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

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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
18 – 20 NOVEMBER 2003 PLENARY MEETING
MONTHLY REPORT

The Committee for Proprietary Medicinal Products (CPMP) held its 98th plenary meeting from 18-20 November 2003.

The CPMP Chairman, on behalf of the Committee, welcomed the new CPMP observer, Mr. Joannis Shiatis, Cyprus, who is replacing Ms Panayota Kokkinou. The Chairman also welcomed Mr Thomasz Jablonski, Poland, and Dr Romaldas Maciulaitis, Lithuania, who were attending the CPMP for the first time as new alternate CPMP observer.

Product related issues

Centralised procedures

The CPMP adopted four opinions on an initial marketing authorisation application at this meeting:

- A positive opinion on the marketing authorisation application for **Cholestagel** (colesevelam), from Genzyme Europe BV, intended for the reduction of elevated total and LDL cholesterol in patients with primary hypercholesterolaemia. EMEA review began on 23 September 2002 and the opinion was adopted on 20 November 2003, with an active review time of 201 days.
- A positive opinion on the marketing authorisation application for **Faslodex** (fulvestrant), from AstraZeneca, intended for the treatment of locally advanced or metastatic breast cancer. EMEA review began on 24 February 2003 and the opinion was adopted on 20 November 2003, with an active review time of 176 days.
- A positive opinion on the marketing authorisation application for **Oxybutynin Nicobrand** (oxybutynin), from Nicobrand Ltd, intended for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with unstable bladder. EMEA review began on 24 February 2003 and the opinion was adopted on 20 November 2003, with an active review time of 180 days.
- A positive opinion on the marketing authorisation application for **Reyataz** (atazanavir sulphate), from Bristol-Myers Squibb Pharma EEIG, intended for the treatment of HIV-1infected, antiretroviral treatment experienced adults, in combination with other antiretroviral medicinal products. EMEA review began on 20 May 2002 and the opinion was adopted on 20 November 2003, with an active review time of 200 days.

The CPMP concluded the appeal process for **Yondelis** (trabectedin), from PharmaMar SA, intended for the treatment of advanced soft tissue sarcoma and did not revise its initial opinion adopted in July 2003. This final opinion followed an oral hearing from the applicant and evaluation of the grounds for appeal.

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

The Committee also adopted six Lists of Questions on initial Marketing Authorisation Applications (one Part A and five Part B).

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

Referrals

The Committee finalised three EU-wide reviews for the following substances:

- The 'COX-2 inhibitor' substances **celecoxib**, **etoricoxib**, **parecoxib**, **rofecoxib** and **valdecoxib**. The review was initiated by France under Article 31 of the Community Code on human medicines in July 2002 because of gastrointestinal and cardiovascular safety concerns. The CPMP concluded that the benefit-risk balance for these products remains positive for the target patient populations. However to promote the safe use of the products, the Committee recommends adding or strengthening warnings, in particular recommending caution for patients with underlying gastrointestinal and cardiovascular risks. The Committee also recommends adding (or modifying) warnings concerning the risk of severe skin and hypersensitivity reactions. The recommendations apply to all these substances whether authorised through the European centralised procedure or through mutual recognition procedures.
- **Loratadine** containing medicinal products, including combinations of loratadine and pseudoephedrine. The review was initiated by Sweden under Article 31 of the Community Code on human medicines in April 2002 because of safety concerns relating to hypospadias in new-born boys following use of loratadine during pregnancy. The Committee concluded that a causal relationship could neither be confirmed nor excluded and as a precautionary measure the product information for loratadine was revised to state that the use of loratadine during pregnancy is not recommended. Furthermore the Committee recommended that use of combinations of loratadine and pseudoephedrine should be contra-indicated in pregnancy because pseudoephedrine decreases maternal uterine blood flow.

  A parallel review for desloratadine containing medicines (desloratadine is the major metabolite of loratadine) was finalised in December 2002. The Committee also concluded that a causal relationship could neither be confirmed nor excluded and as a precautionary measure the product information for desloratadine was revised to state that the use of desloratadine during pregnancy is not recommended.
- **Pravachol (pravastatin)** and associated product names from Bristol-Myers Squibb. The purpose of this referral was to harmonise the Summary of Product Characteristics for these products in all the EU Member States. The harmonised indications recommended by the Committee are hypercholesterolemia (treatment of primary hypercholesterolemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments is inadequate), Primary prevention (reduction of cardiovascular mortality and morbidity in patients with moderate or severe hypercholesterolemia and at high risk of a first cardiovascular event, as an adjunct to diet), Secondary prevention (reduction of cardiovascular mortality and morbidity in patients with a history of myocardial infarction or unstable angina pectoris and with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors) and Post transplantation (reduction of post transplantation hyperlipidaemia in patients receiving immunosuppressive therapy following solid organ transplantation. The referral was made to the EMEA in November 2002 by the European Commission under Article 30 of Directive 2001/83/EC, as amended.

Invented Name Review Group

The Invented Name Review Group held its 43d meeting on 17 November 2003, and the conclusions were subsequently adopted by the CPMP.

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 03-04 November 2003. For further details, please see **Annex 4**.
- Documents prepared by the **CPMP Working Parties and Ad Hoc Groups** adopted during the November 2003 CPMP meeting are listed in **Annex 5**.
- The first meeting of the newly created **Therapeutic Advisory Group** (TAG) **in Oncology** was held on 17 November 2003. The TAG Oncology discussed questions raised by CPMP and provided its comments to the Committee on ongoing procedures in particular for two of the previously mentioned products, Faslodex and Yondelis.

Upcoming meetings following the November 2003 CPMP plenary meeting:

- CPMP – EUCAST (European Committee on Antimicrobial Susceptibility Testing): A meeting on Breakpoints will be held at the EMEA on 15 December 2003.

Organisational Matters

The 27th CPMP Organisational Matters (**ORGAM**) meeting took place on Monday 17 November 2003, 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** on the Work Programmes for 2004-2005 and several Notes for Guidance, Concept Papers and Discussion Papers (**see Annex 5**).
- Proposals for definition of **"similarity" with Orphan Medicinal products** in respect of the mechanism of action were made. Once adopted the proposals will be forwarded to the European Commission for consideration in the drafting of a procedural Guideline on similarity of Orphan Medicinal Products.
- Review of 2003 **Scientific Advice Working Group activities** (SAWG) following the change in the procedure. The review includes performance analysis and feedback from Co-ordinators and Applicants on the new Scientific Advice and Protocol Assistance procedures.
- Proposals suggested by the CPMP Biotechnology Working Party for changes to the **Variation Regulation 1085/2003/EC** with regard to biological medicinal products which will be forwarded to the European Commission.
- Supporting **IT services and tools** for CPMP in order to improve the access to information in the meeting rooms and the delegates' offices. As part of the improvement proposals, the CPMP agreed to a trial period with the SAWG of further use/development of videoconferencing with National Competent Authorities and experts.

The next CPMP Organisational Matters meeting is scheduled to take place on Monday 15 December 2003.

PROCEDURAL ANNOUNCEMENTS

- **Submission of Type IA, Type IB and Type II variations in December 2003**

  Please note that the EMEA will be closed between 24 December 2003 and 2 January 2004.

  Marketing Authorisation Holders are therefore requested not to submit Type IA variation applications to the EMEA between 15 and 23 December 2003 because the 14-day timeframe for the Agency to acknowledge the validity of the submitted Type IA variation (see article 4 of Commission Regulation (EC) No 1085/2003) would coincide with the official closure of the EMEA.

  Type IA variation applications submitted not later than 12 December 2003 will be finalised before the EMEA Christmas break. Type IA variation applications submitted to the EMEA between 24 December 2003 and 2 January of 2004 will start on the 5 January 2004.

  Marketing Authorisation Holders intending to apply for Type IB or Type II variations in December 2003 are encouraged to liaise with the EMEA prior to their submission.

- **Marketing Authorisation Applications transitional requirements for the New Member States in view of the EU Enlargement**

  As announced in the CPMP Monthly Report in September 2003 and October 2003, the EMEA recommends Applicants to submit their Applications, namely Module 1 and 2, to the Contact Points of the New Member States. An updated table with the dossier requirements is published on the EMEA website (http://www.emea.eu.int/htms/human/presub/q23-2.htm).
  Please note that the details of the Maltese Contact Point will be provided in this table as soon as available.

- **Dossier requirements for CPMP Members**

  Applicants/MAHs are reminded to respect the dossier requirements (paper and electronic version) when submitting centralised applications to CPMP Members. An updated table is provided at the EMEA website (http://www.emea.eu.int/htms/human/presub/q23-2.htm).

Mutual Recognition procedure

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

The 99th plenary meeting of the CPMP will be held from 16-18 December 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
Scientific Advice	302	62	364
Follow-up to Scientific Advice	50	9	59
Protocol Assistance	13	17	30
Follow-up to Protocol Assistance	4	4	8

	1995-2002			2003			
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Applications submitted	127	239	366	6	31	37	403
Consultation for Medical Device[1]	0	1	1	0	0	0	1
Withdrawals	20	53	73	2	2	4	77
Positive CPMP opinions[2]	92	155	247	7	16	23	270[3]
Negative CPMP opinions[4]	1	4	5	1	1	2	7[5]
Marketing authorisations granted by the Commission	88	146	234	3	16	19	253[6]

	1995-2002			2003			Overall Total
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Variations type I	585	1132	1717	177	345	522	2239
Positive opinions, variations type II	405	511	916	166	173	339	1258
Negative opinions, variations type II	1	6	7	0	0	0	7
Extensions (Annex II applications)	44	44	88	5	12	17	105

[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] 14 positive opinion corresponding to 14 Orphan Medicinal Products
[3] 270 positive opinions corresponding to 206 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] 253 marketing authorisations corresponding to 191 substances

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

Invented Name	Emtriva
INN	emtricitabine
Marketing Authorisation Holder	Triangle Pharma Limited
ATC code	JO5AF09
Indication	Treatment of HIV-1 infection in combination with other antiretroviral agents
CPMP Opinion date	24/07/2003

Invented Name	Emend
INN	aprepitant
Marketing Authorisation Holder	Merck Sharp & Dohme
ATC code	A04A
Indication	Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy
CPMP Opinion date	24/07/2003

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

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
0 Extension of indication	N/A
38 SPC changes	38 Positive opinions
13 Quality changes	13 Positive opinions

Opinions for Annual Re-Assessment applications		
Name of Medicinal Product (INN) **MAH**	**Outcome**	**Comments**
Ceprotin (protein C) Baxter AG	Positive opinion	Marketing Authorisation to remain under exceptional circumstances
Remicade (infliximab) Centocor B.V	Positive opinion	Exceptional circumstances to be lifted
Xigris (drotrecogin alfa (activated)) Eli Lilly Nederland B.V	Positive opinion	Marketing Authorisation to remain under exceptional circumstances
Foscan (temoporfin) Biolitec Pharma Limited	Positive opinion	Marketing Authorisation to remain under exceptional circumstances

Opinion for Renewal applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Temodal (temozolomide) SP Europe	Positive opinion	---

OUTCOME OF THE NOVEMBER 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	Pneumococcal vaccination*	X				X		X	
Chemical	Rapid (premature) ejaculation	X						X	
Biological	Hypereosinophilic syndrome	X						X	
Biological	Angioedema		X			X	X	X	
Biological	All-cause mortality in patient who undergo primary percutaneous transluminary coronary intervention	X						X	
Chemical	Non-small cell lung cancer			X				X	
Chemical	Type II diabetes	X						X	
Biological	Age related macular degeneration	X						X	
Chemical	Weight loss	X					X	X	
Chemical	Diabetic microvascular complications in the eye	X						X	
Chemical	Psoriasis	X						X	
Chemical	Gaucher disease				X			X	

* Scientific Advice letter adopted through a written procedure in August 2003

SA: Scientific Advice

PA: Protocol Assistance

In November 2003, the above-mentioned 8 Scientific Advice letters, 1 Protocol Assistance letter, 1 Follow-up Scientific Advice letter and 1 Follow-up Protocol Assistance letter were adopted.
The Committee accepted 8 Initial Scientific Advice Requests, 2 Initial Protocol Assistance Requests, 1 Follow-up Scientific Advice Request and 2 Follow-up Protocol Assistance Requests.

ANNEX 5 to CPMP Monthly Report November 2003

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

EFFICACY WORKING PARTY

Reference number	Document	Status
CPMP/EWP/4713/03	Concept Paper on the development of a CPMP Points to Consider on Clinical Investigation of Medicinal Products for the treatment of Sepsis	Adopted
CPMP/EWP/2454/02	Note for Guidance on Clinical Investigation of Medicinal Products indicated for the treatment of Psoriasis	Released for 6 months consultation

BIOTECH WORKING PARTY

Reference number	Document	Status
EMEA/CPMP/BWP/5136/03	Discussion paper on the investigation of manufacturing processes for plasma-derived medicinal products with regard to VCJD risk	Adopted

VACCINES EXPERT GROUP

Reference number	Document	Status
CPMP/VEG/4717/03	Note for Guidance on dossier structure and content for pandemic influenza vaccine marketing authorisation application	Released for 3 months consultation
CPMP/VEG/4986/03	Guideline on submission of marketing authorisation applications for pandemic influenza vaccines through the centralised procedure	Released for 3 months consultation

ICH

Reference number	Document	Status
CPMP/ICH/5716/03	ICH – E2E Pharmacovigilance Planning (PVP): Note for Guidance on Planning Pharmacovigilance activities	Released for 6 months consultation
CPMP/ICH/3945/03	ICH – E2D Post-Approval Safety data management: Note for Guidance on definitions and standards for expedited reporting	Adopted
CPMP/ICH/5721/03	ICH – Q5E Comparability of Biotechnical / Biological Products: Note for Guidance on Biotechnological / Biological products subject to changes in their manufacturing process	Released for 6 months consultation

CPMP WORK PROGRAMMES ADOPTED DURING THE NOVEMBER 2003 CPMP MEETING:

- **CPMP Safety Working Party:** Work programme 2004-2005 (CPMP/SWP/5105/03)
- **CPMP Biotechnology Working Party**: Work Programme for 2004-2005 (EMEA/CPMP/BWP/5092/03)
- **CPMP Efficacy Working Party**: Work programme 2004-2005 (CPMP/EWP/5178/03)
- **Joint CPMP/CVMP Quality Working Party**: Work Programme 2004-2005 (CPMP/QWP/2533/03)
- **Blood Products Working Group (BPWG)**: Work programme 2004-2005 (CPMP/BPWG/4317/03)
- **Ad Hoc Working Group on (pre) clinical comparability of Biotechnology products:** Work programme for 2004 (EMEA/H/26646/03)
- **Ad Hoc Expert Group on Gene Therapy**: Work programme 2004 – 2005 (CPMP/326/03 rev. 1 draft 3)
- **Vaccines Expert Group**: Work programme for 2004-2005 (CPMP/VEG/5246/03)
- **Paediatric Expert Group (PEG)**: Work programme for 2004-2005 (CPMP/PEG/22896/03)

Some of these adopted CPMP Work Programmes will be available on the EMEA web site (www.emea.eu.int) at a later stage.

Report from the meeting held on 17 November 2003

Mutual Recognition Monitoring

The MRFG noted that **50** new mutual recognition procedures were finalised during the months of October 2003, as well as **243** type I variations and **71** type II variations.

The status as of 30 September 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	363	220	2302	241	627	220	8 N.A. and 1 Variation

39 new procedures (regarding **95** products) started in October 2003. The categories of these procedures are as follows:

2 known active substances (already authorised in at least one member state),

33 abridged applications; including 18 multiple applications,

4 line extension application and

the new procedures started related to **6** full dossiers, **32** generics, and **1** other.

The procedures consisted of **37** chemical substances and **2** biological vaccine products[1] .

All of these procedures were prescription-only medicinal products[2] in the reference Member State.

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 October 2003

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
AT (1)	3
AT (1)	14
AT (1)	1
AT (1)	1

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
AT (1)	1
AT (1)	1
DE (2)	1
DE (2)	1
DE (2)	1
DK (2)	7
DK (3)	4
DK (1)	1
DK (2)	1
FI (2)	2
FI (2)	3
FI (2)	6
FI (4)	11
FI (4)	1
FI (4)	1
FI (4)	1
FI (4)	1
FI (4)	1
FI (4)	5
FI (4)	6
FI (2)	1
FI (4)	3
FI (4)	1
FI (4)	1
FI (2)	1
IR (3)	1
NL (1)	12
NL (2)	6
NL (2)	2
NL (2)	1
NL (2)	1
UK (1)	15
UK (3)	2
UK (4)	12
UK (1)	1

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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