

PRODUCT MONOGRAPH

BOOSTRIX

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

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

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Submission Control No: 212380

Date of Approval: March 05, 2018

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BOOSTRIX

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

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal 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.	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.

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.

INDICATIONS AND CLINICAL USE

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.

BOOSTRIX is not intended for primary immunization.

CONTRAINDICATIONS

- BOOSTRIX (combined diphtheria, tetanus, acellular pertussis (adsorbed) vaccine) is contraindicated in patients who are hypersensitive to any component of the vaccine or subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, or pertussis vaccines. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- BOOSTRIX is contraindicated if the subject 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 subjects who have experienced transient thrombocytopenia or neurological complications following an earlier immunization against diphtheria and/or tetanus.

WARNINGS AND PRECAUTIONS

General

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

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 subjects 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 $\geq 40.0^{\circ}\text{C}$ 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.

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.

Hematologic

BOOSTRIX should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects. 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.

Sensitivity

As with other injectable vaccines, appropriate medication (eg. 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.

Special Populations

Pregnant Women:

Safety data from a 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 have shown no vaccine related adverse effect on pregnancy or on the health of the fetus/newborn child.

The use of BOOSTRIX may be considered during the third trimester of pregnancy.

Human data from prospective clinical studies on the use of BOOSTRIX during the first and second trimester of pregnancy are not available.

Limited data indicate that maternal antibodies may reduce the magnitude of the immune response to some vaccines in infants born from mothers vaccinated with BOOSTRIX during pregnancy. The clinical relevance of this observation is unknown.

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 TOXICOLOGY).

BOOSTRIX should only be used during pregnancy when the possible advantages outweigh the possible risks for the fetus.

Nursing Women:

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.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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 1 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 1 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
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

The safety profile below is based on data from clinical trials where BOOSTRIX was administered to 839 children (from 4 to 9 years of age) and 1,931 adults, adolescents and children (above 10 years of age).

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
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
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
	conjunctivitis	Eye disorders
	rash	Skin and subcutaneous tissue disorders

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
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

Post Marketing Data

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).

Subjects fully primed with 4 doses of DTPw followed by a BOOSTRIX dose around 10 years of age show an increase of local reactogenicity after an additional BOOSTRIX dose administered 10 years later.

DRUG INTERACTIONS

Drug-Drug Interactions

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, patients receiving immunosuppressive therapy or patients with immunodeficiency may not achieve an adequate response.

Drug-Lifestyle Interactions

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

DOSAGE AND ADMINISTRATION

Recommended Dose

A single 0.5 mL dose of the vaccine is recommended.

Tetanus Prophylaxis in Wound Management

The following table 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 2 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 patient 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).

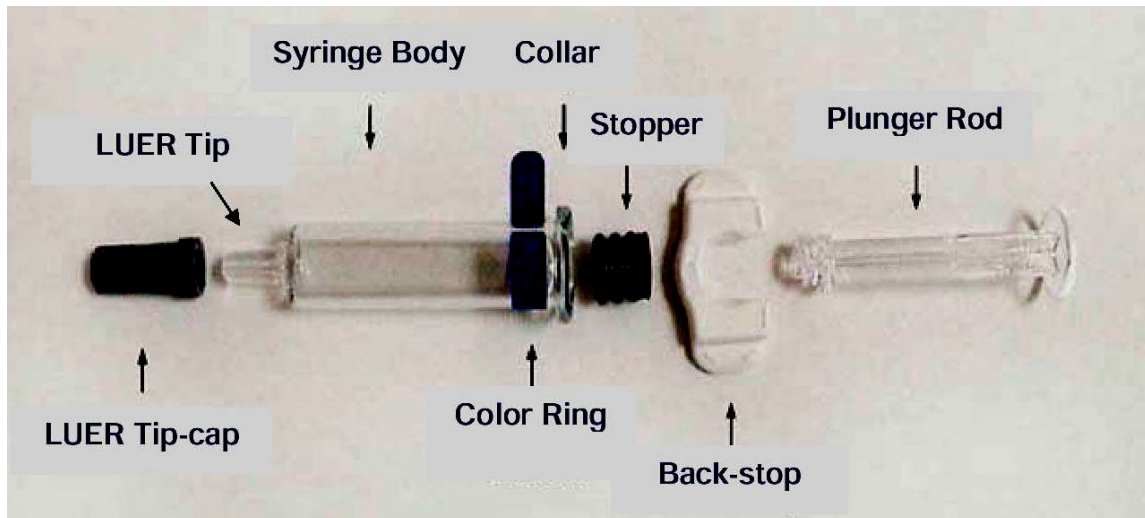
‡Yes, if > 10 years since last booster.

§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 patient 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.

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, discard the vaccine.

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.

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.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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

ACTION AND CLINICAL PHARMACOLOGY

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 whose 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 (attack rates in unimmunized household contacts of up to 90% have been reported) and can affect individuals of any age; however, severity is greatest among young infants. Precise epidemiologic data do not exist, since bacteriological confirmation of pertussis can be obtained in less than half of the suspected cases. Most reported illness from *B. pertussis* occurs in infants and young children in whom complications can be severe. Older children, adolescents and adults, in whom classic signs of pertussis infection are often absent, may go undiagnosed, and may serve as reservoirs of disease and may act as the primary source of transmission of the bacillus to infants.

Pertussis epidemics are cyclic, occur every 3 to 4 years, and outbreaks continue to occur due to 1) the decline in immunity in individuals who received the whole cell vaccine during childhood; 2) a decline in the population that may have acquired natural infection with longer lasting immunity; 3) improvements in diagnosis and surveillance; and 4) possible genetic changes in current strains compared with the strains of *B. pertussis* from which the original whole cell vaccine was prepared. With the licensure of acellular pertussis vaccines, which have better safety and efficacy profiles, the use of whole cell pertussis vaccines is no longer recommended in Canada.

During the 1980s pertussis incidence was low, but has increased since 1990 in spite of high vaccine coverage. Over the past 10 years, the annual number of reported cases of pertussis in Canada has ranged from 2,400 to 10,000 although these figures likely under represent the true incidence because of incomplete reporting.

Active surveillance for pertussis has found that 1 to 25% of patients with prolonged cough had *B. pertussis* infection. Using a combination of laboratory methods, the Sentinel Health Unit Surveillance System has documented pertussis infection in 9 to 20% of non improving cough illness of 7 days or more in adolescents and adults.

Canadian studies have estimated that the secondary attack rate of pertussis in adolescents and adults by household contact ranged between 12 and 14% in contacts aged 12 to 17 years, 11 to 18% for those 18 to 29 years of age and 8 to 33% in those 30 years of age or older. It can be concluded that between 10 to 25% of adolescents and adults are susceptible to pertussis and thus play a role in its transmission.

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.

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.

STORAGE AND STABILITY

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.

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

DO NOT FREEZE; discard if vaccine has been frozen.

DOSAGE FORMS, COMPOSITION AND PACKAGING

BOOSTRIX (combined diphtheria, tetanus, acellular pertussis (adsorbed) vaccine) contains diphtheria toxoid, three purified pertussis antigens [pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (69 kDalton outer membrane protein)], and tetanus toxoid. It also contains aluminum (as 0.5 mg aluminum salts), sodium chloride, water for injection. Residues from the manufacturing process: disodium phosphate, formaldehyde, glutaraldehyde, glycine, monopotassium phosphate, polysorbate 80, and potassium chloride.

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).

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

PART II: SCIENTIFIC INFORMATION

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.

CLINICAL TRIALS

A summary of the pivotal and follow-up trials of BOOSTRIX in vaccinees of different ages is presented in Table 3.

Table 3 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 4)				
APV-118	Single blind, randomised	dTpa (BOOSTRIX)	211	47.9%
		DTPa (INFANRIX)	107	5 years
		Td (TD-PUR) + Pa (PACMERIEUX) / pa (GSK)	103	(4-6)
dTpa-001	Single blind, randomised	dTpa (BOOSTRIX)	46	53.6%
		pa (GSK) + Td (LEDERJECT) one month later	46	13 years (11-17)
		Td (TD-PUR) + Pa (GSK) one month later	46	
dTpa-002	Single blind, randomised	dTpa (BOOSTRIX)	440	40.9%
		pa (GSK) + Td (LEDERJECT) one month later	55	39 years (19-70)
		Td (LEDERJECT) + pa (GSK) one month later	55	
dTpa-003	Blinded, randomised, single centre, phase III	dTpa (BOOSTRIX)	99	49.2%
		pa (GSK)	100	30 years
		Td (TD-RIX)	100	(18-73)
dTpa-004	Single blind,	dTpa (BOOSTRIX) lot A	150	45.3%

	randomised	dTpa (BOOSTRIX) lot B dTpa (BOOSTRIX) lot C Td (LEDERJECT)+ pa (GSK)	150 150 60	11 years (10-13)
Persistence up to 5-6 years after vaccination of children with BOOSTRIX (see Table 5)				
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 5) and second booster dose with BOOSTRIX (see Table 6)				
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 5) and second booster dose with BOOSTRIX (see Table 6)				
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 dTpa (BOOSTRIX) pa (GSK) + Td (LEDERJECT) one month later Td (LEDERJECT) + pa (GSK) one month later	240 34 30	27.6% 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	155	41.3% 57.0 years (40-85)
		1 dose dTpa-IPV at month 0 and 2 doses of Td (TEDIVAX) at month 1 and 6	152	
		3 doses of Td (TEDIVAX) at month 0, 1 and 6	153	

* 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

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 the table below. Approximately one month following booster vaccination with BOOSTRIX, the following seroprotection/seropositivity rates were observed.

Table 4 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	≥ 5 EL.U/ml	97.8%	99.0%
-Filamentous haemagglutinin	≥ 5 EL.U/ml	99.9%	100.0%
-Pertactin	≥ 5 EL.U/ml	99.4%	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:

Table 5 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		
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 6).

Table 6 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.

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).

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PART III: CONSUMER INFORMATION**BOOSTRIX**

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

This leaflet is Part III of a three-part "Product Monograph" published when BOOSTRIX (Combined diphtheria, tetanus, acellular pertussis (adsorbed) vaccine for booster vaccination) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about BOOSTRIX. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

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

Vaccination is the best way to protect against these diseases.

What it does:

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

When it should not be used:

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 (whooping cough) 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 doctor first.
- you are pregnant.

What the medicinal ingredient is:

The active substances contained in BOOSTRIX are: 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.

What the nonmedicinal ingredients are:

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.

What dosage form it comes in:

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.

WARNINGS AND PRECAUTIONS

BEFORE you use BOOSTRIX talk to your doctor or pharmacist 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 pregnant or breastfeeding.

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

INTERACTIONS WITH THIS MEDICATION

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

PROPER USE OF THIS MEDICATION

Usual dose:

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

The doctor will give BOOSTRIX as an injection into the muscle.

The vaccine should never be given into a vein.

Missed Dose:

If you or your child misses a scheduled injection, talk to your doctor and arrange another visit.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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 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 doctor or nurse.

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 doctor'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 doctor 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.

This is not a complete list of side effects. For any unexpected effects while taking BOOSTRIX, contact your doctor or pharmacist.

HOW TO STORE IT

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 reach and sight 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.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following immunization.

For health care professionals:

If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local Health Unit in [your province/territory](#).

For the General Public:

Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.

If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada:

By toll-free telephone: 1-866-844-0018

By toll-free fax: 1-866-844-5931

By email: caefi@phac-aspc.gc.ca

At the following website:

<http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php>

By regular mail:

The Public Health Agency of Canada

Vaccine Safety Section

130 Colonnade Road

Ottawa, Ontario

K1A 0K9 Address Locator 6502A

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

This leaflet was prepared by GlaxoSmithKline Inc.

Last revised: February 28, 2018

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MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

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or by contacting the sponsor,

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