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

01 August 2003
EMEA/CPMP/3754/03

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
22-24 JULY 2003 PLENARY MEETING
MONTHLY REPORT

The Committee for Proprietary Medicinal Products (CPMP) held its 95th plenary meeting from 22-24 July 2003.

The CPMP Chairman, Dr Daniel Brasseur, welcomed the participation of Dr. Kokkinou from Cyprus, who was attending the CPMP for the first time.

Product related issues

Centralised procedures

Five opinions were adopted for initial applications for marketing authorisation:

- A positive opinion for **Dukoral** (vibrio cholerae and recombinant cholera toxin B-subunit), from SBL Vaccin AB, intended for the active immunisation against Vibrio cholerae. EMEA review began on 26 March 2002 and the opinion was adopted on 24 July 2003, with an active review time of 200 days.
- A positive opinion for **Emend** (aprepitant), from Merck Sharp & Dohme, intended for prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy (EMEND is given as part of a combination therapy). EMEA review began on 18 November 2002 and the opinion was adopted on 24 July 2003, with an active review time of 182 days.
- A positive opinion for **Emtriva** (emtricitabine), from Gilead Science International Ltd, intended for the treatment of HIV-1 infected adults and children in combination with other antiretroviral agents. EMEA review began on 6 January 2003 and the opinion was adopted on 24 July 2003, with an active review time of 170 days.
- A positive opinion for **Xagrid** (anagrelide), from Shire Pharmaceutical Contracts Ltd, intended for the reduction of platelet counts in essential thrombocythaemia patients. EMEA review began on 22 April 2002 and the opinion was adopted on 24 July 2003, with an active review time of 179 days. Xagrid was designated an orphan medicinal product on 29 December 2000 and is the **thirteenth orphan medicinal product** to receive a positive CPMP opinion.
- A negative opinion for **Yondelis** (trabectedin), from PharmaMar S.A, intended for the treatment of patients with advanced soft tissue sarcoma, having failed anthracyclines and ifosfamide, or having failed ifosfamide and unsuitable to receive anthracyclines. EMEA review began on 20 November 2001and the opinion was adopted on 24 July 2003, with an active review time of 207 days. Yondelis was designated an orphan medicinal product on 30 May 2001.

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

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The Committee also gave positive opinions for a number of new indications for medicinal products that are already authorised in the EU:

- Extension of indication for **Bondronat** (ibandronic acid) from Roche Registration Ltd to include prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases. Bondronat was first authorised in the European Union on 25 June 1996.
- Extension of indication for **Synagis** (palivizumab) from Abbott Laboratories to include use in children less than 2 years of age and with haemodynamically significant congenital heart disease. Synagis was first authorised in the European Union on 13 August 1999.
- Extension of indication for **Zerit** (stavudine) from Bristol Myers Squibb Pharma EEIG to include HIV infected paediatric patients below 3 months of age. Zerit was first authorised in the European Union on 08 May 1996.
- Extension of indication for **Zyprexa** and **Zyprexa Velotab** (olanzapine) from Eli Lilly to include prevention of recurrence in patients with bipolar disorder whose manic episode has responded to olanzapine treatment. Zyprexa was first authorised in the European Union on 27 September 1996 and Zyprexa Velotab was first authorised in the European Union on 3 February 2000.

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

The Committee also adopted 7 opinions on “line extension” applications (2 Part A and 5 B), 5 Lists of Questions (1 Part A and 4 Part B) on initial Marketing Authorisation applications and 5 Lists of Questions on “line extension” applications (in accordance with Annex II of Commission Regulation (EC) No. 542/95, as amended) (Part B).

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

Referrals

The Committee concluded its Community-wide reviews for:

- **Cardiostad** (lisinopril) and associated product names from Stada, **Lisinopril Biochemie** (lisinopril) and associated product names from Biochemie GmbH. The CPMP considered that a positive opinion for a revised indication "treatment of renal disease in hypertensive patients with type 2 diabetes mellitus and incipient nephropathy" would address the concerns and points of disagreement raised at the start of the referral. The referral was made by the Netherlands in July 2002 under Article 7(5) of Commission Regulation (EC) No 541/95, following the refusal of the Reference Member State to grant a variation submitted under the Mutual Recognition Procedure.
- **Fluconazol Tiefenbacher** (fluconazole) from Tiefenbacher GmbH & Co. The purpose of the referral was related to public health concerns over the use of the product in pregnancy and lactation and also to potential cardiac toxicity. The CPMP concluded that the objections raised should not prevent the granting of a Marketing Authorisation and that the Summary of Product Characteristics should be amended. This arbitration referral was made to the EMEA by Germany in January 2003 under Article 29(2) of Directive 2001/83/EC.
- **Coversyl** (perindopril) and associated product names from Servier. 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 in the treatment of hypertension and symptomatic heart failure. The referral was made to the EMEA in January 2003 by the European

Commission under Article 30 of Directive 2001/83/EC. The referral was not initiated as a result of any established safety or efficacy concern with this product.

- **Nimesulide** containing medicinal products (Aulin, Mesulide, Nimed and associated product names). The CPMP considered that the benefit-risk profile of nimesulide containing products for systemic and topical use is favourable and that Marketing Authorisations should be maintained/granted. The CPMP recommended to restrict the use of nimesulide to the indications of treatment of acute pain, symptomatic treatment of painful osteoarthritis and primary dysmenorrhoea for the systemic formulations and symptomatic relief of pain associated with sprains and acute traumatic tendinitis for the topical formulation. The referral was made to the EMEA in April 2002 by Finland under Article 31 of Directive 2001/83/EC.

Invented Name review Group

The Invented Name review Group held its 40th meeting on 21 July 2003 and the conclusions of the group were subsequently adopted by the CPMP. The next meeting will take place on 22 September 2003.

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 7-8 July 2003. For further details, please see **Annex 4**.

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

ICH

The ICH meeting was held in Brussels on 15-18 July 2003. For further details of CPMP/ICH documents released for consultation or information at this plenary CPMP meeting, please see **Annex 5**.

Organisational Matters

The 25th CPMP Organisational Matters meeting took place on Monday 21st July 2003, chaired by Dr D. Brasseur. Topics addressed during the meeting related to:

- Follow-up discussion on section 4.1 (Therapeutic indications) versus section 5.1 (Pharmacodynamic properties) of the Summary of Product Characteristics (SPC). A "Discussion Paper on Note for Guidance on SPC concerning sections 4.1 and 5.1" was presented. The CPMP agreed to release this Discussion Paper on the EMEA web site for 3 months consultation.
- A draft "Post-Authorisation Guidance", giving practical and procedural advice on the handling of variations and line-extensions following the adoption of the new Regulation on Variations, was presented and discussed. This Guidance document is released on the EMEA web site for comments (preferably via the Industry Associations) by the 10th September 2003.
- Procedural Guidance on Plasma Master File (PMF) and Vaccine Antigen Master File (VAMF) were presented and discussed. The CPMP agreed to release these Guidance documents on the EMEA web site for comments by the 31st August 2003.
- Follow-up on the improvement of IT tools in particular with relation to the results of a CPMP questionnaire on IT tools.

- Follow-up discussion on the "Rules of the Procedure of EMEA/CPMP Therapeutic Advisory Groups". The CPMP adopted this document.

The next CPMP Organisational Matters meeting is scheduled to take place on Monday 22 September 2003.

GUIDANCE DOCUMENTS AND PROCEDURAL ANNOUNCEMENTS

Guidance documents

- **First draft of the "Post-Authorisation Guidance"**

  Released on the EMEA web site (http://www.emea.eu.int) for comments (preferably via the Industry Associations) by the 10th September 2003.

- **Update on Plasma Master File (PMF) and Vaccine Antigen Master File (VAMF)**

  Released on the EMEA web site (http://www.emea.eu.int) for comments by the 31st August 2003:

  -Procedural Guidance on Plasma Master File (PMF) and Vaccine Antigen Master File (VAMF)

  -Note for Guidance on the Scientific data requirements for a Vaccine Antigen Master File (VAMF)

  -Note for Guidance on Scientific data requirements for Plasma Master File (PMF)

  The above documents are being released further to the adoption of Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use, which introduces the concept of EMEA certification of Plasma Master File and Vaccine Antigen Master File by replacing Annex I to the Community code. Due to the fact that the implementation date of the legislation is 01 July 2003 for the centralised procedure and the deadline for implementation into national legislation is 31 October 2003**,** in this exceptional circumstance, the CPMP is publishing these "Working Documents" for parallel consultation with Industry Associations and Member States/ CPMP review. Written comments are therefore requested by 31 August 2003.

- **Discussion Paper on Note for Guidance on SPC concerning sections 4.1 and 5.1.** Released on the EMEA web site for 3 months consultation:

  http://www.emea.eu.int/pdfs/human/regaffair/358303en.pdf.

- **Rules of the Procedure of EMEA/CPMP Therapeutic Advisory Groups**.

  Released on the EMEA web site: http://www.emea.eu.int.

- **Communication addressed to all Marketing Authorisation Holders (MAHs) in the European Economic Area on the implementation of the Electronic Submission of**

Individual Case Safety Reports in the European Economic Area.

This Communication to all MAHs is available on the EMEA website (http://www.emea.eu.int) and the dedicated EudraVigilance website (http://eudravigilance/).

Procedural announcements

- The CPMP agreed to replace the August 2003 plenary meeting by written procedures to be established for certain ongoing applications.
- Marketing Authorisation Holders are informed that variation and line-extension applications submitted as of 01 October 2003 will be validated and processed in accordance with the new Variation Regulation (EC) No 1085/2003.

Mutual Recognition procedure

The CPMP noted the report from the Mutual Recognition Facilitation Group (MRFG) meeting held on 21st July 2003. For further details, please see **Annex 6.**

The 96th plenary meeting of the CPMP will be held from 23-25 September 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

EMEA CENTRALISED PROCEDURES

	1995 - 2002	2003	Overall Total
Initial Scientific Advice	302	46	348
Follow-up to Scientific Advice	50	8	58
Initial Protocol Assistance	13	8	21
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	6	21	27	393
Consultation for Medical Device[1]	0	1	1	0	0	0	1
Withdrawals	20	53	73	1	2	3	76
Positive CPMP opinions[2]	92	155	247	5	9	14	261[3]
Negative CPMP opinions[4]	1	4	5	1	1	2	7[5]
Marketing authorisations granted by the Commission	88	146	234	1	11	12	246[6]

	1995-2002			2003			Overall Total
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Variations type I	585	1132	1717	99	231	330	2047
Positive opinions, variations type II	405	511	916	96	109	205	1121
Negative opinions, variations type II	1	6	7	0	0	0	7
Extensions (Annex II applications)	44	44	88	3	7	10	98

[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] 13 positive opinion corresponding to 13 Orphan Medicinal Products
[3] 261 positive opinions corresponding to 198 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] 246 marketing authorisations corresponding to 185 substances

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

Invented Name	Busilvex
INN	busulfan
Marketing Authorisation Holder	Pierre Fabre Medicament
ATC code	L01AB01
Indication	Conditioning treatment prior to haematopoietc progenitor cell transplantation
CPMP Opinion date	19/03/2003

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

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
6 Extension of indications	6 Positive opinions
20 SPC changes	20 Positive opinions
11 Quality changes	11 Positive opinions

Opinion for Annual Re-Assessment applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Tracleer (bosentan), Actelion	Positive opinion	Marketing Authorisation to remain under exceptional circumstances

Opinions for Renewal applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Aldara (imiquimod), Laboratories 3M Sante	Positive opinion	---
Comtess (entacapone), Orion Corporation	Positive opinion	---
Comtan (entacapone), Novartis Europharm Ltd	Positive opinion	---
Simulect (basiliximab), Novartis Europharm Ltd	Positive opinion	---
Viagra (sildenafil), Pfizer Limited	Positive opinion	---
Xenical (orlistat) Roche Registration Ltd	Positive opinion	This renewal was approved during the June 2003 CPMP meeting

OUTCOME OF THE JULY 2003 CPMP MEETING IN RELATION TO SCIENTIFIC ADVICE PROCEDURES

Substance	Intended indications(s)	Type of Request				Topic			
		Initial		Follow-up		Pharmaceutical	Pre-clinical	Clinical	Significant Benefit
		SA	PA	SA	PA				
Chemical	Schizophrenia	X				X	X	X	
Biological	*Streptococcus Pneumoniae* infections	X				X		X	
Chemical	Atopic keratoconjunctivitis	X						X	
Biological	Short Bowel Syndrome		X					X	
Chemical	Vascular dementia	X						X	
Chemical	Venous thromboembolic events (VTE)	X						X	
Biological	Multiple sclerosis	X						X	
Biological	Glioma		X			X	X	X	
Biological	Anemia	X				X	X	X	
Chemical	Type 2 diabetes	X						X	
Chemical	Hereditary or acquired angioedema caused by C1 inhibitor deficiency		X					X	X
Chemical	Generalised Anxiety disorder	X						X	
Chemical	*Aspergillus* spp. and *Candida* spp. infections	X					X		
Chemical	Allergic rhinitis	X					X		
Biological	Anemia	X				X	X	X	
Chemical	Manic episodes			X				X	

SA: Scientific Advice

PA: Protocol Assistance

In July 2003, the above-mentioned 12 Scientific Advice letters, 1 Follow-up Scientific Advice letter and 3 Protocol Assistance letters were adopted.
The Committee accepted 6 Initial Scientific Advice Requests, 4 Initial Protocol Assistance Requests and 2 Follow-up Protocol Assistance Requests.

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

BIOTECH WORKING PARTY

Reference number	Document	Status
CPMP/BWP/3752/03	Position Statement on West Nile Virus and Plasma-Derived Medicinal Products	Adopted
CPMP/BWP/3068/03	Guidance on the Description of composition of pegylated (conjugated) proteins in the SPC	Adopted. Published on the EMEA website (in the list of guidelines and notes for guidance on QRD)
CPMP/BWP/1793/01	Note for Guidance on the Use of bovine serum in the manufacture of human biological medicinal products	Adopted
CPMP/BWP/3715/03 Draft 3	Procedural Guidance on Plasma Master File (PMF) and Vaccine Antigen Master File (VAMF)	Released for consultation. Comments by 31 August 2003
CPMP/BWP/3734 Draft 3	Note for Guidance on the Scientific data requirements for a Vaccine Antigen Master File (VAMF)	Released for consultation. Comments by 31 August 2003
CPMP/BWP/3794/03	Note for Guidance on Scientific data requirements for Plasma Master File (PMF)	Released for consultation. Comments by 31 August 2003

SAFETY WORKING PARTY

Reference number	Document	Status
CPMP/SWP/4447/00	Note for Guidance on Environmental Risk Assessment of Medicinal Products for Human Use.	Released for 6 months consultation

EFFICACY WORKING PARTY

Reference number	Document	Status
CPMP/EWP/205/95 rev. 2	Note for Guidance on Evaluation of Anticancer medicinal products in man including Addendum (CPMP/EWP/569/02) on Paediatric oncology	Adopted
CPMP/EWP/2986/03	Note for Guidance on Clinical Investigation of medicinal products for the treatment of Cardiac Failure – Addendum on Acute Cardiac Failure	Released for 6 months consultation
CPMP/EWP/2998/03 rev. 5	Note for Guidance on the inclusion of appendices to clinical study reports in Marketing Authorisation Applications	Released for 3 months consultation

BLOOD PRODUCTS WORKING GROUP

Reference number	Document	Status
CPMP/BPWG/220/02	Note for Guidance on the Clinical investigation of human plasma derived von Willebrand Factor Products	Released for 6 months consultation
CPMP/BPWG/4222/02	Core SPC for human plasma-derived Hepatitis-B immunoglobulins for intramuscular administration	Released for 6 months consultation
CPMP/BPWG/4027/02	Core SPC for human plasma-derived Hepatitis-B immunoglobulins for intravenous administration	Released for 6 months consultation
CPMP/BPWG/278/02	Core SPC for human plasma derived von Willebrand Factor	Released for 6 months consultation
CPMP/BPWG/3735/02	Core SPC for human plasma Prothrombin Complex Concentrate	Released for 6 months consultation

ORGAM

Reference number	Document	Status
EMEA/CPMP/3583/03/Draft	Discussion Paper on Note for Guidance on SPC concerning sections 4.1 and 5.1	Released for 3 months consultation
EMEA/CPMP/257/03/Rev.1/ Final	Rules of the Procedure of EMEA/CPMP Therapeutic Advisory Groups	Adopted

ICH

Reference number	Document	Status
CPMP/ICH/3945/03	Note for Guidance on Definitions and standards for expedited reporting	Released for 3 months consultation
CPMP/ICH/5552/02	General Questions and Answers/ Common technical document for the registration of Pharmaceuticals for human use	Released for information
CPMP/ICH/820/03	ICH M2 – Questions and answers/ Common Technical Document for the registration of Pharmaceuticals for human use	Released for information
CPMP/ICH/5552/03	ICH M4 – General Questions and Answers/ Common Technical Document for the registration of pharmaceuticals for Human Use	Released for information
CPMP/ICH/5549/02	ICH M4S – Questions and Answers/ Common Technical Document for the Registration of Pharmaceuticals for human use – Safety	Released for information
CPMP/ICH/4680/02	ICH M4Q – Questions and Answers/ Location Issues for Common Technical Document for the Registration of	Released for information

	Pharmaceuticals for human use – Quality	
CPMP/ICH/3943/03	ICH E2B (M) – Questions and Answers /Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports	Released for information

Report from the meeting held on 21 July 2003

General Issues

Position Paper on Repeat Use of the MRP
The Group agreed on a wording which will be integrated in the "Position Paper on Repeat Use of the MRP" in order to include the case of simplified CADREAC procedure:
"Although the normal timeframe for the repeat-use procedure is 90 days, in the case of existing marketing authorisations for the identical product granted via the 'simplified CADREAC procedure' this period may be reduced to 30 days with the agreement of all member states involved in the procedure. Agreement means that the new member states can accept the current MR-SPC in the repeat use without any comments and are therefore prepared to grant a marketing authorisation. If all MSs involved in the repeat-use procedure will inform the RMS between day 25 and day 29 at the latest, the RMS will finalise the procedure at day 30."

The final revised "Position Paper on Repeat Use of the MRP" will be adopted at the September meeting.

Best Practice Guides for the Submission and Processing of Variations in the Mutual Recognition Procedures
A final version of the "Best Practice Guides for the Submission and Processing of Variations in the Mutual Recognition Procedures" were adopted by the MRFG after minor changes following consultation of Industry.

The Best Practice Guides will be published on the MRFG website. It should be noted that given that the BPGs are applicable only as of 1st October 2003 when the new Variation Regulation (EC) 1084/2003 comes into force, both the new BPGs and the old guidance documents relating to the old Variation Regulation will have to coexist for a few months on the website. To this purpose the expiry date of the soon to be outdated documents and the new BPGs will be made clearly identifiable on the website.

Application of the Variation Regulations
The European Commission confirmed that the Variations will be handled under the new or the old Regulation according to the date of submission.

Mutual Recognition Monitoring

The MRFG noted that **36** new mutual recognition procedures were finalised during the month of June 2003, as well as **238** type I and **79** type II variations.

The status as of 30th June 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	198	109	1206	381	302	293	2 N.A. and 2 Variations

41 new procedures (regarding **87** products) started in June 2003. The categories of these procedures are as follows:

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

34 abridged applications; including **12** multiple applications and **1** repeat use.

1 line extension application and

2 new active substances.

The new procedures started related to **5** full dossiers, **30** generics, **2** bibliographic applications, **2** informed consents and **2** other.
The procedures consisted of **39** chemical substances, **1** biological-vaccine and **1** biological blood product[1].

38 of these procedures were prescription-only medicinal products in the reference Member State and **3** 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 June 2003

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (1)	13
DE (1)	2
DE (1)	4
DE (1)	1
DE (1)	1
DK (4)	2
DK (4)	4
DK (1)	1
ES (3)	7
ES (2)	2
NL (3)	1
NL (3)	1
NL (3)	3
NL (3)	1
NL (3)	2
NL (3)	5
NL (3)	1
NL (3)	1
NL (3)	1
NL (3)	9
NL (3)	3
NL (3)	5
NL (3)	1
NL (1)	3
NO (3)	8

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
NO (2)	6
NO (3)	3
NO (2)	3
SE (1)	1
UK (1)	1
UK (3)	15

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 from the presiding chair of the MRFG:

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http://heads.medagencies.org/