European Medicines Agency

4 July 2004
EMEA/CHMP/651/04

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE**
**22-23 JUNE 2004 PLENARY MEETING**
**MONTHLY REPORT**

The Committee for Medicinal Products for Human Use (CHMP) held its 2nd plenary meeting from 22-23 June 2004.

**Product related issues**

The Committee adopted 6 positive opinions on initial marketing authorisation applications for:

- **Angiox** (bivalirudin), from The Medicines Company UK Ltd, for use as an anticoagulant in patients undergoing percutaneous coronary intervention. EMEA review began on 18 August 2003, with an active review time of 176 days.
- **Alimta** (pemetrexed), from Eli Lilly Nederland B.V., for the treatment of malignant pleural mesothelioma and non-small cell lung cancer. EMEA review began on 18 August 2003, with an active review time of 197 days.
- **Protelos** and **Osseor** (strontium ranelate), from Les Laboratoires Servier, for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures. EMEA review began on 21 July 2003, with an active review time of 194 days.
- **Raptiva** (efalizumab), from Serono Europe Ltd, for the treatment of moderate to severe chronic plaque psoriasis. EMEA review began on 24 February 2003, with an active review time of 185 days.
- **Wilzin** (zinc acetate dihydrate), from Orphan Europe SARL, for the treatment of Wilson's disease. EMEA review began on 24 March 2003 with an active review time of 195 days. Wilzin was designated an orphan medicinal product on 31 July 2001 and is the eighteenth orphan medicinal product to receive a positive CHMP opinion.

Summaries of these opinions, including the full indications for each product, are available on the EMEA web site: http://www.emea.eu.int.

The Committee adopted positive opinions on the extension of indication for two medicinal products that are already authorised in the EU:

- **Mabthera** (rituximab), Roche Registration Ltd, to extend its use in combination with CVP (cyclophosphamide, vincristine and prednisolone) chemotherapy for the treatment of previously untreated patients with indolent non-Hodgkin's Lymphoma. Mabthera was first authorised in the European Union on 2 June 1998.
- **Prevenar** (pneumococcal conjugate vaccine), Wyeth-Lederle Vaccines SA, to extend the age range of vaccination from 2 years to up to 5 years of age. Prevenar was first authorised in the European Union on 2 February 2001.

Further information on these extensions will be included in the public assessment report (EPAR) once the European Commission has granted final approval.

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The Committee adopted a positive opinion on a "line extension" application, a List of Questions on a "line extension" application (in accordance with Annex II of Commission Regulation (EC) No. 1085/2003), and also two Lists of Questions on initial applications.

An overview of centralised procedures since 1995 is given in **Annex 1**. The list of medicinal products for which marketing authorisations have been granted by the European Commission since the CHMP plenary meeting on 1 - 3 June 2004 is provided in **Annex 2.** The post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 3**.

**Non-product related issues**

*CHMP Working Parties and Ad Hoc Groups*

The CHMP was informed of the outcome of the discussions of the Scientific Advice Working Group (SAWG) meeting, which was held on 7 - 8 June 2004. For further details, please see **Annex 4**.

Documents prepared by the CHMP Working Parties and Ad Hoc Groups adopted during the 22-23 June 2004 CHMP meeting are listed in **Annex 5**.

*Organisational Matters*

The 1st CHMP Organisational Matters meeting took place on Monday 21 June 2004, chaired by Dr D. Brasseur. The main topics addressed during the meeting related to:

- The establishment of Scientific Advisory Groups and Working Parties in the framework of Regulation (EC) 726/2004.
- The potential integration of the ORGAM meeting into the CHMP plenary meeting from September 2004 onwards. Such integration will lead to plenary CHMP meetings starting on Mondays at 13.00 with discussions on organisational matters / ongoing Working Party activities.
- The establishment of an internal procedure for the nomination of Plasma Master File / Vaccine Master File Coordinators with regards to evaluation of an application for certification.
- The adoption of updated Day 70 Assessment Report Templates.

*Upcoming meetings following the July 2004 CHMP plenary meeting:*

- The 3rd plenary meeting of the CHMP will be held on 27-29 July 2004.
- The next CHMP Organisational Matters meeting is scheduled to take place on Monday 26 July 2004.
- An EMEA Interested Parties meeting on the Invented Names procedure will take place on 13 September 2004.

**PROCEDURAL ANNOUNCEMENTS**

- **Reminder on the intended date of submission**

Applicants are reminded of the necessity to specify their intended date of marketing authorisation application submission to the EMEA at least four to six months before the submission takes place. This can be specified e.g. in requests for Part B status, invented name checks and at the time of the pre-submission meeting. However, such dates must be reconfirmed at the time of the (Co)-Rapporteurs appointment. Filing dates should be as realistic as possible as such information is crucial to the EMEA and to the CHMP members and their assessment teams for planning purposes. Any anticipated change to the filing dates must be notified in advance to EMEA / CHMP. In such case, applicants should be aware that potential re-appointment of (Co)-Rapporteurs may become necessary due to competing evaluation demands.

- **Advisory note on dossier requirements**

Marketing Authorisation Holders and applicants are advised that a revised list on dossier requirements and contact information regarding initial Marketing Authorisation applications has been published (http://www.emea.eu.int/htms/human/presub/q23-2.htm.).

*Mutual Recognition procedure*

The CHMP noted the report from the Mutual Recognition Facilitation Group (MRFG) meeting held on 21 June 2004. For further details, please see **Annex 6.**

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This CHMP Monthly Report and other documents are available on the Internet at the following address:
http://www.emea.eu.int

## EMEA CENTRALISED PROCEDURES

| | 1995 - 2003 | 2004 | Overall Total |
|---|---|---|---|
| **Scientific Advice** | 367 | 28 | 395 |
| **Follow-up to Scientific Advice** | 60 | 2 | 62 |
| **Protocol Assistance** | 30 | 13 | 43 |
| **Follow-up to Protocol Assistance** | 9 | 1 | 10 |

| | 1995-2003 | | | 2004 | | | |
|---|---|---|---|---|---|---|---|
| | **Part A** | **Part B** | **Total** | **Part A** | **Part B** | **Total** | |
| **Applications submitted** | 134 | 271 | 405 | 9 | 11 | 20 | 425 |
| **Consultation for Medical Device**[1] | 0 | 1 | 1 | 0 | 0 | 0 | 1 |
| **Withdrawals** | 22 | 55 | 77 | 0 | 4 | 4 | 81 |
| **Positive opinions**[2] | 99 | 172 | 271 | 5 | 13 | 18 | 289[3] |
| **Negative opinions**[4] | 2 | 5 | 7 | 0 | 0 | 0 | 7[5] |
| **Marketing authorisations granted by the Commission** | 91 | 164 | 255 | 5 | 11 | 16 | 271[6] |

| | 1995-2003 | | | 2004 | | | Overall Total |
|---|---|---|---|---|---|---|---|
| | **Part A** | **Part B** | **Total** | **Part A** | **Part B** | **Total** | |
| **Variations type I** | 771 | 1505 | 2276 | 30 | 200 | 230 | 2506 |
| **Positive opinions, variations type II** | 583 | 697 | 1280 | 71 | 65 | 136 | 1416 |
| **Negative opinions, variations type II** | 1 | 6 | 7 | 0 | 0 | 0 | 7 |
| **Extensions (Annex II applications)** | 49 | 56 | 105 | 3 | 3 | 6 | 111 |

[1] Consultation in accordance with Council Directive 93/42/EEC concerning medical devices as amended by Directive 2000/70/EC as regards medical devices incorporating stable derivatives of human blood or plasma and Directive 2001/104/EC.
[2] 17 positive opinion corresponding to 17 Orphan Medicinal Products
[3] 289 positive opinions corresponding to 222 substances
[4] In case of appeal, the opinion will not be counted twice
[5] 7 negative opinions corresponding to 6 substances (2 of these negative opinions correspond to 2 Orphan Medicinal Products)
[6] 271 marketing authorisations corresponding to 206 substances

# MEDICINAL PRODUCTS GRANTED A COMMUNITY MARKETING AUTHORISATION UNDER THE CENTRALISED PROCEDURE SINCE 1 - 03 JUNE 2004 CHMP MONTHLY REPORT

| | |
|---|---|
| **Invented Name** | Oxybutynin Nicobrand |
| **INN** | oxybutynin |
| **Marketing Authorisation Holder** | Nicobrand Limited |
| **ATC code** | G04BD04 |
| **Indication** | Symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with unstable bladder |
| **CPMP Opinion date** | 20/11/2003 |

| | |
|---|---|
| **Invented Name** | Levemir |
| **INN** | insulin detemir |
| **Marketing Authorisation Holder** | Novo Nordisk A/S |
| **ATC code** | A10AE |
| **Indication** | Treatment of diabetes mellitus |
| **CPMP Opinion date** | 26/02/2004 |

| | |
|---|---|
| **Invented Name** | Abilify |
| **INN** | aripiprazole |
| **Marketing Authorisation Holder** | Otsuka Pharmaceuticals Europe Ltd |
| **ATC code** | N05A |
| **Indication** | Treatment of schizophrenia |
| **CPMP Opinion date** | 26/02/2004 |

| | |
|---|---|
| **Invented Name** | Tachosil |
| **INN** | Human Fibrinogen + Human Thrombin |
| **Marketing Authorisation Holder** | Nycomed Austria GMBH |
| **ATC code** | B02BC + V03AK |
| **Indication** | Supportive treatment in surgery for improvement of haemostasis where standard techniques are insufficient |
| **CPMP Opinion date** | 26/02/2004 |

# OUTCOME OF THE 22-23 JUNE 2004 CHMP MEETING IN RELATION TO CENTRALISED APPLICATIONS IN THE POST-AUTHORISATION PHASE

| **Opinions for Type II Variation applications** | |
|---|---|
| **Number of Opinions** | **Outcome** |
| 2 Extensions of indication | 2 Positive opinions |
| 19 SPC changes | 19 Positive opinions |
| 17 Quality changes | 17 Positive opinions |

| **Opinions for Annual Re-Assessment applications** | | |
|---|---|---|
| **Name of Medicinal Product (INN)**<br>**MAH** | **Outcome** | **Comments** |
| N/A | N/A | N/A |

| **Opinions for Renewal applications** | | |
|---|---|---|
| **Name of Medicinal Product (INN) MAH** | **Outcome** | **Comments** |
| **Ferriprox** (deferiprone)<br>Apotex | Positive opinion | --- |
| **Integrilin** (eptifibatide)<br>SP Europe | Positive opinion | --- |
| **Remicade** (infliximab)<br>Centocor B.V | Positive opinion | --- |
| **Synagis** (palivizumab)<br>Abbott Laboratories | Positive opinion | --- |

## OUTCOME OF THE 22-23 June 2004 CHMP MEETING IN RELATION TO SCIENTIFIC ADVICE PROCEDURES

| Substance | Intended indications(s) | Type of Request | | | | Topic | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | New | | Follow-up | | Pharmaceutical | Pre-clinical | Clinical | Significant Benefit |
| | | SA | PA | SA | PA | | | | |
| Chemical | Congestive heart failure | X | | | | | | X | |
| Chemical | Vein graft failure | X | | | | | X | X | |
| Chemical | Type 2 diabetes | | | X | | | | X | |
| Chemical | Type 2 diabetes | | | X | | | X | X | |
| Biological | Anaemia | X | | | | | | X | |

SA: Scientific Advice

PA: Protocol Assistance

The above-mentioned 3 Scientific Advice letters and 2 Follow-up Scientific Advice letters were adopted at the 22-23 June CHMP meeting.

The Committee accepted 6 initial Scientific Advice requests, 6 Initial Protocol Assistance Requests and 1 Follow-up Protocol Assistance Request.

# DOCUMENTS PREPARED BY THE CHMP WORKING PARTIES AND AD HOC GROUPS ADOPTED DURING THE 22-23 June 2004 CHMP MEETING

## QUALITY WORKING PARTY

| Reference number | Document | Status |
|---|---|---|
| CHMP/QWP/1888/04 | Concept Paper on the Development of a CHMP Guideline on Dosing Delivery of Injectable Liquids | Adopted |
| CHMP/QWP/297/97 Rev 1 and CVMP/1069/02 | Joint CHMP/CVMP Guideline on summary of requirements for active substances in the quality part of the dossier | Adopted |

## SAFETY WORKING PARTY

| Reference number | Document | Status |
|---|---|---|
| CHMP/SWP/8/04 | Concept Paper on the Development of a CHMP Guideline for the Non-Clinical Development of Fixed Combinations of Medicinal Products | Adopted |
| CPMP/SWP/5199/02 | Guideline on the Limits of Genotoxic Impurities | Released for 6 months consultation |
| CPMP/SWP/2599/02 rev1 | Position Paper on the non-clinical safety studies to support clinical trials with a single microdose | Adopted |
| CPMP/3833/03 | Discussion Paper on Contraindications in Pregnancy concerning sections 4.3, 4.6 and 5.3 of the SPC | Adopted |
| CPMP/SWP/2592/02 rev1 | CHMP SWP Conclusions and Recommendations on the Use of Genetically Modified Animal Models for Carcinogenicity Assessment | Adopted |
| CHMP/SWP/10/04 | Concept Paper on the development of a CHMP guideline on detection of early signals for hepatotoxicity from non-clinical documentation | Adopted |

## EFFICACY WORKING PARTY

| Reference number | Document | Status |
|---|---|---|
| CHMP/EWP/225/02 | Note for Guidance on the Evaluation of the Pharmacokinetics of Medicinal Products in patients with impaired renal function | Adopted |
| CHMP/EWP/238/95 rev2 | Note for Guidance on Clinical Investigation of Medicinal Products in the treatment of hypertension | Adopted |
| CHMP/EWP/519/98rev 1 | Note for Guidance on Clinical Investigation of steroid contraceptives in women | Released for 3 months consultation |
| CHMP/EWP/2998/03 | Note for Guidance on the inclusion of appendices to clinical study reports in Marketing Authorisation Applications | Adopted |
| CHMP/EWP/1470/04 | Concept Paper on the Development of a CHMP Note for Guidance on The Need for Regulatory Guidance in the Evaluation of Medicinal Products for the Secondary Cardiovascular Prevention | Adopted |

**BIOTECH WORKING PARTY**

| Reference number | Document | Status |
|---|---|---|
| EMEA/CPMP/BWP/2879/02/rev 1 | CHMP Position Statement on CJD and plasma-derived and urine-derived medicinal products | Adopted |

**VACCINES EXPERT GROUP**

| Reference number | Document | Status |
|---|---|---|
| CHMP/VEG/1820/04 | Concept paper on the development of a CHMP revised guideline on clinical evaluation of new vaccines | Adopted |

**AD HOC EXPERT GROUP ON THE USE OF MEDICINAL PRODUCTS DURING PREGNANCY**

| Reference number | Document | Status |
|---|---|---|
| CHMP/PhVWP/EWP/1889/04 | Note for Guidance on the exposure to medicinal products during pregnancy. Need for Post-Authorisation data | Released for 6 months consultation |

# Report from the meeting held on 21 June 2004

## General Issues

MRFG Recommendation on Implementation of Article 30 Decisions for Generic Products

An updated version of the document has been adopted by the group and will be published on the website. The updated document includes the web link to the European Commission Decisions on Community Referrals for Human Medicinal Products and updates the classification of a variation to the SPC of an essentially medicinal product following an Article 30 Referral for an original medicinal product as a Type IB, No 46, in accordance with the Commission Regulation (EC) No 1084/2003.

MRFG Best Practice Guides for the Submission and Processing of Variations in the Mutual Recognition Procedure

An updated version of the Annex I (MRP Numbering System) to Chapter 1, to include the initials of the new Member States, has been adopted by the group and will be published on the website.

Bibliographical Applications

In accordance with Commission communication on the Community marketing authorisation procedures for medicinal products 98/C 229/03, national independent procedures may still be followed in the case of a medicinal product with a well-established use, demonstrated in accordance with Article 10 (1.)(a)(ii) of Directive 2001/83/EC (bibliographical applications), based on data referring to an existing group of products with different SPCs in the Member States and for which no Community harmonisation of the use of the constituent(s) exists.

Point E.7 of the Communication mentions the cases in which authorisations have to be considered as being harmonised in all the concerned Member States and for these products, purely national procedures cannot be used.

Change in the EU-Presidency

The June 2004 MRFG meeting was the last one under the Ireland presidency. The Netherlands will take over the presidency in July 2004. Truus Janse-de Hoog will be the next MRFG chairperson and should be contacted in case of any questions regarding the MRP.

Meeting schedule

The next MRFG meeting will be held on 26 July 2004.

**Mutual Recognition Monitoring**

The MRFG noted that **42** new mutual recognition procedures were finalised during the month of May 2004, as well as **1** type I variation, **222** type IA variations, **187** type IB variations and **63** type II variations.

The status as of 31st May of procedures under mutual recognition is as follows:

| Year | Procedures from New applications finalised | Procedures from New applications in process | Procedures from Type I variations finalised | Procedures from Type IA variations finalised | Procedures from Type IB variations finalised | Procedures from Type II variations finalised | Arbitrations referred to CPMP |
|---|---|---|---|---|---|---|---|
| 2004 | 217 | 244 | 43 | 1142 | 834 | 368 | 1 N.A |

**33** new procedures (regarding **70** products) started in May 2004. The categories of these procedures are as follows:

**3** new active substances (first authorisation in the European Community after RMS approval).

**1** known active substance (already authorised in at least one member state).

**25** abridged applications including **10** multiple applications and **1** repeat use.

**4** line extension applications including 2 repeat use.

The new procedures started related to **6** full dossiers, **22** generics, **2** fixed combinations and **3** for different use, route or dose.

The procedures consisted of **31** chemical substances, 1 biological-blood product and **1** biological-vaccine[1].

**32** of these procedures were prescription-only medicinal products in the reference Member State and **1** procedure were classified as a Non-prescription (including OTC) medicinal product[2].

1. As considered by RMS.
2. In this category products are classified as prescription-only or Non-prescription (OTC) products when the RMS has approved them accordingly, although the legal status is not part of the Mutual Recognition Procedure.

Number of countries involved in the new applications procedures started in May 2004

| Reference Member State (number of products involved in the procedure) | Number of CMSs involved in the procedure |
|---|---|
| AT (1) | 4 |
| AT (1) | 1 |
| DE (1) | 8 |
| DE (2) | 13 |
| DK (2) | 2 |
| DK (1) | 9 |
| DK (5) | 1 |
| DK (5) | 10 |
| DK (5) | 1 |
| DK (5) | 1 |
| DK (2) | 3 |
| DK (2) | 1 |
| ES (2) | 11 |
| FI (2) | 7 |
| FI (2) | 2 |
| FI (2) | 2 |
| FI (2) | 2 |

| Reference Member State (number of products involved in the procedure) | Number of CMSs involved in the procedure |
|---|---|
| FI (2) | 2 |
| NL (3) | 2 |
| NL (3) | 11 |
| NL (2) | 16 |
| NL (1) | 1 |
| NL (1) | 2 |
| NL (1) | 1 |
| NL (1) | 2 |
| NL (1) | 1 |
| SE (1) | 1 |
| UK (1) | 13 |
| UK (1) | 6 |
| UK (3) | 1 |
| UK (1) | 1 |
| UK (4) | 4 |
| UK (2) | 2 |

*All documents mentioned in this press release can be found at the MRFG website at the European Medicines Authorities Windows under the heading* MRFG Guidance.

*Information on the above mentioned issues can be obtained from the presiding chair of the MRFG:*


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**http://heads.medagencies.org/**