The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

30 April 2004
EMEA/CPMP/11951/04

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
20 – 22 APRIL 2004 PLENARY MEETING
MONTHLY REPORT

The Committee for Proprietary Medicinal Products (CPMP) held its 103rd plenary meeting from 20 –22 April 2004. This meeting was the last meeting of the CPMP in its current form. The next meeting of the Committee will be under its new name of the Committee for Medicinal Products for Human Use, CHMP (see procedural announcement for more information). At the end of the meeting, the Chairman thanked the members and congratulated them for their outstanding work and input.

Product related issues

Centralised procedures

The CPMP adopted one opinion on an initial marketing authorisation application at this meeting:

- A positive opinion by consensus for **Pedea** (ibuprofen), from Orphan Europe SARL, which is indicated for the treatment of a haemodynamically significant patent *ductus arteriosus* in preterm newborn infants less than 34 weeks of gestational age. The EMEA review began on 21 July 2003 and the opinion was adopted on 22 April 2004, with an active review time of 176 days.

  Pedea was designated as an orphan medicinal product on 14 February 2001 and is the seventeenth orphan medicinal product to receive a positive opinion for marketing authorisation from the CPMP.

The Committee also gave positive opinions on the extension of indication for four medicinal products that are already authorized in the EU:

- **Herceptin** (trastuzumab), Roche Registration Limited, to extend its use in combination with docetaxel for the treatment of HER2-positive patients with metastatic breast cancer who have not received chemotherapy for their metastatic disease. Herceptin was first authorised in the European Union on 28 August 2000.

- **Humira** and **Trudexa** (adalimumab), Abbott Laboratories, to change its therapeutic indication to include reduction of the rate of progression of structural damage and improvement of physical function. Humira was first authorised in the European Union on 8 September 2003. Trudexa was first authorised in the European Union on 1 September 2003.

- **NovoMix 30** (insulin aspart), Novo Nordisk A/S, to specify its use in combination with metformin in patients with type 2 diabetes mellitus that are insufficiently controlled on metformin alone. NovoMix 30 was first authorised in the European Union on 1 August 2000.

- **Remicade** (infliximab), Centocor B.V., to extend its use for the treatment of methotrexate-naïve patients with early rheumatoid arthritis. Remicade was first authorised in the European Union on 13 August 1999.

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Further information on these extensions will be included in the European Public Assessment Report (EPAR) once the European Commission has granted final approval.

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

The CPMP recommended lifting the suspension of marketing authorisation for **Tasmar** (tolcapone) from Roche Registration Limited, which was approved for use in the treatment of Parkinson's disease. Tasmar was first authorised in the European Union in August 1997 and was suspended in November 1998 on the basis of concerns over hepatotoxicity and neuroleptic malignant syndrome. On the basis of new data, including a clinical trial conducted by the marketing authorisation holder during the period of the suspension, the Committee has recommended more stringent liver function monitoring and monitoring for signs and symptoms of liver disease. The CPMP also recommends that Tasmar should be contra-indicated for patients with certain medical histories, including liver disease and neuroleptic malignant syndrome. A detailed public statement has been published on the EMEA website on 29 April 2004.

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 CPMP plenary meeting in March 2004 is provided in **Annex 2.** The post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 3**.

Referrals

The Committee finalised its EU-wide review for **paroxetine** containing medicines. The review was initiated by the UK in June 2003 under Article 31 of the Community Code on human medicines. The referral was made on the basis of safety concerns relating to potential risk of emotional changes (such as crying, mood fluctuations, hostility, self-harm, suicidal thoughts and attempted suicide) and withdrawal reactions associated with the use of paroxetine.

The Committee concluded that the benefit-risk remains positive for these products but made the following recommendations.

The Committee recommends that paroxetine should not be used in children and adolescents as clinical trials have found paroxetine to be associated with increased risk of suicidal behaviour and hostility. In addition, trials in children and adolescents did not adequately demonstrate efficacy. The Committee noted that paroxetine is not authorised in any EU Member State for use in children.

There is a possibility of an increased risk of suicide-related behaviour in young adults. As a consequence young adults should be monitored carefully throughout treatment.

The Committee also recommends strengthened warnings concerning withdrawal symptoms. Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt and the Committee underlines that patients must not stop their treatment abruptly, except on medical advice.

A question and answer document has been published on the EMEA web site on Friday 23 April. This is in line with the Agency's new transparency policy adopted in October 2003 aimed at providing more information to patients and the general public.

Non-product related issues

CPMP Working Parties and Ad Hoc Groups

- The CPMP was informed of the outcome of the discussions of the Scientific Advice Working Group (SAWG) meeting, which was held on 05-06 April 2004. For further details, please see **Annex 4**.
- Documents prepared by the CPMP Working Parties and Ad Hoc Groups adopted during the April 2004 CPMP meeting are listed in **Annex 5**.

Organisational Matters

The 32nd CPMP Organisational Matters meeting took place on Monday 19 April 2004, chaired by Dr D. Brasseur. During the meeting the following principle topics were presented/discussed:

- Issues related to CPMP Working Parties/Ad Hoc Working Groups (Guidelines, Notes for Guidance, Concept Papers and Position Statements) (see Annex 4).
- The scientific report from the CPMP Gene Therapy Expert Group (GTEG) Meeting held on 26-27 February 2004 which was presented and subsequently adopted by the CPMP. This report addressed the following topics: Lentiviral vectors, Germline integration, Insertional oncogenesis, Environmental risk assessment of gene transfer medicinal products, Oncolytic conditionally replication-competent viruses, Adenovirus type 5 Reference Material (ARM). The report will be published on the EMEA website in due time.
- The need to establish a CPMP cell therapy Working Group.
- CHMP draft Rules of Procedure and Procedure for the nomination and appointment of co-opted members of the CHMP. This will be further discussed at the informal CPMP meeting in Ireland.
- The agenda of the Informal CPMP meeting to be held on 28-30 April 2004 in Dublin. The Committee will discuss, amongst other items, the role of the Scientific Advisory Groups (SAGs), Working Parties etc. in providing support to the evaluation process. The implications of implementation of the new legislation, and the EMEA Road Map to 2010 will also be discussed. An analysis of marketing authorisations of Orphan medicinal products will figure on the agenda.

Upcoming meetings following the April 2004 CPMP plenary meeting:

- The 1st plenary meeting of the CHMP will be held from 01-03 June 2004. This meeting was initially planned end of May 2004. However, as the new legislation will not be in force for the Management Board and the CHMP in early May, it will only be possible for the Management Board to be consulted on the composition of the new Committee on May 24th 2004. It was therefore decided to hold the CHMP one week later.
- There will be no ORGAM meeting in May 2004.
- The next Invented Name Review Group meeting is scheduled to take place on Monday 24 May 2004.

PROCEDURAL ANNOUNCEMENTS

The CHMP will meet for the first time from 1-3 June 2004. In line with new requirements in the legislation, this change of date is in order to allow the EMEA Management Board to be consulted on the composition of the new scientific committee. The Management Board will meet on 24 May, the first working day following the entry into force of the new Regulation. The scheduled 22-24 June 2004 CHMP meeting will be maintained.

- **Advisory note on Dossier requirements during the Enlargement**

Marketing Authorisation Holders and Applicants are advised that they should continue to provide Module 1 and 2 of their initial Marketing Authorisation applications and Variation Applications for new clinical indications to the currently nominated observers of the 10 Accession Countries until the first meeting of the CHMP in 01-03 June 2004. Following that meeting, a revised dossier requirements/contact information will be published.

- **Reminder note on dossier requirements applying to Type II Variation and Extension applications**

Marketing Authorisation Holders are reminded to always provide CHMP Members (when not (Co)-Rapporteurs) with one paper copy of Modules 1 and 2 of Type II Variation and Extension applications, in addition to the full electronic copy on CD Rom.

- **Notification of change to contact person**

Owing to an ever increasing number of procedures and resultant data management requirements relating to the SIAMED database, all Applicants and Marketing Authorisation Holders are kindly asked to notify the EMEA of changes to contact persons exclusively in writing and by fax (see template in **Annex 6**).

Any such change should be submitted on company-headed paper, addressed to the Product Team Leader, with a copy to the SIAMED Database Administrator.

Also, there is a requirement for an additional company contact person at the address of the Applicant/Marketing Authorisation Holder, for the purpose of receiving courier mail from the European Commission. It is not possible for this address to be entered into the SIAMED database on a per-product basis, but only on a per-company basis. Therefore, companies should be aware that any change to this contact person is valid for ALL products pertaining to that specific company.

Mutual Recognition procedure

The CPMP noted the report from the Mutual Recognition Facilitation Group (MRFG) meeting held on 19 April 2004. For further details, please see **Annex 7.**

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

EMEA CENTRALISED PROCEDURES

	1995 - 2000	2004	Overall Total
Scientific Advice	367	19	386
Follow-up to Scientific Advice	60	0	60
Protocol Assistance	30	10	40
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	5	5	10	415
Consultation for Medical Device[1]	0	1	1	0	0	0	1
Withdrawals	22	55	77	0	1	1	78
Positive CPMP opinions[2]	99	172	271	3	8	11	282[3]
Negative CPMP opinions[4]	2	5	7	0	0	0	7[5]
Marketing authorisations granted by the Commission	91	164	255	2	6	8	263[6]

	1995-2003			2004			Overall Total
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Variations type I	771	1505	2276	20	103	123	2399
Positive opinions, variations type II	583	697	1280	29	31	60	1340
Negative opinions, variations type II	1	6	7	0	0	0	7
Extensions (Annex II applications)	49	56	105	0	1	1	106

[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] 16 positive opinion corresponding to 16 Orphan Medicinal Products
[3] 282 positive opinions corresponding to 216 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] 263 marketing authorisations corresponding to 198 substances

ANNEX 2 to CPMP Monthly Report April 2004

MEDICINAL PRODUCTS GRANTED A COMMUNITY MARKETING AUTHORISATION UNDER THE CENTRALISED PROCEDURE SINCE MARCH 2004 CPMP MONTHLY REPORT

Invented Name	Advate
INN	octocog alfa
Marketing Authorisation Holder	Baxter AG
ATC code	B02BD02
Indication	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency)
CPMP Opinion date	22.10.2003

Invented Name	Faslodex
INN	fulvestrant
Marketing Authorisation Holder	AstraZeneca
ATC code	L02BA03
Indication	Treatment of locally advanced or metastatic breast cancer
CPMP Opinion date	20.11.2003

Invented Name	Cholestagel
INN	colesevelam hydrocholride
Marketing Authorisation Holder	Genzyme B.V
ATC code	C10AC04
Indication	Adjunctive therapy to diet for the reduction of elevated total and LDL cholesterol (total-C and LDL-C)
CPMP Opinion date	20.11.2003

Invented Name	Photobarr
INN	porfimer sodium
Marketing Authorisation Holder	Axcan International Pharma BV
ATC code	L01CD01
Indication	Ablation of high-grade dysplasia (HGD) in patients with Barrett's Esophagus (BE)
CPMP Opinion date	18.12.2003

OUTCOME OF THE APRIL 2004 CPMP MEETING IN RELATION TO CENTRALISED APPLICATIONS IN THE POST-AUTHORISATION PHASE

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
5 Extensions of indications	5 Positive opinions
13 SPC changes	13 Positive opinions
14 Quality changes	14 Positive opinions

Opinions for Annual Re-Assessment applications		
Name of Medicinal Product (INN) **MAH**	**Outcome**	**Comments**
Viread (tenofovir) Gilead Science International Limited	Positive opinion	Marketing Authorisation will remain under exceptional circumstances
Neurobloc (botulinum toxin type B) Elan Pharma International Ltd.	Positive opinion	Marketing Authorisation will remain under exceptional circumstances

Opinions for Renewal applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Rebetol (ribavirin) SP Europe	Positive opinion	---

OUTCOME OF THE APRIL 2004 CPMP 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				
Biological	Anemia	**X**				**X**	**X**	**X**	
Biological	Multiple sclerosis	**X**					**X**	**X**	
Chemical	Neovascular glaucoma		**X**				**X**	**X**	
Chemical	Parkinson's disease	**X**						**X**	
Chemical	Acute coronary syndrome	**X**						**X**	
Biological	Angioedema		**X**			**X**	**X**		
Chemical	Impetigo, Secondarily-infected dermatoses, Secondarily-infected traumatic lesions	**X**					**X**	**X**	
Biological	Ovarian cancer		**X**				**X**		

SA: Scientific Advice

PA: Protocol Assistance

In April 2004, the above-mentioned 5 Scientific Advice letters and 3 Protocol Assistance letters were adopted.
The Committee accepted 4 Initial Scientific Advice new Requests and 1 Follow-up Protocol Assistance new Request.

DOCUMENTS PREPARED BY THE CPMP WORKING PARTIES AND AD HOC GROUPS ADOPTED DURING THE APRIL 2004 CPMP MEETING

QUALITY WORKING PARTY

Reference number	Document	Status
CPMP/QWP/1542/04	CPMP Concept Paper on the development of a CPMP Guideline on the requirements for the quality part of a Request for Authorisation of a clinical trial	Adopted
CPMP/QWP/1525/04	CPMP Concept Paper on the Revision of the CPMP Notes for Guidance on Dry Powder Inhalers and Pressurised Metered Dose Inhalers and the Development of a CPMP Guideline on Nasal Products, Products for Nebulisation and Hand-Held Nebuliser Products.	Adopted
CPMP/QWP/1526/04	Request for Comments from Industry on the Application of the Future Harmonised PhEur Text "Uniformity of Dosage Units" to New and Existing Marketing Authorisations.	Adopted for release for 3-months consultation after discussion in May CVMP

BIOTECH WORKING PARTY

Reference number	Document	Status
CPMP/BWP/2458/03	Position Statement on Development and Manufacture of Lentiviral Vectors.	Released for 6 months consultation

EFFICACY WORKING PARTY

Reference number	Document	Status
CPMP/EWP/4151/00	Points to consider on the requirements for clinical documentation for orally inhaled products (OIP).	Adopted
CPMP/558/95 rev. 1	Note for Guidance on Evaluation of Medicinal Products indicated for treatment of bacterial infections.	Adopted

VACCINES EXPERT GROUP

Reference number	Document	Status
CPMP/VEG/4986/03	Guideline on Submission of Marketing Authorisation Applications for Pandemic Influenza Vaccines through the Centralised Procedure	Adopted in March by written procedure and subsequently published on EMEA website
CPMP/VEG/4717/03	Guideline on Dossier Structure and Content for Pandemic Influenza Vaccine Marketing Authorisation Application	Adopted in March by written procedure and subsequently published on EMEA website

TEMPLATE LETTER FOR NOTIFICATION OF CHANGES TO CONTACT PERSONS

[Company-headed paper]

To:

[PTL name]
EMEA
7 Westferry Circus
Canary Wharf
London E14 4HP

CC:

SIAMED Database Administrator

Dear **[PTL name]**,

{Notification of change of contact person; with the following details required:}

I Contact person role

[*Please specify:*
Contact person for the product – main regulatory
Contact person in charge of pharmacovigilance
Contact person in charge of scientific services
Contact person in charge of product defects/recalls
Contact person in charge of batch release
OR:
Contact person at the site of the Marketing Authorisation Holder - explanation]

II Full contact details

[*Must contain:*
Name
Full company address
Phone number(s)
Fax number(s)
Email]

{Signed}

Report from the meeting held on 19 April 2004

General Issues

Assessment Reports for Mutual Recognition Procedure CTD Format
An updated version of the following documents has been adopted by the group and will be published on the website:

- Template for the Assessment Report Overview
- Assessment Report Overview Guidance Document
- Guideline on the Assessment Report

Questions/Answers on Mutual Recognition Procedure and Enlargement
A final compilation of questions and the related answers was agreed and will be published on the website.

Meeting schedule
The next MRFG meeting will be held on 24 May 2004.

Mutual Recognition Monitoring

The MRFG noted that **49** new mutual recognition procedures were finalised during the month of March 2004, as well as **4** type I variations, **181** type IA variations, **240** type IB variations and **124** type II variations. 1 arbitration from new applications under Article 29(2) of Directive 2001/83/EC was referred to CPMP.

The status as of 31st March 2004 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	133	182	36	678	507	230	1 N.A

105 new procedures (regarding **216** products) started in March 2004. The categories of these procedures are as follows:

5 new active substance (first authorisation in the European Community after RMS approval), of which **2** are classified as multiple applications.

17 known active substances (already authorised in at least one member state), of which **2** are classified as multiple applications and 3 are repeat use.

76 abridged applications including **19** multiple applications and **7** repeat use.

7 line extension applications, of which **3** are classified as multiple applications.

The new procedures started related to **24** full dossiers, **75** generics, **1** bibliographic applications, **2** informed consent applications and **3** for different use, route or dose.

The procedures consisted of **102** chemical substances, **2** biological-vaccines and **1** biological-other[1].

99 of these procedures were prescription-only medicinal products in the reference Member State and **6** procedures 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 March 2004

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
AT (2)	1
AT (2)	1
AT (2)	1
AT (2)	1
AT (2)	1
DE (1)	8
DE (1)	3
DE (2)	6
DK (2)	1
DK (3)	6
DK (3)	2
DK (3)	1
DK (1)	1
DK (3)	1
DK (3)	1

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DK (3)	5
DK (1)	5
DK (1)	2
DK (1)	5
DK (1)	7
DK (3)	7
DK (3)	1
DK (3)	3
DK (3)	6
DK (2)	2
DK (3)	3
DK (3)	1
DK (3)	2
DK (3)	1
DK (3)	1
DK (3)	1
DK (3)	6
DK (3)	1
DK (3)	1
DK (3)	3
DK (4)	1
DK (1)	14
DK (1)	1
DK (1)	1
DK (2)	1
DK (2)	2
DK (2)	6
DK (1)	3
DK (2)	4
DK (2)	5
DK (2)	7
DK (2)	1
DK (2)	11
DK (2)	3
DK (1)	7
DK (2)	10
DK (2)	1
DK (4)	3
DK (4)	2
DK (4)	4
DK (4)	3
DK (4)	2
DK (4)	1
DK (2)	1
DK (2)	2
DK (2)	2
DK (4)	6
DK (4)	2
DK (1)	6
DK (1)	4
DK (1)	2
FI (2)	8
FI (2)	1
FI (1)	1
FI (2)	4
FI (2)	1
FR (2)	12
FR (1)	1
NL (2)	16
NL (2)	4
NL (2)	3
NL (1)	1
NL (1)	1

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
NL (1)	2
NL (1)	1
NL (3)	2
NL (3)	8
NL (1)	1
NL (1)	1
NL (1)	12
NL (1)	15
PT (1)	1
PT (1)	1
SE (1)	10
SE (1)	1
SE (1)	16
SE (1)	13
SE (1)	3
SE (4)	5
SE (1)	15
SE (1)	9
UK (1)	11
UK (4)	1
UK (1)	1
UK (1)	3
UK (1)	7
UK (1)	11
UK (2)	1
UK (1)	16
UK (4)	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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*Or you could visit the **MRFG web site** at the EUROPEAN NATIONAL MEDICINES AUTHORITIES WINDOW:*
http://heads.medagencies.org/

