

1 AHFS Category: 36:84  
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**Tuberculin Purified Protein Derivative  
(Mantoux)  
TUBERSOL®**



3 **Diagnostic Antigen**

4 (Aid in the detection of infection with *Mycobacterium tuberculosis*)

5 **FOR INTRADERMAL USE**

6 **Polysorbate 80 Stabilized Solution of Tuberculin Purified Protein Derivative for**  
7 **Tuberculin Testing in Humans**

8 **DESCRIPTION**

9 TUBERSOL®, Tuberculin Purified Protein Derivative (Mantoux) (PPD) (1) for intradermal  
10 tuberculin testing is prepared from a large Master Batch Connaught Tuberculin (CT68) (2) and  
11 is a cell-free purified protein fraction obtained from a human strain of *Mycobacterium*  
12 *tuberculosis* grown on a protein-free synthetic medium and inactivated. (2) The use of a  
13 standard preparation derived from a single batch (CT68) has been adopted in order to eliminate  
14 batch to batch variation by the same manufacturer. (2)

15 TUBERSOL is a clear, colorless liquid.

16 TUBERSOL contains:

17 Purified protein derivative of <i>M. tuberculosis</i>	5 TU per 0.1 mL
18 Polysorbate 80	0.0006%
19 Phenol	0.22% to 0.35% w/v
20 in sterile isotonic phosphate buffered saline.	

21 Before release, each successive lot is tested for potency in comparison with the US Standard  
22 Tuberculin PPD-S. (3)  
23 Independent studies conducted by the US Public Health Service in humans have determined the  
24 amount of CT68 in stabilized solution necessary (4) (5) (6) to produce bio-equivalency with  
25 Tuberculin PPD-S (in phosphate buffer without polysorbate 80) using 5 US units (TU)  
26 Tuberculin PPD-S as the standard.

## 27 **CLINICAL PHARMACOLOGY**

### 28 **MECHANISM OF ACTION**

29 The sensitization following infection with mycobacteria occurs primarily in the regional lymph  
30 nodes. Small lymphocytes (T lymphocytes) proliferate in response to the antigenic stimulus to  
31 give rise to specifically sensitized lymphocytes. After 3-8 weeks, these lymphocytes enter the  
32 blood stream and circulate for years. (7) Subsequent restimulation of these sensitized  
33 lymphocytes with the same or a similar antigen, such as the intradermal injection of  
34 TUBERSOL, evokes a local reaction mediated by these cells. (8)

35 Characteristically, delayed hypersensitivity reactions to tuberculin begin at 5 to 6 hours, are  
36 maximal at 48 to 72 hours and subside over a period of days. The resultant immune response  
37 consists of induration due to cell infiltration and occasionally vesiculation and necrosis.

38 Clinically, a delayed hypersensitivity reaction to tuberculin is a manifestation of previous  
39 infection with *M tuberculosis* or a variety of non-tuberculosis bacteria. In most cases  
40 sensitization is induced by natural mycobacterial infection or by vaccination with BCG  
41 Vaccine.

### 42 **INDICATIONS AND USAGE**

43 TUBERSOL, Tuberculin Purified Protein Derivative (Mantoux), is indicated to aid diagnosis of  
44 tuberculosis infection (TB) in persons at increased risk of developing active disease.

45 The Centers for Disease Control and Prevention (CDC) have published guidelines regarding  
46 populations that would benefit from tuberculin skin testing (TST). Current recommendations  
47 can be accessed at: <http://www.cdc.gov/tb/publications/factsheets/testing.htm>.

48 Previous BCG vaccination is not a contraindication to tuberculin testing. The skin-test results of  
49 BCG vaccinated persons can be used to support or exclude the diagnosis of TB infection.

50 However, an FDA-approved interferon gamma release assay is preferred over tuberculin skin  
51 test for persons 5 years of age and older who were previously vaccinated with BCG. (9)

## 52 **CONTRAINDICATIONS**

53 Allergy to any component of TUBERSOL or an anaphylactic or other allergic reaction to a  
54 previous test of tuberculin PPD is a contraindication to the use of TUBERSOL. (See

55 [DESCRIPTION](#) and [HOW SUPPLIED](#).)

56 TUBERSOL should not be administered to:

- 57 • Persons who have had a severe reaction (e.g., necrosis, blistering, anaphylactic shock or  
58 ulcerations) to a previous TST,
- 59 • Persons with documented active tuberculosis or a clear history of treatment for TB  
60 infection or disease, (10)
- 61 • Persons with extensive burns or eczema.

## 62 **WARNINGS**

### 63 Hypersensitivity

64 Allergic reactions may occur following the use of TUBERSOL even in persons with no prior  
65 history of hypersensitivity to the product components. (11) Epinephrine injection (1:1,000) and  
66 other appropriate agents used for the control of immediate allergic reactions must be  
67 immediately available.

### 68 Syncope

69 Syncope (fainting) can occur in association with administration of injectable medicines,  
70 including TUBERSOL. Procedures should be in place to avoid falling injury and to restore  
71 cerebral perfusion following syncope.

## 72 **PRECAUTIONS**

### 73 **GENERAL**

#### 74 **Diagnostic Limitations**

75 False positive or false negative tuberculin skin test reactions may occur in some individuals.  
76 (See [Interpretation of the Test.](#))

77 False positive tuberculin reaction tests occur in individuals who have been infected with other  
78 mycobacteria, including vaccination with BCG.

79 Not all infected persons will have a delayed hypersensitivity reaction to a tuberculin test.

80 Many factors have been reported to cause a decreased ability to respond to the tuberculin test in  
81 the presence of tuberculous infection. (See [Interpretation of the Test.](#))

### 82 **INFORMATION FOR PATIENTS**

83 Prior to administration of TUBERSOL, the patient's current health status and medical history  
84 should be reviewed. The physician should review the patient's immunization history for  
85 possible sensitivity to components of TUBERSOL.

86 The healthcare provider should inform the patient of the need to return for the reading of the  
87 test. Self-reading of the test has been shown to be inaccurate and unreliable.

88 The healthcare provider should give the patient a permanent personal record. In addition, it is  
89 essential that the health professional record the testing history in the permanent medical record  
90 of each patient. This permanent office record should contain the name of the product, date  
91 given, dose, manufacturer and lot number, as well as the test result in millimeters of induration

92 (including 0 mm, if appropriate). Reporting results only as negative or positive is not  
93 satisfactory.

#### 94 DRUG INTERACTIONS

95 Reactivity to the test may be depressed or suppressed in persons who are receiving  
96 corticosteroids or immunosuppressive agents. (8)

97 Reactivity to TUBERSOL may be temporarily depressed by certain live virus vaccines  
98 (measles, mumps, rubella, oral polio, yellow fever, and varicella). If a parenteral live attenuated  
99 virus vaccine has been administered recently, tuberculin testing should be delayed for >1 month  
100 after vaccination. (8) (12) (See Interpretation of the Test.)

101 When tuberculin screening is required at the same time as a measles-containing vaccine or other  
102 parenteral live attenuated virus vaccine, simultaneous administration of TUBERSOL and the  
103 vaccine at separate sites is the preferred option.

#### 104 CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

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

#### 107 PREGNANCY

108 Animal reproduction studies have not been conducted with TUBERSOL. It is also not known  
109 whether TUBERSOL can cause fetal harm when administered to a pregnant woman or can  
110 affect reproduction capacity. TUBERSOL should be given to a pregnant woman only if clearly  
111 needed.

#### 112 NURSING MOTHERS

113 It is not known whether TUBERSOL is excreted in human milk. Because many drugs are  
114 excreted in human milk, caution should be exercised when TUBERSOL is administered to a  
115 nursing woman.

116 PEDIATRIC USE

117 There is no contraindication to tuberculin skin testing of infants. Infants <6 months of age who  
118 are infected with *M. tuberculosis* may not react to TUBERSOL. (See Interpretation of the  
119 Test.)

120 GERIATRIC USE

121 Clinical studies of TUBERSOL did not include sufficient numbers of subjects aged 65 and over  
122 to determine whether they respond differently from younger subjects.

123 **ADVERSE REACTIONS**

124 Induration at the TUBERSOL injection site is the expected reaction for a positive skin test. (See  
125 [Interpretation of the Test.](#))

126 The information pertaining to adverse events has been compiled from historical clinical studies  
127 and post-marketing experience with TUBERSOL.

128 **General disorders and administration site conditions**

129 Injection site pain, injection site pruritus and injection site discomfort.

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

132 Injection site hemorrhage and injection site hematoma up to three days after the  
133 administration of the test.

134 Injection site vesicles, injection site ulcer or injection site necrosis in highly sensitive  
135 persons.

136 Injection site scar as a result of strongly positive reactions.

137 Pyrexia

138 **Immune system disorders**

139 Hypersensitivity, including anaphylaxis/anaphylactic reactions, angiodema, urticaria

140 **Respiratory, thoracic and mediastinal disorders**

141 Stridor, dyspnea

142 **Skin and subcutaneous tissue disorders**

143 Rash, generalized rash

144 **Nervous system disorders**

145 Presyncope, syncope (including syncope associated with tonic-clonic movements and other  
146 seizure-like activity) sometimes resulting in transient loss of consciousness with injury

147 **REPORTING OF ADVERSE EVENTS**

148 To report SUSPECTED ADVERSE REACTIONS, contact the Pharmacovigilance Department,  
149 Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463 (1-800-  
150 VACCINE) or Food and Drug Administration (FDA) MEDWATCH Program at 1-800-332-  
151 1088 and [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

152 **DOSAGE AND ADMINISTRATION**

153 **DOSAGE**

154 Five (5) tuberculin units (TU) per test dose of 0.1 mL is the standard strength used for  
155 intradermal (Mantoux) testing.

156 **METHOD OF ADMINISTRATION**

157 **TUBERSOL is indicated for intradermal injection only. Do not inject intravenously,**  
158 **intramuscularly, or subcutaneously.** If subcutaneous injection occurs, the test cannot be  
159 interpreted.

160 Inspect for extraneous particulate matter and/or discoloration before use. If these conditions  
161 exist, do not administer the product.

162 Use a separate syringe and needle for each injection. (13)

163 The following procedure is recommended for performing the Mantoux test:

- 164 1. The preferred site of the test is the volar aspect of the forearm. Avoid areas on the skin that  
165 are red or swollen. Avoid visible veins.
- 166 2. Clean the skin site with a suitable germicide and allow the site to dry prior to injection of  
167 the antigen.
- 168 3. Administer the test dose (0.1 mL) of TUBERSOL with a 1 mL syringe calibrated in tenths  
169 and fitted with a short, one-quarter to one-half inch, 26 or 27 gauge needle.
- 170 4. Wipe the stopper of the vial with a suitable germicide and allow to dry before needle  
171 insertion. Then insert the needle gently through the stopper and draw 0.1 mL of  
172 TUBERSOL into the syringe. Avoid injection of excess air with removal of each dose so as  
173 not to over pressurize the vial and possibly cause seepage at the puncture site.
- 174 5. Insert the point of the needle into the most superficial layers of the skin with the needle  
175 bevel pointing upward and administer the dose by slow **intra**dermal injection. If the  
176 intra
- 177 dermal injection is performed properly, a definite pale bleb will rise at the needle point,  
178 about 10 mm ( $\frac{3}{8}$ " ) in diameter. This bleb will disperse within minutes. Do not dress the  
179 site.
- 179 6. A drop of blood may appear at the administration site following injection. Blot the site  
180 lightly to remove the blood but avoid squeezing out the injected tuberculin test fluid.
- 181 In the event of an improperly performed injection (ie, no bleb formed), repeat the test  
182 immediately at another site, at least 2 inches from the first site and circle the second injection  
183 site as an indication that this is the site to be read.
- 184 Inform the patient of the need to return for the reading of the test by a trained health  
185 professional. Self-reading may be inaccurate and is strongly discouraged.

186 INTERPRETATION OF THE TEST



187 The skin test should be read by a trained health professional 48 to 72 hours after administration  
188 of TUBERSOL. Skin test sensitivity is indicated by induration only; redness should not be  
189 measured.

190 Measure the diameter of induration transversely to the long axis of the forearm and record the  
191 measurement in millimeters (including 0 mm). (8) The tip of a ballpoint pen, gently pushed at a  
192 45° angle toward the site of injection, will stop at the edge of induration.

193 Also record presence and size (if present) of necrosis and edema, although these are not used in  
194 the interpretation of the test.

#### 195 Positive Reactions

196 Tuberculin reactivity may indicate latent infection, prior infection and/or disease with *M.*  
197 *tuberculosis* and does not necessarily indicate the presence of active tuberculous disease.

198 Persons showing positive tuberculin reactions should be considered positive by current public  
199 health guidelines and referred for further medical evaluation. (8) (10) The repeated testing of  
200 uninfected persons does not sensitize them to TUBERSOL. (7) (8) (10)

201 The significance of induration measurements in diagnosing latent TB infection must be  
202 considered in terms of the patient's history and the risk of developing active TB disease as  
203 indicated in Table 1. (10)

204 **Table 1: Criteria for tuberculin positivity, by risk group**

Reaction $\geq 5$ mm of Induration	Reaction $\geq 10$ mm of Induration	Reaction $\geq 15$ mm of Induration
<p>HIV-positive persons</p> <p>Recent contacts of tuberculosis (TB) case patients</p> <p>Fibrotic changes on chest radiograph consistent with prior TB</p> <p>Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of <math>\geq 15</math> mg/d of prednisone for 1 month or more)*</p>	<p>Recent immigrants (i.e., within the last 5 yrs) from high prevalence countries</p> <p>Injection drug users</p> <p>Residents or employees† of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other healthcare facilities, residential facilities for patients with acquired immunodeficiency syndrome (AIDS) and homeless shelters</p> <p>Mycobacteriology laboratory personnel</p> <p>Persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head or neck and lung), weight loss of <math>\geq 10\%</math> of ideal body weight, gastrectomy and jejunioileal bypass</p> <p>Children younger than 4 yrs of age or infants, children, and adolescents exposed to adults at high-risk</p>	<p>Persons with no risk factors for TB</p>

\* Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.

† For persons who are otherwise at low risk and are tested at the start of employment, a reaction of  $\geq 15$  mm induration is considered positive.

205 A TST conversion is defined as an increase of  $\geq 10$  mm of induration within a 2-year period,  
206 regardless of age. (10)

207 The possibility should be considered that the skin test sensitivity may also be due to a previous  
208 contact with atypical mycobacteria or previous BCG vaccination. (8) (10)

### 209 Negative Reactions

210 An individual who does not show a positive reaction to 5 TU on the first test, but is suspected  
211 of being TB positive, may be retested with 5 TU. (See [Booster Effect and Two-Step Testing](#).)

212 Any individual who does not show a positive reaction to an initial injection of 5 TU, or a  
213 second test with 5 TU may be considered as tuberculin negative.

### 214 False Positive Reactions

215 False positive tuberculin reactions can occur in individuals who have been infected with other  
216 mycobacteria, including vaccination with BCG. (8) However, a diagnosis of *M. tuberculosis*  
217 infection and the use of preventive therapy should be considered for any BCG-vaccinated  
218 person who has a positive TST reaction, especially if the person has been, or is, at increased  
219 risk of acquiring TB infection. (See [INDICATIONS AND USAGE](#).) (14) (15)

### 220 False-Negative Reactions

221 Not all infected persons will have a delayed hypersensitivity reaction to a tuberculin test.

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

224 Since tuberculin sensitivity may take up to 8 weeks to develop following exposure to *M.*

225 *tuberculosis* (see [Mechanism of Action](#)), persons who have a negative tuberculin test <8 weeks

226 following possible TB exposure should be retested  $\geq 8$ -10 weeks following the last known or  
227 suspected exposure. (16)

### 228 *Altered Immune Status*

229 Impaired or attenuated cell mediated immunity (CMI) can potentially cause a false negative  
230 tuberculin reaction. Many factors have been reported to cause a decreased ability to respond to  
231 the tuberculin test in the presence of tuberculous infection including viral infections (e.g.,  
232 measles, mumps, chickenpox and HIV), live virus vaccinations (e.g., measles, mumps, rubella,  
233 oral polio and yellow fever), overwhelming tuberculosis, other bacterial infections, leukemia,  
234 sarcoidosis, fungal infections, metabolic derangements, low protein states, diseases affecting  
235 lymphoid organs, drugs (corticosteroids and many other immunosuppressive agents), and  
236 malignancy or stress. (8) (17) (18) A TST should be deferred for patients with major viral  
237 infections or live-virus vaccination in the past month. Persons with the common cold may be  
238 tuberculin tested.

239 Because TST results in HIV-infected individuals are less reliable as CD4 counts decline,  
240 screening should be completed as early as possible after HIV-infection occurs. (18)

### 241 **BOOSTER EFFECT AND TWO-STEP TESTING**

242 If tuberculin testing will be conducted at regular intervals, for instance among healthcare  
243 workers or prison workers, two-step testing should be performed as a baseline to avoid  
244 interpreting a booster effect as a tuberculin conversion. If the first test showed either no reaction  
245 or a small reaction, the second test should be performed one to four weeks later. Both tests  
246 should be read and recorded at 48 to 72 hours. Patients with a second tuberculin test (booster)  
247 response of  $\geq 10$  mm should be considered to have experienced past TB infection. (14) (19)

248 Persons who do not boost when given repeat tests at one week, but whose tuberculin reactions  
249 change to positive after one year, should be considered to have newly acquired tuberculosis  
250 infection and managed accordingly. (7)

251 **HOW SUPPLIED**

252 TUBERSOL, Tuberculin Purified Protein Derivative (Mantoux), bioequivalent to 5 US units  
253 (TU) PPD-S per test dose (0.1 mL) is supplied in:

254 10-test vial, 1 mL. NDC No. 49281-752-78; package of 1 vial, NDC No. 49281-752-21

255 50-test vial, 5 mL. NDC No. 49281-752-98; package of 1 vial, NDC No. 49281-752-22

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

257 **STORAGE**

258 Store at 2° to 8°C (35° to 46°F). (20) **Do not freeze.** Discard product if exposed to freezing.

259 **Protect from light.** Tuberculin PPD solutions can be adversely affected by exposure to light.

260 The product should be stored in the dark except when doses are actually being withdrawn from  
261 the vial. (21)

262 **A vial of TUBERSOL which has been entered and in use for 30 days should be discarded.**

263 (22)

264 Do not use after expiration date.

265

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