BOOSTRIX®

(Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed)

DESCRIPTION

BOOSTRIX® (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed) (Tdap) is a noninfectious, sterile, vaccine for intramuscular administration manufactured by GlaxoSmithKline Biologicals. It contains tetanus toxoid, diphtheria toxoid, and pertussis antigens (inactivated pertussis toxin [PT] and formaldehyde-treated filamentous hemagglutinin [FHA] and pertactin [69 kiloDalton outer membrane protein]) adsorbed onto aluminum hydroxide. The antigens are the same as those in INFANRIX® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed), 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 3 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. All antigens are then diluted and combined to produce the final formulated vaccine. Each 0.5-mL dose is formulated to contain 2.5 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, 2.5 mcg of pertactin, 8 mcg of FHA, and 8 mcg of inactivated PT.

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).

This vaccine does not contain a preservative.

The vaccine must be well shaken before administration to obtain a homogeneous, turbid, white suspension.

Diphtheria and Tetanus Toxoids Adsorbed Combined Bulk (For Further Manufacturing Use) and Tetanus Toxoid Concentrate (For Further Manufacturing Use) are manufactured by Chiron Behring GmbH & Co KG, Marburg, Germany. The acellular pertussis antigens are manufactured by GlaxoSmithKline Biologicals, Rixensart, Belgium. Formulation, filling, testing, packaging, and release of the vaccine are also performed by GlaxoSmithKline Biologicals.

CLINICAL PHARMACOLOGY

Tetanus: Tetanus is a condition manifested primarily by neuromuscular dysfunction caused by a potent exotoxin released by *C. tetani*. 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.[1] 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.[2,3] A level ≥0.1 to 0.2 IU/mL has been considered as protective.[4] Following immunization, protection persists for at least 10 years.[1]

Efficacy of tetanus toxoid used in BOOSTRIX was determined on the basis of a US immunogenicity study (see Immunological Evaluation of BOOSTRIX).

Diphtheria: Diphtheria is an acute toxin-mediated infectious disease caused by toxigenic strains of *C. diphtheriae*. Diphtheria in the United States has been controlled through the use of diphtheria toxoid-containing vaccines. Protection against disease is due to the development of neutralizing antibodies to the diphtheria toxin. Following adequate immunization with diphtheria toxoid, protection persists for at least 10 years. 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.[5] Levels of 1.0 IU/mL are associated with long-term protection.[5] Immunization with diphtheria toxoid does not, however, eliminate carriage of *C. diphtheriae* in the pharynx or nares or on the skin.[1]

Efficacy of diphtheria toxoid used in BOOSTRIX was determined on the basis of a US immunogenicity study (see Immunological Evaluation of BOOSTRIX).

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. However, the pertussis components in BOOSTRIX (i.e., inactivated PT and formaldehyde-treated FHA and pertactin) have been shown to prevent pertussis in clinical trials of INFANRIX (for details see INFANRIX prescribing information).[6,7]

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).[6,7] Serological data from a subset of infants immunized with INFANRIX in the household contact study were compared to the sera of adolescents immunized with BOOSTRIX (see Immunological Evaluation of BOOSTRIX). 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% to 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% to 78%) and against ≥7 days of paroxysmal cough was 81% (95% CI: 68% to 89%) (for details see INFANRIX prescribing information).[6]

Immunological Evaluation of BOOSTRIX: The efficacy of the tetanus and diphtheria toxoid components of BOOSTRIX is based on the immunogenicity of these antigens compared to a US-licensed Tetanus and Diphtheria Toxoids Adsorbed For Adult Use (Td) vaccine manufactured by Massachusetts Public Health Biologic Laboratories using established serologic correlates of protection. The efficacy of the pertussis components of BOOSTRIX was evaluated by comparison of the immune response of adolescents 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.

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 one 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 Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTwP) or a combination of DTwP and Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (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 the Tetanus and Diphtheria Toxoids: The antibody responses to the tetanus and diphtheria toxoids of BOOSTRIX compared to Td vaccine are shown in Table 1.

Table 1. Pre-vaccination and Post-vaccination Antibody Responses to Tetanus and Diphtheria Toxoids Following BOOSTRIX as Compared to 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)

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.

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

One month after a single dose, non-inferiority of BOOSTRIX compared to the control Td vaccine was demonstrated for anti-tetanus and anti-diphtheria seroprotective rates (≥0.1 IU/mL) and booster response rates.

Response to the Pertussis Antigens of BOOSTRIX: The booster response rates of adolescents to the pertussis antigens are shown in Table 2.

Table 2. 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.

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.

Immune Response of Adolescents to BOOSTRIX Compared to the Immune Response of Infants to INFANRIX: The geometric mean antibody concentrations (GMCs) to each of the pertussis antigens one month following a single dose of BOOSTRIX in the US adolescent study (N = 2,941-2,979) were compared to 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 3 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 INFANRIX study 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 PHARMACOLOGY).

Table 3. Ratio of Geometric Mean Antibody Concentrations to Pertussis Antigens Following BOOSTRIX as Compared to INFANRIX (Total Immunogenicity Cohort)

	GMC Ratio: GMC BOOSTRIX/GMC 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 on the ratio of GMC for BOOSTRIX divided by INFANRIX >0.67).

Although a serologic correlate of protection for pertussis has not been established, anti-PT, anti-FHA, and anti-pertactin antibody concentrations of adolescents one month after a single dose of BOOSTRIX were non-inferior to those of infants following a primary vaccination series with INFANRIX.

Immune Response to Concomitantly Administered Vaccines: Immunogenicity data are not available on the concurrent administration of BOOSTRIX with other vaccines.

INDICATIONS AND USAGE

BOOSTRIX is indicated for active booster immunization against tetanus, diphtheria, and pertussis as a single dose in individuals 10 through 18 years of age.

The use of BOOSTRIX as a primary series or to complete the primary series has not been studied.

As with any vaccine, BOOSTRIX may not protect 100% of individuals receiving the vaccine.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine is a contraindication (see DESCRIPTION).

It is a contraindication to use this vaccine after a serious allergic reaction (e.g., anaphylaxis) following any other tetanus toxoid, diphtheria toxoid or pertussis-containing vaccine, or any component of this vaccine (see DESCRIPTION). Because of the uncertainty as to which component of the vaccine might be responsible, no further vaccination with any of these components should be given. Alternatively, such individuals may be referred to an allergist for evaluation if immunizations are to be considered.[1]

In addition, the following events are contraindications to administration of any pertussis-containing vaccine, including BOOSTRIX:[4]

- Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days of administration of a previous dose of a pertussis-containing vaccine that is not attributable to another identifiable cause;
- Progressive neurologic disorder, uncontrolled epilepsy, or progressive encephalopathy. Pertussis vaccine should not be administered to individuals with these conditions until a treatment regimen has been established and the condition has stabilized.

WARNINGS

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.

If any of the following events occurred in temporal relation to previous receipt of a DTwP vaccine or a vaccine containing an acellular pertussis component, the decision to give BOOSTRIX should be based on careful consideration of the potential benefits and possible risks:[8,9]

- Temperature of ≥40.5°C (105°F) within 48 hours not due to another identifiable cause;
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours;
- Persistent, inconsolable crying lasting ≥3 hours, occurring within 48 hours;
- Seizures with or without fever occurring within 3 days.

When a decision is made to withhold pertussis vaccine, immunization with Td vaccine (Tetanus and Diphtheria Toxoids Adsorbed For Adult Use) should be given.

Persons who experienced serious Arthus-type hypersensitivity reactions following a prior dose of tetanus toxoid usually have high serum tetanus antitoxin levels and should not be given Td or Tdap vaccines or even emergency doses of Td more frequently than every 10 years, even if the wound is neither clean nor minor.[1,9]

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of 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.[4]

The decision to administer a pertussis-containing vaccine to individuals with stable central nervous system (CNS) disorders must be made by the physician on an individual basis, with consideration of all relevant factors, and assessment of potential risks and benefits for that individual. The Advisory Committee on Immunization Practices (ACIP) has issued guidelines for such individuals.[8] The patient, parent, or guardian should be advised of the potential increased risk involved (see PRECAUTIONS, Information for Vaccine Recipients and Parents or Guardians).

A family history of seizures or other CNS disorders is not a contraindication to pertussis vaccine.[8]

The ACIP has published guidelines for vaccination of persons with recent or acute illness (www.cdc.gov).[4]

As with other intramuscular injections, BOOSTRIX should not be given to individuals with bleeding disorders such as hemophilia or thrombocytopenia, or to persons on anticoagulant therapy unless the potential benefit clearly outweighs the risk of administration. If the decision is made to administer BOOSTRIX to such persons, it should be given with caution with steps taken to avoid the risk of hematoma following the injection.[4]

PRECAUTIONS

General: Before the injection of any biological, the physician should take all reasonable precautions to prevent allergic or other adverse reactions, including understanding the use of the biological concerned, and the nature of the side effects and adverse reactions that may follow its use.

Prior to immunization, the patient's current health status and medical history should be reviewed. The physician should review the patient's immunization history for possible vaccine sensitivity, previous vaccination-related adverse reactions and occurrence of any adverse–event-related symptoms and/or signs, in order to determine the existence of any contraindication to immunization with BOOSTRIX and to allow an assessment of benefits and risks. Epinephrine injection (1:1,000) and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

A separate sterile syringe and sterile disposable needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another. Needles should be disposed of properly and should not be recapped.

Special care should be taken to prevent injection into a blood vessel.

As with any vaccine, if administered to immunosuppressed persons, including individuals receiving immunosuppressive therapy, the expected immune response may not be obtained.[10]

Information for Vaccine Recipients and Parents or Guardians: Patients, parents or guardians should be informed by the healthcare provider of the potential benefits and risks of the vaccine. It is important that the vaccine recipient, parent or guardian be questioned concerning occurrence of any symptoms and/or signs of an adverse reaction after a previous dose of a diphtheria, tetanus and pertussis vaccine. The healthcare provider should inform the patients, parents or guardians about the potential for adverse events that have been temporally associated with administration of BOOSTRIX or other vaccines containing similar components. The patient, or parent or guardian accompanying the recipient, should be told to report severe or unusual adverse events to the physician or clinic where the vaccine was administered.

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).

The United States Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events

required by the National Childhood Vaccine Injury Act of 1986.[4] The VAERS toll-free number is 1-800-822-7967. Reporting forms may also be obtained at the VAERS website at www.vaers.hhs.gov.

Drug Interactions: BOOSTRIX should not be mixed with any other vaccine in the same syringe or vial.

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. The ACIP has published guidelines for vaccination of such persons and those with immunodeficiency disorders (www.cdc.gov).[10]

Carcinogenesis, Mutagenesis, Impairment of Fertility: BOOSTRIX has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

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 reproductive 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 to the human dose of BOOSTRIX on a body weight basis), by intramuscular injection. No adverse affect 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.

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.

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.

Geriatric Use: BOOSTRIX is not indicated for use in individuals older than 18 years.

Pediatric Use: BOOSTRIX is not indicated for use in individuals younger than 10 years (see DOSAGE AND ADMINISTRATION). For immunization of infants and children younger than 7 years against diphtheria, tetanus, and pertussis, refer to the manufacturers' package inserts for DTaP vaccines.

ADVERSE REACTIONS

A total of 3,608 adolescents were vaccinated with a single dose of BOOSTRIX during clinical trials. 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.

The primary safety study, conducted in the United States, was a randomized, observer-blinded, controlled study in which 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 DTwP or a combination of DTwP and DTaP in childhood. Data on adverse events were collected by the subjects, parents and/or guardians using standardized diaries for 15 consecutive days following the vaccine dose (i.e., day of vaccination and the next 14 days). Subjects were monitored for unsolicited adverse events that occurred within 31 days of vaccination (day 0-30) using diary cards (day 0-14) supplemented by spontaneous reports and a medical history as reported by subjects, parents, and/or guardians. 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-containing vaccines, 193 of these subjects had previously received 5 doses of INFANRIX. 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.

The adverse event information from clinical trials provides a basis for identifying adverse events that appear to be related to vaccine use and for approximating rates. However, because clinical trials are conducted under widely varying conditions, adverse event 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.

Serious Adverse Events in All Safety Studies: In the US-safety study and German-safety study, 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 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.

Solicited Adverse Events in the US-Safety Study: Table 4 presents the solicited local and general adverse events within 15 days of vaccination with BOOSTRIX or Td vaccine for the total vaccinated cohort (all enrolled, vaccinated subjects with safety data available analyzed by vaccine received) in a US study. The most common local adverse events following administration of BOOSTRIX were pain, redness, and swelling at the injection site. The most common general adverse events were headache and fatigue. Most of these events were reported at a similar frequency in recipients of both BOOSTRIX and Td. Any pain, grade 2 or 3 pain (but not grade 3 alone), and grade 2 or 3 headache (but not grade 3 alone) were reported at a higher rate in recipients of BOOSTRIX.

The primary safety endpoint of the US study 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 ≤4%).

Table 4. Percentage of Individuals 10 to 18 Years of Age Reporting Solicited Local Adverse Events or Solicited General Adverse Events Within the 15-day* Post-Vaccination Period (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	13.5	13.1
Fever,[‖] >100.4˚F	5.0	4.7
Fever,[‖] >102.2˚F	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 the limb was 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 (upper limit of two-sided 95% CI for the difference 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.

Mid-upper arm circumference was measured by the adolescent or their parent/guardian prior to injection and daily for 15 days following vaccination. There was no significant difference between BOOSTRIX recipients and Td recipients in the proportion of subjects reporting an increase in mid-upper arm circumference in the vaccinated arm.

The incidence of unsolicited adverse events reported in the 31 days after vaccination was comparable between the 2 groups.

Solicited Adverse Events in the German Safety Study: Table 5 presents the rates of solicited local adverse events 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 spontaneously 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 5. 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

Adverse Event	BOOSTRIX (N = 193) % (95% CI)
Pain, any	62.2 (54.9-69.0)
Pain, grade 2 or 3	33.2 (26.6-40.3)
Pain, grade 3	5.7 (2.9-10.0)
Redness, any	47.7 (40.4-55.0)
Redness, >20 mm	15.0 (10.3-20.9)
Redness, ≥50 mm	10.9 (6.9-16.2)
Swelling, any	38.9 (31.9-46.1)
Swelling, >20 mm	17.6 (12.5-23.7)
Swelling, ≥50 mm	14.0 (9.4-19.7)
Fever, ≥99.5	8.8 (5.2-13.7)
Fever, >100.4	4.1 (1.8-8.0)
Fever, >102.2	1.0 (0.1-3.7)

N = number of subjects with local/general symptoms sheets completed.
Grade 2 = Painful when the limb was moved.
Grade 3 = Spontaneously painful and/or prevented normal activity.
*Day of vaccination and the next 14 days.

As with any vaccine, there is the possibility that broad use of BOOSTRIX could reveal adverse events not observed in clinical trials.

Additional Adverse Events: Rarely, an anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) has been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.[9] Death following vaccine-caused

anaphylaxis has been reported.[1] Arthus-type hypersensitivity reactions, characterized by severe local reactions, may follow receipt of tetanus toxoid. A review by the IOM found evidence for a causal relationship between receipt of tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome.[11] A few cases of demyelinating diseases of the CNS have been reported following some tetanus toxoid-containing vaccines or tetanus and diphtheria toxoid-containing vaccines, although the IOM concluded that the evidence was inadequate to accept or reject a causal relationship.[11] A few cases of peripheral mononeuropathy and of cranial mononeuropathy have been reported following tetanus toxoid administration, although the IOM concluded that the evidence was inadequate to accept or reject a causal relationship.

Postmarketing Reports: Worldwide voluntary reports of adverse events received for BOOSTRIX in persons 10 to 18 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 vaccine exposure.

Blood and lymphatic system disorders: Lymphadenitis, lymphadenopathy.

Cardiac disorders: Myocarditis.

Injection site reactions: Induration, inflammation, mass, nodule, warmth, local reaction.

Metabolism and nutrition disorders: Diabetes mellitus insulin-dependent.

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.

In addition, extensive swelling of the injected limb has been reported following administration of BOOSTRIX.

Reporting Adverse Events: The National Childhood Vaccine Injury Act requires that the manufacturer and lot number of the vaccine administered be recorded by the healthcare provider in the vaccine recipient's permanent medical record, along with the date of administration of the vaccine and the name, address, and title of the person administering the vaccine.[12] The Act further requires the healthcare provider to report to the US Department of Health and Human Services the occurrence following immunization of any event set forth in the Vaccine Injury Table including: Anaphylaxis or anaphylactic shock within 7 days, encephalopathy or encephalitis within 7 days, brachial neuritis within 28 days, or an acute complication or sequelae (including death) of an illness, disability, injury, or condition referred to above, or any events that would contraindicate further doses of vaccine, according to this prescribing information.[12,13] These events should be reported to VAERS. The VAERS toll-free number is 1-800-822-7967. Reporting forms may also be obtained at the VAERS website at www.vaers.hhs.gov.

DOSAGE AND ADMINISTRATION

Preparation for Administration: BOOSTRIX contains an adjuvant; therefore, shake vigorously to obtain a homogeneous, turbid, white suspension before administration. DO NOT

USE IF RESUSPENSION DOES NOT OCCUR WITH VIGOROUS SHAKING. Inspect visually for particulate matter or discoloration prior to administration. After removal of the dose, any vaccine remaining in the vial should be discarded. Before injection, the skin at the injection site should be cleaned and prepared with a suitable germicide. The recommended needle size for administration of BOOSTRIX is a 22-25 gauge needle, 1-1¼ inches in length.[4]

Recommended Dose: BOOSTRIX should be administered as a single 0.5 mL injection by the intramuscular route into the deltoid muscle of the upper arm in individuals 10 through 18 years of age. Do not administer this product subcutaneously or intravenously.

There are no data to support repeat administration of BOOSTRIX.

Five years should elapse between the subject's last dose of the recommended series of childhood DTwP and/or DTaP vaccine and the administration of BOOSTRIX. Limited data are available on the use of BOOSTRIX following Tetanus and Diphtheria Toxoids Adsorbed For Adult Use (Td) vaccine.

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] Adolescents 10 to 18 years of age 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 missles, crushing, burns, and frostbite) in an adolescent who is in need of tetanus toxoid, BOOSTRIX can be used as an alternative to Tetanus and Diphtheria Toxoids Adsorbed For Adult Use (Td) vaccine in patients for whom the pertussis component is also indicated (see INDICATIONS AND USAGE).

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

Diphtheria Prophylaxis for Case Contacts: The ACIP has published recommendations for diphtheria prophylaxis in individuals who have had contact with a person with confirmed or suspected diphtheria (www.cdc.gov).[1]

Concomitant Vaccine Administration: There are no immunogenicity or safety data for the concomitant administration of BOOSTRIX with other vaccines. When concomitant administration of other vaccines is required, they should be given with separate syringes and at different injection sites.

STORAGE

Store BOOSTRIX refrigerated between 2º and 8ºC (36º and 46ºF). **Do not freeze.** Discard if the vaccine has been frozen. Do not use after expiration date shown on the label.

HOW SUPPLIED

BOOSTRIX is supplied as a turbid white suspension in single-dose (0.5 mL) 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)

CPT® Code: 90715

REFERENCES

1. Centers for Disease Control. Diphtheria, tetanus, and pertussis: Recommendations for vaccine use and other preventive measures — Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR* 1991;40(RR-10):1-28. **2.** Wassilak SGF, Roper MH, Murphy TV and Orenstein WA. Tetanus Toxoid. In: Plotkin SA and Orenstein WA, eds. *Vaccines.* 4th ed. Philadelphia, PA: Saunders Press; 2003:745-781. **3.** Department of Health and Human Services, Food and Drug Administration. Biological products; Bacterial vaccines and toxoids; Implementation of efficacy review; Proposed rule. *Federal Register* December 13, 1985;50(240):51002-51117. **4.** Centers for Disease Control and Prevention. General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). *MMWR* 2002;51(RR-2):1-35. **5.** Wharton M and Vitek CR. Diphtheria Toxoid. In: Plotkin SA and Orenstein WA, eds. *Vaccines.* 4th ed. Philadelphia, PA: Saunders Press; 2003:211-218. **6.** Schmitt H-J, von König CHW, Neiss A, et al. Efficacy of acellular pertussis vaccine in early childhood after household exposure. *JAMA* 1996;275(1):37-41. **7.** Greco D, Salmaso S, Mastrantonio P, et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. *N Engl J Med* 1996;334(6):341-348. **8.** Centers for Disease Control and Prevention. Pertussis vaccination: Use of acellular pertussis vaccines among infants and young children — Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1997;46(RR-7):1-25. **9.** Centers for Disease Control and Prevention. Update: Vaccine side effects, adverse reactions, contraindications, and precautions — Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1996;45(RR-12):1-35. **10.** Centers for Disease Control and Prevention. Use of vaccines and immune globulins in persons with altered immunocompetence: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1993;42(RR-4):1-18. **11.** Institute of Medicine (IOM). Stratton KR, Howe CJ, Johnston RB, eds. *Adverse events associated with childhood vaccines. Evidence bearing on causality.* Washington, DC: National Academy Press; 1994. **12.** Centers for Disease Control. National Childhood Vaccine Injury Act: Requirements for permanent vaccination records and for reporting of selected events after vaccination. *MMWR* 1988;37(13):197-200. **13.** National Vaccine Injury Compensation Program: Vaccine injury table. www.hrsa.gov/osp/vicp/table.htm. Accessed April 14, 2005.

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