Tuberculin Purified Protein Derivative (Mantoux) Tubersol®

℞ only

Diagnostic Antigen

DESCRIPTION

Tuberculin Purified Protein Derivative[1] (Mantoux) - TUBERSOL® for intradermal (Mantoux) tuberculin testing is available in a stabilized solution bio-equivalent to 5 U.S. units (TU) PPD-S per test dose (0.1 mL).

TUBERSOL® is prepared by Aventis Pasteur Limited from a large Master Batch, Connaught Tuberculin (CT68) 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]

TUBERSOL® is a sterile isotonic solution of Tuberculin in phosphate buffered saline containing Tween 80 (0.0005%) as a stabilizer. Phenol 0.28% is added as a preservative.[3,4,5]

Prior to release, each successive lot is tested for potency in sensitized guinea pigs in comparison with the U.S. Standard Tuberculin PPD-S.[6]

CLINICAL PHARMACOLOGY

The number of tuberculosis (TB) cases reported in the United States 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] The excess number of cases is due to many factors, including the human immunodeficiency virus (HIV) epidemic, a deterioration in the health-care infrastructure, and increases in the number of cases among foreign-born persons.[7]

Case rates of tuberculosis for all ages are highest in urban, low-income areas, and in non-white racial and ethnic groups, among whom more than two-thirds of reported cases in the United States now occur. Some rural areas also have high rates. Foreign-born children in recent years accounted for nearly one-quarter of newly diagnosed pediatric cases. More than 35% of those cases 5 to 14 years are foreign-born in comparison to approximately 15% of those younger than 5 years. Specific groups with the highest rates of infection and disease include first-generation immigrants from high-risk countries (e.g., in Asia); Native Americans, including Alaskan natives; the homeless; and residents of correctional facilities.[8]

Tuberculosis has become a relatively uncommon disease in Canada. From 1988 to 1992 over 2,000 active cases were diagnosed annually, and fewer than 200 deaths annually were attributed to tuberculosis. However, declines in tuberculosis notification rates, which characterized the 1960s through the early 1980s, ceased in the late 1980s. In Canada, groups at high risk for tuberculosis include Aboriginal Canadians, foreign-born residents from countries with a high prevalence of the disease and certain disadvantaged inner-city groups, including the poor, the unemployed and the homeless, particularly single men. The proportion of active cases of tuberculosis due to reactivated disease has been quite constant, at about 10% during the 1980s. Tuberculosis rates are similar for males and females until middle age. After 55, the rates rise progressively, with particularly steep increases among men. [9]

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

Independent studies conducted by the U.S. 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 Tween 80) using 5 U.S. units (TU) Tuberculin PPD-S as the standard.[10]

The reaction to intradermally injected tuberculin is a delayed (cellular) hypersensitivity reaction. The reaction which characteristically shows a delayed course, reaching its peak more than 48-72 hours after administration, consists of induration caused by cellular infiltration of lyphocytes. Clinically, a delayed hypersensitivity reaction to tuberculin is a manifestation of previous infection with *M. tuberculosis* or a variety of non-tuberculosis bacteria. Sensitization may be 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 about 6 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 tuberculin, evokes a local reaction caused by infiltration of these cells.

The tuberculin reaction is characterized by the early predominance of mononuclear cells (small and medium sized lymphocytes and monocytes). Only a small proportion of these cells appear to be lymphocytes sensitized to tuberculin. Most cells are brought into the reaction through the release of biologically active substances by sensitized lymphocytes. An increase in vascular permeability leading to erythema and edema also occurs in tuberculin reactions.

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

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.[11,12]

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. Those HIV-infected patients at high risk for continuing exposure to patients who have TB should be screened periodically for TB infection. If they have TB symptoms or if they are exposed to a patient who has pulmonary TB, HIV-infected persons should be evaluated promptly for TB. Because active disease can develop rapidly in HIV-infected persons, the highest priority for contact investigation should be given to persons potentially coinfected with HIV and TB.[13]

Two-step testing should be performed on the initial testing if tuberculin testing will subsequently be conducted at regular intervals, for instance among health-care workers.[9] If the first test showed either or 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.[9] Patients with a second tuberculin test (booster) response of 10 mm or more should be considered to have experienced past or old infection.[14]

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.[15]

The repeated testing of uninfected persons does not sensitize them to tuberculin.[13,14,16,17]

INDICATIONS AND USAGE

Tuberculin Purified Protein Derivative (Mantoux) - TUBERSOL® is indicated as an aid in the detection of infection with *M. tuberculosis*.

For the intradermal (Mantoux) tuberculin test, the dose is 5 U.S. units (TU) per test dose of 0.1 mL.

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

HIV-infected individuals should receive tuberculin skin testing as recommended.[13,18]

CONTRAINDICATIONS

Allergy to any component of Tuberculin Purified Protein Derivative (Mantoux) - TUBERSOL®, (see components listed in DESCRIPTION) or an allergic reaction to a previous test of TUBERSOL® are contraindications to the use of TUBERSOL®.

TUBERSOL® should not be administered to persons who previously experienced a severe reaction (eg. vesiculation, ulceration or necrosis) because of the severity of reactions that may occur at the test site.

WARNINGS

Avoid injecting TUBERSOL® subcutaneously. If this occurs, no local reaction will develop and the test cannot be interpreted.

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.[11,12]

Anything that impairs or attenuates cell mediated immunity (CMI) potentially can cause a false negative tuberculin reaction (viral infections, particularly HIV, live virus vaccines, severe protein malnutrition, lymphoma, leukemia, sarcoidosis, use of glucocorticosteroids and other immunosuppressant drugs).

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. Those HIV-infected patients at high risk for continuing exposure to patients who have TB should be screened periodically for TB infection. If they have TB symptoms or if they are exposed to a patient who has pulmonary TB, HIV-infected persons should be evaluated promptly for TB. Because active disease can develop rapidly in HIV-infected persons, the highest priority for contact investigation should be given to persons potentially coinfected with HIV and TB.[13]

TUBERSOL® should be administered with caution, or not at all, in persons with documented active tuberculosis or documented treatment in the past because of the severity of reactions (e.g. vesiculation, ulceration or necrosis) that may occur at the test site.

PRECAUTIONS

General

Effective use of tuberculin testing requires an understanding of the characteristics inherent to the test and extrinsic factors relating that have influence on interpertation of the results. The utility of the tuberculin test depends on the prevalance of infection with *M. tuberculosis* and the relative prevalence of cross-reaction with nontuberculous mycobacteria.[16,19]

A separate, **sterile** syringe and needle, or a sterile disposable unit, must be used for each patient to prevent the transmission of infectious agents from one person to another. There have been case reports of transmission of HIV and hepatitis by failure to scrupulously observe sterile technique. In particular, the same needle must never be used to re-enter a multidose vial even when it is to be used on the same patient. This may lead to the contamination of the vial contents and infection of patients who subsequently receive product from the vial.[20]

Special care should be taken to ensure the product is given intradermally and on the volar aspect of the forearm. Do not administer intravenously, intramuscularly or subcutaneously.

Needles should not be recapped and should be disposed of according to applicable biohazard waste guidelines.

Epinephrine Hydrochloride Solution (1:1,000) and other appropriate agents should be readily available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs. Before using this product, all appropriate precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible hypersensitivity to the product, determination of previous use of Tuberculin Purified Protein Derivative (Mantoux) - TUBERSOL®, and the presence of any contraindications to the test.

Failure to store and handle TUBERSOL® as recommended will result in a loss of potency and potentially inaccurate test results.[21,22,23]

Reactivity to the test may be depressed or suppressed for as long as 5 to 6 weeks in individuals who have received recent immunization with certain live virus vaccines (measles, mumps, rubella, oral polio, yellow fever, and varicella), who have had viral infections (rubeola, influenza, mumps and probably others)[11,12] or who are receiving corticosteroids or immunosuppressive agents.

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.[24]

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

Laboratory Tests

Tuberculin reactivity may indicate prior infection and/or disease with *M. tuberculosis* and does not necessarily indicate the presence of active tuberculous disease. Individuals showing tuberculin reactions considered positive by current public health guidelines should be evaluated by other diagnostic procedures, such as x-ray examination of the chest and microbiological examination of the sputum.[13]

Drug Interactions

Reactivity to the test may be depressed or suppressed for up to 6 weeks in individuals who are receiving corticosteroids or immunosuppressive agents.[12]

Reactivity to PPD may be temporarily depressed by certain live virus vaccines (measles, mumps, rubella, oral polio, yellow fever, and varicella). Therefore, if a tuberculin test is to be performed, it should be administered either before or simultaneously, at separate sites, with these vaccines in combined form or as separate antigens, or testing should be postponed for 4-6 weeks.[8,25]

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

The product should not be used for extended treatment over a long period of time.

Pregnancy Category C (Tuberculin)

Animal reproduction studies have not been conducted with TUBERSOL®. However, the Advisory Council for Elimination of Tuberculosis states: Tuberculin skin testing is considered valid and safe throughout pregnancy. No teratogenic effects of testing during pregnancy have been documented.[13]

The risk of unrecognized tuberculosis and the close post partum contact between a mother with active disease and an infant leaves the infant in grave danger of tuberculosis and complications such as tuberculous meningitis. Therefore, the prescribing physician should consider if the potential benefits outweigh the possible risks for performing the tuberculin test on a pregnant woman or a woman of childbearing age, particularly in certain high risk populations.[13,26]

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 6 weeks or more after initial infection. 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 ≥ 5 mm. A cutoff of 10 mm is appropriate for children where tuberculosis case rates are high. A cutoff of 15 mm is used for children with minimal risk exposure to tuberculosis.[16]

ADVERSE REACTIONS

Local

Very rare: Vesiculation, ulceration or necrosis may appear at the test site in highly sensitive persons. Cold packs or topical steroid preparations may be employed for symptomatic relief of the associated pain, pruritus and discomfort.

Strongly positive reactions may result in scarring at the test site.

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

Systemic

Rare: There have been rare systemic allergic reactions reported that were manifested by immediate skin rash or generalized rash within 24 hours. Two of the reported cases had concurrent symptoms of upper respiratory stridor. These reactions were treated with epinephrine and steroids and resolved. No cause and effect was able to be established with a specific component of skin test.[27]

Reporting of Adverse Events

Reporting by patients, parents or guardians of all adverse events occuring after a tuberculin skin test should be encouraged. Adverse events following the test should be reported by the health-care provider to the Food and Drug Administration (FDA) MEDWATCH Program at 1-800-332-1088.[28]

The health-care provider also may report these events to the Director of Medical Affairs, Aventis Pasteur Inc., Discovery Drive, Swiftwater, PA 18370-0187 or call 1-800-822-2463.

DOSAGE AND ADMINISTRATION

Parenteral biological products should be inspected visually for extraneous particulate matter and/or discoloration before administration. 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, with a syringe and needle, 0.1 mL of TUBERSOL®. For the intradermal (Mantoux) tuberculin test, the dose is 5 US units (TU) per test dose of 0.1 mL.

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

Two-step testing should be performed on the initial testing if tuberculin testing will subsequently be conducted at regular intervals, for instance among health-care workers.[9] If the first test showed either or 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.[9] Patients with a second tuberculin test (booster) response of 10 mm or more should be considered to have experienced past or old infection.[14]

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.[15]

Method of Administration: The following procedure is recommended for performing the Mantoux test:

1. The preferred site of the test is the flexor (volar) surface of the forearm.
2. The skin site is first cleansed with a suitable germicide and should be dry prior to injection of the antigen.
3. The recommended test dose (0.1 mL) of Tuberculin PPD 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 rubber cap of the vial should be wiped with a suitable germicide and should be dry prior to needle insertion. The needle is then inserted gently through the cap and 0.1 mL of Tuberculin PPD is drawn into the syringe. Care should be taken to avoid injection of excess air with removal of each dose so as to not overpressurize the vial thus causing possible seepage at the site of puncture.
5. The point of the needle is inserted into the epidermal (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 is required.

In the event of an improperly performed injection (i.e. no bleb formed), the test should be repeated immediately at another site.

Interpretation of the Test: The test should be read 48 to 72 hours after administration of TUBERSOL®. Sensitivity is indicated by induration only and any erythema is disregarded. Distinctly palpable induration should be measured in millimeters (mm) transversely to the long axis of the forearm and recorded in mm.[14]

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

Sensitivity to tuberculin, may be the result of a previous infection with mycobacteria. This infection, likely due to *M. tuberculosis*, may have occurred years ago or may be of recent origin.

According to the most recent recommendations, reactions should be interpreted as follows:[13,29]

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 (e.g., 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 (e.g., 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 (HCWs)
- In general, the recommendations in section 1, 2, and 3 above should be followed when interpreting skin test results in HCWs.

However, 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* (i.e., minimal- or very low-risk facilities), an induration ≥ 15 mm may be a suitable cut-point for HCWs who have no other risk factors. In facilities where TB patients receive care, the cut-point for HCWs with no other risk factors may be ≥ 10 mm.
- A recent conversion in an HCW should be defined generally as a ≥ 10 mm increase in size of induration within a 2-year period. For HCWs who work in facilities where exposure to TB is very unlikely (e.g., 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.[13,16]

BCG vaccination may produce a PPD reaction that cannot be distinguished reliably from a reaction caused by infection with *M. tuberculosis*. For a person who was vaccinated with BCG, the probability that a PPD reaction results from infection with *M. tuberculosis* increases a) as the size of the reaction increases, b) when the person is a contact of a person with TB, c) when the person's country of origin has a high prevalence of TB, and d) as the length of time between vaccination and PPD testing increases. For example, a PPD test reaction of ≥ 10 mm probably can be attributed to *M. tuberculosis* infection in an adult who was vaccinated with BCG as a child and who is from a country with high prevalence of TB.[29]

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.[30]

False-Negative Reactions
False-negative tuberculin skin-test reactions have many potential causes.[19,31] Non-responsiveness to delayed-type hypersensitivity-inducing antigens like tuberculin is common among persons having impaired immunity (e.g., HIV-infected persons). Delayed-type hypersensitivity can also be assessed with skin-test antigens such as tetanus toxoid, mumps, and Candida. Most healthy persons in the population are sensitized to these antigens. Anergy testing is usually not part of routine screening for TB infection.[32]

All HIV-infected persons should be tuberculin tested.[19,33,34] Those who are tuberculin-positive (greater than or equal to 5 mm) should be evaluated for TB disease and placed on appropriate curative or preventive therapy. Preventive therapy should be administered to tuberculin-positive, HIV-infected persons, regardless of age. If they are at high risk for TB, persons failing to react to tuberculin may be evaluated for anergy,[35] although the lack of standardization of anergy testing practices should be considered.[13]

Booster Effect: Infection of an individual 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 (after several years) the response may be a reaction that is not significant. 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.[14]

Tuberculin reactivity may indicate prior infection and/or disease with *M. tuberculosis* and does not necessarily indicate the presence of active tuberculous disease. Individuals 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. Chest x-ray examination and microbiological examination of the sputum in these cases are recommended as a means of determining the presence or absence of pulmonary tuberculosis.

HOW SUPPLIED
Vial - 5 TU 1 mL - NDC# 49281-752-21
Vial - 5 TU 5 mL - NDC# 49281-752-22

TUBERSOL® solutions do not require further dilution.

STORAGE
Store at 2º to 8ºC (35º to 46ºF).[6,21] DO NOT FREEZE. Discard product if exposed to freezing. Tuberculin 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.[22]

A VIAL OF TUBERCULIN PPD WHICH HAS BEEN ENTERED AND IN USE FOR 30 DAYS SHOULD BE DISCARDED BECAUSE OXIDATION AND DEGRADATION MAY HAVE REDUCED THE POTENCY.[23]

Do not use after expiration date.

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