Dear Colleague

SUPPLIES OF TUBERCULIN FOR HEAF AND MANTOUX TESTING

Purpose

Further to CMO letter issued on 8 July, SEHD/CMO/(2005)5, the purpose of this letter is to inform NHSS that 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 UK licensed PPD) reached their expiry date at the end of May 2005.

Action

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 the attention of all relevant professionals involved in tuberculin skin testing for screening or diagnostic purposes are set out below:

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 the 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 health care 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 vials. The Tuberculin PPD (SSI) is available in two concentrations expressed as the number of units in 0.1ml of PPD solution and is supplied in 1.5 ml vials. **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 (2 TU per 0.1 ml) is negative (less than approx. 6 mm in diameter) and a retest is considered appropriate for clinical purposes.

From the Deputy Chief Medical Officer, Chief Nursing Officer and Chief Pharmaceutical Officer

Professor Peter Donnelly MD FRCP FFPH
Paul Martin RN RHV DMS MBA
Professor Bill Scott BSc MSc FRPharmS

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Edinburgh EH1 3DG
Telephone 0131-244 2836
Fax 0131 244-2835

29 July 2005

SEHD/CMO(2005) 6

For action
Chief Executives, NHS Boards
Medical Directors, NHS Boards (to cascade to Infectious Disease Consultants; Consultant Paediatricians; Consultant Physicians; chest clinics; chest physicians and TB nurses)
Practice Managers(to cascade to Practice Staff and General Practitioners as appropriate)
Chief Pharmacists
Immunisation Co-ordinators
CPHMs
Scottish Prison Service
Directors of Nursing, NHS Boards
Specialists in Pharmaceutical Public Health

For information
Directors of Public Health
Community Pharmacists
General Manager, HPS
Chief Executive, NHS Health Scotland

NHS 24

Further Enquiries
Policy Issues
Mr John Froggatt
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St Andrews House
EDINBURGH EH1 3DG
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.

<table>
<thead>
<tr>
<th></th>
<th>Negative</th>
<th>Positive</th>
<th>Strongly positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiron Vaccines Evans Tuberculin PPD</td>
<td>0-4 mm</td>
<td>5-14 mm</td>
<td>≥15 mm</td>
</tr>
<tr>
<td>SSI Tuberculin PPD</td>
<td>0-5 mm</td>
<td>6-14 mm</td>
<td>≥15 mm</td>
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</table>

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. Health Scotland and NHS Education for Scotland will support the availability of training materials showing how to give and read the Mantoux test. These materials will be available from early October to download from www.healthscotland.com/immunisation/ or available to order from NHS Health Scotland, www.healthscotland.com or tel: 0131 536 5500.

4. The Mantoux test must be read at 48 – 72 hours after administration. Services providing Tuberculin testing by the Heaf method will currently have clinic sessions organised around the need to read the test result at 1 week. In order to ensure that services are able to read Mantoux test results it is now necessary to make arrangements for patients to return after 48 – 72 hours.

5. Tuberculin PPD 2TU and 10TU (SSI) will be available from Vaccine Holding Centres in boxes of 10 x 1.5ml vials. Please note also that the product information supplied with the Tuberculin PPD from SSI is in four languages, including English.

Advice in ‘Immunisation against Infectious Disease 1996’ (The Green Book) is still relevant for the SSI product but it needs to be interpreted in the light of the SSI directions.

A copy of the SSI Summary of Product Characteristics is available at Appendix 1 and from www.ssi.dk/sw4248.asp

Orders should be placed directly with Vaccine Holding Centres using the following product codes:

SSI2 for 2 TU Tuberculin PPD used for routine Mantoux testing
SSI10 for 10 TU presentation.

Thank you for your continued work on this important immunisation programme.

Yours sincerely

[Signature]

Professor Peter Donnelly
Deputy Chief Medical Officer

[Signature]

Mr Paul Martin
Chief Nursing Officer

Professor Bill Scott
Chief Pharmaceutical Officer
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*
0.1 ml 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 appear 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 are 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 millimetres

<table>
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<tr>
<th>Negative</th>
<th>Positive</th>
<th>Strongly positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 mm</td>
<td>6-14 mm</td>
<td>≥15 mm</td>
</tr>
</tbody>
</table>

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 gives 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 (particular 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 node |
| 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.

5.3 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 throughout the time with repeated administration of tuberculin (guinea pig).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Disodium phosphate dihydrate 7.6 mg  
Sodium chloride 4.8 mg  
Potassium dihydrogen phosphate 1.5 mg  
Potassium hydroxychinoline sulphate 100 µg  
Polysorbate 80 50 µg  
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 AUTHOURISATION 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

10. DATE OF REVISION OF THE TEXT

September 2002.
### Appendix 2

**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**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Chiron</th>
<th>SSI</th>
<th>Recommendations/ Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation</td>
<td>1ml ampoules in a pack of 5 ampoules</td>
<td>1.5ml vials in a pack of 10 vials</td>
<td>The SSI vials have a chlorobutyl rubber stopper</td>
</tr>
<tr>
<td>Label Strength</td>
<td>Not available</td>
<td>2 units in 0.1ml</td>
<td>Caution advised due to the difference 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.</td>
</tr>
<tr>
<td><strong>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</strong></td>
<td>100 units per ml</td>
<td>10 units in 0.1ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1000 units per ml</td>
<td>Not available</td>
<td></td>
</tr>
</tbody>
</table>

**Dosage and Administration.**

<table>
<thead>
<tr>
<th>Instructions</th>
<th>1.1.2 hiron</th>
<th>SSI</th>
<th>Recommendations/ Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of Administration</td>
<td>Intradermal</td>
<td>Intracutaneous’</td>
<td>Routes of administration are identical: both mean ‘within the skin’.</td>
</tr>
<tr>
<td>Method of administration</td>
<td>Similar advice is given in both SPCs.</td>
<td>Similar advice is given in both SPCs.</td>
<td>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.</td>
</tr>
<tr>
<td>Routine Dose</td>
<td>Routine dose of (0.1ml) of 100 units per ml PPD</td>
<td>SPC recommends an initial diagnostic test of</td>
<td>Users are strongly recommended to follow the dosage</td>
</tr>
</tbody>
</table>
* The term intracutaneous is used in place of the term intradermal on product information provided by SSI.

## Mantoux Test Results

<table>
<thead>
<tr>
<th>Instructions</th>
<th>Chiron</th>
<th>SSI</th>
<th>Recommendations/ Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test results</td>
<td>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).</td>
<td>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. 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.</td>
<td>Test results should be read after 48 to 72 hours. Thereafter reactivity is likely to wane. Please refer to the Green Book section 32.15.3 page 231.</td>
</tr>
<tr>
<td>Post Mantoux test BCG Vaccination</td>
<td>Tuberculin positive subjects should not be given BCG vaccine.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td></td>
<td>Tuberculin positive subjects should not be given BCG vaccine. Please refer to the Green Book section 32.16 pages 231-232.</td>
</tr>
</tbody>
</table>
Contra-indications, Special Warning and Special Precautions for Use.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Chiron</th>
<th>SSI</th>
<th>Recommendations/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contra-indications</td>
<td>None stated.</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Other vaccines</td>
<td>Testing should not be carried out within three weeks of receiving a live viral vaccine.</td>
<td>No statement on the use of live viral vaccines.</td>
<td>Please refer to the 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.</td>
</tr>
<tr>
<td>Active tuberculosis</td>
<td>Caution should be exercised in the use of PPD in persons who have or are suspected of having active tuberculosis.</td>
<td>No similar caution.</td>
<td>2 units in 0.1ml is recommended for diagnostic screening.</td>
</tr>
<tr>
<td>Pregnancy and Lactation</td>
<td>PPD should only be used in pregnancy where the potential benefits of testing outweigh the possible risk of side effects.</td>
<td>Testing with PPD may be carried out during pregnancy and lactation.</td>
<td>The advice given in the SSI SPC applies.</td>
</tr>
<tr>
<td>Other warning and precautions.</td>
<td>Broadly similar advice is given in both companies SPCs. Please refer to the individual SPC for further information.</td>
<td>Broadly similar advice is given in both companies SPCs. Please refer to the individual SPC for further information.</td>
<td>For further information please refer to the SPCs and Green Book page 232</td>
</tr>
</tbody>
</table>
### Pharmaceutical Particulars.

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

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

The below named patients are eligible for routine Mantoux testing by intradermal injection of Tuberculin PPD (SSI) 2 TU per 0.1ml (20 units in 1ml) and Tuberculin PPD (SSI) 10 TU/0.1 ml

The higher concentration 10 TU/0.1 ml may be used for a second test if the first test (2 TU per 0.1 ml) is negative (less than approx. 6 mm in diameter) and a retest is considered appropriate.

Patients Name

<table>
<thead>
<tr>
<th>Name</th>
<th>Name</th>
<th>Name</th>
<th>Name</th>
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</tbody>
</table>
If you require further information please contact the relevant person below:

Dr Elizabeth Stewart (Medical issues)  Tel: 0131 244 2158
Mr John Froggatt (Policy issues)  Tel: 0131 244 2504
Mrs Norma Darroch (Pharmacy issues)  Tel: 0131 244 2516