HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BOOSTRIX safely and effectively. See full prescribing information for BOOSTRIX.

BOOSTRIX® (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed)
Suspention for Intramuscular Injection
Initial U.S. Approval: 2005

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	12/2008
Warnings and Precautions (5.2)	12/2008

----------INDICATIONS AND USAGE----------

BOOSTRIX is a vaccine indicated for active booster immunization against tetanus, diphtheria, and pertussis as a single dose. BOOSTRIX is approved for use in individuals 10 through 64 years of age. (1)

---------- DOSAGE AND ADMINISTRATION ----------

A single intramuscular injection (0.5 mL) (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

Suspension for injection in 0.5 mL single-dose vials or syringes. (3)

----------CONTRAINDICATIONS----------

- Severe allergic reaction (e.g., anaphylaxis) to any component of BOOSTRIX. (4.1)
- Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days of administration of a previous pertussis antigen-containing vaccine. (4.2)

---------- WARNINGS AND PRECAUTIONS----------

- If Guillain-Barré syndrome occurs within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give BOOSTRIX should be based on potential benefits and risks. (5.1)
- If progressive or unstable neurologic disorders exist, consider risks and benefits of vaccination. (5.2)
- Persons who experienced an Arthus-type hypersensitivity reaction following a prior dose of a tetanus toxoid-containing vaccine should not receive BOOSTRIX unless at least 10 years have elapsed since the last dose of a tetanus toxoid-containing vaccine. (5.3)
- The needleless prefilled syringes contain dry natural latex rubber and may cause allergic reactions. (5.4)

---------- ADVERSE REACTIONS ----------

- Common solicited adverse events (≥15%) in adolescents were pain, redness, and swelling at the injection site, increase in arm circumference of injected arm, headache, fatigue, and gastrointestinal symptoms. (6.1)
- Common solicited adverse events (≥15%) in adults were pain, redness, and swelling at the injection site, headache, fatigue, and gastrointestinal symptoms. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

----------DRUG INTERACTIONS----------

- Lower levels for antibodies to the pertussis antigens FHA and pertactin were observed when BOOSTRIX was administered concomitantly with an inactivated influenza vaccine as compared to BOOSTRIX alone. (7.1)
- Do not mix BOOSTRIX with any other vaccine in the same syringe or vial. (7.1)

---------- USE IN SPECIFIC POPULATIONS ----------

- Safety and effectiveness of BOOSTRIX have not been established in pregnant women, nursing mothers, and children younger than 10 years of age. (8.1, 8.3, 8.4)
- Register women who receive BOOSTRIX while pregnant in the pregnancy registry by calling 1-888-825-5249. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: December 2008
BTX:7PI

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BOOSTRIX is indicated for active booster immunization against tetanus, diphtheria, and pertussis as a single dose in individuals 10 through 64 years of age.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Shake vigorously to obtain a homogeneous, turbid, white suspension before administration. Do not use if resuspension does not occur with vigorous shaking. Inspect BOOSTRIX visually for particulate matter, discoloration, or cracks in the vial or syringe prior to administration. If any of these conditions exist, the vaccine should not be administered. BOOSTRIX should not be combined through reconstitution or mixed with any other vaccine.

Do not administer this product intravenously, intradermally, or subcutaneously.

2.2 Dose

BOOSTRIX is administered as a single 0.5 mL intramuscular injection into the deltoid muscle of the upper arm.

There are no data to support repeat administration of BOOSTRIX.

Five years should elapse between the last dose of the recommended series of Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) and/or Tetanus and Diphtheria Toxoids Adsorbed For Adult Use (Td) vaccine and the administration of BOOSTRIX.

2.3 Additional Dosing Information

Primary Series: The use of BOOSTRIX as a primary series or to complete the primary series for diphtheria, tetanus, or pertussis has not been studied.

Wound Management: Clinicians should refer to guidelines for tetanus prophylaxis in routine wound management.[1] Individuals who have completed a primary series against tetanus and who sustain wounds which are minor and uncomplicated should receive a booster dose of a tetanus toxoid-containing vaccine only if they have not received tetanus toxoid within the preceding 10 years. In case of tetanus-prone injury (e.g., wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite) in an individual who is in need of tetanus toxoid, BOOSTRIX can be used as an alternative to Td vaccine in patients for whom the pertussis component is also indicated.

3 DOSAGE FORMS AND STRENGTHS

BOOSTRIX is a suspension for injection available in 0.5-mL single-dose vials and prefilled TIP-LOK® syringes. See *Description (11)* for the complete listing of ingredients.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

A severe allergic reaction (e.g., anaphylaxis) after a previous dose of any tetanus toxoid-, diphtheria toxoid-, or pertussis antigen-containing vaccine or any component of this vaccine is a contraindication to administration of BOOSTRIX[2,3] *[see Description (11)]*. Because of the uncertainty as to which component of the vaccine might be responsible, none of the components should be administered. Alternatively, such individuals may be referred to an allergist for evaluation if immunization with any of these components is considered.

4.2 Encephalopathy

Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days of administration of a previous dose of a pertussis antigen-containing vaccine that is not attributable to another identifiable cause is a contraindication to administration of any pertussis antigen-containing vaccine, including BOOSTRIX.[2,3]

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome and Brachial Neuritis

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give BOOSTRIX or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks. A review by the Institute of Medicine (IOM) found evidence for a causal relationship between receipt of tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome.[4]

5.2 Progressive or Unstable Neurologic Disorders

Progressive neurologic disorder, uncontrolled epilepsy, progressive encephalopathy or unstable neurological conditions (e.g., cerebrovascular events and acute encephalopathic conditions) are considered reasons to defer Tdap vaccination. In these situations, administration of any pertussis antigen-containing vaccine, including BOOSTRIX, should be based on careful consideration of the potential benefits and possible risks.[2,3]

5.3 Arthus-Type Hypersensitivity

Persons who experienced an Arthus-type hypersensitivity reaction following a prior dose of a tetanus toxoid-containing vaccine usually have a high serum tetanus antitoxin level and should not receive BOOSTRIX or other tetanus toxoid-containing vaccines unless at least 10 years have elapsed since the last dose of tetanus toxoid-containing vaccine.

5.4 Latex

The tip cap and the rubber plunger of the needleless prefilled syringes contain dry natural latex rubber that may cause allergic reactions in latex sensitive individuals. The vial stopper is latex-free.

5.5 Altered Immunocompetence

As with any vaccine, if administered to immunosuppressed persons, including individuals receiving immunosuppressive therapy, the expected immune response may not be obtained.

5.6 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions to allow an assessment of benefits and risks. Epinephrine and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine, and may not reflect the rates observed in practice. As with any vaccine, there is the possibility that broad use of BOOSTRIX could reveal adverse reactions not observed in clinical trials.

In clinical studies, 3,608 adolescents and 2,972 adults were vaccinated with a single dose of BOOSTRIX. Of these adults, 1,450 were vaccinated with BOOSTRIX in a coadministration study with influenza vaccine *[see Drug Interactions (7.1)]*. An additional 1,092 adolescents 10 to 18 years of age received a non-US formulation of BOOSTRIX (formulated to contain 0.5 mg aluminum per dose) in non-US clinical studies.

In a randomized, observer-blinded, controlled study in the US, 3,080 adolescents 10 to 18 years of age received a single dose of BOOSTRIX and 1,034 received the control Td vaccine, manufactured by Massachusetts Public Health Biologic Laboratories. There were no substantive differences in demographic characteristics between the vaccine groups. Among BOOSTRIX and control vaccine recipients, approximately 75% were 10 to 14 years of age and approximately 25% were 15 to 18 years of age. Approximately 98% of participants in this study had received the recommended series of 4 or 5 doses of either Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTwP) or a combination of DTwP and DTaP in childhood. Subjects were monitored for solicited adverse events using standardized diary cards (day 0-14). Unsolicited adverse events were monitored for the 31-day period following vaccination (day 0-30). Subjects were also monitored for 6 months post-vaccination for non-routine medical visits, visits to an emergency room, onset of new chronic illness, and serious adverse events. Information regarding late onset adverse events was obtained via a telephone call 6 months following vaccination. At least 97% of subjects completed the 6-month follow-up evaluation.

In a study conducted in Germany, BOOSTRIX was administered to 319 children 10 to 12 years of age previously vaccinated with 5 doses of acellular pertussis antigen-containing vaccines; 193 of these subjects had previously received 5 doses of INFANRIX® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed). Adverse events were recorded on diary cards during the 15 days following vaccination. Unsolicited adverse events that occurred within 31 days of vaccination (day 0-30) were recorded on the diary card or verbally reported to the investigator. Subjects were monitored for 6 months post-vaccination for physician office

visits, emergency room visits, onset of new chronic illness, and serious adverse events. The 6-month follow-up evaluation, conducted via telephone interview, was completed by 90% of subjects.

A randomized, observer-blinded study in adults, conducted in the US, evaluated the safety of BOOSTRIX compared with ADACEL® (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed), a US-licensed Tdap vaccine, manufactured by Sanofi Pasteur SA. Vaccines were administered as a single-dose booster to adults 19 to 64 years of age (N = 2,284). There were no substantive differences in demographic characteristics between the vaccine groups. Subjects were monitored for solicited adverse events using standardized diary cards (day 0-14). Unsolicited adverse events were monitored for the 31-day period following vaccination (day 0-30). Subjects were also monitored for 6 months post-vaccination for serious adverse events, visits to an emergency room, hospitalizations, and onset of new chronic illness. Approximately 95% of subjects completed the 6-month follow-up evaluation.

Solicited Adverse Events in the US Adolescent Safety Study: Table 1 presents the solicited local adverse reactions and general adverse events within 15 days of vaccination with BOOSTRIX or Td vaccine for the total vaccinated cohort.

The primary safety endpoint was the incidence of grade 3 pain (spontaneously painful and/or prevented normal activity) at the injection site within 15 days of vaccination. Grade 3 pain was reported in 4.6% of those who received BOOSTRIX compared with 4.0% of those who received the Td vaccine. The difference in rate of grade 3 pain was within the pre-defined clinical limit for non-inferiority (upper limit of the 95% CI for the difference [BOOSTRIX minus Td] ≤4%).

Table 1. Rates of Solicited Local Adverse Reactions or General Adverse Events Within the 15-day[*] Post-Vaccination Period in Individuals 10 to 18 Years of Age (Total Vaccinated Cohort)

	BOOSTRIX (N = 3,032) %	Td (N = 1,013) %
Local		
Pain, any[†]	75.3	71.7
Pain, grade 2 or 3[†]	51.2	42.5
Pain, grade 3[‡]	4.6	4.0
Redness, any	22.5	19.8
Redness, >20 mm	4.1	3.9
Redness, ≥50 mm	1.7	1.6
Swelling, any	21.1	20.1
Swelling, >20 mm	5.3	4.9
Swelling, ≥50 mm	2.5	3.2
Arm circumference increase, >5 mm[§]	28.3	29.5
Arm circumference increase, >20 mm[§]	2.0	2.2
Arm circumference increase, >40 mm[§]	0.5	0.3
General		
Fever, ≥99.5°F (37.5°C)[‖]	13.5	13.1
Fever, >100.4°F (38.0°C)[‖]	5.0	4.7
Fever, >102.2°F (39.0°C)[‖]	1.4	1.0
Headache, any	43.1	41.5
Headache, grade 2 or 3[†]	15.7	12.7
Headache, grade 3	3.7	2.7
Fatigue, any	37.0	36.7
Fatigue, grade 2 or 3	14.4	12.9
Fatigue, grade 3	3.7	3.2
Gastrointestinal symptoms, any[¶]	26.0	25.8
Gastrointestinal symptoms, grade 2 or 3[¶]	9.8	9.7
Gastrointestinal symptoms, grade 3[¶]	3.0	3.2

Td = Tetanus and Diphtheria Toxoids Adsorbed For Adult Use manufactured by Massachusetts Public Health Biologic Laboratories.

N = Number of subjects in the total vaccinated cohort with local/general symptoms sheets completed.

Grade 2 = Local: painful when limb moved; General: interfered with normal activity.

Grade 3 = Local: spontaneously painful and/or prevented normal activity; General: prevented normal activity.

[*] Day of vaccination and the next 14 days.

[†] Statistically significantly higher ($p<0.05$) following BOOSTRIX as compared to Td vaccine.

‡ Grade 3 injection site pain following BOOSTRIX was not inferior to Td vaccine (upper limit of two-sided 95% CI for the difference [BOOSTRIX minus Td] in the percentage of subjects ≤4%).

§ Mid-upper region of the vaccinated arm.

‖ Oral temperatures or axillary temperatures.

¶ Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

Unsolicited Adverse Events in the US Adolescent Safety Study: The incidence of unsolicited adverse events reported in the 31 days after vaccination was comparable between the 2 groups (25.4% and 24.5 % for BOOSTRIX and Td vaccine, respectively).

Solicited Adverse Events in the German Adolescent Safety Study: Table 2 presents the rates of solicited local adverse reactions and fever within 15 days of vaccination for those subjects who had previously been vaccinated with 5 doses of INFANRIX. No cases of whole arm swelling were reported. Two individuals (2/193) reported large injection site swelling (range 110 to 200 mm diameter), in one case associated with grade 3 pain. Neither individual sought medical attention. These episodes were reported to resolve without sequelae within 5 days.

Table 2. Rates of Solicited Adverse Events Reported Within the 15-day* Post-Vaccination Period Following Administration of BOOSTRIX in Individuals 10 to 12 Years of Age Who Had Previously Received 5 Doses of INFANRIX

	BOOSTRIX (N = 193) %
Pain, any	62.2
Pain, grade 2 or 3	33.2
Pain, grade 3	5.7
Redness, any	47.7
Redness, >20 mm	15.0
Redness, ≥50 mm	10.9
Swelling, any	38.9
Swelling, >20 mm	17.6
Swelling, ≥50 mm	14.0
Fever, ≥99.5°F (37.5°C)†	8.8
Fever, >100.4°F (38.0°C)†	4.1
Fever, >102.2°F (39.0°C)†	1.0

N = Number of subjects with local/general symptoms sheets completed.

Grade 2 = Painful when limb moved.

Grade 3 = Spontaneously painful and/or prevented normal activity.

* Day of vaccination and the next 14 days.

† Oral temperatures or axillary temperatures.

Solicited Adverse Events in the US Adult Safety Study: Table 3 presents solicited local adverse reactions and general adverse events within 15 days of vaccination with BOOSTRIX or the comparator Tdap vaccine for the total vaccinated cohort.

Table 3. Rates of Solicited Local Adverse Reactions or General Adverse Events Within the 15-day[*] Post-Vaccination Period in Adults (Total Vaccinated Cohort)

	BOOSTRIX (N = 1,480) %	**Tdap (N = 741) %**
Local		
Pain, any	61.0	69.2
Pain, grade 2 or 3	35.1	44.4
Pain, grade 3	1.6	2.3
Redness, any	21.1	27.1
Redness, >20 mm	4.0	6.2
Redness, ≥50 mm	1.6	2.3
Swelling, any	17.6	25.6
Swelling, >20 mm	3.9	6.3
Swelling, ≥50 mm	1.4	2.8
General		
Fever, ≥99.5°F (37.5°C)[†]	5.5	8.0
Fever, >100.4°F (38.0°C)[†]	1.0	1.5
Fever, >102.2°F (39.0°C)[†]	0.1	0.4
Headache, any	30.1	31.0
Headache, grade 2 or 3	11.1	10.5
Headache, grade 3	2.2	1.5
Fatigue, any	28.1	28.9
Fatigue, grade 2 or 3	9.1	9.4
Fatigue, grade 3	2.5	1.2
Gastrointestinal symptoms, any[‡]	15.9	17.5
Gastrointestinal symptoms, grade 2 or 3[‡]	4.3	5.7
Gastrointestinal symptoms, grade 3[‡]	1.2	1.3

Tdap = Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed, a US-licensed Tdap vaccine, manufactured by Sanofi Pasteur SA.
N = Number of subjects in the total vaccinated cohort with local/general symptoms sheets completed.
Grade 2 = Local: painful when limb moved; General: interfered with normal activity.
Grade 3 = Local/General: prevented normal activity.
[*] Day of vaccination and the next 14 days.
[†] Oral temperatures.
[‡] Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

Unsolicited Adverse Events in the US Adult Safety Study: The incidence of

unsolicited adverse events reported in the 31 days after vaccination was comparable between the 2 groups (17.8% and 22.2% for BOOSTRIX and Tdap vaccine, respectively).

Serious Adverse Events (SAEs): In the US and German adolescent safety studies, no serious adverse events were reported to occur within 31 days of vaccination. During the 6-month extended safety evaluation period, no serious adverse events that were of potential autoimmune origin or new onset and chronic in nature were reported to occur. In non-US adolescent studies in which serious adverse events were monitored for up to 37 days, one subject was diagnosed with insulin-dependent diabetes 20 days following administration of BOOSTRIX. No other serious adverse events of potential autoimmune origin or that were new onset and chronic in nature were reported to occur in these studies. In the US adult safety study, serious adverse events were reported to occur during the entire study period (0-6 months) by 1.4% and 1.7% of subjects who received BOOSTRIX and the comparator Tdap vaccine, respectively. During the 6-month extended safety evaluation period, no serious adverse events of a neuroinflammatory nature or with information suggesting an autoimmune etiology were reported in subjects who received BOOSTRIX.

6.2 Postmarketing Experience

In addition to reports in clinical trials, worldwide voluntary reports of adverse events received for BOOSTRIX in persons 10 to 64 years of age since market introduction of this vaccine are listed below. This list includes serious events or events which have causal connection to components of this or other vaccines or drugs. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Blood and Lymphatic System Disorders: Lymphadenitis, lymphadenopathy.

Cardiac Disorders: Myocarditis.

General Disorders and Administration Site Conditions: Extensive swelling of the injected limb, injection site induration, injection site inflammation, injection site mass, injection site pruritus, injection site nodule, injection site warmth, local reaction.

Musculoskeletal and Connective Tissue Disorders: Arthralgia, back pain, myalgia.

Nervous System Disorders: Convulsion, encephalitis, facial palsy, paraesthesia.

Skin and Subcutaneous Tissue Disorders: Exanthem, Henoch-Schönlein purpura, rash, urticaria.

7 DRUG INTERACTIONS

7.1 Concomitant Immunizations

BOOSTRIX was administered concomitantly with FLUARIX® (Influenza Virus Vaccine) in a clinical study *[see Clinical Studies (14.4)]*. Lower geometric mean antibody concentrations (GMCs) for antibodies to the pertussis antigens filamentous hemagglutinin (FHA) and pertactin were observed when BOOSTRIX was administered concomitantly with FLUARIX as compared with BOOSTRIX alone.

There are no immunogenicity or safety data to assess the concomitant use of BOOSTRIX

with other vaccines.

When BOOSTRIX is administered concomitantly with other injectable vaccines, they should be given with separate syringes and at different injection sites. BOOSTRIX should not be mixed with any other vaccine in the same syringe or vial.

Tetanus Immune Globulin, if needed, should be given at a separate site, with a separate needle and syringe.

7.2 Immunosuppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to BOOSTRIX.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with BOOSTRIX. It is also not known whether BOOSTRIX can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. BOOSTRIX should be given to a pregnant woman only if clearly needed.

Animal fertility studies have not been conducted with BOOSTRIX. In a developmental toxicity study, the effect of BOOSTRIX on embryo-fetal and pre-weaning development was evaluated in pregnant rats. Animals were administered INFANRIX prior to gestation and BOOSTRIX during the period of organogenesis (gestation days 6, 8, 11) and later in pregnancy (gestation day 15), 0.1 mL/rat/occasion (a 45-fold increase compared with the human dose of BOOSTRIX on a body weight basis), by intramuscular injection. No adverse effect on pregnancy and lactation parameters, embryo-fetal or pre-weaning development was observed. There were no fetal malformations or other evidence of teratogenesis noted in this study.

Pregnancy Exposure Registry: Healthcare providers are encouraged to register pregnant women who receive BOOSTRIX in the GlaxoSmithKline vaccination pregnancy registry by calling 1-888-825-5249.

8.3 Nursing Mothers

It is not known whether BOOSTRIX is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BOOSTRIX is administered to a nursing woman.

8.4 Pediatric Use

BOOSTRIX is not indicated for use in children younger than 10 years of age. Safety and effectiveness of BOOSTRIX in this age group have not been established.

8.5 Geriatric Use

BOOSTRIX is not indicated for use in individuals older than 64 years. Clinical studies of BOOSTRIX did not include sufficient numbers of subjects older than 65 years to determine whether they respond differently from younger subjects.

11 DESCRIPTION

BOOSTRIX (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed) is a noninfectious, sterile, vaccine for intramuscular administration. It contains tetanus toxoid, diphtheria toxoid, and pertussis antigens (inactivated pertussis toxin [PT] and formaldehyde-treated filamentous hemagglutinin [FHA] and pertactin). The antigens are the same as those in INFANRIX, but BOOSTRIX is formulated with reduced quantities of these antigens.

Tetanus toxin is produced by growing *Clostridium tetani* in a modified Latham medium derived from bovine casein. The diphtheria toxin is produced by growing *Corynebacterium diphtheriae* in Fenton medium containing a bovine extract. The bovine materials used in these extracts are sourced from countries which the United States Department of Agriculture (USDA) has determined neither have nor are at risk of bovine spongiform encephalopathy (BSE). Both toxins are detoxified with formaldehyde, concentrated by ultrafiltration, and purified by precipitation, dialysis, and sterile filtration.

The acellular pertussis antigens (PT, FHA, and pertactin) are isolated from *Bordetella pertussis* culture grown in modified Stainer-Scholte liquid medium. PT and FHA are isolated from the fermentation broth; pertactin is extracted from the cells by heat treatment and flocculation. The antigens are purified in successive chromatographic and precipitation steps. PT is detoxified using glutaraldehyde and formaldehyde. FHA and pertactin are treated with formaldehyde.

Each antigen is individually adsorbed onto aluminum hydroxide. Each 0.5-mL dose is formulated to contain 5 Lf of tetanus toxoid, 2.5 Lf of diphtheria toxoid, 8 mcg of inactivated PT, 8 mcg of FHA, and 2.5 mcg of pertactin (69 kiloDalton outer membrane protein).

Tetanus and diphtheria toxoid potency is determined by measuring the amount of neutralizing antitoxin in previously immunized guinea pigs. The potency of the acellular pertussis components (inactivated PT and formaldehyde-treated FHA and pertactin) is determined by enzyme-linked immunosorbent assay (ELISA) on sera from previously immunized mice.

Each 0.5-mL dose also contains 4.5 mg of NaCl, aluminum adjuvant (not more than 0.39 mg aluminum by assay), ≤100 mcg of residual formaldehyde, and ≤100 mcg of polysorbate 80 (Tween 80).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tetanus: Tetanus is a condition manifested primarily by neuromuscular dysfunction caused by a potent exotoxin released by *C. tetani*. Protection against disease is due to the development of neutralizing antibodies to the tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assays, is considered the minimum protective level.[5,6] A level ≥0.1 IU/mL has been considered as protective.[7]

Diphtheria: Diphtheria is an acute toxin-mediated infectious disease caused by toxigenic

strains of *C. diphtheriae*. Protection against disease is due to the development of neutralizing antibodies to the diphtheria toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection; a level of 0.1 IU/mL is regarded as protective.[8]

Pertussis: Pertussis (whooping cough) is a disease of the respiratory tract caused by *B. pertussis*. The role of the different components produced by *B. pertussis* in either the pathogenesis of, or the immunity to, pertussis is not well understood.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

BOOSTRIX has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

14 CLINICAL STUDIES

The efficacy of the tetanus and diphtheria toxoid components of BOOSTRIX is based on the immunogenicity of the individual antigens compared to US-licensed vaccines using established serologic correlates of protection. The efficacy of the pertussis components of BOOSTRIX was evaluated by comparison of the immune response of adolescents and adults following a single dose of BOOSTRIX to the immune response of infants following a 3-dose primary series of INFANRIX. In addition, the ability of BOOSTRIX to induce a booster response to each of the antigens was evaluated.

14.1 Efficacy of INFANRIX

The efficacy of a 3-dose primary series of INFANRIX in infants has been assessed in 2 clinical studies: A prospective efficacy trial conducted in Germany employing a household contact study design and a double-blind, randomized, active Diphtheria and Tetanus Toxoids (DT)-controlled trial conducted in Italy sponsored by the National Institutes of Health (NIH) (for details see INFANRIX prescribing information). Serological data from a subset of infants immunized with INFANRIX in the household contact study were compared with the sera of adolescents and adults immunized with BOOSTRIX *[see Clinical Studies (14.2, 14.3)]*. In the household contact study, the protective efficacy of INFANRIX, in infants, against WHO-defined pertussis (21 days or more of paroxysmal cough with infection confirmed by culture and/or serologic testing) was calculated to be 89% (95% CI: 77%, 95%). When the definition of pertussis was expanded to include clinically milder disease, with infection confirmed by culture and/or serologic testing, the efficacy of INFANRIX against ≥7 days of any cough was 67% (95% CI: 52%, 78%) and against ≥7 days of paroxysmal cough was 81% (95% CI: 68%, 89%) (for details see INFANRIX prescribing information).

14.2 Immunological Evaluation in Adolescents

In a multicenter, randomized, controlled study conducted in the United States, the immune responses to each of the antigens contained in BOOSTRIX were evaluated in sera obtained approximately 1 month after administration of a single dose of vaccine to adolescent subjects (10 to 18 years of age). Of the subjects enrolled in this study, approximately 76% were 10 to 14 years of age and 24% were 15 to 18 years of age. Approximately 98% of participants in

this study had received the recommended series of 4 or 5 doses of either DTwP or a combination of DTwP and DTaP in childhood. The racial/ethnic demographics were as follows: Caucasian 85.8%, Black 5.7%, Hispanic 5.6%, Oriental 0.8%, and other 2.1%.

Response to Tetanus and Diphtheria Toxoids: The antibody responses to the tetanus and diphtheria toxoids of BOOSTRIX compared with Td vaccine are shown in Table 4. One month after a single dose, anti-tetanus and anti-diphtheria seroprotective rates (≥0.1 IU/mL) and booster response rates were comparable between BOOSTRIX and the control Td vaccine.

Table 4. Antibody Responses to Tetanus and Diphtheria Toxoids Following BOOSTRIX as Compared With Td Vaccine in Individuals 10 to 18 Years of Age (ATP Cohort for Immunogenicity)

	N	% ≥0.1 IU/mL (95% CI)	% ≥1.0 IU/mL (95% CI)	% BR* (95% CI)
Anti-Tetanus				
BOOSTRIX	2,469-2,516			
Pre-vaccination		97.7 (97.1, 98.3)	36.8 (34.9, 38.7)	-
Post-vaccination		100 (99.8, 100)†	99.5 (99.1, 99.7)‡	89.7 (88.4, 90.8)†
Td	817-834			
Pre-vaccination		96.8 (95.4, 97.9)	39.9 (36.5, 43.4)	-
Post-vaccination		100 (99.6, 100)	99.8 (99.1, 100)	92.5 (90.5, 94.2)
Anti-Diphtheria				
BOOSTRIX	2,463-2,515			
Pre-vaccination		85.8 (84.3, 87.1)	17.1 (15.6, 18.6)	-
Post-vaccination		99.9 (99.7, 100)†	97.3 (96.6, 97.9)‡	90.6 (89.4, 91.7)†
Td	814-834			
Pre-vaccination		84.8 (82.1, 87.2)	19.5 (16.9, 22.4)	-
Post-vaccination		99.9 (99.3, 100)	99.3 (98.4, 99.7)	95.9 (94.4, 97.2)

Td manufactured by Massachusetts Public Health Biologic Laboratories.

ATP = according-to-protocol; CI = Confidence Interval; BR = booster response.

* Booster response: In subjects with pre-vaccination <0.1 IU/mL, post-vaccination concentration ≥0.4 IU/mL. In subjects with pre-vaccination concentration ≥0.1 IU/mL, an increase of at least 4 times the pre-vaccination concentration.

† Seroprotection rate or booster response rate to BOOSTRIX was non-inferior to Td (upper limit of two-sided 95% CI on the difference for Td minus BOOSTRIX ≤10%).

‡ Non-inferiority criteria not prospectively defined for this endpoint.

Response to Pertussis Antigens: The booster response rates of adolescents to the pertussis antigens are shown in Table 5. For each of the pertussis antigens the lower limit of the two-sided 95% CI for the percentage of subjects with a booster response exceeded the pre-defined lower limit of 80% for demonstration of an acceptable booster response.

Table 5. Booster Responses to the Pertussis Antigens Following BOOSTRIX in Individuals 10 to 18 Years of Age (ATP Cohort for Immunogenicity)

	N	BOOSTRIX % BR* (95% CI)
Anti-PT	2,677	84.5 (83.0, 85.9)
Anti-FHA	2,744	95.1 (94.2, 95.9)
Anti-pertactin	2,752	95.4 (94.5, 96.1)

ATP = according-to-protocol; CI = Confidence Interval; BR = booster response.

* Booster response: In initially seronegative subjects (<5 EL.U./mL), post-vaccination antibody concentrations ≥20 EL.U./mL. In initially seropositive subjects with pre-vaccination antibody concentrations ≥5 EL.U./mL and <20 EL.U./mL, an increase of at least 4 times the pre-vaccination antibody concentration. In initially seropositive subjects with pre-vaccination antibody concentrations ≥20 EL.U./mL, an increase of at least 2 times the pre-vaccination antibody concentration.

The GMCs to each of the pertussis antigens 1 month following a single dose of BOOSTRIX in the US adolescent study (N = 2,941-2,979) were compared with the GMCs of infants following a 3-dose primary series of INFANRIX administered at 3, 4, and 5 months of age (N = 631-2,884). Table 6 presents the results for the total immunogenicity cohort in both studies (vaccinated subjects with serology data available for at least one pertussis antigen; the majority of subjects in the study of INFANRIX had anti-PT serology data only). These infants were a subset of those who formed the cohort for the German household contact study in which the efficacy of INFANRIX was demonstrated *[see Clinical Studies (14.1)]*. Although a serologic correlate of protection for pertussis has not been established, anti-PT, anti-FHA, and anti-pertactin antibody concentrations of adolescents 1 month after a single dose of BOOSTRIX were non-inferior to those of infants following a primary vaccination series with INFANRIX.

Table 6. Ratio of GMCs to Pertussis Antigens Following One Dose of BOOSTRIX in Individuals 10 to 18 Years of Age as Compared With 3 Doses of INFANRIX in Infants (Total Immunogenicity Cohort)

	GMC Ratio: BOOSTRIX/INFANRIX (95% CI)
Anti-PT	1.90 (1.82, 1.99)*
Anti-FHA	7.35 (6.85, 7.89)*
Anti-pertactin	4.19 (3.73, 4.71)*

GMC = geometric mean antibody concentration, measured in arbitrary ELISA units;
CI = Confidence Interval.
Number of subjects for BOOSTRIX GMC evaluation: Anti-PT = 2,941, anti-FHA = 2,979, and anti-pertactin = 2,978.
Number of subjects for INFANRIX GMC evaluation: Anti-PT = 2,884, anti-FHA = 685, and anti-pertactin = 631.
* GMC following BOOSTRIX was non-inferior to GMC following INFANRIX (lower limit of 95% CI for the GMC ratio of BOOSTRIX/INFANRIX >0.67).

14.3 Immunological Evaluation in Adults

A multicenter, randomized, observer-blinded study, conducted in the United States, evaluated the immunogenicity of BOOSTRIX compared with the licensed comparator Tdap vaccine (Sanofi Pasteur SA). Vaccines were administered as a single-dose booster to adults 19 to 64 years of age (N = 2,284), who had not received a tetanus-diphtheria booster within 5 years. The immune responses to each of the antigens contained in BOOSTRIX were evaluated in sera obtained approximately 1 month after administration. Approximately 33% of patients were 19 to 29 years of age, 33% were 30 to 49 years of age and 34% were 50 to 64 years of age. Among subjects in the combined vaccine groups, 62% were female; 84% of subjects were Caucasian, 8% Black, 1% Asian, and 7% were of other racial groups.

Response to Tetanus and Diphtheria Toxoids: The antibody responses to the tetanus and diphtheria toxoids of BOOSTRIX compared with the control Tdap vaccine are shown in Table 7. One month after a single dose, anti-tetanus and anti-diphtheria seroprotective rates (≥0.1 IU/mL) were comparable between BOOSTRIX and the control Tdap vaccine.

Table 7. Antibody Responses to Tetanus and Diphtheria Toxoids Following One Dose of BOOSTRIX as Compared With the Control Tdap Vaccine in Adults 19 to 64 Years of Age (ATP Cohort for Immunogenicity)

	N	% ≥0.1 IU/mL (95% CI)	% ≥1.0 IU/mL (95% CI)
Anti-Tetanus			
BOOSTRIX	1,445-1,447		
Pre-vaccination		95.9 (94.8, 96.9)	71.9 (69.5, 74.2)
Post-vaccination		99.6 (99.1, 99.8)*	98.3 (97.5, 98.9)*
Tdap	727-728		
Pre-vaccination		97.2 (95.8, 98.3)	74.7 (71.4, 77.8)
Post-vaccination		100 (95.5, 100)	99.3 (98.4, 99.8)
Anti-Diphtheria			
BOOSTRIX	1,440-1,444		
Pre-vaccination		85.2 (83.3, 87.0)	23.7 (21.5, 26.0)
Post-vaccination		98.2 (97.4, 98.8)*	87.9 (86.1, 89.5)†
Tdap	720-727		
Pre-vaccination		89.2 (86.7, 91.3)	26.5 (23.3, 29.9)
Post-vaccination		98.6 (97.5, 99.3)	92.0 (89.8, 93.9)

Tdap = Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed manufactured by Sanofi Pasteur SA.

ATP = according-to-protocol; CI = Confidence Interval.

* Seroprotection rates for BOOSTRIX were non-inferior to the comparator Tdap vaccine (lower limit of 95% CI on the difference of BOOSTRIX minus Tdap ≥-10%).

† Non-inferiority criteria not prospectively defined for this endpoint.

Response to Pertussis Antigens: The GMCs and booster response rates to the pertussis antigens are shown in Table 8. For the FHA and pertactin antigens, the lower limit of the 95% CI for the booster responses exceeded the pre-defined limit of 80% demonstrating an acceptable booster response following BOOSTRIX. The PT antigen booster response lower limit of the 95% CI (74.9%) did not exceed the pre-defined limit of 80%.

Table 8. GMCs and Booster Responses for the Pertussis Antigens Following One Dose of BOOSTRIX in Adults 19 to 64 Years of Age (ATP Cohort for Immunogenicity)

	N	GMC EL.U./mL	% BR* (95% CI)
BOOSTRIX	1,419-1,444		
Anti-PT		63.6	77.2 (74.9, 79.3)†
Anti-FHA		624.4	96.9 (95.8, 97.7)‡
Anti-pertactin		401.0	93.2 (91.8, 94.4)‡

GMC = geometric mean antibody concentration; ATP = according-to-protocol; BR = booster response; CI = Confidence Interval.

* Booster response: In initially seronegative subjects (<5 EL.U./mL), post-vaccination antibody concentrations ≥20 EL.U./mL. In initially seropositive subjects with pre-vaccination antibody concentrations ≥5 EL.U./mL and <20 EL.U./mL, an increase of at least 4 times the pre-vaccination antibody concentration. In initially seropositive subjects with pre-vaccination antibody concentrations ≥20 EL.U./mL, an increase of at least 2 times the pre-vaccination antibody concentration.

† The PT antigen booster response lower limit of the 95% CI did not exceed the pre-defined limit of 80%.

‡ The FHA and pertactin antigens booster response lower limit of the 95% CI exceeded the pre-defined limit of 80%.

The GMCs to each of the pertussis antigens 1 month following a single dose of BOOSTRIX in the US adult study were compared with the GMCs of infants following a 3-dose primary series of INFANRIX administered at 3, 4, and 5 months of age. Table 9 presents the results for the total immunogenicity cohort in both studies (vaccinated subjects with serology data available for at least one pertussis antigen). These infants were a subset of those who formed the cohort for the German household contact study in which the efficacy of INFANRIX was demonstrated *[see Clinical Studies (14.1)]*. Although a serologic correlate of protection for pertussis has not been established, anti-PT, anti-FHA, and anti-pertactin antibody concentrations of adults 1 month after a single dose of BOOSTRIX were non-inferior to those of infants following a primary vaccination series with INFANRIX.

Table 9. Ratio of GMCs to Pertussis Antigens Following One Dose of BOOSTRIX in Adults 19 to 64 Years of Age as Compared With 3 Doses of INFANRIX in Infants (Total Immunogenicity Cohort)

	GMC Ratio: BOOSTRIX/INFANRIX (95% CI)
Anti-PT	1.39 (1.32, 1.47)*
Anti-FHA	7.46 (6.86, 8.12)*
Anti-pertactin	3.56 (3.10, 4.08)*

GMC = geometric mean antibody concentration; CI = Confidence Interval.
Number of subjects for BOOSTRIX GMC evaluation: Anti-PT = 1,460, anti-FHA = 1,472, and anti-pertactin = 1,473.
Number of subjects for INFANRIX GMC evaluation: Anti-PT = 2,884, anti-FHA = 685, and anti-pertactin = 631.
* BOOSTRIX was non-inferior to INFANRIX (lower limit of 95% CI for the GMC ratio of BOOSTRIX/INFANRIX ≥0.67).

14.4 Concomitant Vaccine Administration

The concomitant use of BOOSTRIX and FLUARIX was evaluated in a multicenter, open-label, randomized, controlled study of 1,497 adults aged 19 to 64 years of age. In one group, subjects received BOOSTRIX and FLUARIX concurrently (n = 748). The other group received FLUARIX at the first visit, then 1 month later received BOOSTRIX (n = 749). Sera was obtained prior to and 1 month following concomitant or separate administration of BOOSTRIX and/or FLUARIX, as well as 1 month after the separate administration of FLUARIX.

Immune responses following concurrent administration of BOOSTRIX and FLUARIX were non-inferior to separate administration for diphtheria (seroprotection defined as ≥0.1 IU/mL), tetanus (seroprotection defined as ≥0.1 IU/mL and based on concentrations ≥1.0 IU/mL), pertussis toxin (PT) antigen (anti-PT GMC) and influenza antigens (percent of subjects with hemagglutination-inhibition [HI] antibody titer ≥1:40 and ≥4-fold rise in HI titer). Non-inferiority criteria were not met for the anti-pertussis antigens FHA and pertactin. The lower limit of the 95% CI of the GMC ratio was 0.64 for anti-FHA and 0.60 for anti-pertactin and the pre-specified limit was ≥0.67.

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16 HOW SUPPLIED/STORAGE AND HANDLING

BOOSTRIX is available in 0.5-mL single-dose vials and disposable prefilled TIP-LOK syringes.

Single-Dose Vials

NDC 58160-842-11 (package of 10)

Single-Dose Prefilled Disposable TIP-LOK Syringes (packaged without needles)

NDC 58160-842-46 (package of 5)

Store refrigerated between 2º and 8ºC (36º and 46ºF). Do not freeze. Discard if the vaccine has been frozen.

17 PATIENT COUNSELING INFORMATION

- Patients, parents or guardians should be informed by the healthcare provider of the potential benefits and risks of immunization with BOOSTRIX.
- The healthcare provider should inform the patients, parents or guardians about the potential for adverse reactions that have been temporally associated with administration of BOOSTRIX or other vaccines containing similar components.
- The patient, or parent/guardian accompanying the recipient, should be instructed to report any adverse events to their healthcare provider.
- The patient, parent or guardian should be given the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control

and Prevention (CDC) website (www.cdc.gov/nip).

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