



Pfizer Global Manufacturing

21 DIC. 2007

Ascoli Piceno, _____

TO WHOM IT MAY CONCERN

• **MEDROL 16MG & 32MG TABLETS.**

I, the undersigned, Sylvia Orsini, TSE/BSE Responsible for the pharmaceutical plant Pfizer Italia S.r.l., located in Via del Commercio 25/27, 63046 Marino del Tronto – Ascoli Piceno (Italy), declare the following:

The above mentioned products contain the following ingredients:

- | | |
|---|--------------------------------------|
| • Methylprednisolone (Active ingredient) | TSE – Specified risk material |
| • Sucrose | TSE – Non specified risk material |
| • Maize starch | TSE – Non specified risk material |
| • Lactose | TSE – Non specified risk material |
| • Calcium stearate | TSE – Specified risk material |
| • Liquid paraffin | TSE – Non specified risk material |

An extensive TSE/BSE investigation has been performed on the components of the above mentioned products and the "Specified risk materials" are:

- **Methylprednisolone (Active substance)**
(Certificate's of Suitability – Nutrient broth: R1-CEP 2000-248-Rev 00, Oleic acid: R1-CEP 2001-079-Rev 00 & Catalase: R1-CEP 2001-168-Rev 00).
- **Calcium stearate**
(Certificate of Suitability N°: R1-CEP 2000-269-Rev 00 / Stearic acid)

The "Certificate of Suitability" has been issued by the European Directorate for the Quality of Medicines (EDQM), thus meaning that our plant is in full compliance to the TSE Commission Directive 1999/82/EEC. (The above mentioned certificate is attached to this statement).

The Ascoli Piceno Plant is also in full compliance to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMA/410/01 Rev. 2) which is adopted by the Committee for Proprietary Medicinal Products (CPMP) and by the Committee for Veterinary Medicinal Products (CVMP).



Pharmaceutical grade lactose is scientifically classified as "safe" with regards to BSE. Please find attached our suppliers' Declaration explaining their compliance to the Note for Guidance EMEA/410/01 Rev. 2 which is based on the Public report EMEA/CPMP/BWP/337/02/Public/Final and the Public statement EMEA/CPMP/571/02 (attached).

All the other ingredients are classified as "Non Specified Risk Materials" and therefore do not present risks for TSE/BSE.

A handwritten signature in black ink, appearing to read "Sylvia Orsini", written over a horizontal dotted line.

Sylvia Orsini
TSE/BSE Responsible
Site Compliance Department
Ascoli Piceno.

METHYLPREDNISOLONE

| Component | Origin of the material (synthetic/ animal/ vegetal) | Country of origin and Tissue used | CEP # |
|--|---|--|---------------------------|
| <u>Methylprednisolone</u> | | | |
| 1. Nutrient broth is used in the fermentation process to generate an early intermediate which is used in the synthesis of drug substance. | 1. Animal | 1. Australia, Canada and USA Bovine: bile, skeletal muscle, connective tissue, skin, bones free from skulls, spinal cord and vertebrae. | 1. R1-CEP 2000-248-Rev 00 |
| 2. Oleic acid is used as starting material for a reagent (Polysorbate 80) used in the master cell bank and working cell bank and during the bioconversion of an early intermediate, used in the synthesis of drug substance. | 2. Animal | 2. USA and Canada Tallow | 2. R1-CEP 2001-079-Rev 00 |
| 3. Catalase is used in the fermentation process to generate an early intermediate which is used in the synthesis of drug substance. | 3. Animal | 3. USA Bovine, liver | 3. R1-CEP 2001-168-Rev 00 |
| 4. Lard oil is used in the fermentation process to produce a precursor to the starting material for the active substance | 4. Animal | 4. USA Porcine | 4. N/A |
| 5. Soy flour hydrolyzate is used in the fermentation process to generate an early intermediate which is used in the synthesis of drug substance. | 5. Animal | 5. USA and Canada Porcine | 5. N/A |
| 6. Edamin S is used in the fermentation process to generate an early intermediate which is used in the synthesis of drug substance. | 6. Edamin S | 6. USA and Canada, Porcine, Pancreas; USA, Australia and New Zealand, Bovine, milk | 6. N/A |

An extensive TSE/BSE assessment has been performed on Methylprednisolone as described in the *Joint CPMP/CVMP Note for Guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human or veterinary medicinal products - EMEA 410/01 Revision 02*.

The Certificates of Suitability for Nutrient broth, Oleic acid and Catalase have been issued by the European Directorate for the Quality of Medicines and attached hereafter.

Lard oil and soy flour hydrolyzate are from porcine origin and to date porcine species have not been reported to be susceptible to transmissible spongiform encephalopathy and are out of the scope of the Guideline mentioned above.

The Edamin S is manufactured from milk taken from healthy animals, in the same conditions as milk collected for human consumption. No other product from ruminant origin has been used to prepare the lactose except calf rennet. The calf rennet is in compliance with the requirements defined in Regulation 999/2001 and other applicable EU legislation. No other product from ruminant origin has been used to prepare the Edamin.

edqm



European Directorate for the Quality of Medicines
Division Certification of Substances

Certificate of suitability
No. R1-CEP 2000-248-Rev 00

1 *Name of the substance:*
2 **NUTRIENT BROTH**
3 (codes 231000, 232000, 233000 and 234000)

4 *Name of holder:*
5 **BECTON, DICKINSON AND COMPANY**
6 7 Loveton Circle
7 USA - 21152 Sparks, Maryland

8 *Sites of production:*
9 **BECTON, DICKINSON AND COMPANY**
10 39 Loveton Circle
11 USA - 21152 Sparks, Maryland

12 **BECTON, DICKINSON AND COMPANY**
13 920 Henry Street
14 USA - 48201 Detroit, Michigan

15 **THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE**
16 **R0-CEP 2000-248-REV 01**

17 After examination of the information provided on the origin of raw material(s) and type of
18 tissue(s) used and on the manufacturing process for this substance on the sites of production
19 mentioned above, USA - 21152 Sparks, Maryland and USA - 48201 Detroit, Michigan, we
20 certify that the substance **NUTRIENT BROTH** meets the criteria described in the current version of
21 the monograph Products with risk of transmitting agents of animal spongiform encephalopathies
22 no. 1483 of the European Pharmacopoeia, current edition including supplements.

23 - countries of origin of source materials: Australia, Canada and United States of
24 America
25 - nature of animal tissues used in manufacture: Bovine bile, bovine skeletal muscle, bovine
26 connective tissue, bovine skin, and bovine
27 bones free from skulls, spinal cord and
28 vertebrae

29 The submitted dossier must be updated after any significant change that may alter the quality,
30 safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform
31 encephalopathy agents.

- 32 Manufacture of the substance shall take place in accordance with a suitable quality assurance
33 system such as ISO 9001 and GMP, and in accordance with the dossier submitted.
34 Failure to comply with these provisions will render this certificate void.
35 The certificate is valid provided that there has been no deterioration in the TSE status of the
36 country(ies) of origin of the source material.
37 This certificate is renewed from 1 October 2006 according to the provisions of Resolution AP-
38 CSP (93) 5 as amended, and of Directive 2001/83/EC and Directive 2001/82/EC and any
39 subsequent amendment, and the related guidelines.
40 This certificate has 40 lines only.



Dr. A. ARTIGES
Director of the Quality of Medicines

Strasbourg, 3 October 2006

DECLARATION OF ACCESS (to be filled in by the certificate holder under their own responsibility)

BECTON, DICKINSON AND COMPANY, as holder of the certificate of suitability

R1-CEP 2000-248-Rev 00 for NUTRIENT BROTH

hereby authorises
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing
Authorisation(s): (name of product(s) and marketing number(s), if known)

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been
made since the granting of this version of the certificate.

Date and Signature (of the CEP holder):

Postal Address: 226 Avenue de Colmar (entrance rue Schertz) B.P. 907 — F 67029 Strasbourg Cedex 1
Telephone: 03.88.41.30 30 - Fax 03.88.41.27.71 - Web site : <http://www.pheur.org>



European Directorate for the Quality of Medicines
Certification Unit

Certificate of suitability
No. R1-CEP 2001-168-Rev 00

1 *Name of the substance:*

2 **CATALASE**

3 **Product No C9322**

4 *Name of holder:*

5 **SIGMA-ALDRICH CORPORATION**

6 **3050 Spruce Street**

7 **USA – 63103 Saint Louis, Missouri**

8 *Site of production:*

9 **SIGMA-ALDRICH CORPORATION**

10 **3500 Dekalb Street**

11 **USA – 63118 Saint Louis, Missouri**

12 **THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE**

13 **R0-CEP 2001-168-Rev 02**

14 After examination of the information provided on the origin of raw material(s) and type of
15 tissue(s) used and on the manufacturing process for this substance on the site of production
16 mentioned above, USA – 63118 Saint Louis, Missouri, we certify that the substance CATALASE
17 meets the criteria described in the current version of the monograph Products with risk of
18 transmitting agents of animal spongiform encephalopathies no. 1483 of the European
19 Pharmacopoeia, current edition including supplements.

20 - country of origin of source materials: **New Zealand**

21 - nature of animal tissues used in manufacture: **Bovine liver**

22 The submitted dossier must be updated after any significant change that may alter the quality,
23 safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform
24 encephalopathy agents.

25 Manufacture of the substance shall take place in accordance with a suitable quality assurance
26 system such as ISO 9001, and in accordance with the dossier submitted.

27 Failure to comply with these provisions will render this certificate void.

28 The certificate is valid provided that there has been no deterioration in the TSE status of the
29 country(ies) of origin of the source material.

- 30 This certificate is renewed from 11 June 2006 according to the provisions of Resolution AP-
31 CSP (93) 5 as amended, and of Directive 2001/83/EC and Directive 2001/82/EC and any
32 subsequent amendment, and the related guidelines.
33 This certificate has 33 lines only.



Dr. A. ARTIGES
Director of the Quality of Medicines

Strasbourg, 12 May 2006

DECLARATION OF ACCESS (to be filled in by the certificate holder under their own responsibility)

SIGMA-ALDRICH CORPORATION, as holder of the certificate of suitability

R1-CEP 2001-168-Rev 00 for CATALASE

hereby authorises Pfizer
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing
Authorisation(s): (name of product(s) and marketing number(s), if known)

Unknown

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been
made since the granting of this version of the certificate.

Date and Signature (of the CEP holder): Mike Shannon 05/19/06



European Directorate for the Quality of Medicines
Division Certification of Substances



Certificate of suitability
No. R1-CEP 2001-079-Rev 00

1 *Name of the substance:*
2 **OLEIC ACID**
3 **Uniqema Chicago (USA)**

4 *Name of holder:*
5 **UNIQEMA**
6 **4650 South Racine Avenue**
7 **USA - IL 60609-3321 Chicago**

8 *Site of production:*
9 **UNIQEMA**
10 **4650 South Racine Avenue**
11 **USA - IL 60609-3321 Chicago**

12 **THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE**
13 **R0-CEP 2001-079-Rev 01**

14 After examination of the information provided on the origin of raw material(s) and type of
15 tissue(s) used and on the manufacturing process for this substance on the site of production
16 mentioned above, USA - IL 60609-3321 Chicago, we certify that the substance **OLEIC ACID**
17 meets the criteria described in the current version of the monograph Products with risk of
18 transmitting agents of animal spongiform encephalopathies, no. 1483 of the European
19 Pharmacopoeia, current edition including supplements.

20 The submitted dossier must be updated after any significant change that may alter the quality,
21 safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform
22 encephalopathy agents.

23 Manufacture of the substance shall take place in accordance with a suitable quality assurance
24 system such as ISO 9001, and in accordance with the dossier submitted.

25 Failure to comply with these provisions will render this certificate void.

26 The certificate is valid provided that there has been no deterioration in the TSE status of the
27 country(ies) of origin of the source material.

- 28 This certificate is renewed from **25 January 2007** according to the provisions of Resolution AP-
29 CSP (93) 5 as amended, and of Directive 2001/83/EC and Directive 2001/82/EC and any
30 subsequent amendment, and the related guidelines.
31 This certificate has 31 lines only.



Dr. A. ARTIGES
Director of the Quality of Medicines

Strasbourg, 10 January 2007

DECLARATION OF ACCESS (to be filled in by the certificate holder under their own responsibility)

UNIQEMA, as holder of the certificate of suitability

R1-CEP 2001-079-Rev 00 for OLEIC ACID

hereby authorises **Pfizer**

(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): (name of product(s) and marketing number(s), if known)

Products containing **TWEEN® 80 Polysorbate 80 NF**

***** Products Not Specified *****

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature (of the CEP holder):
25-Jan-2007

