

From the Chief Medical Officer
Dr Henrietta Campbell CB

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Consultants in Communicable Disease Control, HSS Boards
Chief Executives of HSS Boards
Chief Executives of HSS Trusts (for circulation to Occupational Health Departments)
Medical Directors, HSS Trusts
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Your Ref:
Our Ref: HSS(MD)25/2005
– Follow-Up Letter
Date: 8th August 2005

Dear Colleague

SUPPLIES OF TUBERCULIN PPD FOR HEAF AND MANTOUX TESTING

This letter is a follow up to the Chief Professionals' letter dated 15th July 2005 (HSS(MD)25/2005). This information will be required by all relevant professionals involved in tuberculin skin testing for screening or diagnostic purposes.

Chiron Vaccines Evans has ceased production of Tuberculin PPD for both Heaf and Mantoux testing for the foreseeable future. Current stocks of Tuberculin PPD for Mantoux testing from Chiron Vaccines Evans (the sole supplier of the UK licensed PPD) reached their expiry date at the end of May 2005.

This will mean that, until further notice, once Heaf strength PPD has been used up all Tuberculin PPD testing will be by the Mantoux intradermal method using an alternative Tuberculin product manufactured by the Statens Serum Institut (SSI) in Denmark.

Key issues for your attention

- 1. Tuberculin PPD from SSI is available as an unlicensed medicine in the UK** (although it has a Marketing Authorisation for use in other European countries). As a Tuberculin PPD (SSI) is unlicensed in the UK, this product cannot be administered using a Patient Group Direction. Instead, it should be administered on a **Patient Specific Direction** (written instruction by an independent prescriber to another healthcare professional, to supply and/or administer a medicine directly to a named patient, or to several named patients). For convenience, where several individuals require Mantoux testing, a list of these named individuals can be printed and authorisation signed by a doctor or extended formulary nurse prescriber. (See appendix three for an example Patient Specific Direction for Mantoux testing using Tuberculin PPD (SSI).)
- 2. There are important differences between Tuberculin Mantoux PPD from SSI and Tuberculin Mantoux PPD formerly provided by Chiron Vaccines Evans**

- (a) The Chiron Vaccines Evans Tuberculin PPD preparation for routine use in the Mantoux test contained 100 units/ml and was supplied in 1.0 ml ampoules. The Tuberculin PPD (SSI) is available in two concentrations expressed as the number of units in 0.1 ml of PPD solution and is supplied in 1.5 ml ampoules. **Users must carefully read the label and package insert.**

Tuberculin PPD (SSI) for routine use in the Mantoux test is labelled as 2 TU per 0.1ml dose (20 units in 1ml). The higher concentration 10 TU/0.1 ml may be used for a second test if the first test (2TU per 0.1ml) is negative (less than approx. 6mm in diameter) and a retest is considered appropriate for clinical purposes.

- (b) **Interpreting reactions to the Tuberculin PPD (SSI) Mantoux test.** Different commercial Tuberculin PPD reagents vary in potency. Tuberculin PPD (SSI) and Chiron Vaccines Evans Tuberculin PPD are both internationally standardised products and should give comparable results when interpreted using the following cut off measurements.

	Negative	Positive	Strongly positive
Chiron Vaccines Evans Tuberculin PPD	0-4 mm	5-14 mm	≥15 mm
SSI Tuberculin PPD	0-5 mm	6-14 mm	≥15 mm

- 3. Any member of staff who has been assessed as competent to perform BCG can administer the Mantoux test as the technique is the same.** The Department of Health is producing a variety of training materials showing how to give and read the Mantoux test. These materials will be available from early August to download from www.immunisation.nhs.uk or available to order from DH Publications: dh@prolog.uk.com or tel: 08701 555 455.

CORE SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tuberculin PPD RT 23 SSI, 2 T.U./0.1 ml, solution for injection.
Tuberculin PPD RT 23 SSI, 10 T.U./0.1 ml, solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tuberculin PPD RT 23 SSI, 2 T.U./0.1 ml, solution for injection:

1 dose = 0.1 ml contains 0.04 microgram Tuberculin PPD.

Tuberculin PPD RT 23 SSI, 10 T.U./0.1 ml, solution for injection:

1 dose = 0.1 ml contains 0.20 microgram Tuberculin PPD.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless to light yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mantoux tuberculin skin testing for diagnostic use in patients infected with tuberculous mycobacteria.

Some countries also recommend tuberculin testing in conjunction with BCG vaccination, either to ensure that only tuberculin-negative individuals are vaccinated or as a post-vaccination test.

4.2 Posology and method of administration

Injection Technique

0.1ml Tuberculin PPD RT 23 SSI should be administered with a 1 ml graduated syringe fitted with a short bevel needle (gauge 25 or 26). The injection should be given strictly intradermally in the middle third of the forearm, as a reaction might be weaker near the wrist or the elbow joint.

The skin is slightly stretched, and the needle point (held almost parallel with the skin surface, bevel upwards) is inserted into the superficial layer of the dermis. The needle should be visible through the epidermis during insertion. The solution is slowly injected and a small papule of 8-10 mm in diameter appears and remains for about 10 minutes. If a papule does not appear the solution has been injected too deeply, and the test should be repeated on the other arm. If the same arm is used the injection site should be separated at least 4 cm from the first injection site.

The injection may result in an induration surrounded by an area of erythema a few hours after the injection.

Dosage and strength

The dosage is always 0.1 ml by strictly intradermal injection.

The strength 2 T.U./0.1 ml is recommended. 10 T.U./0.1 ml may be used for a second test if the first test is negative (less than approx. 6 mm in diameter) and a retest is considered appropriate, refer to section 4.5.

Evaluating the reaction

The reaction should be evaluated 48-72 hours after the injection.

A positive reaction to Tuberculin PPD RT 23 SSI is defined as a flat, uneven, slightly raised induration having a diameter of at least 6 millimetres, surrounded by a more or less defined area of redness. Only the induration is assessed. The diameter of the induration in millimetres is measured transversely to the long axis of the forearm with a clear, flexible, plastic ruler.

HOW TO READ THE MANTOUX TEST

Diameter of induration in millimeters

Negative	Positive	Strongly positive
0-5 mm	6-14 mm	≥15 mm

A positive reaction indicates a response of the immune system due to one or more of the following reasons:

- a. infection with Mycobacterium tuberculosis complex (*M. tuberculosis*, *M. bovis*, *M. africanum* or *M. microti*)
- b. infection with non-tuberculous mycobacteria
- c. previous BCG vaccination (BCG vaccinated persons normally become tuberculin positive after 4-8 weeks)

Reactions with a diameter larger than 15 millimetres are defined as strongly positive and give a strong indication of infection with Mycobacterium tuberculosis complex.

4.3 Contraindications

Tuberculin PPD RT 23 SSI should not be administered to patients known to be hypersensitive to any component of the medicinal product or to patients who previously have experienced a severe skin reaction to Tuberculin products.

4.4 Special warnings and precautions for use

No special precautions need to be considered. Although anaphylaxis is extremely rare, facilities for its management should always be available during skin testing.

Repeated tuberculin skin testing in patients previously vaccinated with BCG vaccine may be complicated by a booster phenomenon. Repetition of the skin test in a short period of time (less than 1 year) should be avoided, or apparent conversions of the reaction from negative to positive may be created.

4.5 Interaction with other medicinal products and other forms of interaction

A variety of host-related factors such as young or old age, poor nutrition, immunosuppression by disease or drugs, viral infections (particularly measles, mononucleosis, varicella and influenza) can lower tuberculin reactivity. After vaccinations with vaccines containing live virus (e.g. vaccines against measles, mumps and rubella) a reduced reactivity may be observed. This decreased reactivity may result in false negative reactions. Many patients co-infected with HIV and Mycobacterium tuberculosis have anergy for tuberculin with or without anergy to other skin test antigens. In patients with severe tuberculosis (e.g. miliary tuberculosis) tuberculin reactivity may be suppressed.

Recent infection with environmental non-tuberculous mycobacteria can result in cross-sensitization and a false-positive reaction to a Mantoux test.

4.6 Pregnancy and lactation

Testing with Tuberculin PPD RT 23 SSI may be carried out during pregnancy and lactation.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Common(>1/100)	Local: Pain, irritation or discomfort at the injection site immediately after the injection.
Uncommon(<1/100)	Systemic: Headache, fever Local: Enlargement of regional lymph nodes
Rare(<1/1,000)	Systemic: Anaphylactic reactions Local: Hypersensitivity to tuberculin can cause vesiculation and skin necrosis.

Though anaphylactic reactions are extremely rare, facilities for their management should always be available.

4.9 Overdose

No case of overdose has been reported.

5. **PHARMACOLOGICAL PROPERTIES**

5.1 Pharmacodynamic properties

Pharmacotherapeutic group (ATC code): V 04 CF 01.

5.2 Pharmacokinetic properties - Not relevant.

5.2 Preclinical safety data

Studies with non sensitised animals have revealed that, in the absence of sensitisation, the injection of tuberculin provokes a slight local reaction (rabbit) and this reaction does not increase through out the time with repeated administration of tuberculin (guinea pig).

6. **PHARMACEUTICAL PARTICULARS**

6.1 List of excipients

Disodium phosphate dihydrate	7.6mg
Sodium chloride	4.8mg
Potassium dihydrogen phosphate	1.5mg
Potassium hydroxychinoline sulphate	100µg
Polysorbate	80 50µg
Water for Injections to	1 ml

6.2 Incompatibilities

Do not mix with other medicinal products

6.3 Shelf life

36 months

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C -8°C.

6.4 Special precautions for storage
Store at 2°C - 8°C, protected from light.

6.5 Nature and contents of container
Type I glass vials (Ph Eur)
Stoppers of chlorobutyl rubber (Ph.Eur).

Presentations:

Tuberculin PPD RT 23 SSI 2 T.U./0.1 ml: 1.5 ml: 1 and 10 vials.
5 ml: 1 and 10 vials.

Tuberculin PPD RT 23 SSI 10 T.U./0.1 ml: 1.5 ml: 1 and 10 vials.
Not all pack sizes may be marketed.

6.6 Instructions for use and handling
Refer to section 4.2.

Any unused product or waste material should be disposed of in accordance with local requirements. The product does not contain live materials or other hazardous agents.

7. MARKETING AUTHORISATION HOLDER

Statens Serum Institut, 5,
Artillerivej,
DK - 2300 Copenhagen S.

8. MARKETING AUTHORISATION NUMBER(S)

XXXXXX

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION XXXXXX
MARKETING AUTHORISATION NUMBER(S)**

XXXXXX

10. DATE OF REVISION OF THE TEXT

September 2002.

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Differences Between the Summary of Product Characteristics of the Tuberculin PPD Solutions available from Chiron Vaccines Evans and SSI

This table provides a summary of the difference between the licensed Tuberculin PPD dilutions manufactured by Chiron Vaccines Evans and the solutions available from Statens Serum Institute (SSI) as indicated in the latest Summary of Product Characteristics (SPC).

Presentations

Characteristics	Chiron	SSI	Reccommendations/Notes
Presentation	1ml ampoules in a pack of 5 ampoules	1.5 vials in a pack of 10 vials	The SSI vials have a chlorobutyl rubber stopper
Label Strength <i>NB. Please refer to the Dosage and Administration Section. 1 unit of PPD from SSI may not be equivalent to 1 unit of PPD from Chiron</i>	Not available 100 units per ml 1000 units per ml	2 units in 0.1ml 10 units in 0.1ml Not available	Caution advised due to the differences in the labelling format using units per ml (Chiron) compared to units in 0.1ml. (SSI). The use of decimal points in labelling can cause misinterpretation of the strength

Dosage and Administration

Instructions	Chiron	SSI	Recommendations / Notes
Route of Administration	Intradermal	Intracutaneous*	Routes of administration are identical: both mean 'within the skin'
Method of administration	Similar advice is given in both SPCs.	Similar advice is given in both SPCs.	For further information please refer to the guidance on skin preparation and test site definition given in 'Immunisation against Infectious Disease 1996' (Green Book) section 32.15.2 page 231.
Routine Dose	Routine dose of (0.1ml) of 100 units per ml PPD (equivalent to 10 units)	SPC recommends an initial diagnostic test of 2 units in 0.1 ml PPD.	Users are strongly recommended to follow the dosage instructions as indicated in the SSI SPC as the standard test for screening purposes.

* The term intracutaneous is used in place of the term intradermal on product information provided by the SSI.

Mantoux Test Results

Instructions	Chiron	SSI	Recommendations / Notes
Test Results	<p>A positive reaction is characterised by an area of 5mm or greater of palpable induration, which may sometimes be surrounded by erythema. The results should be read 48 to 96 hours after the test, (preferably after 72 hours).</p>	<p>The reaction should be evaluated 48 to 72 hours after the injection. A positive reaction is defined as a flat, uneven, slightly raised induration having a diameter of at least 6 mm, surrounded by a more or less defined area of redness. <u>Only the induration is assessed.</u> The diameter of the induration in millimetres is measured transversely to the long axis of the forearm with a clear, flexible, plastic ruler.</p>	<p>Test results should be read after 48 to 72 hours. Thereafter reactivity is likely to wane. Please refer to Green Book section 32.15.3 page 231.</p>
Post Mantoux test BCG Vaccination	<p>Tuberculin positive subjects should not be given BCG vaccine.</p>	<p>An indication of grading is given together with a list of reasons for a positive reaction. This does not include a statement on BCG vaccination.</p>	<p>Tuberculin positive subjects should not be given BCG vaccine. Please refer to the Green Book section 32.16 pages 231-232.</p>

Contra-indications, Special Warning and Special Precautions for Use.

Instructions	Chiron	SSI	Recommendations/Notes
Contra-indicators	None stated.	PPD Should not be administered to patients known to be hypersensitive to any component of the medicinal products or to patients who previously have experienced a severe skin reaction to Tuberculin products.	
Other vaccines	Testing should not be carried out within three weeks of receiving a live viral vaccine.	No statement on the use of live viral vaccines.	Please refer to Green Book section 32.17 page 232. Chiron guidance should be followed. Immunisation programmes should be arranged so the tuberculin testing is carried out before live vaccines are given.
Active tuberculosis	Caution should be exercised in the use of PPD in persons who have or are suspected of having active tuberculosis.	No similar caution.	2 units in 0.1 ml is recommended for diagnostic screening.
Pregnancy and Lactation	PPD should only be used in pregnancy where the potential benefits of testing outweigh the possible risk of side effects.	Testing with PPD may be carried out during pregnancy and lactation.	The advice given in the SSI SPC applies.
Other warnings and precautions	Broadly similar advice is given in both companies SPCs. Please refer to the individual SPC for further information.	Broadly similar advice is given in both companies SPCs. Please refer to the individual SPC for further information.	For further information please refer to SPCs and Green Book page 232.

Pharmaceutical Particulars

Instructions	Chiron	SSI	Recommendations / Notes
Excipients	Excipients listed in the Summary of Product Characteristics (SPC)	Minor difference in most excipients when compared with the Chiron presentation. Product contains an additional excipient Potassium hydroxychinoline sulphate.	Control solution for Mantoux Test available from Chiron is not a suitable control for the SSI solutions.
Maximum Shelf Life	12 months	36 months	
Instructions of use/handling	Use the contents of the ampoule as soon as possible and within 1 hour of opening provided adequate aseptic precautions are taken.	The contents of the vial should not be used more than 24 hours after the first dose has been removed.	Follow the SSI SPC instructions. It is recommended that the SSI vials are marked with the date and time of opening.
Storage	Between 2°C and 8°C. Do not freeze.	Between 2°C and 8°C	DH recommends that the product is not frozen.
Disposal	Disposal should be by incineration at a temperature not less than 1100°C at a registered waste disposal contractor.	Disposal in accordance with local requirements.	Disposal of all Tuberculin solutions from either manufacturer should be by incineration at a temperature not less than 1100°C at a registered waste disposal contractor.

PATIENT SPECIFIC DIRECTION FOR ADMINISTRATION OF TUBERCULIN PPD (SSI) FOR MANTOUX TESTING

Tuberculin PPD from SSI is available as an unlicensed medicine in the UK (although it has a Marketing Authorisation for use in other European countries). As the Tuberculin PPD (SSI) is unlicensed in the UK, this product cannot be administered using a Patient Group Direction (PGD). Instead, it should be administered on the basis of a Patient Specific Direction (PSD) i.e. a written instruction by a doctor or an Extended Formulary Nurse Prescriber to administer the medicine directly to one or more named patients.

When it is anticipated that a group of patients will require Mantoux testing using Tuberculin PPD(SSI), wherever possible, a list of eligible patients should be drawn up in advance of a session and signed by a doctor or extended formulary nurse prescriber. An example form is attached. If additional patients present for testing, approval for their inclusion should be sought from a doctor or extended formulary nurse prescriber. Approval can be granted as a verbal instruction.

For more information on the use of PGDs and PSDs, please refer to:

http://www.dh.gov.uk/AboutUs/HeadsOfProfession/ChiefHealthProfessionsOfficer/CHPOPolicyAreas/CHPOPolicyAreasArticle/fs/en?CONTENT_ID=4061507&chk=kpOWot

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