TUBERCULIN PPD RT 23 AJV FOR MANTOUX TEST

Artillerivej 5
DK-2300, Copenhagen S
Denmark

Composition

1 ml of Tuberculin PPD strength 2 T.U. contains:

Tuberculin PPD RT 23 AJV	
Mycobacterium tuberculosis	0.4 microgram
Disodium phosphate dihydrate	7.6 mg
Potassium dihydrogen phosphate	1.5 mg
Sodium chloride	4.8 mg
Potassium hydroxyquinoline sulphate (as preservative)	100 microgram
Polysorbat 80	50 microgram
Water for injection	to 1 ml

Description

Tuberculin Purified Protein Derivative (PPD) RT 23 is a clear liquid consisting of PPD from selected strains of the bacterium *Mycobacterium tuberculosis.* Tuberculin PPD RT 23 is produced in strengths of 2 tuberculin units (T.U.) Recommended dose 0.1 ml of 2 T.U.contains 0.04 microgram of *Mycobacterium tuberculosis*, respectively.
Tuberculin solution contains polysorbate 80 as a stabiliser, potassium hydroxyquinoline sulphate, in a phosphate buffer, as a preservative.

Product Registration Holder:

Pharmaniaga LifeScience Sdn Bhd (198201002939)
Lot 7, Jalan PPU 3,
Taman Perindustrian Puchong Utama,
47100 Puchong,
Selangor Darul Ehsan, Malaysia

Manufacturer:

AJ Vaccines A/S
Artillerivej 5
DK-2300 Copenhagen S
Denmark

Pharmacodynamics

Intradermally injected tuberculin PPD causes a delayed (cellular) hypersensitivity reaction in individual sensitised by mycobacterial infection. Following infection with mycobacteria, sensitisation of T-cell occurs primarily in the regional lymph nodes. Natural infection with *M. tuberculosis* usually initiates a cell mediated immune response against mycobacterial antigens. T-cells proliferate in response to the infection and give rise to T-cells specifically sensitised to mycobacterial antigens. After several weeks, these T-lymphocytes enter the bloodstream and circulate for a long period of time. Subsequent restimulation of these T-lymphocytes with intradermal injection of tuberculin PPD evokes a local reaction mediated by these cells.
The reaction to intradermal injected tuberculin is a delayed (cellular) hypersensitivity reaction. The reaction which characteristically shows a delayed course, reaching its peak more than 24 hours after administration, consists of induration due to cell infiltration. 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 sensitisation is induced by a natural mycobacterial infection or by vaccination with BCG Vaccine. The sensitisation 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 sensitised lymphocytes.

After several weeks, these lymphocytes enter the blood stream and circulate for long periods of time. Subsequent restimulation of these sensitised lymphocytes with the same or a similar antigen, such as the intradermal injection of tuberculin, evokes a local reaction mediated by these cells.

Pharmacokinetics

The tuberculin injected into the skin is mostly removed within a few hours via the lymphatics. The remainder is engulfed at the site by macrophages and there is soon a mild inflammatory reaction with the appearance of polymorphs and some mononuclear cell into both the non-sensitive and sensitive subjects. In non-sensitive subjects the inflammatory response soon stops. In sensitive subjects oedema and hyperaemia continue to increase and three is intense perivascular infiltration with mononuclear cells.

The product has been widely tested in animal models, not as much in the form of preclinical safety tests, as in the form of testing performed in relation to the control of potency and comparison of potencies between different preparations. The documentation for this testing is provided as part of the clinical and pharmaceutical documentation.

The tuberculin reaction is characterised 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 sensitised to tuberculin. Most cells are brought into the reaction through the release of biologically active substances by sensitised lymphocytes. An increase in vascular permeability leading to erythema and oedema 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. 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 reactions to tuberculin or to constituents of the diluent can also occur.

Indications

For diagnostic purposes: Mantoux testing with Tuberculin PPD RT 23 AJV is an accepted aid to determine whether a person has ever been infected with *Mycobacterium tuberculosis.*

Contraindications

Tuberculin PPD RT 23 AJV should not be administered to:

- Individuals known to be hypersensitive (Type I) to the active substance or any of the excipients.
- Individuals who have experienced a severe local reaction to tuberculin products. A severe local reaction may include vesicles and ulceration at the injection site and skin necrosis at the centre of a widespread tuberculin reaction. The necrosis will generally disappear after a few days.

Special warnings and precautions for use

Although anaphylaxis is rare, facilities for its management should always be available during the Mantoux tuberculin skin test. Whenever possible skin tested individuals should be observed for allergic reactions for up to 20 minutes after administration.

Interactions with other medical products and other forms of interactions

Vaccinations with live virus vaccines (for example the MMR vaccine against measles, mumps, and rubella) or virus infections, such as measles, HIV or influenza, can temporarily decrease the tuberculin reaction. Other diseases, including cancer and sarcoidosis, can lower sensitivity to tuberculin. Persons who are undernourished and those undergoing immunosuppressive treatment (i.e. Corticosteroids) may suppress the reactivity to the tuberculin test.

A person with active tuberculosis may demonstrate a reaction of less than 6 mm if the immune system is severely depressed by the tuberculosis infection.

An individual may demonstrate a positive Mantoux test although no infection with tuberculosis is/was present. This may be due either to a previous BCG vaccination, or to an earlier infection with an environmental non-tuberculous mycobacterium which did not cause overt disease.

Pregnancy and lactation

Testing with Tuberculin PPD RT 23 AJV may be performed during pregnancy or lactation.

Dosage and method of administration

Skin-testing should be performed using the Mantoux method. When used for a medical diagnostic purpose, it is recommended to apply 0.1 ml of 2 T.U. of Tuberculin PPD RT 23 AJV. The dose is 0.1 ml of the PPD RT 23 solution. The injections should be given intradermal in the middle third of the forearm, as reactions are weaker near the wrist and the elbow-joint.

A 1 ml graduated syringe with a short-beveled 25-26 gauge needle (0.5 x 10 mm) is recommended for administration. Slightly more than 0.1 ml of the tuberculin solution should be drawn up.
An excess volume, as well as any air bubbles, is removed, leaving exactly 0.1 ml Tuberculin PPD solution.
The skin is slightly stretched, and the needle point (bevel upwards) is inserted in the superficial layer of the skin, after which the entire dose of 0.1 ml is slowly injected.
It is essential that the injection be given in the uppermost layer of the skin, as the subsequent reaction is difficult to interpret if the Tuberculin PPD solution is injected too deeply.
A suitable injection will result in the immediate formation of a small round wheal or papule of 8-10 mm in diameter, which will remain visible for about 10 minutes.
If no wheal is formed, the solution may have been given too deeply, and the skin test should be repeated at another site, 4 or more centimetres away from the first injection.

Evaluation and interpretation of the Mantoux Test

48-72 hours after an injection, an induration, possibly surrounded by an area of redness, can be observed in positive reactors. Measure only the induration, however, approximately 3 days after the application of Tuberculin PPD RT 23 AJV.
The skin reaction can be felt as a flat, uneven, slightly

raised induration which should be measured using a clear, flexible plastic ruler.

A positive reaction to Tuberculin PPD RT 23 AJV is defined as an induration having a diameter of more than 6 mm.

HOW TO READ A MANTOUX TEST Diameter of induration in mm		
Negative 0-5 mm	Positive 6-14 mm	Strongly positive 15 + mm

Countries where BCG vaccination is practised may wish to choose a higher cut-off point as indicating a positive reaction. Under certain circumstances, immunosuppressed individuals may be considered to react positively to tuberculin, even though the induration is less than 6 mm in diameter.

Undesirable effects
Immediately after the injection, pain, irritation or discomfort may rarely develop at the test site, subsiding after a short period of time. In individuals who are extremely sensitive to tuberculin, vesicles, ulceration or necrosis may occur at the injection site. Mild fever, lymph node swelling, hypersensitivity, including anaphylactic reactions, headache or urticaria have been reported.

Overdose
Not applicable.

Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Storage
Solutions of Tuberculin PPD RT 23 AJV must be stored cold between +2ºC to +8ºC and protected from light. The date of expiration specified on the label must not be exceeded. After removal of the first dose, the capped vial must be stored between +2ºC to +8ºC.
Any remaining contents must be used within 24 hours.

Registration number:
MAL 20031943 AZ

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