HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TENIVAC safely and effectively. See full prescribing information for TENIVAC. TENIVAC (Tetanus and Diphtheria Toxoids Adsorbed) Suspension for Intramuscular Injection Initial US Approval: 2003

INDICATIONS AND USAGE
• TENIVAC is a vaccine indicated for active immunization for the prevention of tetanus and diphtheria in persons 7 years of age and older. (1)

DOSE AND ADMINISTRATION
• Each 0.5 mL dose should be administered intramuscularly. (2.5)
• Primary immunization with TENIVAC consists of 3 doses. The first 2 doses are administered 2 months apart and the third dose is administered 6-8 months after the second dose. (2.1)
• TENIVAC may be used for booster immunization against tetanus and diphtheria. Routine booster immunization against tetanus and diphtheria is recommended at 11-12 years of age and every 10 years thereafter. (2.2)
• For post-exposure diphtheria prophylaxis and for management of a tetanus prone wound, a booster dose of TENIVAC may be administered if at least 5 years have elapsed since previous receipt of a diphtheria toxoid and tetanus toxoid containing vaccine. (2.3) (2.4)

DOSE FORMS AND STRENGTHS
• Suspension for injection supplied in 0.5 mL single-dose vials or syringes. (3)

CONTRAINDICATIONS
• Severe allergic reaction (e.g., anaphylaxis) to a previous dose of TENIVAC, or any other tetanus or diphtheria toxoid-containing vaccine, or any component of this vaccine. (4.1)

WARNINGS AND PRECAUTIONS
• The tip caps of the prefilled syringes may contain natural rubber latex which may cause allergic reactions in latex sensitive individuals. (5.2)
• More frequent administration of TENIVAC than described in Dosage and Administration (2.1, 2.2, 2.3, 2.4) may be associated with increased incidence and severity of adverse reactions. (5.3)

ADVERSE REACTIONS
• Persons who experienced an Arthus-type hypersensitivity reaction following a prior dose of a tetanus toxoid-containing vaccine should not receive TENIVAC more frequently than every 10 years, even for tetanus prophylaxis as part of wound management. (5.4)
• Carefully consider benefits and risks before administering TENIVAC to persons with a history of Guillain-Barré syndrome within 6 weeks of a previous tetanus toxoid-containing vaccine. (5.5)

WARNINGS AND PRECAUTIONS
• The most frequent solicited injection site reaction within 0-3 days following TENIVAC was pain, reported in 78.3% of study participants 11-59 years of age and 35.3% of participants ≥60 years of age. (6.1)
• The most frequent solicited systemic reaction within 0-3 days following TENIVAC was headache, reported in 17.9% of participants, overall. (6.1)
• Other common (≥10%) solicited adverse reactions within 0-3 days following TENIVAC were injection site redness, injection site swelling, malaise, muscle weakness and pain in joints. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1 800 822-7967 or http://vaers.hhs.gov

DRUG INTERACTIONS
• No safety and immunogenicity data are available on the concomitant administration of TENIVAC with other US licensed vaccines. (7.1)
• If passive protection against tetanus is required, Tetanus Immune Globulin (TIG) (Human) may be administered concomitantly at a separate site with a separate needle and syringe. (7.2)
• Immunosuppressive therapies may reduce the immune response to TENIVAC. (7.3)

USE IN SPECIFIC POPULATIONS
Pre- and post-vaccination tetanus and diphtheria seroprotection rates were lower in study participants ≥65 years of age compared to younger participants. In general, rates of solicited adverse reactions were not higher in participants ≥65 years of age compared to younger participants. (8.5)

See 17 PATIENT COUNSELING INFORMATION
Revised: [April 2013]

FULL PRESCRIBING INFORMATION: CONTENTS*
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 Primary Immunization
  2.2 Routine Booster Immunization
  2.3 Diphtheria Prophylaxis for Case Contacts
  2.4 Tetanus Prophylaxis in Wound Management
  2.5 Administration
3 DOSE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
  4.1 Hypersensitivity
5 WARNINGS AND PRECAUTIONS
  5.1 Management of Acute Allergic Reactions
  5.2 Latex
  5.3 Frequency of Administration
  5.4 Arthus Reactions
  5.5 Guillain-Barré Syndrome and Brachial Neuritis
  5.6 Limitations of Vaccine Effectiveness
  5.7 Altered Immunocompetence
6 ADVERSE REACTIONS
  6.1 Data from Clinical Studies
  6.2 Data from Post-marketing Experience
7 DRUG INTERACTIONS
  7.1 Concomitant Vaccine Administration
  7.2 Tetanus Immune Globulin (Human)
  7.3 Immunosuppressive Treatments
8 USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy
  8.3 Nursing Mothers
  8.4 Pediatric Use
  8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
  12.1 Mechanism of Action
13 NONCLINICAL TOXICOLOGY
  13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
  14.1 Primary Immunization
  14.2 Booster Immunization
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.
Because of uncertainty as to which component of the vaccine may be responsible, none of the components should be administered. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are to be considered.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Epinephrine hydrochloride solution (1:1,000) and other appropriate agents and equipment must be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs.

5.2 Latex

The tip caps of the TENVAC prefilled syringes may contain natural rubber latex, which may cause allergic reactions in latex sensitive individuals.

5.3 Frequency of Administration

More frequent doses of TENVAC vaccine than described in Section 2, Dosage and Administration, may be associated with increased incidence and severity of adverse reactions. [See Dosage and Administration (2.1, 2.2, 2.3, 2.4)]

5.4 Arthus Reactions

Persons who experienced an Arthus-type hypersensitivity reaction following a prior dose of a tetanus toxoid-containing vaccine usually have high serum tetanus antitoxin levels and should not receive TENVAC vaccine more frequently than every 10 years, even for tetanus prophylaxis as part of wound management.

5.5 Guillain-Barré Syndrome and Brachial Neuritis

A review by the Institute of Medicine found evidence for a causal relation between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome. (2) If Guillain-Barré syndrome occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give TENVAC vaccine or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks.

5.6 Limitations of Vaccine Effectiveness

Vaccination with TENVAC vaccine may not protect all individuals.

5.7 Altered Immunocompetence

If TENVAC vaccine is administered to immunocompromised persons, including persons receiving immunosuppressive therapy, the expected immune response may not be obtained. [See Drug Interactions (7.3)]

6 ADVERSE REACTIONS

6.1 Data from Clinical Studies

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events.

In a primary immunization study conducted in Canada, 18 participants, 8 of whom were 6 to 9 years of age and 10 of whom were 17 to 56 years of age, received three doses of TENVAC vaccine. In four booster immunization studies conducted in either the US or Canada, TENVAC vaccine was administered to 3,723 participants overall, ranging in age from 11 to 93 years.

In one of these studies, a US multi-center booster immunization study (TDC01), 2,250 adolescents and adults ages 11-59 years of age received TENVAC vaccine in an open-label design and adults 60 years of age and over were randomized to receive either TENVAC vaccine (N = 700) or DECAVAC vaccine (US licensed Td manufactured by Sanofi Pasteur Inc.) (N = 701). Vaccine assignment for participants ≥60 years of age was unblinded to pharmacists and vaccination nurses, but was blinded to other study personnel and participants. Among participants who received TENVAC vaccine, overall, 80.4% were Caucasian, 3.3% Black, 5.1% Hispanic, 4.5% Asian and 6.6% other races. Among participants ≥60 years of age, the racial distribution was similar for the TENVAC vaccine and DECAVAC vaccine groups. Among participants who received TENVAC vaccine, the proportion of participants who were female varied by age group (44.4% of participants 11-18 years of age, 70.1% of participants 19-59 years of age and 62.4% of participants ≥60 years of age). Among participants ≥60 years of age who received DECACV vaccine, 57.6% were female. Nearly all (99.8%) enrolled participants and all participants in the per-protocol immunogenicity population had a reported or documented history of previous immunization against tetanus and diphtheria and, by report, had not received a vaccine containing tetanus or diphtheria toxoid within 5 years prior to enrollment.

In the US multi-center booster immunization study, solicited injection site reactions and systemic adverse events were monitored on diary cards for a subset of participants 11-59 years of age and for all participants ≥60 years of age. The incidence and severity of solicited injection site reactions and selected solicited systemic adverse events that occurred within 3 days following vaccination are shown in Table 2.
General disorders and administration site conditions

Injection site reactions (including inflammation, mass, edema, induration, warmth, pruritus, cellulitis, discomfort)

Fatigue, edema peripheral

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administration

No safety and immunogenicity data are available on the concomitant administration of TENIVAC vaccine with other US licensed vaccines.

7.2 Tetanus Immune Globulin (Human)

If passive protection against tetanus is required, TIG (Human) may be administered according to its prescribing information, concomitantly with TENIVAC vaccine at a separate site with a separate needle and syringe. [See Dosage and Administration (2.4)].

7.3 Immunosuppressive Treatments

Immunosuppressive therapies, including irradiation, antimitobolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to TENIVAC vaccine. [See Warnings and Precautions (5.7)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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

Animal fertility studies have not been conducted with TENIVAC vaccine. The effect of TENIVAC vaccine on embryo-fetal and pre-weaning development was evaluated in one developmental toxicity study using pregnant rabbits. Animals were administered TENIVAC vaccine twice prior to gestation, during the period of organogenesis (gestation day 6) and later during pregnancy on gestation day 29, 0.5 mL/rabbit/occasion (a 17-fold increase compared to the human dose of TENIVAC vaccine on a body weight basis), by intramuscular injection. No adverse effects on pregnancy, parturition, lactation, embryo-fetal or pre-weaning development were observed. There were no vaccine related fetal malformations or other evidence of teratogenesis noted in this study.

8.3 Nursing Mothers

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

8.4 Pediatric Use

TENIVAC vaccine is not approved for use in infants and children younger than 7 years of age. Safety and effectiveness of TENIVAC vaccine in this age group have not been established.

8.5 Geriatric Use

In one clinical study, (TDCC1) 449 participants 65 years of age and over, including 192 participants who were 75 years of age and over received a dose of TENIVAC vaccine. A lower proportion of participants 65 years of age and over had a pre-vaccination seroprotective level of antibody to tetanus toxoid and diphtheria toxoid compared to adolescents and adults less than 65 years of age. The proportion of participants 65 years of age and over with a seroprotective level of antibody following TENIVAC vaccine was marginally lower for tetanus and lower for diphtheria compared to younger participants. In general, rates of solicited adverse events were not higher in participants 65 years of age and over compared to younger participants. [See Adverse Reactions (6), Clinical Pharmacology (12.1), and Clinical Studies (14.2)].

11 DESCRIPTION

TENIVAC vaccine, Tetanus and Diphtheria Toxoids Adsorbed, is a sterile isotonic suspension of tetanus and diphtheria toxoids adsorbed on aluminum phosphate.

Each 0.5 mL dose of TENIVAC vaccine contains the following active ingredients:

- Tetanus Toxoid
- Diphtheria Toxoid

Other ingredients per 0.5 mL dose include 1.5 mg of aluminum phosphate (0.33 mg of aluminum) as the adjuvant and ≤5.0 mcg of residual formaldehyde.

Clostridium tetani is grown in modified Mueller-Miller casamino acid medium without beef heart infusion. (3) Tetanus toxoid is detoxified with formaldehyde and purified by ammonium sulfate fractionation and dialfiltration. Corynebacterium diphtheriae is grown in modified Mueller’s growth medium. (4) After purification by ammonium sulfate fractionation, diphtheria toxin is detoxified with formaldehyde and dialfiltrated. Tetanus and diphtheria toxoids are individually adsorbed onto aluminum phosphate.

The adsorbed tetanus and diphtheria toxoids are combined with aluminum phosphate (as adjuvant), sodium chloride and water for injection. This product contains no preservative.

In the guinea pig potency test, the tetanus toxoid component induces at least 2 neutralizing units/mL of serum and the diphtheria toxoid component induces at least 0.5 neutralizing units/mL of serum.

The tip caps of the prefilled syringes may contain natural rubber latex. The vial stoppers do not contain latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tetanus

Tetanus is an acute disease caused by an extremely potent neurotoxin produced by C. tetani. Protection against disease is due to the development of neutralizing antibodies to tetanus toxin. A serum tetanus antitoxin level of at least 0.1 IU/mL measured by neutralization assay is considered the minimum protective level. (5) (6) A tetanus antitoxin level of ≥0.1 IU/mL as
Diphtheria is an acute toxin-mediated disease caused by toxigenic strains of *C. diphteriae*. Protection against disease is due to the development of neutralizing antibodies to diphtheria toxin. A serum diphtheria antitoxin level of 0.1 IU/mL is the lowest level giving some degree of protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective. (5) A level of at least 1.0 IU/mL has been associated with long-term protection. (7)

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

TENIVAC vaccine has not been evaluated for carcinogenic or mutagenic potential or impairment of fertility.

### 14 CLINICAL STUDIES

#### 14.1 Primary Immunization

A three-dose primary immunization series with TENIVAC vaccine was evaluated in 17 participants ages 6 to 56 years in a study conducted in Canada. (See Adverse Reactions (6.1)). The first two doses were administered two months apart, followed by a third dose six to eight months after the second dose. Serum tetanus antitoxin levels were measured by an in vivo neutralizing assay and serum diphtheria antitoxin levels were measured by an in vitro neutralizing assay. (See Clinical Pharmacology (12.1)). All 17 participants had serum tetanus and diphtheria antitoxin levels pre-vaccination and 7 days post-vaccination <0.1 IU/mL, consistent with no previous immunization. Four weeks following the second dose, 17 participants had a serum tetanus antitoxin level >0.1 IU/mL and a serum diphtheria antitoxin level >0.01 IU/mL.

### 14.2 Booster Immunization

In the US multicenter booster immunization study (TDC01) (see Adverse Reactions (6.1)), the immune response to a dose of TENIVAC vaccine was evaluated in an open-label manner in a subset of participants 11 to 59 years of age, and in comparison to DECAVAC vaccine in participants ≥60 years of age who were randomized to receive a dose of either TENIVAC vaccine or DECAVAC vaccine. Tetanus immune responses, measured by ELISA (see Clinical Pharmacology (12.1)), are presented in Table 3. Diphtheria immune responses, measured by a microneutralization assay (see Clinical Pharmacology (12.1)), are presented in Table 4.

Among adults 65 years of age and over who received TENIVAC vaccine (N = 419), 94.5% (95% confidence interval 91.9, 96.5) had a post-vaccination tetanus antitoxin level ≥0.1 IU/mL and 61.1% (95% confidence interval 56.2, 65.8) had a post-vaccination diphtheria antitoxin level ≥0.01 IU/mL.

#### Table 4: Diphtheria Antitoxin Levels and Booster Response Rates Following a Dose of TENIVAC Vaccine, by Age Group, and for Adults >60 Years of Age, Compared to DECAVAC Vaccine, per Protocol Immunogenicity Population

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Age Group</th>
<th>Timing</th>
<th>Percent of Participants With Specified Level of Diphtheria Antitoxin and Booster Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥0.01 IU/mL (95% CI)</td>
</tr>
<tr>
<td><strong>TENIVAC vaccine</strong></td>
<td>Ado. 11-18 yrs (N = 670)</td>
<td>Pre-</td>
<td>97.9 (96.1, 99.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-</td>
<td>99.9 (99.2, 100.0)</td>
</tr>
<tr>
<td></td>
<td>Adults 19-59 yrs (N = 237)</td>
<td>Pre-</td>
<td>97.5 (94.6, 99.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-</td>
<td>100.0 (98.5, 100.0)</td>
</tr>
<tr>
<td></td>
<td>Adults ≥60 yrs (N = 661)</td>
<td>Pre-</td>
<td>76.2 (72.8, 79.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-</td>
<td>96.1 (94.3, 97.4)</td>
</tr>
<tr>
<td><strong>DECAVAC vaccine</strong></td>
<td>Ado. 11-18 yrs (N = 670)</td>
<td>Pre-</td>
<td>75.2 (71.7, 78.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-</td>
<td>97.3 (95.7, 98.4)</td>
</tr>
</tbody>
</table>

* Booster response: If pre-vaccination level <0.10 IU/mL, 4-fold increase and post-vaccination level ≥0.10 IU/mL. If pre-vaccination level ≥0.10 IU/mL and ≥2.0 IU/mL, 4-fold increase. If pre-vaccination level >2.0 IU/mL, 2-fold increase.

† TENIVAC vaccine non-inferior to DECAVAC vaccine [upper limit of 95% CI for difference (DECAVAC vaccine minus TENIVAC vaccine) <10%].

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

§ TENIVAC vaccine non-inferior to DECAVAC vaccine [upper limit of 95% CI for difference (DECAVAC vaccine minus TENIVAC vaccine) <10%].

Pre- indicates pre-vaccination bleed.

Post- indicates 26-42 days post-vaccination bleed.