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

London, 28 March 2003
EMEA/CPMP/1358/03

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
MARCH 2003 PLENARY MEETING
MONTHLY REPORT

The Committee for Proprietary Medicinal Products (CPMP) held its 91st plenary meeting from 18 – 19 March 2003.

Product related issues

Centralised procedures

The CPMP adopted 2 opinions on initial marketing authorisation applications at this meeting:

- A positive opinion for **Fuzeon** (enfuvirtide) from Roche, which is intended for the treatment in combination with other antiretroviral products for HIV-infected patients with few remaining treatment options. It belongs to a new class of antiretroviral products called fusion inhibitors.

  EMEA review began on 21 October 2002 and the opinion was adopted on 19 March 2003, with an active review time of 121 days. Fuzeon was evaluated as an **accelerated procedure** , agreed to by the CPMP at its July 2002 meeting prior to submission of the application.

- A positive opinion for **Busilvex** (busulfan) from Pierre Fabre Médicament, which is part of a conditioning treatment prior to haematopoietic progenitor cell transplantation in adults.

  EMEA review began on 26 March 2002 and the opinion was adopted on 19 March 2003, with an active review time of 171 days.

  Busilvex was designated an orphan medicinal product on 29 December 2000 and is the **tenth orphan medicinal product** to receive a positive CPMP opinion for marketing authorisation.

Summaries of these two opinions are available on the EMEA web site: http://www.emea.eu.int.

The Committee also adopted 3 Lists of Questions (1 Part A and 2 Part B).

The Committee also gave a positive opinion to extend the indication for **Thyrogen** (thryotrophon alfa) from Genzyme to include the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy (THST) to be used with serum thyroglobulin (Tg) testing with or without radioiodine imaging. Thyrogen was first authorised in the European Union in March 2000. Further information on this extension will be included in the public assessment report (EPAR) once the European Commission has granted final approval.

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 February 2003 is provided in **Annex 2.** The post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 3**.

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Referrals

The Committee concluded its Community-wide reviews for Genotropin and Norditropin (somatropin) from Pharmacia and from NovoNordisk concerning two separate applications under the mutual recognition procedure for new indications to include the treatment of growth-retarded children born small for gestational age (SGA). The referrals for arbitration were made for Genotropin by Germany and Sweden in December 2001 and for Norditropin by Sweden in May 2002. The referrals for arbitration were based on concerns that the data were not adequate to support the change requested as well as safety concerns. The CPMP considered that, based on currently available information, there is a positive benefit-risk balance for Genotropin and Norditropin in the indication *"Growth disturbance (current height SDS <-2.5 and parental adjusted height SDS <-1) in short children born small for gestational age (SGA), with a birth weight and/or length below -2 SD, who failed to show catch-up growth (HV SDS <0 during the last year) by 4 years of age or later"* and recommended the approval of the new indication.

The CPMP also concluded its Community-wide review for **Lederfoline** and associated product names (calcium folinate) from Wyeth Research. The purpose of the referral was to harmonise the product information for these products in all EU Member States. The harmonised indications recommended by the Committee are for the product's use to diminish the toxicity and counteract the action of folic acid antagonists such as methotrexate in cytotoxic therapy and overdose in adults and children (in cytotoxic therapy this procedure is commonly known as 'Calcium Folinate Rescue') and in combination with 5-fluorouracil in cytotoxic therapy. The procedure was initiated by France in October 2000.

Invented Name Review Group

The Invented Name Review Group held its 36th meeting on 17 March 2003 and the conclusions of the group were subsequently adopted by the CPMP. The next meeting will take place on 22 April 2003. The second EMEA/EFPIA Workshop on Invented Names will take place at the EMEA premises on 22 April 2003.

Non-product related issues

CPMP Working Parties and Ad Hoc Groups

The CPMP endorsed the outcome of the discussions of the Scientific Advice Working Group (SAWG) meeting, which was held on 3 – 4 March 2003. For further details, please see **Annex 4**.

The Herbal Medicinal Product Working Party, chaired by Dr Konstantin Keller, held its' meeting on 24 – 25 March 2003. The HMPWP proposals for Core data on Primula radix (http://www.emea.eu.int/pdfs/human/hmpwp/024303en.pdf) and Lini semen (http://www.emea.eu.int/pdfs/human/hmpwp/024403en.pdf) were released for four months consultation. For further details on the meeting, please see the published Press Release of the meeting on the following web link: http://www.emea.eu.int/pdfs/human/hmpwp/109003en.pdf.

The Committee agreed on a list of CPMP Members and Experts to participate at the EMEA/CPMP Working Group with Patient's Associations. The participation of the European Patient's Forum to the working group was agreed.

Documents prepared by the CPMP Working Parties and Ad Hoc Groups adopted during the March 2003 CPMP meeting are listed in **Annex 5**.

Upcoming meetings following the March 2003 CPMP plenary meeting:

- The next Ad Hoc Working Group on (pre) clinical comparability of Biotechnology products (Chairperson Dr P. Kurki) will take place on 29 April 2003.
- The Informal CPMP meeting will be held on 5 - 6 May 2003 in Athens, Greece.

Organisational Matters

- The CPMP finalised its discussions on the handling of safety concerns for pre- and post-authorisation applications submitted in accordance with the centralised procedure and agreed on the future handling of such concerns. The outcome of this discussion will be used as a contribution to the revision of the mandate of the Pharmacovigilance Working Party, which is undertaken as part of the development of a European Risk Management Strategy.

  A document providing guidance to applicants/MAHs will be prepared and published in the near future at the EMEA website.

- The 21st CPMP Organisational Matters meeting took place on Monday 17 March 2003, chaired by Dr D. Brasseur. During the meeting the following principle topics were presented/discussed:
  - Proposals on the improvement of the use of EMEA IT tools and audio-videoconferencing in order to ensure the optimum flow of CPMP meetings
  - SPC Expert Group proposals on the content reflected in section 4.1 (Therapeutic indications) versus section 5.1 (Pharmacodynamic properties) of the SPC. These proposals will be considered in a future revision of the SPC Guideline
  - Implementation of the revised Draft Variation Regulation (Commission Regulation (EC) No 542/95)
  - Experience on Risk Management Programmes' related to centralised procedures
  - The rules of procedure and composition of the different Therapeutic Advisory Groups (Oncology, Diagnostics and Anti-Infectives)

  The next CPMP Organisational Matters meeting is scheduled to take place on Tuesday 22 April 2003.

PROCEDURAL ANNOUNCEMENT

The Commission Regulation (EC) No 494/2003 amending Council Regulation (EC) 297/95 on the fees payable to the European Agency for the Evaluation of Medicinal Products (EMEA) has entered into force since the 20 March 2003 following its publication in the Official Journal of the European Communities on the 19 March 2003. Please see:
http://europa.eu.int/eur-lex/en/dat/2003/l_073/l_07320030319en00060007.pdf

All validated applications as of this date will be handled according to the new Regulation on fees.

Mutual Recognition procedure

The CPMP noted the report from the Mutual Recognition Facilitation Group (MRFG) meeting held on 17 March 2003. For further details, please see **Annex 6.**

The 92nd plenary meeting of the CPMP will be held from 23 – 25 April 2003.

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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

ANNEX 1 to CPMP Monthly Report March 2003

EMEA CENTRALISED PROCEDURES (FINALISED)

	1995 - 2000	2003	Overall Total
Scientific Advice	302	18	320
Follow-up to Scientific Advice	50	1	51
Protocol Assistance	13	3	16
Follow-up to Protocol Assistance	4	1	5

	1995-2002			2003			
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Applications submitted	127	239	366	2	12	14	380
Consultation for Medical Device[1]	0	1	1	0	0	0	1
Withdrawals	20	53	73	1	1	2	75
Positive CPMP opinions[2]	92	155	247	1	2	3	250[3]
Negative CPMP opinions[4]	1	4	5	0	0	0	5[5]
Marketing authorisations granted by the Commission	88	146	234	0	5	5	241[6]

	1995-2002			2003			Overall Total
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Variations type I	585	1132	1717	18	68	86	1803
Positive opinions, variations type II	405	511	916	39	44	83	999
Negative opinions, variations type II	1	6	7	0	0	0	7
Extensions (Annex II applications)	44	44	88	1	0	1	89

[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] 2 positive opinion corresponding to 2 Orphan Medicinal Product
[3] 250 positive opinions corresponding to 188 substances
[4] In case of appeal, the opinion will not be counted twice
[5] 5 negative opinions corresponding to 4 substances
[6] 241 marketing authorisations corresponding to 180 substances

MEDICINAL PRODUCTS GRANTED A COMMUNITY MARKETING AUTHORISATION UNDER THE CENTRALISED PROCEDURE SINCE FEBRUARY 2003 CPMP MONTHLY REPORT

Invented Name	Vivanza
INN	vardenafil
Marketing Authorisation Holder	Bayer AG
ATC code	G04B E09
Indication	Treatment of erectile dysfunction
CPMP Opinion date	21.11.2002

Invented Name	Levitra
INN	vardenafil
Marketing Authorisation Holder	Bayer AG
ATC code	G04B E09
Indication	Treatment of erectile dysfunction
CPMP Opinion date	21.11.2002

Invented Name	Hepsera
INN	adefovir dipivoxil
Marketing Authorisation Holder	Gilead Science International Limited
ATC code	pending
Indication	Treatment of chronic hepatitis B in adults
CPMP Opinion date	21.11.2002

OUTCOME OF THE MARCH 2003 CPMP MEETING IN RELATION TO CENTRALISED APPLICATIONS IN THE POST-AUTHORISATION PHASE

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
1 Extensions of indication	1 Positive opinion by consensus
28 SPC changes	28 Positive opinions by consensus
10 Quality changes	10 Positive opinions by consensus

Opinions for Annual Re-Assessment applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Ceprotin (protein C) Baxter AG	Positive opinion by consensus	Marketing Authorisation to remain under exceptional circumstances
Foscan (temoporfin) Biolitech Pharma Ltd	Positive opinion by consensus	Marketing Authorisation to remain under exceptional circumstances
Glivec (imatinib mesilate) Novartis Europharm Ltd	Positive opinion by consensus	Marketing Authorisation to remain under exceptional circumstances

Opinions for Renewal applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Exelon (rivastigmine) Novartis Europharm	Positive opinion by consensus	---
Prometax (rivastigmine) Novartis Europharm Ltd	Positive opinion by consensus	---
Pylobactell (13C-urea) Torbet	Positive opinion by consensus	---
Rebif (interferon beta-1a) Ares Serono (Europe) Ltd,	Positive opinion by consensus	---
Combivir (lamivudine/zidovudine) GlaxoSmithKline	Positive opinion by consensus	---

DOCUMENTS PREPARED BY THE CPMP WORKING PARTIES AND AD-HOC GROUPS ADOPTED DURING THE MARCH 2003 CPMP MEETING

EFFICACY WORKING PARTY

The EWP has considered the need for revision of the following guidelines adopted:

- CPMP Note for Guidance on the clinical investigation of medicinal products in the treatment of hypertension (CPMP/EWP/293/03)
- CPMP Note for Guidance on the clinical investigation of anitangial medicinal products in stable angina pectoris (CPMP/EWP/293/03)

A review for both of the guidelines was considered necessary. Concept papers will therefore be proposed for adoption by the CPMP. The CPMP adopted these recommendations during its March 2003 plenary meeting.

Reference number	Document	Status
CPMP/EWP/633/02	Note for Guidance on the clinical development of medicinal products for treatment of HIV infection	Adopted
CPMP/EWP/225/02	Note for Guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function	Released for 6 months consultation
CPMP/EWP/785/97	Points to consider on the evaluation of medicinal products for the treatment of irritable bowel syndrome	Adopted

BIOTECH WORKING PARTY

Reference number	Document	Status
CPMP/BWP/6011/03	Final EU recommendations for the influenza vaccine composition for the season 2003/2004	Adopted

BLOOD PRODUCTS WORKING GROUP

Reference number	Document	Status
CPMP/PhVWP/BPWG/2231/99	Core SPC for human albumin	Released for 2 months consultation
CPMP/BPWG/2048/01	Core SPC for human plasma coagulation factor VII concentrate	Released for 6 months consultation
CPMP/BPWG/1089/00	Note for guidance on the clinical investigation of plasma derived fibrin sealant products	Release for 2 months consultation
CPMP/BPWG/153/00	Core SPC for Plasma derived fibrin sealant products	Released for 6 months consultation

Report from the meeting held on 17 March 2003

General issues:

The updated Questions and Answers will be published on the HoA/MRFG website (http://heads.medagencies.com).

Cross reference in a mutual recognition "informed consent" procedure to a centrally authorised product

The requirement for the use of 'informed consent' is stated in Article10. 1 a) i). It requires that the medicinal product is essentially similar to a medicinal product authorised in the Member State concerned by the application and that the holder of the marketing authorisation for the original product has consented to the use of the dossier.

The basic principle of 'informed consent' is the fact that the competent authority has already evaluated the dossier in question and granted a marketing authorisation.

The European Commission confirmed that as dossiers submitted for the centralised procedure have not been approved by competent authorities in the Member States this basic principle is not fulfilled and the 'informed consent' according to Article 10.1 a) I) cannot be relied upon. A cross reference to centralised marketing authorisations is therefore not possible.

Annual update of influenza vaccines

Given that the vaccine composition for the vaccination period is the same as in the previous year, the group sees no need for clinical trials for this season's vaccine provided that there are no production changes. As in previous years changes to the production process should be made outside of the annual update variation.

Product literature should be amended to show that the composition is reflective of the new season's recommendations (2003/2004).

Provided that the working seeds are prepared from the master seeds authorised last year, the following quality data are required:
results from three monovalent bulks for each virus train.

In any case, the following should be provided:
stability data for bulks and finished product from last year's production.

No new inactivation studies are required unless the production has changed.

In the unlikely event that a new master seed would be prepared, the current requirements (both quality and clinical) for the annual update, as specified in the Note for Guidance on Harmonisation of Requirements for Influenza Vaccines (CPMP/BWP/214/96) would apply.

It should be noted that for the annual update of the influenza vaccines the templates in the old NtA format could be used.

OUTCOME OF THE MARCH 2003 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	Stable angina	X				X	X	X	
Biological	Haemophilia B	X						X	
Chemical	Amyotrophic lateral sclerosis	X					X	X	
Chemical	Gaucher's disease				X		X	X	
Chemical	Schizophrenia	X					X	X	
Biological	Crohn's Disease	X						X	

SA: Scientific Advice

PA: Protocol Assistance

In March 2003, the above-mentioned 5 Scientific Advice letters and 1 Follow-up Protocol Assistance letter were adopted. The Committee accepted 9 Scientific Advice New Requests, 2 Follow-up Scientific Advice Requests and 1 Protocol Assistance New Request.

CPMP Position Statement on the use of fibrinolytics in diabetic patients
A CPMP position statement on the use of fibrinolytics in diabetic patients has been published on the EMEA website: http://www.emea.eu.int/pdfs/human/press/pos/008203en.pdf.
Marketing authorisation holders are advised to contact their competent authorities to implement this amendment for mutual recognition - and national marketing authorisations.

Corrigendum in the Mutual Recognition Monitoring of the February Press Release:
29 new procedures (regarding **44** products) started in January 2003. The categories of these procedures are as follows:

3 new active substances, classified as repeat use.

10 known active substances (already authorised in at least one member state), including **1** multiple application and **2** repeat use.

11 abridged applications including **3** multiple applications and **2** repeat use.

5 *Line extension applications.*

Meeting schedule
The next MRFG meeting will be held on Thursday 24 April 2003.

Annex 1

Joint CPMP/ MRFG working group on harmonisation of SPCs:
During the meeting the group reviewed the ongoing referral procedures and decided to inform HoA in May of the current situation. The April meeting with EMACOLEX was also discussed.

Mutual Recognition Monitoring
The MRFG noted that **23** new mutual recognition procedures were finalised during the month of February 2003, as well as **161** type I and **36** type II variations.

The status as of 28th February 2003 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 I variations pending	Procedures from Type II variations finalised	Procedures from Type II variations pending	Arbitrations referred to CPMP
2003	55	105	325	317	75	282	1 N.A.

33 new procedures (regarding **54** products) started in February 2003. The categories of these procedures are as follows:

4 new active substances, including **3** repeat use.

7 known active substances (already authorised in at least one member state), including **2** repeat use.

17 abridged applications including **6** multiple applications and **2** repeat use.

5 Line extension applications, including **1** repeat use.

The new procedures started related to **10** full dossiers, **14** generics, **5** bibliographic applications, **1** fixed combination and **3** for different use, route or dose.

The procedures consisted of **32** chemical substances and **1** biological- vaccine[1].

21 of these procedures were prescription-only medicinal products in the reference Member State and **12** were Non-prescription (including OTC) medicinal products[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 February 2003

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (1)	13
DK (2)	6
DK (1)	1
DK (1)	1
DK (1)	1
DK (1)	1
DK (1)	1
DK (1)	1
DK (1)	3
DK (3)	1
DK (3)	1
DK (3)	1
DK (3)	1
DK (3)	1
FR (1)	6
FR (1)	9
FR (1)	7
NL (1)	1
NL (5)	1
SE (1)	2
SE (1)	12
SE (1)	1
SE (1)	4
SE (2)	11
SE (2)	3
SE (1)	16
SE (1)	2
SE (1)	3
UK (1)	1
UK (1)	12
UK (1)	5
UK (2)	1
UK (1)	9
UK (4)	7

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

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

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