NEW ZEALAND DATA SHEET

1 TUBERSOL® (TUBERCULIN PPD) (5 TU/0.1 ML, SOLUTION FOR INJECTION)

Tubersol (Tuberculin PPD) 5 TU/0.1 mL Solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tuberculin Purified Protein Derivative (Mantoux) for intradermal tuberculin testing is prepared by the Sanofi Pasteur Laboratories Limited from a large Master Batch Connaught Tuberculin (CT68) 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 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 containing polysorbate 80 (0.0006%) as a stabiliser. Phenol 0.28% is added as a preservative.

Independent studies conducted by the US Public Health Service in humans have determined the amount of CT68 in stabilised solution necessary to produce bio-equivalency with Tuberculin PPD-S (in phosphate buffer without polysorbate 80) using 5 US units Tuberculin PPD-S as the standard.

Prior to release, each successive lot is tested for potency in sensitised guinea pigs in comparison with a reference standard.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Tubersol is a clear, colourless solution for injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Tuberculin PPD is indicated as an aid in the detection of infection with *Mycobacterium tuberculosis.*

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

The Mantoux test is performed by injection intradermally, with a syringe and needle, 0.1 mL of Tuberculin PPD. For the intradermal (Mantoux) tuberculin test, the dose is 5 tuberculin units (TU) per test dose of 0.1 mL.

Method of administration

Do not inject intravenously or intramuscularly.

Do not inject subcutaneously. If this occurs, the test cannot be interpreted.

The vial should be inspected for extraneous particulate matter and/or discoloration before use. If these conditions exist, the product should not be administered.

1. The site of the test is the flexor surface of the forearm about 10 cm below the bend of the elbow.
2. The skin of the forearm is first cleansed with alcohol and allowed to dry.
3. The test dose (0.1 mL) of Tubersol is administered with a 1 mL syringe calibrated in tenths and fitted with a short (0.6 cm to 1.3 cm) 26 or 27 gauge needle.
4. Disposable sterile syringes and needles may be used.
5. Wipe the rubber cap of the vial with an alcohol swab. The needle is then inserted gently through the cap and 0.1 mL of Tubersol is drawn into the syringe.
6. The point of the needle is inserted into the most superficial layers of the skin with the needle bevel pointing upward and the dose delivered by slow intradermal injection. 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 will disappear within minutes. No dressing is required.
7. A separate sterile syringe and needle must be used for each individual injection to prevent the possibility of transmission of viral hepatitis or other infectious agents from one person to another. 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 patient who subsequently receive product from the vial.

In the event of an improperly performed injection (i.e., no bleb formed), the test should be repeated immediately at another site, at least 5.08 cm from the first site.

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

Interpretation of the test

Intradermal tuberculin testing is an accepted aid in the diagnosis of tuberculosis. A positive reaction indicates sensitivity to tuberculin, which may be the result of a previous infection with mycobacteria. This infection, likely due to *Mycobacterium tuberculosis*, may have occurred years ago or may be of recent origin.

The test should be read by a trained individual 48 to 72 hours after administration of the tuberculin. 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 (mm). Presence of oedema or necrosis should also be recorded, although it is not used in the interpretation of the test.

Any palpable induration measuring 10 mm or more is considered a positive reaction. Induration measuring 5-9 mm indicates a doubtful reaction. Induration of less than 5 mm is considered a negative reaction.

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. 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.

Two-step testing - Two-step testing is performed when there is a need to establish a true baseline tuberculin reaction. Two-step testing is done to distinguish boosting from conversion in people who are having serial tuberculin testing for instance health-care workers. If the first test showed either no reaction or small reaction, the second test should be performed one week after the first test.

In the case of doubtful tuberculin reactions (5-9 mm) to 5 TU, the possibility should be considered that the skin sensitivity is due to previous contact with atypical mycobacteria or previous BCG vaccination.

Since 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.

4.3 CONTRAINDICATIONS

Previous hyper-sensitivity to PPD antigen or any component of Tubersol (see Section 6.1 List of excipients).

Tubersol should not be administered to:

- Persons who have had a severe reaction (e.g. necrosis, blistering, anaphylactic shock or ulcerations) to a previous tuberculin skin test
- Persons with extensive burns or eczema because of greater likelihood of adverse reactions or severe reactions
- Persons with documented active tuberculosis or a clear history of treatment for TB infection or disease

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Do not inject intravenously or intramuscularly.

Do not inject subcutaneously. If this occurs, the test cannot be interpreted.

Proper use of the tuberculin skin test requires knowledge of the antigen (tuberculin), the immunological basis for the reaction to this antigen, the technique(s) of administering and reading the test and the results of epidemiologic and clinical experience with the test.

Reactivity to the test may be depressed or suppressed for as long as 4 to 6 weeks in individuals who have had viral infections (rubella, influenza, mumps and probably others) or in those who are receiving corticosteroids or immunosuppressive agents. Reactivity to PPD may be temporarily depressed by certain live virus vaccines (measles, mumps, rubella). Therefore, if a tuberculin test is to be performed it should be administered either before or simultaneously with the injection of measles, mumps and rubella vaccines.

Adrenaline injection (1:1000) and other appropriate agents should be readily available for use in case an anaphylactic or acute hypersensitivity reaction occurs. The possibility of allergic reactions in persons sensitive to components of Tubersol should be evaluated. Allergic reactions may occur following the use of Tubersol even in persons with no prior history of hypersensitivity to the product components.

False Positive Test

False positive tuberculin reaction tests occur in individuals who have been exposed to other mycobacteria, including vaccination with BCG. 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 (see Section 4.2 Dose ad method of administration - Interpretation of the Test).

False Negative Test

Not all persons infected with *M. tuberculosis* will have a delayed hypersensitivity reaction to Tubersol. There is no age contraindication to tuberculin skin testing of infants. Many infants <6 months of age who are infected with *M. tuberculosis* do not react to tuberculin tests due to immature immune systems. Older infants and children develop tuberculin sensitivity 3-6 weeks or more after initial infection.

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

Altered Immune Status

Impaired or attenuated cell mediated immunity (CMI) may cause a false negative tuberculin reaction. A large number of factors have been reported to cause a decreased ability to respond to the tuberculin test in the presence of tuberculous infection (TB) including viral infections (measles, mumps, chickenpox and HIV infection cutaneous anergy associated with progressive HIV-associated immunosuppression), live virus vaccinations (e.g., measles, mumps, rubella, varicella and yellow fever vaccines), overwhelming tuberculosis, other bacterial infections, fungal infections, metabolic derangements, low protein states, diseases affecting lymphoid organs, immunosuppressive drugs, malignancy and stress.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Drug interactions

Reactivity to the skin test with Tubersol may be depressed or suppressed in persons who are taking corticosteroids or other immunosuppressive agents.

Vaccine interactions

Reactivity to Tubersol may be temporarily depressed by certain live virus vaccines (e.g., measles, mumps, rubella, yellow fever, and varicella). If a parenteral live virus vaccine has been administered recently, tuberculin testing should be delayed for >1 month post vaccination.

When tuberculin screening is required at the same time as a measles-containing vaccine or other parenteral live virus vaccine, separate syringes, separate injection sites and preferably separate

limbs should be used for administration of Tubersol (see Section 4.2 Dose and method of administration).

4.6 FERTILITY, PREGNANCY AND LACTATION

Fertility

Tubersol has not been evaluated for the effects on fertility.

Use in pregnancy

Animal reproduction studies have not been conducted with Tubersol. It is not known if Tubersol can cause fetal harm when administered to pregnant women.

Tubersol should be administered to pregnant women only if clearly needed following an assessment of the risks and benefit, and in accordance with local guidelines.

Use in lactation

It is not known whether Tubersol is excreted in human milk. Caution must be exercised when Tubersol is administered to a nursing mother. Tubersol should be administered to nursing mothers only if clearly needed following an assessment of the risks and benefit, and in accordance with local guidelines.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of Tubersol on the ability to drive or use machines have been performed.

4.8 UNDESIRABLE EFFECTS

There have been rare severe systemic hypersensitivity reactions (anaphylactic/anaphylactoid reactions) following Tubersol administration that were manifested by angioedema, upper respiratory stridor, dyspnea, skin rash, generalised rash and/or urticaria reported within 24 hours. These were treated with epinephrine, diphenhydramine and/or steroids. 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 the skin test.

Induration at the Tubersol injection site is the expected reaction for a positive skin test. See Section 4.2 Dose and method of administration - Interpretation of the test.

Adverse reactions occurring after Tubersol administration are ranked under headings of frequency using the following convention:

Very common	(≥1/10)
Common	(≥1/100 to <1/10)

Uncommon	(≥1/1,000 to <1/100)
Rare	(≥1/10,000 to <1/1,000)
Very Rare	(<1/10,000), including individual cases

General disorders and administration site conditions

Common: Injection site pain, injection site pruritus, injection site discomfort.

Uncommon: Injection site erythema or injection site rash (without induration) occurring within 12 hours of testing. These reactions do not indicate TB infection.

Injection site haemorrhage and injection site haematoma and bruising up to three days after the administration of the test have been seen.

Very Rare: Injection site vesicles, injection site ulcer or injection site necrosis may appear at the test site in highly sensitive persons.

Injection site scar as a result of strongly positive reactions.

Immune system disorders

Rare: Hypersensitivity, anaphylaxis/anaphylactic reaction, angioedema, urticaria

Respiratory, thoracic and mediastinal disorders

Rare: Stridor, dyspnoea

Skin and subcutaneous tissue disorders

Rare: Rash, generalized rash

Post-marketing experience

Based on spontaneous reporting, the following adverse events have been reported following commercial use of Tubersol. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Tubersol exposure. Therefore, their frequency is qualified as "Not known".

General disorders and administration site conditions

Not known: Pyrexia

Nervous system disorders

Not known: Presyncope, syncope.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

The standard dose of Tubersol is 5 TU. Use of 250 TU/test dose is associated with a very high rate of false-positive reactions.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Diagnostic Agents, ATC code: V04CF01

5.2 PHARMACOKINETIC PROPERTIES

No pharmacokinetic studies have been performed.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Tubersol has not been evaluated for genotoxic potential.

Carcinogenicity

Tubersol has not been evaluated for carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Polysorbate 80
Phenol
Isotonic phosphate buffered saline

6.2 INCOMPATIBILITIES

Tubersol must not be mixed with other medicines except those mentioned above (see Section 4.5 Interactions with other medicines and other forms of interaction).

6.3 SHELF LIFE

36 months.

A vial containing any unused product 30 days after the first dose is withdrawn should be discarded since oxidation and degradation may reduce the potency.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Tubersol should be stored between 2° and 8°C (35°-48°F).

Refrigerate. Do not freeze.

Tubersol 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.

For storage conditions after first opening of the medicine, see section 6.3 Shelf life.

6.5 NATURE AND CONTENTS OF CONTAINER

Tubersol bioequivalent to 5 US units (TU) PPD-S per test dose (0.1 mL) is available in 1 mL (equivalent to 10 tests) and 5 mL (equivalent to 50 tests) vials.

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

Tubersol solutions are ready for immediate use without further dilution.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

sanofi-aventis new zealand limited
Level 8
56 Cawley St
Ellerslie
Auckland
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Tel: 0800 283 684

9 DATE OF FIRST APPROVAL

5 February 1975

10 DATE OF REVISION OF THE TEXT

02 May 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformat and addition of standard text in line with the new form
1	Add product name, strength and dose form
3	Add pharmaceutical form
4.2	Addition of safety information; Method of administration and editorial changes
4.3	Addition of safety information; Contraindications
4.5	Add Interactions with other medicines and other forms of interactions
4.6	Addition of safety information; Fertility, Use in Pregnancy and Use in Lactation
4.7	Addition of standard text for mandatory subheading
4.8	Addition of standard text for mandatory subheading and deletion of duplicate text
5.1	Add pharmacotherapeutic group and ATC code
5.2	Add pharmacokinetic properties under mandatory subheadings
5.3	Add Preclinical safety data under mandatory subheadings
6.1	Addition of excipients and preservative
6.2	Add incompatibilities
6.3	Add shelf life and minor editorial changes
6.4	Add Special precautions for storage and minor editorial changes
6.5	Add Nature and contents of container and deletion of text
6.6	Add Special precautions for disposal
8	Update sponsor details
9	Add date of first approval