Tuberculin Purified Protein Derivative (Mantoux) TUBERSOL®

Diagnostic Antigen
(Aid in the detection of infection with Mycobacterium tuberculosis)

FOR INTRADERMAL USE
Polyoxymethylbutane-0-Stabilized Solution of Tuberculin Purified Protein Derivative for Tuberculin Testing in Humans

DESCRIPTION
TUBERSOL®, Tuberculin Purified Protein Derivative (Mantoux) (PPD) is for intradermal tuberculin testing. It is prepared from a large M. tuberculosis strain (CT8) and is a cell-free purified protein fraction obtained from a human strain of Mycobacterium tuberculosis grown on a protein-free synthetic medium and inactivated. (2) The use of a standard preparation derived from a single batch (CT8) has been adopted in order to eliminate batch to batch variation by the same manufacturer. (2)

TUBERSOL is a clear, colorless liquid.

TUBERSOL contains:
Purified protein derivative of M. tuberculosis 5 TU per 0.1 mL
Polyoxymethylbutane-0 0.006%
Phenol 0.25% to 0.36% w/v in sterile isotonic phosphate buffered saline.

Before release, each successive lot is tested for potency in comparison with the US Standard Tuberculin PPD-S (3)

Independent studies conducted by the US Public Health Service in humans have determined the amount of CT8 in stabilized solution necessary (4) (5) (6) to produce bio-equivalency with Tuberculin PPD-S (in phosphate buffer without polysorbate 80) using 5 US units (TU) Tuberculin PPD-S as the standard.

CLINICAL PHARMACOLOGY
MECHANISM OF ACTION
The sensitization following infection with mycobacteria occurs primarily in the regional lymph nodes. Small lymphocytes (T lymphocytes) proliferate in response to the antigenic stimulus to give rise to specifically sensitized lymphocytes. After 3-6 weeks, these lymphocytes enter the blood stream and circulate for years. (7) Subsequent reactivation of these sensitized lymphocytes with the same or a similar antigen, such as the intradermal injection of TUBERSOL, evokes a local reaction mediated by these cells. (8)

Characteristically, delayed hypersensitivity reactions to tuberculin begin at 5 to 6 hours, are measurable at 48 to 72 hours and resolve over a period of days. The resultant immune response consists of induction due to cell infiltration and consequent vasodilatation and necrosis. Clinically, a delayed hypersensitivity reaction to tuberculin is a manifestation of previous infection with M. tuberculosis or a variety of non-tuberculosis bacteria. In most cases sensitization is induced by natural mycobacterial infection or by vaccination with BCG Vaccine.

INDICATIONS AND USAGE
TUBERSOL, Tuberculin Purified Protein Derivative (Mantoux), is indicated to aid diagnosis of tuberculosis infection (TB) in persons at increased risk of developing active disease. The Centers for Disease Control and Prevention (CDC) have published guidelines regarding populations that would benefit from tuberculin skin testing (TST). Current recommendations can be accessed at http://www.cdc.gov/tb/publications/factsheets/testing.htm.

Previous BCG vaccination is not a contraindication to tuberculin testing. The skin-test results of BCG vaccinated persons can be used to support or exclude the diagnosis of TB infection. However, an FDA-approved interferon-gamma release assay is preferred over tuberculin skin test for persons 5 years of age and older who were previously vaccinated with BCG. (9)

CONTRAINDICATIONS
Allergy to any component of TUBERSOL, or an anaphylactic or other allergic reaction to a previous test of Tuberculin PPD is a contraindication to the use of TUBERSOL. (See DESCRIPTION and HOW SUPPLIED.)

TUBERSOL should not be administered to:
• Persons who have had a severe reaction (e.g., necrosis, blistering, anaphylactic shock or ulcerations) to a previous TST.
• Persons with documented active tuberculosis or a clear history of treatment for TB infection or disease. (10)
• Persons with extensive burns or eczema.

WARNINGS
Hypersensitivity
Allergic reactions may occur following the use of TUBERSOL even in persons with no prior history of hypersensitivity to the product components. (11) Intradermal injection (1:1,000) and other appropriate agents used for the control of immediate allergic reactions must be immediately available.

Syncope
Syncope (fainting) can occur in association with administration of injectable medicines, including TUBERSOL. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

PRECAUTIONS
GENERAL
Diagnostic Limitations
False positive or false negative tuberculin skin test reactions may occur in some individuals. (See Interpretation of the Test.)
False positive tuberculin reaction tests occur in individuals who have been infected with other mycobacteria, including vaccination with BCG.

Not all infected persons will have a delayed hypersensitivity reaction to a tuberculin test.

Many factors have been reported to cause a decreased ability to respond to the tuberculin test in the presence of previous infection. (See Interpretation of the Test.)

INFORMATION FOR PATIENTS
Prior to administration of TUBERSOL, the patient's current health status and medical history should be reviewed. The physician should review the patient's immunization history for possible hypersensitivity to components of TUBERSOL.

The healthcare provider should inform the patient of the need to return for the reading of the test. Self-reading of the test has been shown to be inaccurate and unreliable.

The healthcare provider should give the patient a permanent personal record. In addition, it is essential that the health professional record the testing history in the permanent medical record of each patient. This permanent office record should contain the name of the product, date given, dose, manufacturer and lot number, as well as the test result in millimeters of induration (including 0 mm, if appropriate). Reporting results only as negative or positive is not satisfactory.

DRUG INTERACTIONS
Reactivity to the test may be depressed or suppressed in persons who are receiving corticosteroids or immunosuppressive agents. (8)

Reactivity to TUBERSOL may be temporarily depressed by certain live virus vaccines (measles, mumps, rubella, oral polio, yellow fever, and varicella). If a parenteral live attenuated virus vaccine has been administered recently, tuberculin testing should be delayed for >1 month after vaccination. (8) (12) (See Interpretation of the Test.)

When tuberculin screening is requested at the same time as a measles-containing vaccine or other parenteral live attenuated virus vaccine, simultaneous administration of TUBERSOL and the vaccine at separate sites is the preferred option.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
TUBERSOL has not been evaluated for its carcinogenic or mutagenic potentials or impairment of fertility.

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

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

PEDIATRIC USE
There is no contraindication to tuberculin skin testing of infants. Infants <6 months of age who are infected with M. tuberculosis may not react to TUBERSOL. (See Interpretation of the Test.)

GERIATRIC USE
Clinical studies of TUBERSOL did not include sufficient numbers of subjects aged 65 and over and to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS
Injection of the TUBERSOL injection site is the expected reaction for a positive skin test. (See Interpretation of the Test.)

The information pertaining to adverse events has been compiled from historical clinical studies and post-marketing experience with TUBERSOL.

General disorders and administration site conditions
Injection site pain, injection site pruritus and injection site discomfort.
Injection site erythema or injection site rash (without induration) occurring 12 hours after testing. These reactions do not indicate TB infection.
Injection site hemangoma and injection site hematoma up to three days after the administration of the test.
Injection site vesicles, injection site ulcer or injection site necrosis in highly sensitive persons.
Injection site scar as a result of strongly positive reactions.

Pyrexia
Immune system disorders
Hypersensitivity, including anaphylaxis/anaphylactic reactions, angioedema, urticaria
Respiratory, thoracic and mediastinal disorders
Stridor, dyspnea
Skin and subcutaneous tissue disorders
Rash, generalized rash
Nervous system disorders
Presyncope, syncope (including syncope associated with tonic-clonic movements and other seizure-like activity) sometimes resulting in transient loss of consciousness with injury

REPORTING OF ADVERSE EVENTS
To report SUSPECTED ADVERSE REACTIONS, contact the Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-262-9493 (1-800-MUCONE) or Food and Drug Administration (FDA) MEDWORTH Program at 1-800-332-1088 and www.fda.gov/medwatch.

DOSAGE AND ADMINISTRATION
DOSEAGE
Five (5) tuberculin units (TU) per test dose of 0.1 mL is the standard strength used for intradermal (Mantoux) testing.

METHOD OF ADMINISTRATION
TUBERSOL is indicated for intradermal injection only. Do not inject intravenously, intramuscularly, or subcutaneously. If subcutaneous injection occurs, the test cannot be interpreted.

Inject for extravasation particle matter and/or discrimination before use. If these conditions exist, do not administer the product.

Use a separate syringe and needle for each injection. (13)

The following procedure is recommended for performing the Mantoux test.

1. The preferred site of the test is the volar aspect of the forearm. Avoid areas on the skin that are red or swolten, avoid visible veins.

2. Clean the skin site with a suitable germicide and allow the site to dry prior to injection of the antigen.

3. Administer the test dose (0.1 mL) of TUBERSOL, with a 1 mL syringe calibrated in tenths and fitted with a short, one-quarter to one-half inch, 26 or 27 gauge needle.

4. Wipe the stop of the vial with a suitable germicide and allow to dry before needle insertion. Then insert the needle gently through the stopper and draw 0.1 mL TUBERSOL into the syringe. Avoid injection of excess air with removal of dose so as not to over pressure of tuberculin and possibly cause seepage at the puncture site.

5. Insert the point of the needle into the most superficial layers of the skin with the needle bevel pointing upward and administer the dose by slow intradermal injection. If the needle is over-inserted, it will not release the antigen.

6. A drop of blood may appear on the site of the administration site following injection. But the site lightly to remove the blood but avoid squeezing out the injected tuberculin test fluid.

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In the event of an improperly performed injection (ie, no bleb formed), repeat the test immediately at another site at least 2 inches from the first site and circle the second injection site as an indication that this is the site to be read.

Inform the patient of the need to return for the reading of the test by a trained health professional. Self-reading may be inaccurate and is strongly discouraged.

**INTERPRETATION OF THE TEST**

The skin test should be read by a trained health professional 48 to 72 hours after administration of TUBERSOL. Skin test sensitivity is indicated by induration only; redness should not be measured. Measure the diameter of induration transversely to the long axis of the forearm and record the measurement in millimeters (including 0 mm). (8) The tip of a ballpoint pen, gently pushed at a 45° angle toward the site of injection, will stop at the edge of induration. Also record presence and size (if present) of necrosis and edema, although these are not used in the interpretation of the test.

**Positive Reactions**

Tuberculin reactivity may indicate latent infection, prior infection and/or disease with M. tuberculosis and does not necessarily indicate the presence of active tuberculosis disease.

Persons showing positive tuberculin reactions should be considered positive by current public health guidelines and referred for further medical evaluation. (6) (10) The repeated testing of uninfected persons does not sensitize them to TUBERSOL. (7) (8) (10)

The significance of induration measurements in diagnosing latent TB infection must be considered in terms of the patient's history and the risk of developing active TB disease as indicated in Table 1. (10)

**Table 1: Criteria for tuberculin positivity, by risk group**

<table>
<thead>
<tr>
<th>Reaction ≥5 mm of Induration</th>
<th>Reaction ≥10 mm of Induration</th>
<th>Reaction ≥15 mm of Induration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons with recent contacts of tuberculosis (TB) case patients</td>
<td>Persons with positive reaction to Mantoux reactors (ie, within the last 5 years) from high prevalence countries</td>
<td>Persons with positive reaction to Mantoux reactors (ie, within the last 5 years) from high prevalence countries</td>
</tr>
<tr>
<td>Injection drug users</td>
<td>Reaction to Mantoux is equivalent of ≥15 mm of induration for 1 month or more</td>
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</tr>
</tbody>
</table>

*Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.*

1. For persons who are otherwise at low risk and are tested at the start of employment, a reaction of ≥15 mm induration is considered positive.

1A. A TST conversion is defined as an increase of ≥10 mm of induration within a 2-year period, regardless of age.

1B. The possibility should be considered that the skin test sensitivity may also be due to a previous contact with atypical mycobacteria or previous BCG vaccination. (6) (10)

Negative Reactions

Any individual who does not show a positive reaction to 5 TU on the first test, but is suspected of being TB positive, may be retested with 5 TU. (See Booster Effect and Two-Step Testing.)

Persons who have a positive test result to Mantoux reactors (ie, within the last 5 years) from high prevalence countries have a positive test result to Mantoux reactors (ie, within the last 5 years) from high prevalence countries.

False Positive Reactions

False positive tuberculin reactivity can occur in individuals who have been infected with other mycobacteria, including vaccination with BCG. (6) However, a diagnosis of M. tuberculosis infection and the use of preventive therapy should be considered for all BCG-vaccinated persons who have a positive TST reaction, especially if the person has been, or is, at increased risk of acquiring TB infection. (See INDICATIONS AND USAGE.)

False Nega tive Reactions

All inflected persons will have a delayed hypersensitivity reaction to a tuberculin test. In those who are elderly or those who are being treated for the first time, reactions may develop slowly and may not peak until after 72 hours.

Since tuberculin sensitivity may take up to 8 weeks to develop following exposure to M. tuberculosis (see Mechanism of Action), persons who have a negative tuberculin test at 4 weeks following possible TB exposure should be retested at 8-10 weeks following the last known or suspected exposure. (16)

**Altered Immune Status**

Immunosuppressed persons, such as those with HIV, transplant recipients, patients with malignancy, hematologic disorders, diabetes mellitus, chronic renal failure, those with AIDS (acquired immunodeficiency syndrome) and homeless shelters. (3) (22)

**False-Negative Reactions**

Persons who do not show a positive reaction at one week, whose tuberculin reactions change to positive after one year, should be considered to have newly acquired tuberculosis infection and managed accordingly. (7)

**HOW SUPPLIED**

TUBERSOL, Tuberculin Purified Protein Derivative (Mantoux), bioequivalent to 5 US units (TU) PPD-D per tuberculin dose (0.1 mL) is supplied in:

- 10-tube vial, 1 mL. NDC No. 45891-752-78; package of 1 vial. NDC No. 45891-752-21
- 50-tube vial, 1 mL. NDC No. 45891-752-96; package of 1 mL. NDC No. 45891-752-22

The stopper of the vial for this product does not contain natural latex rubber.

**STORAGE**

Store at 2° to 8°C (35° to 46°F). (20)

**PRODUCT INFORMATION**

50-test vial, 5 mL. NDC No. 49281-752-98; package of 1 vial. NDC No. 49281-752-22

The product should be stored in the dark except when doses are actually being withdrawn for use. (21)

A vial of TUBERSOL which has been entered and in use for 10 days should be discarded. (22)

Do not use after expiration date.

**REFERENCES**

18. CDC. Prevention and control of tuberculosis in correctional and detention facilities: Recommendations from the CDC. MMWR 2006;55(RR-9):1-44.

**Product Information as of April 2016**

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