

APLISOL®
(Tuberculin Purified Protein Derivative, Diluted
[Stabilized Solution])
Diagnostic Antigen
For Intradermal Injection Only

45256320

DESCRIPTION

Aplisol (tuberculin PPD, diluted) is a sterile aqueous solution of a purified protein fraction for intradermal administration as an aid in the diagnosis of tuberculosis. The solution is stabilized with polysorbate (Tween) 80, buffered with potassium and sodium phosphates and contains approximately 0.35% phenol as a preservative. This product is ready for immediate use without further dilution.

The purified protein fraction is isolated from culture media filtrates of a human strain of *Mycobacterium tuberculosis* by the method of F.B. Seibert.^{1,2} Tuberculin PPD, diluted, is prepared from Tuberculin PPD Powder Master Lot 154616 which is clinically bioequivalent in potency to the standard PPD-S* (5 TU** per 0.1 mL) of the U.S. Public Health Service, National Centers for Disease Control. This product is made from a single master lot (No. 154616) to eliminate lot to lot variation inherent in manufacturing.

The potency of each lot of tuberculin PPD, diluted is determined in sensitized guinea pigs.

CLINICAL PHARMACOLOGY

In the United States, the prevalence of *Mycobacterium tuberculosis* infection and active disease varies for different segments of the population; however, the risk for *M. tuberculosis* infection in the overall population is low. Tuberculosis (TB) case rates declined steadily for decades in the United States. However, in 1985 the TB case rate stabilized and subsequently increased through 1992, accompanied by a 14% increase in the TB mortality rate in 1988. This has been attributed to several complex social and medical factors, including the human immunodeficiency virus (HIV) epidemic, the occurrence of TB in foreign-born persons from countries that have a high prevalence of TB, the emergence of drug-resistant strains of TB, and the transmission of *M. tuberculosis* in congregate settings. (e.g., health-care facilities, correctional facilities, drug-treatment centers, and homeless shelters). Because the overall risk of acquiring *M. tuberculosis* is low for the total U.S. population, the primary strategy for preventing and controlling TB in the United States is to minimize the risk of transmission by the early identification and treatment of patients who have active infectious TB, finding and screening persons who have been in contact with active infectious TB patients and screening high-risk populations.

Tuberculin PPD is recommended by the American Lung Association as an aid in the detection of infection with *Mycobacterium tuberculosis*.^{3,4} After a person becomes infected with mycobacteria, T lymphocytes proliferate and become sensitized. These sensitized T cells enter the bloodstream and circulate for months or years. This sensitization process occurs principally in the regional lymph nodes and may take 2–10 weeks to develop following infection. Once acquired, tuberculin sensitivity tends to persist, although it often wanes with time and advancing age. The injection of tuberculin into the skin stimulates the lymphocytes and activates the series of events leading to a delayed-type hypersensitivity (DTH) response. This response is called “delayed” because the reaction becomes evident hours after injection. Dermal reactivity involves vasodilation, edema, and the infiltration of lymphocytes, basophils, monocytes, and neutrophils into the site of antigen injection. Antigen-specific T lymphocytes proliferate and release lymphokines, which mediate the accumulation of other cells at the site. The area of induration reflects DTH activity.⁵ In most tuberculin-sensitive individuals, the delayed hypersensitivity reaction is evident 5–6 hours after administration of a tuberculin skin test and is maximal 48–72 hours. In geriatric patients or in patients receiving a tuberculin skin test for the first time, the reaction may develop more slowly and may not be maximal until after 72 hours.⁶ Because their immune systems are immature, many neonates and infants < 6 weeks of age, who are infected with *M. tuberculosis*, do not react at all to tuberculin tests.⁵

Immediate erythematous or other hypersensitivity reactions to tuberculin or the constituents of the diluent may occur at the injection site.

A possible decrease in responsiveness to skin testing may occur in the

presence of tuberculous infections including viral infections, live virus vaccination, overwhelming tuberculosis, other bacterial infections, drugs and malignancy.

Tuberculin skin-test results are also less reliable as CD4 counts decline in HIV infected individuals.³

The 5TU dose of Tuberculin PPD intradermally (Mantoux) is recommended as the standard tuberculin test, and Tuberculin PPD is recommended by the American Lung Association as an aid in the detection of infection with *Mycobacterium tuberculosis*. Reactions to the Mantoux test are interpreted on the basis of a quantitative measurement of the response to a specific dose (5 TU PPD-S or equivalent) of Tuberculin PPD.⁷

To determine that Tuberculin PPD Master Lot 154616 is clinically bioequivalent in potency to standard 5TU PPD-S*, 3 dose-response studies were conducted in the following populations (1) persons with a history of bacteriologically confirmed TB; (2) healthy volunteers in a geographical region of low endemicity of atypical mycobacterial infection; and (3) healthy volunteers in a geographical location of high endemicity of atypical mycobacterial infection.

INDICATIONS AND USAGE

Tuberculin PPD is recommended by the American Lung Association as an aid in the detection of infection with *Mycobacterium tuberculosis*. The standard tuberculin test recommended employs the intradermal (Mantoux) test using a 5 TU dose of tuberculin PPD.⁷ The 0.1 mL test dose of Aplisol (tuberculin PPD, diluted) is equivalent to the 5 TU dose recommended as clinically established and standardized with PPD-S. Tuberculin skin testing is not contraindicated for persons who have been vaccinated with BCG and the skin-test results of such persons are used to support or exclude the diagnosis of *M. tuberculosis* infections.⁴ HIV infection is a strong risk factor for the development of TB disease in persons having TB infection. All HIV-infected persons should receive a PPD-tuberculin skin test.³

CONTRAINDICATIONS

Aplisol is contraindicated in patients with known hypersensitivity or allergy to Aplisol or any of its components. Aplisol should not be administered to persons who have previously experienced a severe reaction (e.g., vesiculation, ulceration, or necrosis) because of the severity of reactions that may occur at the test site.

WARNINGS

Aplisol should not be administered to persons who previously experienced a severe reaction (e.g., vesiculation, ulceration, or necrosis) because of the severity of reactions that may occur at the test site (see **CONTRAINDICATIONS**).

Not all infected persons will have a delayed hypersensitivity reaction to a tuberculin test. A number of factors have been reported to cause a decreased ability to respond to the tuberculin test, such as the presence of tuberculous infection or viral infections (measles, mumps, chickenpox, and HIV), live virus vaccination (measles, mumps, rubella, oral polio and yellow fever), overwhelming tuberculosis, other bacterial infections, drugs (corticosteroids and other immunosuppressive agents) and malignancy.^{8,9}

Any condition that impairs or attenuates cell mediated immunity potentially can cause a false negative reaction.

Tuberculin skin test results are less reliable in HIV-infected individuals as CD4 counts decline (see **CLINICAL PHARMACOLOGY**).³

Avoid injecting tuberculin subcutaneously. If this occurs, no local reaction develops, but a general febrile reaction and/or acute inflammation around old tuberculous lesions may occur in highly sensitive individuals.

PRECAUTIONS

General

The predictive value of the tuberculin skin test depends on the prevalence of infection with *M. tuberculosis* and the relative prevalence of cross-reactions with nontuberculous mycobacteria.^{9,10}

A separate, sterile, single-use disposable syringe and needle should be used for each individual patient to prevent possible transmission of serum hepatitis virus and other infectious agents from one person to another. Special care should be taken to ensure that the product is injected intradermally and not into a blood vessel.

Before administration of Aplisol, a review of the patient's history with

respect to possible immediate-type hypersensitivity to the product, determination of previous use of Aplisol and the presence of any contraindication to the test should be made (see **CONTRAINDICATIONS**).

As with any biological product, epinephrine should be immediately available in case an anaphylactoid or acute hypersensitivity reaction occurs.

Failure to store and handle Aplisol as recommended may result in a loss of potency and inaccurate test results.^{11,8}

Reactivity to the test may be depressed or suppressed for as long as 5–6 weeks in individuals following immunization with certain live viral vaccines, viral infections or discontinuation of corticosteroids or immunosuppressive agents.^{8,9}

Information to Patients

Patients should be instructed to report adverse events such as vesiculation, ulceration or necrosis which may occur at the test site in highly sensitive individuals. Patients should be informed that pain, pruritus and discomfort may occur at injection site.

Patient should be informed of the need to return to their physician or health care provider for the reading of the test and of the need to keep and maintain a personal immunization record.

Drug Interactions

In patients who are receiving corticosteroids or immunosuppressive agents, reactivity to the test may be depressed or suppressed. This reduced reactivity may be present for as long as 5–6 weeks after discontinuation of therapy (see **PRECAUTIONS – General**).⁹

The reactivity to PPD may be temporarily depressed by certain live virus vaccines. Therefore, if a tuberculin test is to be performed, it should be administered either before or simultaneously with the use of oral polio and/or injection of measles, mumps and rubella vaccines in combined form or as separate antigens, or testing should be postponed for 4–6 weeks.¹⁰

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long term studies have been conducted in animals or in humans to evaluate carcinogenic or mutagenic potential or effects on fertility with Aplisol.

Pregnancy

Teratogenic effects: Pregnancy Category C. Animal reproduction studies have not been conducted with Aplisol. It is also not known whether Aplisol can cause fetal harm when administered to a pregnant woman or can affect the reproduction capacity. Aplisol should be given to a pregnant woman only if clearly needed.

However, the risk of unrecognized tuberculosis and the postpartum contact between a mother with active disease and an infant leaves the infant in grave danger of tuberculosis and complications such as tuberculous meningitis. Although there have not been any reported adverse effects upon the fetus recognized as being due to tuberculosis skin testing, the prescribing physician will want to 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.

Tuberculin skin testing is considered valid and safe throughout pregnancy.³

ADVERSE REACTIONS

In highly sensitive individuals, strongly positive reactions including vesiculation, ulceration or necrosis may occur at the test site; however, there were no reports of these reactions for the period 1995 through 1998. Cold packs or topical steroid preparations may be employed for symptomatic relief of the associated pain, pruritus and discomfort.

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

Immediate erythematous or other reactions may occur at the injection site.

DOSAGE AND ADMINISTRATION

Aplisol vials should be inspected visually for both particulate matter and discoloration prior to administration and discarded if either is seen. Vials in use for more than 30 days should be discarded.

Standard Method (Mantoux Test)

The Mantoux test is performed by **intra**dermally injecting with a syringe and needle exactly 0.1mL of Aplisol. The result is read 48 to 72 hours later and **induration only is considered in interpreting the test**. Induration is a hard, raised area with clearly defined margins at and around the injection site. Erythema may develop at the injection site but has no diagnostic

value. The standard test is performed as follows:

1. The site of the test is usually the flexor or dorsal surface of the forearm about 4" below the elbow. Other skin sites may be used, but the flexor surface of the forearm is preferred. The use of a skin area free of lesions and away from any veins is recommended.⁷
2. The skin at the injection site is cleansed with 70% alcohol and allowed to dry.
3. The test material is administered with a tuberculin syringe (0.5 or 1.0mL) fitted with a short (1/2") 26 or 27 gauge needle.
4. A separate, sterile, single-use disposable syringe and needle should be used for each individual patient.
5. The diaphragm of the vial-stopper should be wiped with 70% alcohol.
6. The needle is inserted through the stopper diaphragm of the inverted vial. Exactly 0.1mL is filled into the syringe with care being taken to exclude air bubbles and to maintain the lumen of the needle filled.
7. The point of the needle is inserted into the most superficial layers of the skin with the needle bevel pointed upward. **As the Tuberculin solution is injected, a pale bleb 6 to 10mm in size (1/3") will rise over the point of the needle.** This is quickly absorbed and no dressing is required.

In the event the injection is delivered subcutaneously (i.e., no bleb will form), or if a significant part of the dose leaks from the injection site, the test should be repeated immediately at another site at least 5 cm (2") removed.

The Mantoux test is the standard of comparison for all other tuberculin tests.

Interpretation of Tuberculin Reaction

Readings of Mantoux reactions should be made during the period from 48 to 72 hours after the injection. **Induration only should be considered in interpreting the test.** The diameter of induration should be measured transversely to the long axis of the forearm and recorded in millimeters. Erythema has no diagnostic value and should be disregarded. The presence and size of necrosis and edema if present should be recorded although not used in the interpretation of the test. In the absence of induration, an area of erythema greater than 10 mm in diameter may indicate the injection was made too deeply and retesting is indicated.

Reactions should be interpreted as follows:

Positive – A positive reaction to the tuberculin skin test may not be seen until 2–10 weeks after the infection.⁷ Based in current guidelines,^{3,12} interpretation of positive reactions (depending on the age, immune status or risk factors of the persons tested) is:

1. An induration of >5 mm is classified as positive in the following:
 - Persons who have had recent close contact with persons who have active TB;
 - Persons who have human immunodeficiency virus (HIV) infection or risk factors for HIV infection but unknown HIV status;
 - 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 above criteria, but who belong to one or more of the following groups at high risk for TB:
 - Injecting-drug users known to be HIV seronegative;
 - Persons who have other medical conditions that have been reported to increase the risk for progressing from latent TB infection to active TB. These medical conditions include diabetes mellitus, conditions requiring prolonged high-dose corticosteroid therapy and other immunosuppressive therapy (including bone marrow and organ transplantation), chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head or neck), weight loss of >10% below ideal body weight, silicosis, gastrectomy, jejunal bypass;
 - Residents and employees of high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, health-care facilities (including some residential mental health facilities), and homeless shelters;
 - Foreign-born persons recently arrived (i.e., within the last 5 years) from countries having a high prevalence or incidence of TB;
 - Some medically underserved, low-income populations, including migrant farm workers and homeless persons;

- High-risk racial or ethnic minority populations, as defined locally;
- Children <4 years of age or infants, children and adolescents exposed to adults in high-risk categories.

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

Negative – Induration of less than 5 mm. This indicates a lack of hypersensitivity to tuberculo-protein and tuberculous infection is highly unlikely.

Booster Effect – Infection of an individual with tubercle bacilli or other mycobacteria or BCG vaccination 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, a significant reaction may not be detected. 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. This booster effect can be seen on a second test done one week after the initial stimulating test and can persist for a year, and perhaps longer. When routine periodic tuberculin testing of adults is done, initially two-stage testing should be considered to minimize the likelihood of interpreting a boosted reaction as a conversion.^{13,14}

It should be noted that reactivity to tuberculin may be depressed or suppressed for as long as 5–6 weeks by viral infections, live virus vaccines (i.e., measles, smallpox, polio, rubella and mumps), or after discontinuation of therapy with corticosteroids or immunosuppressive agents. Malnutrition may also have a similar effect. When of diagnostic importance, a negative test should be accepted as proof that hypersensitivity is absent only after normal reactivity to non-specific irritants has been demonstrated. A primary injection of tuberculin may possibly have a boosting effect on subsequent tuberculin reactions. A pediatric patient who is known to have been exposed to a person with tuberculosis must not be adjudged free of infection until that patient has a negative tuberculin reaction at least ten weeks after contact with tuberculous person has ceased.¹⁵ Annual testing is generally recommended for pediatric patients in high risk populations, such as persons from countries with a high prevalence of tuberculosis and low-income groups.¹⁶

A positive tuberculin reaction does not necessarily signify the presence of active disease. Further diagnostic procedures (e.g., chest radiograph, sputum smear and/or culture examination) should be carried out before a diagnosis of tuberculosis is made. A small percentage of responders may not have been infected with *M. tuberculosis* but by some other mycobacterium. The negative tuberculin skin test should never be used to exclude the possibility of active tuberculosis among persons for whom the diagnosis is being considered (symptoms compatible with tuberculosis).

How Supplied

Tuberculin PPD-Aplisol bioequivalent to 5US units (TU) PPD-S per test dose (0.1mL) is available in the following presentations:

NDC 64029-4525-1 (Bio. 1525)

1 mL (10 tests) – rubber-diaphragm-capped vial

NDC 64029-4525-2 (Bio. 1607)

5 mL (50 tests) – rubber-diaphragm-capped vial

This product is ready for use without further dilution.

Storage

DO NOT FREEZE

This product should be stored at 2°–8°C (36°–46°F) and protected from light.

Vials in use more than 30 days should be discarded due to possible oxidation and degradation which may affect potency.

REFERENCES

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¹⁶ ACET(CDC): Screening for tuberculosis and tuberculosis infection in high risk populations. Recommendations of the ACET, 1990. MMWR 39(8):1–7.

Rx only.

Prescribing Information as of May 2002



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