AHFS Category: 36:84

Tuberculin Purified Protein Derivative (Mantoux)

℞ only

TUBERSOL®

Diagnostic Antigen

(Aid in the detection of infection with *Mycobacterium tuberculosis*)

FOR INTRADERMAL USE

Polysorbate 80 Stabilized Solution of Tuberculin Purified Protein Derivative for Tuberculin Testing in Humans

DESCRIPTION

TUBERSOL®, [Tuberculin Purified Protein Derivative (Mantoux)] (PPD) (1) for intradermal tuberculin testing is prepared from a large Master Batch Connaught Tuberculin (CT68) (2) 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 (CT68) 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
Polysorbate 80	0.0006%
Phenol	0.22% to 0.35% w/v

in sterile isotonic phosphate buffered saline. (3) (4) (5)

Before release, each successive lot is tested for potency in comparison with the US Standard Tuberculin PPD-S.(6)

Independent studies conducted by the US Public Health Service in humans have determined the amount of CT68 in stabilized solution necessary 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. (9)

CLINICAL PHARMACOLOGY

BACKGROUND

The number of tuberculosis (TB) cases reported in the United States (US) declined from more than 84,000 cases in 1953 to 22,255 cases in 1984. However, since 1984 dramatic changes in TB morbidity trends have occurred, and these changes jeopardize the control of TB. From 1985 through 1991, reported TB cases increased 18% - representing approximately 39,000 more cases than expected had the previous downward trend continued. (7)

MECHANISM OF ACTION

TUBERSOL, Tuberculin Purified Protein Derivative (Mantoux), is indicated for the detection of a delayed hypersensitivity reaction to tuberculin as an aid in the detection of infection with *Mycobacterium tuberculosis*.

The reaction to intradermally injected tuberculin is a delayed (cellular) hypersensitivity reaction. The reaction, which characteristically shows a delayed course, reaching its peak 48-72 hours after administration, consists of induration due to cell infiltration and occasionally vesiculation 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.

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 several weeks, these lymphocytes enter the blood stream and circulate for years. Subsequent restimulation 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.

Characteristically, delayed hypersensitivity reactions to tuberculin begin at 5 to 6 hours, are maximal at 48 to 72 hours and subside over a period of days. In those who are elderly or those who are being tested for the first time reactions may develop slowly and may not peak until after

72 hours. Immediate hypersensitivity (allergic) reactions to tuberculin or to constituents of the solution may also occur, but these allergic reactions have no diagnostic importance.

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. There are two general situations where risk of disease is increased:

- Recent infection - most commonly contacts of a recently diagnosed patient with active contagious pulmonary TB, or immigrants from countries where TB is still common. (12)
- Increased risk of reactivation due to impaired immunity. This includes HIV infection, diabetes, renal failure, corticosteroids or other immuno-suppressant medication and pulmonary silicosis. (12)

All health-care workers (pre-placement and presently employed) should have their TB infection status documented. Ongoing surveillance for TB in health-care workers includes both regular ongoing screening and post-exposure screening. (12)

Travelers at high risk of exposure to TB due to travel in a high-endemic environment, who have a medical condition increasing the risk of TB, have "high-risk" lengths of travel (>1 month), or participate in high-risk activities leading to probable exposure should have a pre-exposure Tuberculin Skin Test (TST). Post-exposure TST, or testing at least every 2 years, should be done for all tuberculin-negative reactors. (12)

HIV-infected persons should be given a TST as soon as possible after HIV infection is diagnosed and as recommended. (12)

Staff members in all correctional facilities should have tuberculin skin test screening (at hiring and routinely thereafter). Inmates in long-term correctional facilities should have tuberculin skin test screening on admission and routinely thereafter. (12)(13)

The tuberculin skin test is useful in epidemiologic surveys to define the prevalence of infection in population groups or to estimate prevalence or risk of infection in certain population groups.

Previous BCG vaccination is not a contraindication to tuberculin testing. (12)(14)

TUBERSOL may be used as an aid in the diagnosis of tuberculosis infection in persons with a history of BCG vaccination.

The repeated testing of uninfected persons does not sensitize them to tuberculin.(12)(15) (16) (17)

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 Sections.)

TUBERSOL should not be administered to:

- Known tuberculin positive reactors because of the severity of reactions (eg, vesiculation, ulceration or necrosis) that may occur at the test site in highly sensitive persons,
- Persons with severe blistering tuberculin reactions in the past,
- Persons with documented active tuberculosis or a clear history of treatment for TB infection or disease, (14)
- Persons with extensive burns or eczema.

DEFERRAL

Tuberculin skin testing should be deferred for patients with major viral infections or live-virus vaccination in the past month, for example vaccination against mumps or measles. Persons with the common cold may be tuberculin tested.

WARNINGS

Not all infected persons will have a delayed hypersensitivity reaction to a tuberculin test. A large number of factors has been reported to cause a decreased ability to respond to the tuberculin test in the presence of tuberculous infection including viral infections (measles, mumps, chickenpox and HIV), live virus vaccinations (measles, mumps, rubella, oral polio and yellow fever), overwhelming tuberculosis, other bacterial infections, drugs (corticosteroids and many other immunosuppressive agents), and malignancy. (10) (11)

Because in HIV-infected individuals, tuberculin skin-test results are less reliable as CD4 counts decline, screening should be completed as early as possible after HIV-infection occurs.

PRECAUTIONS

GENERAL

DO NOT INJECT INTRAVENOUSLY OR INTRAMUSCULARLY.

DO NOT INJECT SUBCUTANEOUSLY. If this occurs, the test cannot be interpreted.

False positive tuberculin reaction tests occur in individuals who have been infected with other mycobacteria, including vaccination with BCG. Some antigens in the tuberculin skin test are shared with other mycobacteria and thus can elicit a skin test response. (15) (16) (18)

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 sensitivity to components of TUBERSOL. Medical treatment and supervision should be readily available for immediate use in case of a rare anaphylatic reaction following the administration of TUBERSOL. Epinephrine injection (1:1,000) and other appropriate agents used for the control of immediate allergic reactions must be immediately available. Allergic reactions may occur following the use of TUBERSOL even in persons with no prior history of hypersensitivity to the product components.

Anything that impairs or attenuates cell mediated immunity (CMI) potentially can cause a false negative tuberculin reaction (eg, viral infections, HIV infection, live virus vaccines, leukemia, sarcoidosis, use of glucocorticosteroids and other immunosuppressant agents, bacterial infections,

fungal infections, metabolic derangements, low protein states, diseases affecting lymphoid organs, age (newborns, elderly) or stress). (15)

A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of other infectious agents from person to person. Needles should be disposed of properly and should not be recapped. In particular, the same needle and/or syringe must never be used to re-enter a multidose vial to withdraw product even when it is to be used for testing of the same patient. This may lead to the contamination of the vial contents and infection of patients who subsequently receive product from the vial. (19)

Special care should be taken to ensure the product is given intradermally and on the volar aspect of the forearm.

Failure to store and handle TUBERSOL as recommended will result in a loss of potency and potentially inaccurate test results. (20) (21) (22)

INFORMATION FOR PATIENTS

The health-care provider should instruct patients to report to the health-care provider adverse events such as vesiculation, ulceration or necrosis, which may appear at the test site in highly sensitive patients. The health-care provider should also inform the patient that pain, pruritus and discomfort at the site may also occur.

The health-care 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 unreliable. (23)

The health-care provider should inform the patient of the need to maintain a personal immunization record.

LABORATORY TESTS

Tuberculin reactivity may indicate latent infection prior infection and/or disease with *M tuberculosis* and does not necessarily indicate the presence of active tuberculous disease. Persons showing positive tuberculin reactions should be considered positive by current public health guidelines and referred for further medical evaluation. (12) (15)

DRUG INTERACTIONS

Reactivity to the test may be depressed or suppressed in persons who are receiving corticosteroids or immunosuppressive agents. (11)

Reactivity to PPD may be temporarily depressed by certain live virus vaccines (measles, mumps, rubella, oral polio, yellow fever, and varicella). When tuberculin screening is required 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. If a parenteral live attenuated virus vaccine has been administered recently, tuberculin testing should be delayed for >1 month after vaccination. (11)(15)

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

TUBERSOL has not been evaluated for its carcinogenic or mutagenic potentials or impairment of fertility.

PREGNANCY CATEGORY C

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.

PEDIATRIC USE

There is no age contraindication to tuberculin skin testing of infants. Because their immune systems are immature, many infants <6 weeks of age who are infected with *M tuberculosis* do not react to tuberculin tests. Older infants and children develop tuberculin sensitivity 3-6 weeks or more after initial infection. (25) Very young children are at increased risk for active tuberculosis once infected; therefore, during contact investigations, priority with regard to skin testing and evaluation for preventive therapy should be given to infants and young children who have been exposed to persons with active tuberculosis. These children should receive preventive therapy if their reactions to a tuberculin skin test measure ≥5mm. A cut-off of 10 mm is appropriate for children where tuberculosis case rates are high. A cut-off of 15 mm is used for children with minimal risk exposure to tuberculosis. (16)

GERIATRIC USE

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

ADVERSE REACTIONS

LOCAL

Pain, pruritus and discomfort at the test site may occur.

Uncommon: Immediate erythematous or other reactions may occur at the injection site. The reason(s) for these occurrences are presently unknown.

Two to three percent of tested persons will have localized redness or rash (without induration) occurring within 12 hours of testing. These reactions do not indicate TB infection.

Injection site bleeding after the needle is withdrawn and hematoma and bruising up to three days after the administration of the test have been seen.

Very rare: Vesiculation, ulceration or necrosis may appear at the test site in highly sensitive persons. Strongly positive reactions may result in scarring at the test site.

SYSTEMIC

Rare: There have been systemic hypersensitivity reactions (anaphylactic/anaphylactoid reactions) following TUBERSOL administration that were manifested by angioedema, upper respiratory stridor, (26) dyspnea, skin rash, generalized rash and/or urticaria reported within 24 hours. These

were treated with epinephrine, diphenhydramine and/or steroids. (27) Some of these events were reported in patients who had no prior exposure to TUBERSOL. No cause and effect was able to be established with a specific component of skin test. (26)

REPORTING OF ADVERSE EVENTS

Reporting by patients, parents or guardians of all adverse events occurring after a tuberculin skin test should be encouraged. To report SUSPECTED ADVERSE REACTIONS, contact the Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463 (1-800-VACCINE) or Food and Drug Administration (FDA) MEDWATCH Program at 1-800-332-1088 and www.fda.gov/medwatch. (28)

DOSAGE AND ADMINISTRATION

~~Inspect for extraneous particulate matter and/or discoloration before use. If these conditions exist,~~ the product should not be administered. In addition, it is essential that the physician or nurse record the test results in millimeters of induration, including 0, in the permanent medical record of each patient. This permanent medical record should contain the name of the product, date given, dose, manufacturer and lot number. Reporting results only as negative or positive is not satisfactory.

THE TEST

The Mantoux test is performed by injecting intradermally, on the volar aspect of the forearm, with a syringe and needle, 0.1 mL of TUBERSOL.

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

The result is read 48 to 72 hours after administration. Only palpable induration is considered in interpreting the test.

METHOD OF ADMINISTRATION

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 swollen. Avoid visible veins.
2. The skin site is first cleansed with a suitable germicide and should be dry prior to injection of the antigen.
3. ~~The test dose (0.1 mL) of TUBERSOL is administered 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. The stopper of the vial should be wiped with a suitable germicide and should be dry before needle insertion. The needle is then inserted gently through the stopper and 0.1 mL of TUBERSOL is drawn into the syringe. Care should be taken to avoid injection of excess air with removal of each dose so as not to over pressurize the vial thus causing possible seepage at the puncture site.
5. The point of the needle is inserted into the most superficial layers of the skin with the needle bevel pointing upward. If the intradermal injection is performed properly, a definite pale bleb will rise at the needle point, about 10 mm ($^3/_8$") in diameter. This bleb will disperse within minutes. No dressing should be used.

6. You may see a drop of blood when you withdraw the needle. This is normal. Offer the patient a gauze pad to remove the blood. Advise the patient not to press the gauze pad over the injection site but just to dab gently to remove the blood. This will avoid squeezing out the tuberculin thereby disrupting the test.

Needles should not be recapped and should be disposed of properly.

In the event of an improperly performed injection (ie, no bleb formed), the test should be repeated immediately at another site, at least 2 inches from the first site and the second injection site circled 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 is 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. Sensitivity is indicated by induration only; redness should not be measured.

The diameter of induration should be measured transversely to the long axis of the forearm and recorded in millimetres (including 0). (15) The tip of a ballpoint pen pushed at a 45° angle toward the site of injection will stop at the edge of induration.

Presence and size of necrosis and edema (if present) should also be recorded, although it is not used in the interpretation of the test.

The significance of induration measurements in diagnosing latent TB infection must be considered in terms of the patient's history and his or her risk of developing active TB disease as indicated below: (12)

Positive Reaction

1) An induration of ≥5 mm is classified as positive in:

   - Persons who have human immunodeficiency virus (HIV) infection or risk factors for HIV infection but unknown HIV status.
   - Persons who have had recent close contact* with persons who have active tuberculosis (TB).
   - Persons who have fibrotic chest radiographs (consistent with healed TB).

2) An induration of ≥10 mm is classified as positive in all persons who do not meet any of the criteria above but who have other risk factors for TB, including:

High-risk groups

   - Injecting-drug users known to be HIV seronegative.
   - Persons who have other medical conditions that reportedly increase the risk for progressing from latent TB infection to active TB (eg, silicosis; gastrectomy or jejuno-ileal bypass; being ≥10% below ideal body weight; chronic renal failure with renal dialysis; diabetes mellitus; high-dose corticosteroid or other immunosuppressive therapy;

some hematologic disorders, including malignancies such as leukemias and lymphomas; and other malignancies).

- Children <4 years of age.

High-prevalence groups

- Persons born in countries in Asia, Africa, the Caribbean, and Latin America that have high prevalence of TB.
- Persons from medically underserved, low-income populations.
- Residents of long-term-care facilities (eg, correctional institutions and nursing homes).
- Persons from high-risk populations in their communities, as determined by local public health authorities.

3) An induration of ≥15 mm is classified as positive in persons who do not meet any of the above criteria.

4) Recent converters are defined on the basis of both size of induration and age of the person being tested:
   - ≥10 mm increase within a 2-year period is classified as a recent conversion for persons <35 years of age.
   - ≥15 mm increase within a 2-year period is classified as a recent conversion for persons ≥35 years of age.

5) PPD skin-test results in health-care workers

- In general, the recommendations in section 1, 2, and 3 above should be followed when interpreting skin test results in health-care workers.

The prevalence of TB in the facility should be considered when choosing the appropriate cut-point for defining a positive PPD reaction. In facilities where there is essentially no risk for exposure to *M tuberculosis* (ie, minimal- or very low-risk facilities), an induration ≥15 mm may be a suitable cut-point for health-care workerswho have no other risk factors. In facilities where TB patients receive care, the cut-point for health-care workers with no other risk factors may be ≥10 mm.

- A recent conversion in health-care workers should be defined generally as a ≥10 mm increase in size of induration within a 2-year period. For health-care workers who work in facilities where exposure to TB is very unlikely (eg, minimal-risk facilities), an increase of ≥15 mm within a 2-year period may be more appropriate for defining a recent conversion because of the lower positive-predictive value of the test in such groups.

* Recent close contact implies either household or social contact or unprotected occupational exposure similar in intensity and duration to household contact. (29)

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. (12) (15) (16)

BCG vaccination may produce a PPD reaction that cannot be distinguished reliably from a reaction caused by infection with *M tuberculosis*. However, a diagnosis of *M tuberculosis* infection and the use of preventive therapy should be considered for any BCG-vaccinated person who has a tuberculin skin-test reaction of ≥10 mm of induration, especially if any of the following circumstances are present:

a) The vaccinated person is a contact of another person who has infectious TB, particularly if the infectious person has transmitted *M tuberculosis* to others;
b) The vaccinated person was born or has resided in a country in which the prevalence of TB is high; or
c) The vaccinated person is exposed continually to populations in which the prevalence of TB is high. (29) (30)

Negative Reaction

Induration of less than 15 mm in normal, healthy persons is considered negative. An 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.

Any individual who does not show a positive reaction to an initial injection of 5 TU, or a second test with 5 TU may be considered as tuberculin negative.

An individual who is considered to be at a high risk for contacting tuberculosis, should have an annual PPD skin test. (31)

False-Negative Reactions

Not all infected persons will have a delayed hypersensitivity reaction to a tuberculin test. A large number of factors has been reported to cause a decreased ability to respond to the tuberculin test in the presence of tuberculous infection including viral infections (measles, mumps, chickenpox and HIV), live virus vaccinations (measles, mumps, rubella, oral polio and yellow fever), overwhelming tuberculosis, other bacterial infections, drugs (corticosteroids and many other immunosuppressive agents), and malignancy. (10) (11)

Because in HIV-infected individuals, tuberculin skin-test results are less reliable as CD4 counts decline, screening should be completed as early as possible after HIV-infection occurs.

Booster Effect and Two-Step Testing

Infection of a person with tubercle bacilli or other mycobacteria results in a delayed hypersensitivity response to tuberculin which is demonstrated by the skin test. The delayed hypersensitivity response may gradually wane over a period of years. If a person receives a tuberculin test at this time (several years after infection) the response may be a reaction that is not significant. However, the stimulus of the test may boost or increase the size of the reaction to a second test, sometimes causing an apparent conversion or development of sensitivity. (15)

To eliminate this potential confusion, two-step testing should be performed as a baseline if tuberculin testing will subsequently be conducted at regular intervals, for instance among health-care workers or prison workers. (12) (13) If the first test showed either no reaction or a small

reaction, the second test should be performed one to four weeks later. Both tests should be read and recorded at 48 to 72 hours. (12) Patients with a second tuberculin test (booster) response of 10 mm or more should be considered to have experienced past or old infection. (12) (15) (17)

Persons who do not boost when given repeat tests at one week, but whose tuberculin reactions change to positive after one year, should be considered to have newly acquired tuberculosis infection and managed accordingly. (17) (32)

Since tuberculin reactivity may not necessarily indicate the presence of active tuberculous disease, persons showing a tuberculin reaction should be further evaluated with other diagnostic procedures.

Those individuals giving a positive tuberculin reaction may or may not show evidence of tuberculosis disease. Subjects should be referred for further medical evaluation.

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, if appropriate). Reporting results only as negative or positive is not satisfactory.

HOW SUPPLIED

TUBERSOL, Tuberculin Purified Protein Derivative (Mantoux), bioequivalent to 5 US units (TU) PPD-S per test dose (0.1 mL) is available in the following presentations:

Vial, 1 mL (5 TU per 0.1 mL test dose). Product No. 49281-752-21

Vial, 5 mL (5 TU per 0.1 mL test dose). Product No. 49281-752-22

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

CPT® Code: 86580

CPT is a registered trademark of the American Medical Association.

STORAGE

Store at 2° to 8°C (35° to 46°F). (20) DO NOT FREEZE. Discard product if exposed to freezing.

PROTECT FROM LIGHT. Tuberculin PPD solutions can be adversely affected by exposure to light. The product should be stored in the dark except when doses are actually being withdrawn from the vial. (21)

A VIAL OF TUBERSOL WHICH HAS BEEN ENTERED AND IN USE FOR 30 DAYS SHOULD BE DISCARDED BECAUSE OXIDATION AND DEGRADATION MAY HAVE REDUCED THE POTENCY. (22)

Failure to store and handle TUBERSOL as recommended will result in a loss of potency and inaccurate test results. (20)

Do not use after expiration date.

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