TENIVAC® (Tetanus and Diphtheria Toxoids Adsorbed) Suspension for Intramuscular Injection

Initial U.S. 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)

DOSAGE 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)

DOSAGE 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)

ADVERSE REACTIONS

- 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 55.3% of participants ≥65 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 1-800-822-7970 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)

US 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 for PATIENT COUNSELING INFORMATION

Revised: 12/2019

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In one of these studies, a US multi-center booster immunization study (TDC01), 2,250 adolescents and adults 19-59 years of age were enrolled. 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.

<table>
<thead>
<tr>
<th>Table 1: Guide for use of Tetanus and Diphteria Toxoids Adsorbed (Td) for Tetanus Prophylaxis in Routine Wound Management in Persons 7 Years of Age and Older</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History of Adsorbed Tetanus Toxoid (Doses)</strong></td>
</tr>
<tr>
<td>Td</td>
</tr>
<tr>
<td>Unknown or &lt; three</td>
</tr>
<tr>
<td>≥ Three</td>
</tr>
</tbody>
</table>

Such as, but not limited to, wounds contaminated with dirt, puncture wounds and traumatic wounds. 

† Only three doses of fluid tetanus toxoid have been received, then a fourth dose of toxoid, preferably an adsorbed toxoid should be given.

‡ Yes, if ≥ 10 years since last dose.

§ Yes, if ≥ 5 years since last dose. (More frequent boosters are not needed and can accentuate side effects.)

2.5 Administration
Just before use, shake the single-dose vial or syringe well until a uniform, white, cloudy suspension results. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If these conditions exist, the product should not be administered.

Administer the 0.5 mL dose of TENIVAC intramuscularly. Discard unused portion.

The preferred site is the deltoid muscle. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk.

Do not administer this product intravenously or subcutaneously.

TENIVAC should not be combined through reconstitution or mixed with any other vaccine.

5.3 Frequency of Administration
TENIVAC is a suspension for injection available in 0.5 mL single-dose vials or syringes. (See Description (11))

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 TENIVAC 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 TENIVAC 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 TENIVAC may not protect all individuals.

5.7 Altered Immunocompetence
If TENIVAC is administered to immunocompromised persons, including persons receiving immunosuppressive therapy, the expected immune response may not be obtained. (See Drug Interactions (7.4))

6. ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. 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 TENIVAC. In four booster immunization studies conducted in either the US or Canada, TENIVAC 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 TENIVAC in an open-label design and adults 60 years of age and over were randomized to receive either TENIVAC (N = 700) or DECAVAC (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 TENIVAC, overall, 80.4% were Caucasian, 3.3% Black, 5.1% Hispanic, 4.5% Asian and 6.8% other races. Among participants ≥ 60 years of age, the racial distribution was similar for the TENIVAC and DECAVAC groups. Among participants who received TENIVAC, 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 DECAVAC, 57.8% 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 diphteria 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.
There were five deaths reported during the study. All of the reported deaths were in participants ≥60 years of age and occurred >30 days post-vaccination: three in the TENVAC group (cardiopulmonary arrest; myocardial infarction and septic shock; and unknown cause) and two in the DECAVAC group (myocardial infarction and congestive heart failure; and liver cancer).

In the primary immunization study (N = 18) in which serious adverse events were monitored for 3 days following each vaccination and in three other booster immunization studies in which serious adverse events were monitored for either four days (N = 347) or one month (N = 426) following vaccination, no serious adverse events were reported.

6.2 Postmarketing Experience
The following adverse events have been spontaneously reported during the postmarketing use of TENVAC. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

The following adverse events were included based on severity, frequency of reporting or the strength of causal association to TENVAC:

- Blood and lymphatic system disorders
  - Lymphadenopathy
- Immune system disorders
  - Allergic reactions (such as erythematous rash, maculopapular rash, urticaria and pruritus; anaphylactic reaction bronchospasm and angioedema).
- Nervous system disorders
  - Paresthesia, dizziness, syncope
  - Guillain-Barré syndrome
- Gastrointestinal disorders
  - Vomiting
- Musculoskeletal, connective tissue and bone disorders
  - Myalgia, pain in extremities

* 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 TENVAC 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 TENVAC at a separate site with a separate needle and syringe. [See Dosage and Administration (2.4).]

7.3 Immunosuppressive Treatments
Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to TENVAC. [See Warnings and Precautions (6.7).]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. There are no adequate and well-controlled studies of TENVAC administration in pregnant women in the US. There are insufficient human data from TENVAC administered during pregnancy to establish the presence or absence of a vaccine-associated risk.

A developmental toxicity study has been performed in female rabbits administered a single human dose of TENVAC prior to mating and during gestation. This study revealed no evidence of harm to the fetus due to TENVAC. [See Animal data]

Data
Animal data
In a developmental toxicity study, female rabbits received a single human dose (0.5 mL) of TENVAC by intramuscular injection 17 and 10 days prior to mating, and on gestation days 6 and 29. No adverse effects on pre-weaning development up to post-natal day 35 were observed. There were no vaccine-related fatal malformations or variations observed.

8.2 Lactation
It is not known whether TENVAC components are excreted in human milk. Data are not available to assess the effect of administration of TENVAC on breastfed infants or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for TENVAC and any potential adverse effects on the breastfed child from TENVAC or the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use
TENVAC is not approved for use in infants and children younger than 7 years of age. Safety and effectiveness of TENVAC in this age group have not been established.

8.5 Geriatric Use
In one clinical study, (TDC01) 449 participants 65 years of age and over, including 192 participants who were 75 years of age and over received a dose of TENVAC. 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 and over with a seroprotective level of antibody following TENVAC 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 (14.3).]

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 toxoid. 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 measured by the ELISA used in some clinical studies of TENVAC is considered protective.

Diphtheria
Diphtheria is an acute toxin-mediated disease caused by toxigenic strains of C diphtheriae. Protection against disease is due to the development of neutralizing antibodies to diphtheria toxoid. A serum diphtheria antitoxin level of 0.01 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
TENVAC has not been evaluated for carcinogenic or mutagenic potential or impairment of male fertility in animals. Vaccination of female rabbits with TENVAC had no effects on fertility. [See Use in Specific Populations (8.1)]

14 CLINICAL STUDIES

14.1 Primary Immunization
A three-dose primary immunization series with TENVAC 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 4 to 6 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 <0.01 IU/mL, consistent with no previous immunization. Four weeks following the second dose, all 17 participants had a serum tetanus antitoxin level >0.1 IU/mL, and a serum diphtheria antitoxin level >0.01 IU/mL. Five weeks following the third dose, all 17 participants had a serum diphtheria antitoxin level >0.1 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 TENVAC was evaluated in an open-label manner in a subset of participants 11 to 59 years of age, and in comparison to DECAVAC in participants ≥60 years of age who were randomized to receive a dose of either TENVAC or DECAVAC. TENVAC immune responses, measured by ELISA [see Clinical Pharmacology (12.1)] are presented in Table 3. Diphtheria immune responses, measured by a neutralization assay [see Clinical Pharmacology (12.1)] are presented in Table 4. Among adults 65 years of age and over who received TENVAC (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 ≥0.1 IU/mL.

Table 3: Tetanus Antitoxin Levels and Booster Response Rates Following a Dose of TENVAC, by Age Group, and for Adults ≥60 Years of Age, Compared to DECAVAC, 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 Tetanus Antitoxin and Booster Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥0.1 IU/mL (% (95% CI))</td>
</tr>
<tr>
<td>Adolescents 11 to 18 years (N = 470)</td>
<td>Pre-</td>
<td>97.9 (96.1, 99.0)</td>
<td>48.7 (44.1, 53.3)</td>
</tr>
<tr>
<td></td>
<td>Post-</td>
<td>100.0 (99.2, 100)</td>
<td>99.8 (98.8, 100)</td>
</tr>
<tr>
<td>Adults ≥60 years (N = 237)</td>
<td>Pre-</td>
<td>97.5 (94.6, 99.1)</td>
<td>77.6 (71.8, 82.8)</td>
</tr>
<tr>
<td></td>
<td>Post-</td>
<td>100.0 (98.5, 100)</td>
<td>99.6 (97.7, 100)</td>
</tr>
<tr>
<td>Adults &lt;60 years (N &lt; 661)</td>
<td>Pre-</td>
<td>76.2 (72.8, 79.4)</td>
<td>43.7 (39.3, 47.6)</td>
</tr>
<tr>
<td></td>
<td>Post-</td>
<td>96.1* (94.3, 97.4)</td>
<td>90.6* (88.1, 92.7)</td>
</tr>
</tbody>
</table>
### Table 3: Tetanus Antitoxin Levels and Booster Response Rates Following a Dose of TENIVAC, by Age Group, and for Adults ≥60 Years of Age, Compared to DECAVAC, per Protocol Immunogenicity Population (continued)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Age Group</th>
<th>Timing</th>
<th>Percent of Participants With Specified Level of Tetanus Antitoxin and Booster Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>DECAVAC</td>
<td>Adults ≥60 years (N = 658)</td>
<td>Pre-</td>
<td>75.2 (71.1, 78.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-</td>
<td>97.3 (95.7, 98.4)</td>
</tr>
</tbody>
</table>

Pre- indicates pre-vaccination bleed.  
Post- indicates 26-42 days post-vaccination bleed.  
*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 ≤0.27 IU/mL, 4-fold increase. If pre-vaccination level ≥0.27 IU/mL, 2-fold increase.  
†TENIVAC non-inferior to DECAVAC (upper limit of 95% CI for difference (DECAVAC minus TENIVAC) <10%).  
‡Non-inferiority criteria not prospectively specified for this endpoint.  
§TENIVAC non-inferior to DECAVAC (upper limit of 95% CI for difference (DECAVAC minus TENIVAC) <5%).

### Table 4: Diphtheria Antitoxin Levels and Booster Response Rates Following a Dose of TENIVAC, by Age Group, and for Adults ≥60 Years of Age, Compared to DECAVAC, 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>TENIVAC</td>
<td>Adolescents 11 to 18 years (N = 470)</td>
<td>Pre-</td>
<td>99.1 (97.8, 99.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-</td>
<td>100.0 (99.2, 100)</td>
</tr>
<tr>
<td></td>
<td>Adults 19 to 59 years (N = 227)</td>
<td>Pre-</td>
<td>96.6 (93.5, 98.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-</td>
<td>99.2 (97.0, 99.9)</td>
</tr>
<tr>
<td></td>
<td>Adults ≥60 years (N = 661)</td>
<td>Pre-</td>
<td>61.9 (58.1, 65.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-</td>
<td>88.0† (85.3, 90.4)</td>
</tr>
<tr>
<td>DECAVAC</td>
<td>Adults ≥60 years (N = 658)</td>
<td>Pre-</td>
<td>61.7 (57.9, 65.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-</td>
<td>87.4 (84.6, 89.8)</td>
</tr>
</tbody>
</table>

Pre- indicates pre-vaccination bleed.  
Post- indicates 26-42 days post-vaccination bleed.  
*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 ≤0.27 IU/mL, 4-fold increase. If pre-vaccination level ≥0.27 IU/mL, 2-fold increase.  
†Non-inferiority criteria not prospectively specified for this endpoint.  
*‡TENIVAC non-inferior to DECAVAC (upper limit of 95% CI for difference (DECAVAC minus TENIVAC) <10%).

### 15 REFERENCES