure should be applied to the injection site (without rubbing) for at least 2 minutes.

Immune
HIV infection is not considered as a contraindication for diphtheria, tetanus and pertussis vaccination. The expected immunological response may not be obtained after vaccination.

Neurologic
In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it is better to defer pertussis (Pa or Pw) immunization until the condition is corrected or stable. However, the decision to give pertussis vaccine must be made on an individual basis after careful consideration of the risks and benefits.

A history or a family history of convulsions and a family history of an adverse event following DTP vaccination do not constitute contraindications.

Sensitivity/Resistance
As with other injectable vaccines, appropriate medication (e.g. Epinephrine 1:1000) should be readily available for immediate use in case of anaphylaxis or anaphylactoid reactions following administration of the vaccine. For this reason, the vaccinee should remain under medical supervision for 30 minutes after immunization.

7.1 Special Populations

7.1.1 Pregnant Women

Safety data from a randomized controlled clinical trial (341 pregnancy outcomes) and from a published prospective observational study where BOOSTRIX was administered to pregnant women during the third trimester (793 pregnancy outcomes), as well as data from post-marketing surveillance where pregnant women were exposed to BOOSTRIX in the second or third trimester have shown no vaccine related adverse effect on pregnancy or on the health of the fetus/newborn child.

Human data from prospective clinical studies on the use of BOOSTRIX during the first and second trimester of pregnancy are not available. Animal studies with BOOSTRIX do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/fetal development, parturition or post-natal development (see 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

The safety of BOOSTRIX when administered to breast-feeding women has not been evaluated.

It is unknown whether BOOSTRIX is excreted in human breast milk.

BOOSTRIX should only be used during breast-feeding when the possible advantages outweigh the potential risks.

8 ADVERSE REACTIONS

8.1 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

A total of 1,243 vaccinees have received a dose of BOOSTRIX (combined diphtheria, tetanus, acellular pertussis (adsorbed) vaccine) in clinical studies of which 1,032 were over 10 years of age.

During controlled clinical studies, diary cards were used to monitor signs and symptoms in all vaccinees following administration of a dose of BOOSTRIX. Table 3 below summarizes data from two pivotal studies for solicited local and general symptoms reported during a 15 day follow up period after vaccination. Onset of the majority of local and general symptoms occurred within 48 hours of vaccination. All symptoms resolved without sequelae. A causal relationship between these events and vaccination has not necessarily been established.

Table 3 - Summary data from 2 pivotal studies for solicited local and general symptoms reported during a 15 day follow up period vaccination

Solicited Symptoms	Incidence (%)					
	BOOSTRIX administered to adolescent subjects aged 10-17 years	Adolescent comparator group who received separate Td and aP (ap) vaccines		BOOSTRIX administered to adult subjects aged 18 years	Adult comparator group who received separate Td and aP (ap) vaccines	
	BOOSTRIX N=448	Td N=60	aP N =59	BOOSTRIX N =438	Td* N=54	aP* N=55
Local reactions						
Pain (All)	**79.0**	83.3	67.8	**72.6**	85.2	56.4
(Grade 3)	**3.8**	10.0	8.5	**0.7**	0	3.65
Redness (All)	**33.0**	53.3	15.3	**32**	38.9	20.0
(≥ 50 mm)	**5.8**	16.7	0	**2.5**	7.4	0
Swelling (All)	**35.0**	46.7	15.3	**20.8**	29.6	10.9
(≥ 50 mm)	**7.8**	10.0	1.7	**2.5**	5.6	0
General Symptoms						
Fever (≥ 37.5°C)	**8.9**	8.3	5.1	**18.5**	33.3	12.7
Fever (≥ 39.1°C)	**0.4**	0	0	**0.2**	0	0
Malaise	**27.7**	26.7	20.3	**19.2**	20.4	14.5
Fatigue	**56.2**	50.0	40.7	**27.2**	25.9	23.6
Vomiting	**4.0**	5.0	3.4	**3.4**	3.7	5.5
Headache	**51.3**	51.7	35.6	**37.0**	44.4	47.3
Dizziness	**20.5**	26.7	13.6	**10.0**	3.7	9.1

Td – Tetanus + diphtheria toxoid
aP – acellular pertussis
* These data are from the first vaccination of either of these comparator vaccine.

Clinical Studies in Children, Adolescents and Adults

Children from 4 to 9 years of age

The safety profile in Table 4 is based on data from clinical trials where BOOSTRIX was administered to 839 children (from 4 to 9 years of age).

Table 4 Children from 4 to 9 years of age

Frequency	Adverse Event	System/Organ Class
Very common: ≥1/10	injection site reactions (including pain, redness and swelling), fatigue	General and administration site conditions
	irritability	Psychiatric disorders
	somnolence	Nervous system disorders

Frequency	Adverse Event	System/Organ Class
Common: ≥1/100 and <1/10	fever ≥ 37.5°C (including fever > 39°C)	General and administration site conditions
	anorexia	Metabolism and nutrition disorders
	headache	Nervous system disorders
	diarrhoea, vomiting, gastrointestinal disorders	Gastrointestinal disorders

Adults, adolescents, and children, from the age of 10 years onwards

The safety profile in Table 5 is based on data from clinical trials where BOOSTRIX was administered to 1,931 adults, adolescents and children (above 10 years of age).

Table 5 Adults, adolescents, and children, from the age of 10 years onwards

Frequency	Adverse Event	System/Organ Class
Very common: ≥1/10	injection site reactions (including pain, redness and swelling), fatigue, malaise	General and administration site conditions
	headache	Nervous system disorders
Common: ≥1/100 and <1/10	fever > 37.5°C, injection site reactions (such as injection site mass and injection site abscess sterile)	General and administration site conditions
	dizziness	Nervous system disorders
	nausea, gastrointestinal disorders	Gastrointestinal disorders

8.2 Less Common Clinical Trial Adverse Reactions

Children from 4 to 9 years of age

The safety profile in Table 6 is based on data from clinical trials where BOOSTRIX was administered to 839 children (from 4 to 9 years of age).

Table 6 Children from 4 to 9 years of age

Frequency	Adverse Event	System/Organ Class
Uncommon: ≥1/1,000 and <1/100	other injection site reactions (such induration), pain	General and administration site conditions
	upper respiratory tract infections	Infections and infestations
	disturbances in attention	Nervous system disorders

Frequency	Adverse Event	System/Organ Class
	conjunctivitis	Eye disorders
	rash	Skin and subcutaneous tissue disorders

Adults, adolescents, and children, from the age of 10 years onwards

The safety profile in **Error! Reference source not found.** is based on data from clinical trials where BOOSTRIX was administered to 1,931 adults, adolescents and children (above 10 years of age).

Table 7 Adults, adolescents, and children, from the age of 10 years onwards

Frequency	Adverse Event	System/Organ Class
Uncommon: ≥1/1,000 and <1/100	fever > 39°C, influenza like illness, pain	General and administration site conditions
	upper respiratory tract infections, pharyngitis	Infections and infestations
	lymphadenopathy	Blood and lymphatic system disorders
	syncope	Nervous system disorders
	cough	Respiratory, thoracic and mediastinal disorders
	diarrhoea, vomiting	Gastrointestinal disorders
	hyperhidrosis, pruritus, rash	Skin and subcutaneous tissue disorders
	arthralgia, myalgia, joint stiffness, musculoskeletal stiffness	Musculoskeletal and connective tissue disorders

8.4 Post-Market Adverse Reactions

Table 8 Post-Market Adverse Reactions

Frequency	Adverse Event	System/Organ Class
Rare: ≥1/10,000 and <1/1,000	extensive swelling of the vaccinated limb, asthenia	General and administration site conditions
	angioedema	Blood and lymphatic system disorders
	convulsions (with or without fever)	Nervous system disorders
	urticaria	Skin and subcutaneous tissue disorders
Very rare: <1/10,000	allergic reactions, including anaphylactic and anaphylactoid reactions	Immune system disorders

Data on 146 subjects suggest a small increase in local reactogenicity (pain, redness, swelling) with repeated vaccination according to a 0, 1, 6 months schedule in adults (> 40 years of age).

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

The vaccine is unlikely to produce an effect on the ability to drive and use machines.

9.4 Drug-Drug Interactions

The drugs listed in this section are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Concomitant use with other inactivated vaccines or with immunoglobulin has not been studied. It is unlikely the coadministration will result in interference with the immune responses. When considered necessary, BOOSTRIX (combined diphtheria, tetanus, acellular pertussis (adsorbed) vaccine) can be administered simultaneously with other vaccines or immunoglobulin, at a different injection site.

As with other vaccines, individuals receiving immunosuppressive therapy or individuals with immunodeficiency may not achieve an adequate response.

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Diphtheria

Diphtheria is a serious communicable disease, primarily a localized and generalized intoxication caused by diphtheria toxin, an extracellular protein metabolite of toxigenic strains of *Corynebacterium diphtheriae*. The disease occurs most frequently in unimmunized or partially immunized individuals. The incidence of diphtheria in Canada has decreased from 9,000 cases reported in 1924 to extremely low levels. Only one or two cases have been reported annually in recent years. The case fatality rate remains 5 to 10%, with the highest death rates in the very young and elderly. If immunization levels are allowed to fall and adults do not receive booster doses, disease re-emergence may appear as demonstrated in the Commonwealth of Independent States (former Soviet Union), where tens of thousands of cases with substantial mortality have been reported. Protection against disease is due to the development of neutralizing antibodies to the diphtheria toxin. Following adequate immunization with diphtheria toxoid, it is generally accepted that protection persists for at least 10 years. Serum antitoxin levels of at least 0.01 antitoxin units per mL are generally regarded as protective. This significantly reduces both the risk of developing diphtheria and the severity of clinical illness. Immunization with diphtheria toxoid does not, however, eliminate carriage of *C. diphtheriae* in the pharynx or nose or on the skin.

Tetanus

Tetanus is an intoxication manifested primarily by neuromuscular dysfunction caused by a potent exotoxin released by *Clostridium tetani*. Immunization is highly effective, provides long lasting protection and is recommended for the entire population. Only 1 to 7 with an average of 5 cases of tetanus are reported annually in Canada while no deaths have been recorded since 1995. The disease continues to occur almost exclusively among persons who are unvaccinated or inadequately vaccinated or whole vaccination histories are unknown or uncertain.

Spores of *C. tetani* are ubiquitous. Naturally acquired immunity to tetanus toxin does not occur. Thus, universal primary immunization and timed booster doses to maintain adequate tetanus antitoxin levels are necessary to protect all age groups. Protection against disease is due to the development of neutralizing antibodies to the tetanus toxin. Tetanus toxoid is a highly effective antigen and a completed primary series generally induces serum antitoxin levels of at least 0.01 antitoxin units per mL, a level which has been reported to be protective. It is generally accepted that protection persists for at least 10 years. To maintain immunity to tetanus following completion of primary immunization, booster doses administered as Td are recommended at 10 yearly intervals.

Pertussis

Pertussis (whooping cough) is a disease of the respiratory tract caused by *Bordetella pertussis*. Pertussis is highly communicable and can affect individuals of any age; however, severity is greatest among young infants.

Although there is no established serologic correlate of protection against pertussis, majority of pregnant women were found to have undetectable anti-pertussis toxin levels. Newborn infants

therefore remain susceptible until their first vaccination at two months of age. Immunization in pregnancy provides newborn infants benefits from the transfer of the maternal antibodies.

Antigenic components of *B. pertussis* believed to contribute to protective immunity include: pertussis toxin; filamentous hemagglutinin; and pertactin (69kDa). Although the role of these antigens in providing protective immunity in humans is not well understood, clinical trials which evaluated candidate acellular DTP vaccines manufactured by GlaxoSmithKline supported the efficacy of three component INFANRIX (DTaP). Recently published data suggests a higher importance of the PT and pertactin (69kDa) components in providing protection against pertussis.

11 STORAGE, STABILITY AND DISPOSAL

BOOSTRIX (combined diphtheria, tetanus, acellular pertussis (adsorbed) vaccine) must be stored at 2 to 8°C. Do not use beyond the expiry date printed on the label and packaging.

Protect from light.

Upon removal from the refrigerator, the vaccine is stable for 8 hours at 21°C.

DO NOT FREEZE; discard if vaccine has been frozen.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Combined diphtheria, tetanus, acellular pertussis (adsorbed) vaccine for booster vaccination

Product Characteristics:

BOOSTRIX (combined diphtheria, tetanus, acellular pertussis (adsorbed) vaccine) contains combined diphtheria and tetanus toxoids, and three purified pertussis antigens [pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (69 kDalton outer membrane protein)], adsorbed onto aluminum salts. The final vaccine is formulated in saline.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

A summary of the pivotal and follow-up trials of BOOSTRIX in vaccinees of different ages is presented in Table 9.

Table 9 - Summary of studies (Total cohort)

Study ID	Trial Design, Study Duration	Study and control vaccines	Number of subjects enrolled	Gender %Male Median Age (range)
One month after vaccination with BOOSTRIX (see Table 1010)				
APV-118	Single blind, randomised	dTpa (BOOSTRIX) DTPa (INFANRIX) Td (TD-PUR) + Pa (PACMERIEUX) / pa (GSK)	211 107 103	47.9% 5 years (4-6)
dTpa-001	Single blind, randomised	dTpa (BOOSTRIX) pa (GSK) + Td (LEDERJECT) one month later Td (TD-PUR) + Pa (GSK) one month later	46 46 46	53.6% 13 years (11-17)
dTpa-002	Single blind, randomised	dTpa (BOOSTRIX) pa (GSK) + Td (LEDERJECT) one month later Td (LEDERJECT) + pa (GSK) one month later	440 55 55	40.9% 39 years (19-70)
dTpa-003	Blinded, randomised, single centre, phase III	dTpa (BOOSTRIX) pa (GSK) Td (TD-RIX)	99 100 100	49.2% 30 years (18-73)

Study ID	Trial Design, Study Duration	Study and control vaccines	Number of subjects enrolled	Gender %Male Median Age (range)
dTpa-004	Single blind, randomised	dTpa (BOOSTRIX) lot A dTpa (BOOSTRIX) lot B dTpa (BOOSTRIX) lot C Td (LEDERJECT)+ pa (GSK)	150 150 150 60	45.3% 11 years (10-13)
Persistence up to 5-6 years after vaccination of children with BOOSTRIX (see Table 1011)				
APV-124	Open	No vaccine administered dTpa (BOOSTRIX) DTPa (INFANRIX) Td (TD-PUR) + Pa (PACMERIEUX) / pa (GSK)	 125 67 56	48.1% 5 years (4-6)
dTap 0.3-004	Double-blind, randomized, multicentre, phase III	dTpa (BOOSTRIX) DTPa (INFANRIX) Td (TD-PUR) + Pa (PACMERIEUX) / pa (GSK) Subjects received a dose of dTpa but with a different formulation and so data not shown.	83 195 42	51.1% 11 years (10-12)
Persistence up to 10 years after vaccination of adolescents with BOOSTRIX (see Table 1011) and second booster dose with BOOSTRIX (see Table 1112)				
dTpa-017	Open	No vaccine administered dTpa (BOOSTRIX) (pooled groups**) Td (LEDERJECT)+ pa (GSK)	 269 30	46.6% 14 years (13-15)
dTpa-030	Open	No vaccine administered dTpa (BOOSTRIX) (pooled groups**) Td (LEDERJECT)+ pa (GSK)	 267 36	43.3% 16 years (15-17)
dTpa-040	Open, non-randomised, single-centre, phase IV	dTpa (BOOSTRIX) (pooled groups**) Td (LEDERJECT)+ pa (GSK) All subjects received a dose of BOOSTRIX	75 7	12.2% 21.0 years (21-22)
Persistence up to 10 years after vaccination of adults with BOOSTRIX (see Table 1011) and second booster dose with BOOSTRIX (see Table 1112)				
dTpa-021	Open	No vaccine administered dTpa (BOOSTRIX) pa (GSK) + Td (LEDERJECT) one month later Td (LEDERJECT) + pa (GSK) one month later	 310 40 37	28.7% (age not evaluated)
dTpa-027	Open	No vaccine administered		27.6%

Study ID	Trial Design, Study Duration	Study and control vaccines	Number of subjects enrolled	Gender %Male Median Age (range)
		dTpa (BOOSTRIX) pa (GSK) + Td (LEDERJECT) one month later Td (LEDERJECT) + pa (GSK) one month later	240 34 30	46 years (25-74)
dTpa-039	Open, non-randomised, single-centre, phase IV	dTpa (BOOSTRIX) Pooled pa + Td groups *** All subjects received a dose of BOOSTRIX	164 39	31.4% 52.0 years (29-74)
Vaccination of subjects ≥ 40 years of age with BOOSTRIX or BOOSTRIX-POLIO				
dTpa-034	Double blind, randomised, multicentre, phase III	3 doses dTpa (BOOSTRIX) at month 0, 1 and 6 1 dose dTpa-IPV at month 0 and 2 doses of Td (TEDIVAX) at month 1 and 6 3 doses of Td (TEDIVAX) at month 0, 1 and 6	155 152 153	41.3% 57.0 years (40-85)

* 3 consistency lots of dTpa-IPV

** 3 consistency lots of dTpa from study dTpa-004

*** Pooling of subjects from the two groups, group pa (GSK) + Td (LEDERJECT) one month later and group Td (LEDERJECT) + pa (GSK) one month later

14.2 Study Results

In clinical studies APV-118, dTpa-001, dTpa-002, dTpa-003, and dTpa-004, the immune response to the diphtheria, tetanus, and acellular pertussis components was evaluated. The results are presented in Table 10. Approximately one month following booster vaccination with BOOSTRIX, the following seroprotection/seropositivity rates were observed.

Table 10 - Percent Seroprotection / Seropositivity one month following vaccination with BOOSTRIX

Antigen	Seroprotection / Seropositivity	Adults and adolescents from the age of 10 years onwards, at least 1690 subjects (% vaccinees)	Children from 4 to 9 years of age, at least 415 subjects (% vaccinees)
Diphtheria	≥ 0.1 IU/ml*	97.2%	99.8%
Tetanus	≥ 0.1 IU/ml*	99.0%	100.0%
Pertussis: -Pertussis toxoid -Filamentous haemagglutinin -Pertactin	 ≥ 5 EL.U/ml ≥ 5 EL.U/ml ≥ 5 EL.U/ml	 97.8% 99.9% 99.4%	 99.0% 100.0% 99.8%

*cut-off accepted as indicative of protection

Results of the comparative studies with commercial dT vaccines containing the same antigen content indicates that the degree and duration of protection with BOOSTRIX would not be different from those obtained with these vaccines.

In clinical studies APV-124, dTap 0.3-004, dTpa-017, dTpa-030, dTpa-040, dTpa-021, dTpa-027 and dTpa-039, the persistence of immune response was evaluated. Three to 3.5 years, 5 to 6 years and 10 years following vaccination with BOOSTRIX, the following persistence of responses were observed in Table 11.

Table 11 - Persistence of Responses Observed 3 to 3.5, 5 to 6 and 10 years Following Vaccination with BOOSTRIX

Antigen	Response[1]	Adults and adolescents 10 years and older Percentage of vaccinees demonstrating response (CI)						Children 4 years and older[2] Percentage of vaccinees demonstrating response (CI)	
		3-3.5 years persistence		5 years persistence		10 years persistence		3-3.5 years persistence	5 to 6 years persistence
		Adult[3] N = 309	Adolescent[3] N = 261	Adult[3] N = 232	Adolescent[3] N = 250	Adult[3] N = 158	Adolescent[3] N = 74	N = 118	N = 68
Diphtheria	≥ 0.1 IU/ml	**71.2%** (65.8-76.2)	**91.6%** (87.6-94.7)	**84.1%** (78.7-88.5)	**86.8%** (82.0-90.7)	**64.6%** (56.6-72.0)	**82.4%** (71.8-90.3)	**97.5 %** (93.0-99.5)	**94.2 %** (85.8-98.4)
	≥ 0.016 IU/ml[4]	**97.4%** (95.6-99.2)	**100%** (98.2-100)	**94.4%** (90.6-97.0)	**99.2%** (96.9-99.9)	**89.9%** (84.1-94.1)	**98.6%** (92.7-100)	**100 %** (97.0-100)	Not determined
Tetanus	≥ 0.1 IU/ml	**94.8%** (91.8-97.0)	**100%** (98.6-100)	**96.2%** (93.0-98.3)	**100%** (98.6-100)	**95.0%** (90.4-97.8)	**97.3%** (90.6-99.7)	**98.4 %** (94.2-99.8)	**98.5 %** (92.1-100)
Pertussis									
Pertussis toxoid	≥ 5 EL.U/ml	**90.6%** (86.8-93.6)	**81.6%** (76.4-86.1)	**89.5%** (84.9-93.1)	**76.8%** (71.1-81.9)	**85.6%** (79.2-90.7)	**61.3%** (49.4-72.4)	**58.7%** (49.4-67.6)	**51.5%** (39.0-63.8)
Filamentous Haemagglutinin	≥ 5 EL.U/ml	**100%** (98.8-100)	**100%** (98.6-100)	**100%** (98.5-100)	**100%** (98.6-100)	**99.4%** (96.6-100)	**100%** (95.2-100)	**100%** (96.9-100)	**100%** (94.8-100)
Pertactin	≥ 5 EL.U/ml	**94.8%** (91.7-97.0)	**99.2%** (97.3-99.9)	**95.0%** (91.4-97.4)	**98.1%** (95.5-99.4)	**95.0%** (90.3-97.8)	**96.0%** (88.8-99.2)	**99.2%** (95.5-100)	**100%** (94.9-100)

[1]Response: Where, at the specified time point, a concentration of antibodies against diphtheria and tetanus ≥ 0.1 IU/ml was considered as seroprotection and a concentration of antibodies against pertussis ≥ 5EL.U/ml was considered as seropositivity.
[2]This reflects the age at which children were vaccinated with BOOSTRIX
[3]The terms 'adult' and 'adolescent' reflect the ages at which subjects received their first vaccination with BOOSTRIX.
[4]Percentage of subjects with antibody concentrations associated with protection against disease (≥ 0.1 IU/ml by ELISA assay or ≥ 0.016 IU/ml by an in-vitro Vero-cell neutralisation assay).

N = the minimum number of subjects with available data for each antigen; CI = Confidence Interval (95%)
In clinical studies dTpa-040 and dTpa-039, the immunogenicity of BOOSTRIX, administered 10 years after a previous booster dose with reduced-antigen content diphtheria, tetanus and acellular pertussis vaccine(s) was evaluated. One month post vaccination, > 99 % of subjects were seroprotected against diphtheria and tetanus and seropositive against pertussis (see Table 12).

Table 12 - Immunogenicity of a second booster dose of BOOSTRIX administered 10 years after the first dose in either adolescents or adults

Antigen	Response[1]	Adolescents[2]		Adults[3]	
		Number of subjects (N)	% vaccinees demonstrating response (CI)	Number of subjects (N)	% vaccinees demonstrating response (CI)
Diphtheria[4]	≥ 0.1 IU/mL	73	100% (95.1-100)	152	99.3% (96.4-100)
Tetanus [5]	≥ 0.1 IU/mL	73	100% (95.1-100)	153	100% (97.6-100)
Pertussis					
Pertussis toxoid	≥ 5 EL.U/mL	73	100% (95.1-100)	152	100% (97.6-100)
Filamentous haemagglutinin	≥ 5 EL.U/mL	73	100% (95.1-100)	152	100% (97.6-100)
Pertactin	≥ 5 EL.U/mL	73	100% (95.1-100)	153	100% (97.6-100)

[1] Response: Where, one month after the second booster dose, a concentration of antibodies against diphtheria and tetanus ≥ 0.1 IU/mL was considered as seroprotection, a concentration of antibodies against pertussis ≥ 5 EL.U/mL was considered as seropositivity.
[2] The term 'adolescent' reflects the age at which subjects received their first booster dose (10-13 years) where subjects received a second booster dose 10 years later at 21-22 years of age.
[3] The term 'adult' reflects the age at which subjects received their first booster dose (19-70 years) where subjects received a second booster dose 10 years later at 29-74 years of age.
[4] To demonstrate that the second booster dose elicits seroprotective antibody concentrations in at least 80% of subjects against diphtheria, the lower limit of the 95% confidence interval for concentrations ≥ 0.1 IU/ml must be above 80%.
[5] To demonstrate that the second booster dose elicits seroprotective antibody concentrations in at least 90% of subjects against tetanus, the lower limit of the 95% confidence interval for concentrations ≥ 0.1 IU/ml must be above 90%.
N = number of subjects with available results
CI = Confidence Interval (95%)

In clinical study dTpa-034, after administration of one dose of BOOSTRIX to 139 adults ≥ 40 years of age that had not received any diphtheria and tetanus containing vaccine in the past 20 years, at least 98.5% of adults were seropositive for all three pertussis antigens and 81.5% and 93.4% were seroprotected against diphtheria and tetanus respectively. After administration of two additional doses one and six months after the first dose, the seropositivity rate was 100% for all three pertussis antigens and the seroprotection rates for diphtheria and tetanus reached 99.3% and 100% respectively.

Pertussis
One month post vaccination, the overall response rate for each of the three individual pertussis antigens (pertussis toxoid, filamentous hemagglutinin, pertactin) was between 92.1 – 100%, 95.0 – 99.8% and 97.9 – 100%, respectively.

The pertussis antigens contained in BOOSTRIX are an integral part of the pediatric acellular pertussis combination vaccine (INFANRIX), for which efficacy after primary vaccination has been demonstrated in a household contact efficacy study. The antibody titres to all 3 pertussis components following vaccination with BOOSTRIX are higher than those observed during the household contact efficacy trial. Based on these comparisons, BOOSTRIX provides protection against pertussis, however the degree and duration of protection afforded by the vaccine are undetermined.

Protective efficacy of pertussis

There is currently no correlate of protection defined for pertussis; however, the protective efficacy of GlaxoSmithKline DTPa (INFANRIX) vaccine against WHO defined typical pertussis (≥ 21 days of paroxysmal cough with laboratory confirmation) was demonstrated in the following 3 dose primary studies:

A prospective blinded household contact study performed in Germany (3, 4, 5 months schedule).
Based on data collected from secondary contacts in households where there was an index case with typical pertussis, the protective efficacy of the vaccine was 88.7%. Protection against laboratory confirmed mild disease, defined as 14 days or more of cough of any type was 73 and 67% when defined as 7 days or more of cough of any type.

An NIH sponsored efficacy study performed in Italy (2, 4, 6 months schedule). The vaccine efficacy was found to be 84%. When the definition of pertussis was expanded to include clinically milder cases with respect to type and duration of cough, the efficacy of INFANRIX was calculated to be 71% against > 7 days of any cough and 73% against > 14 days of any cough. In a follow up of the same cohort, the efficacy was confirmed up to 5 years after completion of primary vaccination without administration of a booster dose of pertussis.

As infants cannot begin their pertussis vaccination course until they are at least 6 weeks old and three doses of vaccine need to be given, vaccination does not confer complete protection until infants have received all 3 doses. Several studies have shown that adults are a significant source of pertussis in the first week of life. It could be expected that immunization of immediate close contacts of newborn infants, such as parents, grandparents and healthcare workers, would reduce exposure of pertussis to infants not yet adequately protected through immunization. Booster immunization with BOOSTRIX, an acellular pertussis vaccine with reduced antigen content of diphtheria toxoids and pertussis, has demonstrated that the vaccine was immunogenic and well tolerated in clinical studies in which adolescents and adults have received BOOSTRIX.

<u>Passive protection against pertussis in infants (less than 3 months of age) born to mothers vaccinated during pregnancy</u>

In a randomized, cross-over, placebo-controlled study (DTPA-047), higher pertussis antibody concentrations were demonstrated at delivery in the cord blood of infants born to mothers vaccinated with BOOSTRIX (N=291) versus placebo (N=292) after 27 weeks of pregnancy. The concentrations of

antibodies against the pertussis antigens PT, FHA and PRN were respectively 8, 16 and 21 times higher in the cord blood of infants born to vaccinated mothers versus controls.

Immunogenicity in infants and toddlers born to mothers vaccinated during pregnancy

In two follow-up studies (DTPA-048, -049), more than 500 infants and toddlers. born to mothers vaccinated with BOOSTRIX or placebo after 27 weeks of pregnancy, received primary and booster vaccination of INFANRIX hexa and Prevnar* 13. Antibody response to diphtheria, tetanus, hepatitis B, inactivated polio virus, *Haemophilus influenzae* type b or pneumococcal antigens were comparable between infants/toddlers born to vaccinated mothers and infants/toddlers born to unvaccinated mothers. Lower concentrations of antibodies against all pertussis antigens (PT, FHA and PRN) were observed post primary vaccination and against PT and FHA antigens post booster vaccination in infants/toddlers born to vaccinated mothers compared to infants/toddlers born to unvaccinated mothers. However, 92.1% to 98.1% of infants and toddlers born to vaccinated mothers showed a booster response (post-booster antibody concentration ≥2 times the pre-booster antibody concentration) against these pertussis antigens.

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Effectiveness in the protection against pertussis disease in infants born to women vaccinated during pregnancy:

BOOSTRIX or BOOSTRIX-POLIO vaccine effectiveness (VE) was evaluated in three published observational studies, in UK, Spain and Australia (Amirthalingam G *et al*, 2016 Clin Infect Dis. 63(suppl_4):S236-S243; Bellido-Blasco J *et al*, 2017 Euro Surveill. 22(22); Saul N *et al*, 2018 Vaccine 36(14):1887-1892). The vaccine was used during the third trimester of pregnancy for passive protection of infants below 3 months of age against pertussis disease.

Across the three studies, VE against pertussis disease for infants below 3 months of age born to mothers vaccinated during the third trimester of pregnancy with BOOSTRIX or BOOSTRIX-POLIO ranged between 69% to 90.9%.

If maternal vaccination occurs within two weeks before delivery, VE in the infant may be lower than these figures.

16 NON-CLINICAL TOXICOLOGY

Nonclinical data obtained with BOOSTRIX reveal no specific hazard for humans based on conventional studies of female fertility and embryo-fetal development in rats and rabbits, and also parturition and postnatal toxicity in rats (up to the end of the lactation period).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR VACCINE

BOOSTRIX

Combined diphtheria, tetanus, acellular pertussis (adsorbed) vaccine for booster vaccination

Read this carefully before you receive **BOOSTRIX**. This leaflet is a summary and will not tell you everything about this vaccine. Talk to your healthcare professional and ask if there is any new information about **BOOSTRIX**.

What is BOOSTRIX used for?

BOOSTRIX is a vaccine used in adults and children 4 years of age and above for protection against diphtheria (respiratory and skin disease), tetanus (lockjaw) and pertussis (whooping cough).

Vaccination is the best way to protect against these diseases.

How does BOOSTRIX work?

The vaccine works by causing the body to produce its own protection (antibodies) against these diseases.

The use of BOOSTRIX during pregnancy will help to protect your baby from whooping cough in the first few months of life before their primary immunization.

What are the ingredients in BOOSTRIX?

Medicinal ingredients: combined diphtheria and tetanus toxoids, and three purified pertussis antigens [pertussis toxoid, filamentous haemagglutinin and pertactin (69 kiloDalton outer membrane protein)]. None of the components in the vaccine are infectious. You cannot get the diseases from the BOOSTRIX vaccine.

Non-medicinal ingredients: Aluminum (as aluminum salts), sodium chloride and water for injection. Residues from the manufacturing process: disodium phosphate, formaldehyde, glutaraldehyde, glycine, monopotassium phosphate, polysorbate 80, and potassium chloride.

BOOSTRIX comes in the following dosage form:

BOOSTRIX is presented as a cloudy white sterile suspension in a single dose prefilled syringe. Upon storage, a white solid may be seen. This is normal.

Do not use BOOSTRIX if:

- you or your child has previously had any allergic reaction to BOOSTRIX, or any ingredient contained in this vaccine. The active substances and other ingredients in BOOSTRIX are listed below. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.
- you or your child has previously had an allergic reaction to any vaccine against diphtheria, tetanus or pertussis diseases.
- you or your child experienced problems of the nervous system (encephalopathy) within 7 days after previous vaccination with a vaccine against pertussis disease.
- you or your child experienced problems with the brain or nerves after previous vaccination with a vaccine against diphtheria and/or tetanus.

- you or your child has a severe infection with a high temperature (over 40°C). A minor infection such as a cold should not be a problem, but talk to your healthcare professional first.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you or your child receive BOOSTRIX. Talk about any health conditions or problems you may have, including if:

- you or your child have a family history of convulsions.
- your child is suffering from neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy (disease of brain).
- you or your child has a bleeding problem or bruises easily. BOOSTRIX should be given with caution since bleeding may occur following vaccination.
- you or your child had any problems (such as a high fever, collapse or shock-like state or persistent crying lasting 3 hours or more) within 48 hours or fits (with or without fever) within 3 days of vaccination with a vaccine against pertussis.
- you or your child has a high temperature (over 38°C).
- you or your child has any known allergies.
- you or your child is taking any other medicine or has recently received any other vaccine.
- you or your child has any serious health problem.
- your child is younger than 4 years of age.
- you are breastfeeding.

Fainting can occur following, or even before, any needle injection; therefore, tell the healthcare professional if you or your child fainted with a previous injection.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with BOOSTRIX:

Individuals receiving immunosuppressive therapy or individuals with immunodeficiency may not be fully protected against disease after receiving BOOSTRIX.

How to receive BOOSTRIX:

Usual dose:

The dose of BOOSTRIX (combined diphtheria, tetanus, acellular pertussis (adsorbed) vaccine) is 0.5 mL.

BOOSTRIX will be given as an injection into the muscle.

The vaccine should never be given into a vein.

Overdose:

If you think you, or a person you are caring for, have received too much BOOSTRIX, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you or your child misses a scheduled injection, talk to your healthcare professional and arrange another visit.

What are possible side effects from receiving BOOSTRIX?

These are not all the possible side effects you or your child may feel after being given BOOSTRIX. If you or your child experiences any side effects not listed here, contact your healthcare professional.

Like all vaccines, BOOSTRIX may occasionally cause unwanted effects.

As with other vaccines, you or your child may feel pain at the injection site, or you or your child may see some redness and swelling at this site. However, these reactions usually clear up within a few days.

In children 4 to 9 years of age, very common side effects (in more than 1 in 10 doses of the vaccine) after having BOOSTRIX are irritability, sleepiness, swelling, pain, redness where the injection was given and fatigue.

Common side effects (in more than 1 in 100 dose of the vaccine) after having BOOSTRIX are headache, loss of appetite, vomiting, diarrhea and a fever more than 38°C.

Uncommon side effects (in more than 1 in 1,000 doses of the vaccine) after having BOOSTRIX are upper respiratory tract infection, lack of attention, itchy eyes and crusty eyelids, rash, pain and a hard lump at the injection site.

In adults, teenagers, and children from the age of 10 onwards, very common side effects (in more than 1 in 10 doses of the vaccine) after having BOOSTRIX are headache, fatigue and ill feeling.

Common side effects (in more than 1 in 100 doses of the vaccine) after having BOOSTRIX are dizziness, fever more than 38°C, nausea and a hard lump at the injection site.

Uncommon side effects (in more than 1 in 1,000 doses of the vaccine) after having BOOSTRIX are fainting, vomiting, diarrhea, upper respiratory tract infection, flu-like symptoms (fever, sore throat, runny nose, cough, chills), swollen glands, excessive sweating, itching, rash, joint stiffness and pain, muscle ache and pain.

If these symptoms continue or become severe, tell the healthcare professional.

As with other vaccines in any age group, allergic reactions may occur very rarely (in less than 1 in 10,000 vaccinees). This can be recognized by symptoms such as itchy rash of the hands and feet, swelling of the face, lips, mouth, tongue or throat, difficulty in breathing or swallowing, fits (with or without fever), hives, large swelling of the vaccinated limb, unusual weakness and a sudden drop in blood pressure and loss of consciousness. Such reactions will usually occur before leaving the healthcare professional's office. However, you should seek immediate treatment in any event.

If you or your child develops any other symptom within days following the vaccination, tell your healthcare professional as soon as possible.

Do not be alarmed by this list of possible side effects. It is possible that you or your child will have no side effects from vaccination.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Suspected Side Effects for Vaccines

For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional.

Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and GlaxoSmithKline Inc. cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php) and send it to your local Health Unit.

Storage:

Store BOOSTRIX in a refrigerator at 2°C to 8°C. Store in the original package in order to protect from light. **Do not freeze.** Freezing destroys the vaccine.

Keep out of the sight and reach of children.

Do not use after the expiry date which is stated on the carton. The date for last use corresponds to the last day of that month mentioned.

If you want more information about BOOSTRIX:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals which includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.gsk.ca), or by calling the manufacturer at 1-800-387-7374.

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