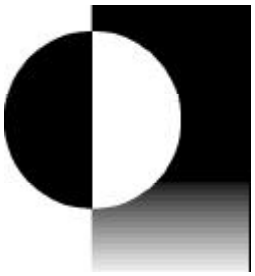
TUBERCULIN PURIFIED PROTEIN DERIVATIVE (MANTOUX)



Tubersol®

Diagnostic Antigen

Tween Stabilized Solution of Tuberculin Purified Protein Derivative for Intracutaneous Tuberculin Testing in Humans

DESCRIPTION

Tuberculin Purified Protein Derivative[1] for intracutaneous (Mantoux) tuberculin testing is prepared by the Aventis Pasteur Limited from a large Master Batch Connaught Tuberculin (CT68)[2] which has been obtained from a human strain of *Mycobacterium tuberculosis* grown on a protein-free synthetic medium. The use of a standard preparation derived from a single batch (CT68) has been recommended[3] in order to eliminate batch to batch variation by the same manufacturer.

It is estimated that this batch is large enough to provide solutions for many years. From this batch, Tuberculin PPD at three concentrations is available:

- in sterile isotonic phosphate buffered saline.[4,5,6]

Purified protein derivative of:

- *Mycobacterium tuberculosis*	1 TU per 0.1 mL, or
	5 TU per 0.1 mL, or
	250 TU per 0.1 mL
- Tween 80	0.0005% per 0.1 mL
- Phenol	0.28% per 0.1 mL

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.

Prior to release, each successive lot is tested for potency in comparison with a Standard.

INDICATIONS

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

Five (5) Tuberculin units (TU) per test dose of 0.1 mL is the standard strength tuberculin test used for

intracutaneous (Mantoux) testing. 1 TU per test (0.1 mL) and 250 TU per test dose (0.1 mL) are also available, however, these are not standardized and have limited clinical application in routine or serial (two-step) testing.[7,8] Under no circumstances is the 250 TU per test dose (0.1 mL) to be used for the initial injection. See Administration

Section for the two step testing and booster phenomenon.

Previous BCG vaccination is not a contraindication to tuberculin testing.[7,9]

The repeated testing of uninfected persons does not sensitize them to tuberculin.[10,11]

CONTRAINDICATIONS

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

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.[7]

· Patients with severe blistering tuberculin reactions in the past.[7]

· Patients with extensive burns or eczema.[7]

· Persons with documented active TB or documented treatment (active or passive) in the past.[7]

WARNINGS

Tuberculin Purified Protein Derivative (Mantoux) - Tubersol®, 250 U.S. units (TU) per test dose (0.1 mL) is not, under any circumstances, to be used for the initial injection.

Tuberculin PPD 250 U.S. units (TU) per test dose (0.1 mL) is to be used only after the individual has been tested with, and failed to respond to the 5 TU dose, but is suspected of being infected with *M. tuberculosis*.

Avoid injecting Tuberculin PPD subcutaneously. If this occurs, no local reaction will develop, but a general febrile reaction and/or acute inflammation around old tuberculosis lesions may occur in highly sensitive individuals.

DO NOT INJECT INTRAVENOUSLY.

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 interpretation of the results. The utility of the tuberculin test depends on the prevalence of infection with *M. tuberculosis* and to relative prevalence of cross-reaction with nontuberculous mycobacteria.[8]

The possibility of allergic reactions in individuals sensitive to components of Tuberculin Purified Protein Derivative (Mantoux) - Tubersol® should be evaluated. Epinephrine Hydrochloride Solution (1:1000) and other appropriate agents should be available for immediate use in case an anaphylactic or acute reaction occurs.[12] Before the use of 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 or similar products, determination of previous testing history with Tubersol®, and the presence of any contraindications to the use of Tubersol®. Familiarity with the recommendations for the initial management of anaphylaxis in non-hospital settings is recommended before administering Tubersol®.[13]

Reactivity to the test may be depressed or suppressed for as long as 4 to 6 weeks in individuals who have had viral infections (rubeola, influenza, mumps and probably others) or in those who are receiving corticosteroids or immunosuppressive agents.[14]

Reactivity to PPD may be temporarily depressed by certain live virus vaccines (measles, mumps, rubella, oral polio). Therefore, if a tuberculin test is to be performed it should be administered either before or at the same time as the live virus vaccines (such as MMR), or wait at least 30 days before administering the test.

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).

In HIV-infected individuals, tuberculin skin test results are less reliable as CD4 counts decline[11], and negative tuberculin reactions may occur in more than 40% of HIV-infected persons who have active tuberculosis.[15,16] HIV-infected individuals should receive tuberculin skin testing as recommended.[11]

Special care should be taken to ensure the product is not injected into a blood vessel.

A separate, sterile syringe and needle, or a sterile disposable unit, must be used for each individual patient to prevent the transmission of infectious agents. There have been case reports of transmission of HIV and hepatitis by failure to scrupulously observe sterile technique. In particular, the same needle and/or syringe must never be used to re-enter a multi-dose vial to withdraw product even when it is to be used for testing of the same patient. This may lead to contamination of the vial contents and infection of patients who subsequently receive product from the vial.[17]

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

In those who are elderly or being tested for the first time, reactions may develop slowly and may not peak until after 72 hours.

ADVERSE REACTIONS

Vesiculation, ulceration or necrosis may appear at the test site in highly sensitive persons. Pain, pruritus and discomfort at the test site may also occur.

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

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

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.[18]

Physicians, nurses, and pharmacists should report any adverse occurrences temporally related to the administration of the product in accordance with local requirements and to the Medical Director, Aventis Pasteur Limited, 1755 Steeles Avenue West, Toronto, Ontario, Canada, M2R 3T4.

ADMINISTRATION

Parenteral biological products should be inspected visually for extraneous particulate matter and/or discolouration before administration. If these conditions exist, the product should not be administered.

The Test: For the initial intracutaneous (Mantoux) tuberculin test it is customary to use 5 TU (bioequivalent) per dose (0.1 mL).

Five (5) Tuberculin units (TU) per test dose of 0.1 mL is the standard strength tuberculin test used for intracutaneous (Mantoux) testing. 1 TU per test (0.1 mL) and 250 TU per test dose (0.1 mL) are also available, however, these are not standardized and have limited clinical application in routine or serial (two-step) testing.[7,8] Under no circumstances is the 250 TU per test dose (0.1 mL) to be used for the initial injection.

Method of Administration:

1. The preferred site of the test is the flexor 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 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.
4. The 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.
5. The point of the needle is inserted into the most superficial layers of the skin with the needle bevel pointing upward. If the intracutaneous 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.

Failure to store and handle Tuberculin PPD as recommended will result in a loss of potency and inaccurate test results.

Interpretation of the Test:

Intracutaneous tuberculin testing is an accepted aid in the diagnosis of tuberculosis.

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

The test should be read 48 to 72 hours after administration of the Tuberculin. Sensitivity is indicated by induration, usually accompanied by erythema. Distinctly palpable induration should be measured at the widest diameter in millimeters (mm) and recorded. The tip of a ballpoint pen pushed at a 45° angle toward the site of injection will stop at the edge of induration.[7] Presence and size of necrosis and oedema (if present) should also be recorded.

Interpretation of tuberculin test[7]

Tuberculin reaction size, mm induration	Setting in which reaction considered significant
0-4	HIV infection AND expected risk of tuberculosis infection is high (e.g., patient is an immigrant from a country where TB is endemic, is a household contact, or has an abnormal x-ray). Anergy testing, if done, should show anergy. This reaction size is not normally considered significant but in the presence of immune suppression may be important.
5-9	HIV infection Contact of active contagious case Abnormal chest x-ray with fibronodular disease
≥10	All others

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.[19]

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 received 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.[10]

Although the booster phenomenon may be documented at any age, its frequency increases with age and is highest among persons >55 years old. When the tuberculin skin testing of adults is to be repeated periodically, as in employee-health or institutional screening programs, a two step approach can reduce the likelihood that a boosted reaction will be incorrectly interpreted as representing a recent infection. If the first tuberculin test result is negative, a second 5-TU test should be given 1-3 weeks later. If the second result is positive, it probably indicates the boosting of a remote infection. Persons who have a boosting reaction should be classified as reactors, not converters. If the second result is negative, the person should be considered uninfected, and any positive reaction to subsequent skin test should be considered a true tuberculin skin test conversion.[11]

Since a tuberculin reactivity may 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 tuberculous disease. Chest X-ray examination and microbiological examination of the sputum in these cases is recommended as a means of determining the presence or absence of pulmonary tuberculosis.

The possibility should not be excluded that the skin sensitivity is due to previous contact with atypical mycobacteria or previous BCG vaccination. In the absence of signs of tuberculous disease, differential diagnosis by means of intracutaneous skin tests with PPD derived from atypical mycobacteria may be indicated.

Each person who is tested with Tubersol® should be given a permanent personal record. In addition, it is essential that the physician or nurse 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.

HOW SUPPLIED

Tuberculin PPD (Mantoux)-Tubersol® bioequivalent to 5 U.S. units (TU) PPD-S per test dose (0.1 mL) is available in the following presentations:

Vial - 1 TU 1 mL

Vial - 5 TU 1 mL

Vial - 5 TU 5 mL

Vial - 250 TU 1 mL

Tuberculin PPD (Mantoux)-Tubersol® solutions do not require further dilution.

STORAGE

Tuberculin PPD (Mantoux)-Tubersol® should be stored between 2° and 8°C (35° and 46°F).[4,20]

DO NOT FREEZE. Product which has been exposed to freezing should not be used.

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 TUBERCULIN PPD WHICH HAS BEEN ENTERED AND IN USE FOR ONE MONTH SHOULD BE DISCARDED BECAUSE OXIDATION AND DEGRADATION MAY HAVE REDUCED THE POTENCY.[22]

Do not use product beyond the expiry date.

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