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)
Suspension for Intramuscular Injection
Initial U.S. Approval: 2005

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

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

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

A single intramuscular injection (0.5 mL). (2.2)

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

Single-dose vials and prefilled syringes containing a 0.5-mL suspension for injection. (3)

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

- Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any tetanus toxoid-, diphtheria toxoid-, or pertussis antigen-containing vaccine or 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----------

- The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions. (5.1)
- If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk of Guillain-Barré syndrome may be increased following a subsequent dose of tetanus toxoid-containing vaccine, including BOOSTRIX. (5.2)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including BOOSTRIX. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.3)
- Progressive or unstable neurologic conditions are reasons to defer vaccination with a pertussis-containing vaccine, including BOOSTRIX. (5.4)
- 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. (5.5)

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

- Common solicited adverse events (≥15%) in adolescents (10 to 18 years of age) 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 (19 to 64 years of age) were pain, redness, and swelling at the injection site, headache, fatigue, and gastrointestinal symptoms. (6.1)
- The most common solicited adverse event (≥15%) in the elderly (65 years of age and older) was pain at the injection site. (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----------

- In subjects 11 to 18 years of age, lower levels for antibodies to pertactin were observed when BOOSTRIX was administered concomitantly with meningococcal conjugate vaccine (serogroups A, C, Y, and W-135) as compared with BOOSTRIX administered first. (7.1)
- In subjects 19 to 64 years of age, lower levels for antibodies to FHA and pertactin were observed when BOOSTRIX was administered concomitantly with an inactivated influenza vaccine as compared with 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. (8.1)
- Register women who receive BOOSTRIX while pregnant in the pregnancy registry by calling 1-888-452-9622. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: xx/xxxx

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. BOOSTRIX is approved for use as a single dose in individuals 10 years of age and older.

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. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

For the prefilled syringes, attach a sterile needle and administer intramuscularly.

For the vials, use a sterile needle and sterile syringe to withdraw the 0.5-mL dose and administer intramuscularly. Changing needles between drawing vaccine from a vial and injecting it into a recipient is not necessary unless the needle has been damaged or contaminated. Use a separate sterile needle and syringe for each individual.

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

2.2 Dose and Schedule

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

If tetanus prophylaxis is needed for wound management, BOOSTRIX may be given if no previous dose of any Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Tdap) has been administered.

3 DOSAGE FORMS AND STRENGTHS

BOOSTRIX is a suspension for injection available in 0.5-mL single-dose vials and prefilled TIP-LOK® syringes.

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 *[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.

5 WARNINGS AND PRECAUTIONS

5.1 Latex

The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions.

5.2 Guillain-Barré Syndrome and Brachial Neuritis

If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk of Guillain-Barré syndrome may be increased following a subsequent dose of tetanus toxoid-containing vaccine, including BOOSTRIX. 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.[1]

5.3 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including BOOSTRIX. Syncope can be accompanied by transient neurological signs such as visual

disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

5.4 Progressive or Unstable Neurologic Disorders

Progressive or unstable neurologic conditions (e.g., cerebrovascular events and acute encephalopathic conditions) are reasons to defer vaccination with a pertussis-containing vaccine, including BOOSTRIX. It is not known whether administration of BOOSTRIX to persons with an unstable or progressive neurologic disorder might hasten manifestations of the disorder or affect the prognosis. Administration of BOOSTRIX to persons with an unstable or progressive neurologic disorder may result in diagnostic confusion between manifestations of the underlying illness and possible adverse effects of vaccination.

5.5 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.

5.6 Altered Immunocompetence

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

5.7 Prevention and Management of Acute Allergic 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 with 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, 4,949 adolescents (10 to 18 years of age) and 4,076 adults (19 years of age and older) were vaccinated with a single dose of BOOSTRIX. Of these adolescents, 1,341 were vaccinated with BOOSTRIX in a coadministration study with meningococcal conjugate vaccine *[see Drug Interactions (7.1), Clinical Studies (14.5)]*. Of these adults, 1,104 were 65 years of age

and older *[see Clinical Studies (14.4)]*. A total of 860 adults 19 years of age and older received concomitant vaccination with BOOSTRIX and influenza vaccines in a coadministration study *[see Drug Interactions (7.1), Clinical Studies (14.5)]*. 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 comparator Td vaccine, manufactured by MassBioLogics. There were no substantive differences in demographic characteristics between the vaccine groups. Among BOOSTRIX and comparator 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.

The US adult (19 to 64 years of age) study, a randomized, observer-blinded study, evaluated the safety of BOOSTRIX (N = 1,522) compared with ADACEL® (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed) (N = 762), a Tdap vaccine manufactured by Sanofi Pasteur SA. Vaccines were administered as a single dose. 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.

The US elderly (65 years of age and older) study, a randomized, observer-blinded study,

evaluated the safety of BOOSTRIX (N = 887) compared with DECAVAC® (Tetanus and Diphtheria Toxoids Adsorbed) (N = 445), a US-licensed Td vaccine, manufactured by Sanofi Pasteur SA. Vaccines were administered as a single dose. Among all vaccine recipients, the mean age was approximately 72 years; 54% were female and 95% were white. Subjects were monitored for solicited adverse events using standardized diary cards (Day 0-3). 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. Approximately 99% of subjects completed the 6-month follow-up evaluation.

Solicited Adverse Events in the US Adolescent 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[a] Post-vaccination Period in Adolescents 10 to 18 Years of Age (Total Vaccinated Cohort)

	BOOSTRIX (N = 3,032) %	Td (N = 1,013) %
Local		
Pain, any[b]	75.3	71.7
Pain, Grade 2 or 3[b]	51.2	42.5
Pain, Grade 3[c]	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[d]	28.3	29.5
Arm circumference increase, >20 mm[d]	2.0	2.2
Arm circumference increase, >40 mm[d]	0.5	0.3
General		
Headache, any	43.1	41.5
Headache, Grade 2 or 3[b]	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[e]	26.0	25.8
Gastrointestinal symptoms, Grade 2 or 3[e]	9.8	9.7
Gastrointestinal symptoms, Grade 3[e]	3.0	3.2
Fever, ≥99.5°F (37.5°C)[f]	13.5	13.1
Fever, >100.4°F (38.0°C)[f]	5.0	4.7
Fever, >102.2°F (39.0°C)[f]	1.4	1.0

Td = Tetanus and Diphtheria Toxoids Adsorbed For Adult Use manufactured by MassBioLogics.
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.

[a] Day of vaccination and the next 14 days.
[b] Statistically significantly higher (P <0.05) following BOOSTRIX as compared with Td vaccine.
[c] 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%).
[d] Mid-upper region of the vaccinated arm.
[e] Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.
[f] Oral temperatures or axillary temperatures.

Unsolicited Adverse Events in the US Adolescent 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 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[a] Post-vaccination Period following Administration of BOOSTRIX in Adolescents 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)[b]	8.8
Fever, >100.4°F (38.0°C)[b]	4.1
Fever, >102.2°F (39.0°C)[b]	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.
[a] Day of vaccination and the next 14 days.
[b] Oral temperatures or axillary temperatures.

Solicited Adverse Events in the US Adult (19 to 64 Years of Age) 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[a] Post-vaccination Period in Adults 19 to 64 Years of Age (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		
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[b]	15.9	17.5
Gastrointestinal symptoms, Grade 2 or 3[b]	4.3	5.7
Gastrointestinal symptoms, Grade 3[b]	1.2	1.3
Fever, ≥99.5°F (37.5°C)[c]	5.5	8.0
Fever, >100.4°F (38.0°C)[c]	1.0	1.5
Fever, >102.2°F (39.0°C)[c]	0.1	0.4

Tdap = Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed, a 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.

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

[b] Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

[c] Oral temperatures.

Unsolicited Adverse Events in the US Adult (19 to 64 Years of Age) 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).

Solicited Adverse Events in the US Elderly (65 Years of Age and Older) Study

Table 4 presents solicited local adverse reactions and general adverse events within 4 days of vaccination with BOOSTRIX or the comparator Td vaccine for the total vaccinated cohort.

Table 4. Rates of Solicited Local Adverse Reactions or General Adverse Events within 4 Days[a] of Vaccination in the Elderly 65 Years of Age and Older (Total Vaccinated Cohort)

	BOOSTRIX %	**Td %**
Local	**(N = 882)**	**(N = 444)**
Pain, any	21.5	27.7
Pain, Grade 2 or 3	7.5	10.1
Pain, Grade 3	0.2	0.7
Redness, any	10.8	12.6
Redness, >20 mm	1.4	2.5
Redness, ≥50 mm	0.6	0.9
Swelling, any	7.5	11.7
Swelling, >20 mm	2.2	3.4
Swelling, ≥50 mm	0.7	0.7
General	**(N = 882)**	**(N = 445)**
Fatigue, any	12.5	14.8
Fatigue, Grade 2 or 3	2.5	2.9
Fatigue, Grade 3	0.7	0.7
Headache, any	11.5	11.7
Headache, Grade 2 or 3	1.9	2.2
Headache, Grade 3	0.6	0.0
Gastrointestinal symptoms, any[b]	7.6	9.2
Gastrointestinal symptoms, Grade 2 or 3[b]	1.7	1.8
Gastrointestinal symptoms, Grade 3[b]	0.3	0.4
Fever, ≥99.5°F (37.5°C)[c]	2.0	2.5
Fever, >100.4°F (38.0°C)[c]	0.2	0.2
Fever, >102.2°F (39.0°C)[c]	0.0	0.0

Td = Tetanus and Diphtheria Toxoids Adsorbed, a US-licensed Td vaccine, manufactured by Sanofi Pasteur SA.

N = Number of subjects with a documented dose.

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

Grade 3 = Local/General: prevented normal activity.

[a] Day of vaccination and the next 3 days.

[b] Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

[c] Oral temperatures.

Unsolicited Adverse Events in the US Elderly (65 Years of Age and Older) Study

The incidence of unsolicited adverse events reported in the 31 days after vaccination was comparable between the 2 groups (17.1% and 14.4% for BOOSTRIX and Td 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 (19 to 64 years of age) 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. In the US elderly (65 years of age and older) study, serious adverse events were reported to occur by 0.7% and 0.9% of subjects who received BOOSTRIX and the comparator Td vaccine, respectively, during the 31-day period after vaccination. Serious adverse events were reported to occur by 4.2% and 2.2% of subjects who received BOOSTRIX and the comparator Td vaccine, respectively, during the 6-month period after vaccination.

Concomitant Vaccination with Meningococcal Conjugate Vaccine in Adolescents

In a randomized study in the US, 1,341 adolescents (11 to 18 years of age) received either BOOSTRIX administered concomitantly with MENACTRA® (Meningococcal (Groups A, C, Y, and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine), (Sanofi Pasteur SA), or each vaccine administered separately 1 month apart *[see Drug Interactions (7.1), Clinical Studies (14.5)]*. Safety was evaluated in 446 subjects who received BOOSTRIX administered concomitantly with meningococcal conjugate vaccine at different injection sites, 446 subjects who received BOOSTRIX followed by meningococcal conjugate vaccine 1 month later, and 449 subjects who received meningococcal conjugate vaccine followed by BOOSTRIX 1 month later. Solicited local adverse reactions and general adverse events were recorded on diary cards for 4 days (Day 0-3) following each vaccination. Unsolicited adverse events were monitored for the 31-day period following each vaccination (Day 0-30). Table 5 presents the percentages of subjects experiencing local reactions at the injection site for BOOSTRIX and solicited general events following BOOSTRIX. The incidence of unsolicited adverse events reported in the 31 days after any vaccination was similar following each dose of BOOSTRIX in all cohorts.

Table 5. Rates of Solicited Local Adverse Reactions or General Adverse Events Reported within the 4-Day Post-vaccination Period following Administration of BOOSTRIX in Individuals 11 to 18 Years of Age (Total Vaccinated Cohort)

	BOOSTRIX+MCV4[a] (N = 441) %	BOOSTRIX→MCV4[b] (N = 432-433) %	MCV4→BOOSTRIX[c] (N = 441) %
Local (at injection site for BOOSTRIX)			
Pain, any	70.1	70.4	47.8
Redness, any	22.7	25.7	17.9
Swelling, any	17.7	18.1	12.0
General (following administration of BOOSTRIX)			
Fatigue	34.0	32.1	20.4
Headache	34.0	30.7	17.0
Gastrointestinal symptoms[d]	15.2	14.5	7.7
Fever, ≥99.5°F (37.5°C)[e]	5.2	3.5	2.3

MCV4 = MENACTRA (Meningococcal (Groups A, C, Y, and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine), Sanofi Pasteur SA.

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

[a] BOOSTRIX+MCV4 = Concomitant vaccination with BOOSTRIX and MENACTRA.

[b] BOOSTRIX→MCV4 = BOOSTRIX followed by MCV4 1 month later.

[c] MCV4→BOOSTRIX = MCV4 followed by BOOSTRIX 1 month later.

[d] Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

[e] Oral temperatures.

6.2 Postmarketing Experience

In addition to reports in clinical trials, worldwide voluntary reports of adverse events received for BOOSTRIX in persons 10 years of age and older since market introduction of this vaccine are listed below. This list includes serious events or events that 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.

Immune System Disorders

Allergic reactions, including anaphylactic and anaphylactoid reactions.

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, injection site reaction.

Musculoskeletal and Connective Tissue Disorders

Arthralgia, back pain, myalgia.

Nervous System Disorders

Convulsions (with and without fever), encephalitis, facial palsy, loss of consciousness, paraesthesia, syncope.

Skin and Subcutaneous Tissue Disorders

Angioedema, exanthem, Henoch-Schönlein purpura, rash, urticaria.

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administration

BOOSTRIX was administered concomitantly with MENACTRA in a clinical study of subjects 11 to 18 years of age *[see Clinical Studies (14.5)]*. Post-vaccination geometric mean antibody concentrations (GMCs) to pertactin were lower following BOOSTRIX administered concomitantly with meningococcal conjugate vaccine compared with BOOSTRIX administered first. It is not known if the efficacy of BOOSTRIX is affected by the reduced response to pertactin.

BOOSTRIX was administered concomitantly with FLUARIX® (Influenza Virus Vaccine) in a clinical study of subjects 19 to 64 years of age *[see Clinical Studies (14.5)]*. Lower 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. It is not known if the efficacy of BOOSTRIX is affected by the reduced response to FHA and pertactin.

When BOOSTRIX is administered concomitantly with other injectable vaccines or Tetanus Immune Globulin, 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.

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 B

A developmental toxicity study has been performed in female rats at a dose approximately 40 times the human dose (on a mL/kg basis) and revealed no evidence of harm to the fetus due to BOOSTRIX. Animal fertility studies have not been conducted with BOOSTRIX. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, BOOSTRIX should be given to a pregnant woman only if clearly needed.

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 by intramuscular injection once prior to gestation and BOOSTRIX by intramuscular injection during the period of organogenesis (gestation Days 6, 8, 11, and 15), 0.1 mL/rat/occasion (approximately 40-fold excess relative to the projected human dose of BOOSTRIX on a body weight basis). The antigens in INFANRIX are the same as those in BOOSTRIX, but INFANRIX is formulated with higher quantities of these antigens. No adverse effects on pregnancy, parturition, lactation parameters, and embryo-fetal or pre-weaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis.

Pregnancy Registry

GlaxoSmithKline maintains a surveillance registry to collect data on pregnancy outcomes and newborn health status outcomes following vaccination with BOOSTRIX during pregnancy. Women who receive BOOSTRIX during pregnancy should be encouraged to contact GlaxoSmithKline directly or their healthcare provider should contact GlaxoSmithKline by calling 1-888-452-9622.

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

In clinical trials, 1,104 subjects 65 years of age and older received BOOSTRIX; of these subjects, 299 were 75 years of age and older. In the US elderly (65 years and older) study, immune responses to tetanus and diphtheria toxoids following BOOSTRIX were non-inferior to the comparator Td vaccine. Antibody responses to pertussis antigens following a single dose of

BOOSTRIX in the elderly were non-inferior to those observed with INFANRIX administered as a 3-dose series in infants *[see Clinical Studies (14.4)]*. Solicited adverse events following BOOSTRIX were similar in frequency to those reported with the comparator Td vaccine *[see Adverse Reactions (6.1)]*.

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 contains aluminum hydroxide as adjuvant (not more than 0.39 mg aluminum by assay), 4.5 mg of sodium chloride, ≤100 mcg of residual formaldehyde, and ≤100 mcg of polysorbate 80 (Tween 80).

BOOSTRIX is available in vials and prefilled syringes. The tip caps of the prefilled syringes contain natural rubber latex; the plungers are not made with natural rubber latex. The vial stoppers are not made with natural rubber latex.

BOOSTRIX is formulated without preservatives.

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.[2] A level ≥0.1 IU/mL by ELISA has been considered as protective.

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, measured by neutralization assays, is the lowest level giving some degree of protection; a level of 0.1 IU/mL by ELISA is regarded as protective.[3] Diphtheria antitoxin levels ≥1.0 IU/mL by ELISA have been associated with long-term protection.[3]

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 with 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: white 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 6. One month after a single dose, anti-tetanus and anti-diphtheria seroprotective rates (≥0.1 IU/mL by ELISA) and booster response rates were comparable between BOOSTRIX and the comparator Td vaccine.

Table 6. Antibody Responses to Tetanus and Diphtheria Toxoids following BOOSTRIX Compared with Td Vaccine in Adolescents 10 to 18 Years of Age (ATP Cohort for Immunogenicity)

	N	% ≥0.1 IU/mL[a] (95% CI)	% ≥1.0 IU/mL[a] (95% CI)	% Booster Response[b] (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)[c]	99.5 (99.1, 99.7)[d]	89.7 (88.4, 90.8)[c]
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)[c]	97.3 (96.6, 97.9)[d]	90.6 (89.4, 91.7)[c]
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 MassBioLogics.

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

[a] Measured by ELISA.

[b] 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.

[c] 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%).

[d] 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 7. 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 7. Booster Responses to the Pertussis Antigens following BOOSTRIX in Adolescents 10 to 18 Years of Age (ATP Cohort for Immunogenicity)

	N	BOOSTRIX % Booster Response[a] (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.

[a] 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 to 2,979) were compared with the GMCs observed in infants following a 3-dose primary series of INFANRIX administered at 3, 4, and 5 months of age (N = 631 to 2,884). Table 8 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 observed in adolescents 1 month after a single dose of BOOSTRIX were non-inferior to those observed in infants following a primary vaccination series with INFANRIX.

Table 8. Ratio of GMCs to Pertussis Antigens following One Dose of BOOSTRIX in Adolescents 10 to 18 Years of Age 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)[a]
Anti-FHA	7.35 (6.85, 7.89)[a]
Anti-pertactin	4.19 (3.73, 4.71)[a]

GMC = Geometric mean antibody concentration, measured in 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.

[a] 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 (19 to 64 Years of Age)

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 to subjects (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 white, 8% black, 1% Asian, and 7% were of other racial/ethnic groups.

Response to Tetanus and Diphtheria Toxoids

The antibody responses to the tetanus and diphtheria toxoids of BOOSTRIX compared with the comparator Tdap vaccine are shown in Table 9. One month after a single dose, anti-tetanus and anti-diphtheria seroprotective rates (≥0.1 IU/mL by ELISA) were comparable between BOOSTRIX and the comparator Tdap vaccine.

Table 9. Antibody Responses to Tetanus and Diphtheria Toxoids following One Dose of BOOSTRIX Compared with the Comparator Tdap Vaccine in Adults 19 to 64 Years of Age (ATP Cohort for Immunogenicity)

	N	% ≥0.1 IU/mL[a] (95% CI)	% ≥1.0 IU/mL[a] (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)[b]	98.3 (97.5, 98.9)[b]
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)[b]	87.9 (86.1, 89.5)[c]
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.

[a] Measured by ELISA.

[b] 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%).

[c] Non-inferiority criteria not prospectively defined for this endpoint.

Response to Pertussis Antigens

Booster response rates to the pertussis antigens are shown in Table 10. 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 10. Booster Responses to the Pertussis Antigens following One Dose of BOOSTRIX in Adults 19 to 64 Years of Age (ATP Cohort for Immunogenicity)

	N	BOOSTRIX % Booster Response[a] (95% CI)
Anti-PT	1,419	77.2 (74.9, 79.3)[b]
Anti-FHA	1,433	96.9 (95.8, 97.7)[c]
Anti-pertactin	1,441	93.2 (91.8, 94.4)[c]

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

[a] 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.

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

[c] 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 (19 to 64 years of age) study were compared with the GMCs observed in infants following a 3-dose primary series of INFANRIX administered at 3, 4, and 5 months of age. Table 11 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 observed in adults 1 month after a single dose of BOOSTRIX were non-inferior to those observed in infants following a primary vaccination series with INFANRIX.

Table 11. Ratio of GMCs to Pertussis Antigens following One Dose of BOOSTRIX in Adults 19 to 64 Years of Age 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)[a]
Anti-FHA	7.46 (6.86, 8.12)[a]
Anti-pertactin	3.56 (3.10, 4.08)[a]

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.
[a] BOOSTRIX was non-inferior to INFANRIX (lower limit of 95% CI for the GMC ratio of BOOSTRIX/INFANRIX ≥0.67).

14.4 Immunological Evaluation in the Elderly (65 Years of Age and Older)

The US elderly (65 years of age and older) study, a randomized, observer-blinded study, evaluated the immunogenicity of BOOSTRIX (N = 887) compared with a US-licensed comparator Td vaccine (N = 445) (Sanofi Pasteur SA). Vaccines were administered as a single dose to subjects who had not received a tetanus-diphtheria booster within 5 years. Among all vaccine recipients, the mean age was approximately 72 years of age; 54% were female and 95% were white. The immune responses to each of the antigens contained in BOOSTRIX were evaluated in sera obtained approximately 1 month after administration.

Response to Tetanus and Diphtheria Toxoids and Pertussis Antigens

Immune responses to tetanus and diphtheria toxoids and pertussis antigens were measured 1 month after administration of a single dose of BOOSTRIX or a comparator Td vaccine. Anti-tetanus and anti-diphtheria seroprotective rates (≥0.1 IU/mL) were comparable between BOOSTRIX and the comparator Td vaccine (Table 12).

Table 12. Immune Responses to Tetanus and Diphtheria Toxoids following BOOSTRIX or Comparator Td Vaccine in the Elderly 65 Years of Age and Older (ATP Cohort for Immunogenicity)

	BOOSTRIX	Td
	(N = 844-864)	(N = 430-439)
Anti-tetanus		
% ≥0.1 IU/mL (95% CI)	96.8 (95.4, 97.8)[a]	97.5 (95.6, 98.7)
% ≥1.0 IU/mL (95% CI)	88.8 (86.5, 90.8)[a]	90.0 (86.8, 92.6)
Anti-diphtheria		
% ≥0.1 IU/mL (95% CI)	84.9 (82.3, 87.2)[a]	86.6 (83.0, 89.6)
% ≥1.0 IU/mL (95% CI)	52.0 (48.6, 55.4)[b]	51.2 (46.3, 56.0)

Td = Tetanus and Diphtheria Toxoids Adsorbed, a US-licensed Td vaccine, manufactured by Sanofi Pasteur SA.

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

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

[b] Non-inferiority criteria not prospectively defined for this endpoint.

The GMCs to each of the pertussis antigens 1 month following a single dose of BOOSTRIX 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 13 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 in the elderly (65 years of age and older) 1 month after a single dose of BOOSTRIX were non-inferior to those of infants following a primary vaccination series with INFANRIX.

Table 13. Ratio of GMCs to Pertussis Antigens following One Dose of BOOSTRIX in the Elderly 65 Years of Age and Older Compared with 3 Doses of INFANRIX in Infants (Total Immunogenicity Cohort)

	GMC Ratio: BOOSTRIX/INFANRIX (95% CI)
Anti-PT	1.07 (1.00, 1.15)[a]
Anti-FHA	8.24 (7.45, 9.12)[a]
Anti-pertactin	0.93 (0.79, 1.10)[a]

GMC = Geometric mean antibody concentration; CI = Confidence Interval.
Number of subjects for BOOSTRIX GMC evaluation: Anti-PT = 865, anti-FHA = 847, and anti-pertactin = 878.
Number of subjects for INFANRIX GMC evaluation: Anti-PT = 2,884, anti-FHA = 685, and anti-pertactin = 631.
[a] BOOSTRIX was non-inferior to INFANRIX (lower limit of 95% CI for the GMC ratio of BOOSTRIX/INFANRIX ≥0.67).

14.5 Concomitant Vaccine Administration

Concomitant Administration with Meningococcal Conjugate Vaccine

The concomitant use of BOOSTRIX and a tetravalent meningococcal (groups A, C, Y, and W-135) conjugate vaccine (Sanofi Pasteur SA) was evaluated in a randomized study in healthy adolescents 11 to 18 years of age. A total of 1,341 adolescents were vaccinated with BOOSTRIX. Of these, 446 subjects received BOOSTRIX administered concomitantly with meningococcal conjugate vaccine at different injection sites, 446 subjects received BOOSTRIX followed by meningococcal conjugate vaccine 1 month later, and 449 subjects received meningococcal conjugate vaccine followed by BOOSTRIX 1 month later.

Immune responses to diphtheria and tetanus toxoids (% of subjects with anti-tetanus and anti-diphtheria antibodies ≥1.0 IU/mL by ELISA), pertussis antigens (booster responses and GMCs), and meningococcal antigens (vaccine responses) were measured 1 month (range: 30 to 48 days) after concomitant or separate administration of BOOSTRIX and meningococcal conjugate vaccine. For BOOSTRIX given concomitantly with meningococcal conjugate vaccine compared with BOOSTRIX administered first, non-inferiority was demonstrated for all antigens, with the exception of the anti-pertactin GMC. The lower limit of the 95% CI for the GMC ratio was 0.54 for anti-pertactin (pre-specified limit ≥0.67). For the anti-pertactin booster response, non-inferiority was demonstrated. It is not known if the efficacy of BOOSTRIX is affected by the reduced response to pertactin.

There was no evidence that BOOSTRIX interfered with the antibody responses to the meningococcal antigens when measured by serum bactericidal assays (rSBA) when given concomitantly or sequentially (meningococcal conjugate vaccine followed by BOOSTRIX or BOOSTRIX followed by meningococcal conjugate vaccine).

Concomitant Administration with FLUARIX (Influenza Virus Vaccine)

The concomitant use of BOOSTRIX and FLUARIX was evaluated in a multicenter, open-label, randomized, controlled study of 1,497 adults 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. It is not known if the efficacy of BOOSTRIX is affected by the reduced response to FHA and pertactin.

15 REFERENCES

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3. Vitek CR and Wharton M. Diphtheria Toxoid. In: Plotkin SA, Orenstein WA, and Offit PA, eds. *Vaccines.* 5th ed. Saunders; 2008:139-156.

16 HOW SUPPLIED/STORAGE AND HANDLING

BOOSTRIX is available in 0.5-mL single-dose vials and disposable prefilled TIP-LOK syringes (packaged without needles):

NDC 58160-842-01 Vial in Package of 10: NDC 58160-842-11

NDC 58160-842-05 Syringe in Package of 1: NDC 58160-842-34

NDC 58160-842-43 Syringe in Package of 10: NDC 58160-842-52

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

17 PATIENT COUNSELING INFORMATION

The patient, parent, or guardian should be:

- informed of the potential benefits and risks of immunization with BOOSTRIX.
- informed about the potential for adverse reactions that have been temporally associated with administration of BOOSTRIX or other vaccines containing similar components.
- instructed to report any adverse events to their healthcare provider.
- informed that safety and efficacy have not been established in pregnant women. Register women who receive BOOSTRIX while pregnant in the pregnancy registry by calling 1-888-452-9622.
- 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/vaccines).

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Novartis Vaccines and Diagnostics GmbH

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