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

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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
24-26 JUNE 2003 PLENARY MEETING
MONTHLY REPORT

The Committee for Proprietary Medicinal Products (CPMP) held its 94th plenary meeting from 24 – 26 June 2003.

The CPMP Chairman, Dr Daniel Brasseur, welcomed the participation of Mr Vladas Volbekas from Lithuania, who was attending the CPMP for the first time.

Product related issues

Centralised procedures

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

- A positive opinion for **Avandamet** (rosiglitazone/metformin), from SmithKline Beecham, intended for the treatment of type 2 diabetes mellitus patients, particularly overweight patients, who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone. EMEA review began on 21 October 2002 and the opinion was adopted on 26 June 2003, with an active review time of 176 days.
- A positive opinion for **Omnitrop** (somatropin), from Sandoz, intended for the treatment of growth hormone deficiency in children over three years of age and adolescents due to insufficient secretion of growth hormone and growth disturbance associated with Turner syndrome or chronic renal insufficiency and replacement therapy in adults with pronounced growth hormone deficiency. EMEA review began on 22 May 2001 and the opinion was adopted on 26 June 2003, with an active review time of 206 days.
- A positive opinion for **Onsenal** (celecoxib), from Pharmacia-Pfizer EEIG, intended for the treatment of familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g. endoscopic surveillance, surgery). EMEA review began on 20 November 2001 and the opinion was adopted on 26 June 2003, with a total review time of 206 days. Onsenal was designated an orphan medicinal product on 20 November 2001 and it is the twelfth orphan medicinal product to receive a positive opinion.
- A positive opinion for **Stalevo** (levodopa/carbidopa/entacapone), from Orion Corporation, intended for the treatment of Parkinson's disease. EMEA review began on 23 September 2002 and the opinion was adopted on 26 June 2003, with an active review time of 192 days

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

The Committee also adopted an opinion for 2 "line extension" applications (in accordance with Annex II of Commission Regulation (EC) No. 542/95, as amended) (Part B), 7 Lists of Questions on initial Marketing Authorisation applications (Part B) and 1 List of Questions on a "line extension" application (in accordance with Annex II of Commission Regulation (EC) No. 542/95, as amended) (Part A).

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 16
E-mail: mail@emea.eu.int http://www.emea.eu.int

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

Referrals

- The Committee began a Community-wide benefit-risk review for **paroxetine** containing medicines. The referral was made by the UK 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 CPMP completed its review for **Calcitugg** (calcium 500 mg/1000 mg), **Calcichew-D3 mite** (calcium 500 mg and cholecalciferol 5 µg), **Calcichew-D3** (calcium 500 mg and cholecalciferol 10 µg) and all associated products. This review was initiated by the licence holder Nycomed to harmonise the different indications and product information in the EU Member States. The Committee considered that there was a positive benefit-risk balance for the use of these products in a range of indications related to the prevention and treatment of calcium and vitamin D deficiency, and as an adjunct therapy in the prevention and treatment of osteoporosis. Details of the full indications agreed for each product will be published following adoption of the European Commission Decision.

Invented Name review Group

The Invented Name review Group held its 39th meeting on 23 June 2003 and the conclusions of the group were subsequently adopted by the CPMP. The next meeting will take place on 21 July 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 10 and 11 June 2003. For further details, please see **Annex 4**.

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

The CPMP endorsed the Report of the 1st meeting of the EMEA/CPMP Working Group with Patients' Associations, which was held at the EMEA on 8 May 2003. The Press Release of this meeting was already published on 20 May 2003. The Press Release and the Report are available on the EMEA website: http://www.emea.eu.int/pdfs/human/patientgroup/1253603en.pdf.

The Ad Hoc Expert Group meeting on Revision of the Guideline on Excipients in the Package Leaflet, chaired by Prof. Bass, held its last meeting on 21 March 2003. A revised Guideline was adopted by the CPMP (see **Annex 5**).

The Blood Products Working Group meeting, chaired by Dr Haase, was held on 5 – 6 June 2003. The Group will hold its next meeting on 09-10 September 2003.

The CPMP Vaccine Expert Group meeting, chaired by Dr Dobbelaer, was held on 18 – 20 June 2003. The next meeting of the Group is scheduled to take place on 23-24 October 2003.

Meetings following the June 2003 CPMP plenary meeting:

- The Gene Therapy Expert Group meeting, chaired by Dr. Cichuteck, was held on 26-27 June 2003.
- The Herbal Medicinal Products Working Party meeting, chaired by Dr Keller, was held on 30 June 2003-1 July 2003.
- The Ad Hoc Expert Group meeting on Pharmacogenetics, chaired by Dr Abadie, was held on 2 July 2003.

Organisational Matters

The 24th CPMP Organisational Matters meeting took place on Monday 23 June 2003, chaired by Dr D. Brasseur. During the meeting a number of topics were discussed:

- Improvement of IT Tools (e.g. Wireless Networking) and overview of security links with EudraLink.
- Proposals on the optimum link between ORGAM and CPMP plenary discussions, in particular with emphasis on Working Party discussions.
- Follow-up on SPC Expert Group proposals on the content reflected in section 4.1 versus section 5.1 of the SPC.
- Development of Guidelines to CPMP assessors and applicants concerning the Well Established Use of medicinal products' applications.
- Issues relating to the implementation of EudraVigilance.

The next CPMP Organisational Matters meeting is scheduled to take place on Monday 23 June 2003.

PUBLICATION OF LEGISLATIVE TEXTS

- Review of the Pharmaceutical Legislation
  On the 2nd of June 2003, the Health Council adopted a political agreement on the proposal for Regulation modifying Council Regulation 2309/93 on the centralised procedure and the EMEA and on the proposal modifying Directive 2001/83/EC establishing a Community code on medicinal products for human use. These proposals are now available on the website of the European Commission (http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2003/June/council10449en03.pdf and http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2003/June/council10450en03.pdf)
- Two new Regulations on Variations [Commission Regulation (EC) No 1084/2003 (ex (EC) No 541/95) and Commission Regulation (EC) No 1085/2003 (ex. (EC) No 542/95)] have been published in the European Official Journal on 27/6/03 (See http://pharmacos.eudra.org/F2/review/index.htm and Official Journal L 159 of 27.6.2003). (EMEA Guidance documents for the handling of variations in the centralized procedure are in the process of preparation and will be published in due time).
- The new Annex I to Commission Directive 2001/83/EC has been published in the European Official Journal on 27/6/03 under the reference "Commission Directive 2003/63/EC" (http://pharmacos.eudra.org/F2/review/index.htm and Official Journal L 159 of 27.6.2003). [Applicants are reminded that as of 1 July 2003 all applications in the Centralized Procedure should be submitted in accordance with the EU-CTD Format, as published in Volume 2B of the Notice To Applicants, edition July 2003 (http://pharmacos.eudra.org/F2/eudralex/vol-2/B/ctd2003july.pdf)]

GUIDANCE DOCUMENTS AND PROCEDURAL ANNOUNCEMENT

Guidance documents:

- EMEA guidance for companies requesting scientific advice and protocol assistance (EMEA-H-4260-01-Rev. 2). The EMEA has published this updated guidance on its website (http://www.emea.eu.int/pdfs/human/sciadvice/426001en.pdf)
- EMEA guidance for companies requesting protocol assistance regarding scientific issues (EMEA/H/238/02 Rev.1). The EMEA has published this updated guidance on its website (http://www.emea.eu.int/pdfs/human/sciadvice/023802en.pdf)
- EMEA Public Statement on Fee Reductions for Designated Orphan Medicinal Products (EMEA-H-4042-01-Rev.3). The EMEA has published this updated Public Statement on its website (http://www.emea.eu.int/pdfs/human/comp/404201en.pdf)

Procedural announcement:

- Brief Update on Plasma Master File (PMF) and Vaccine Antigen Master File (VAMF) ~ Implementation of revised Annex I to Directive 2001/83 of the European Parliament and of the Council on the Community code relating to medicinal products for human use.

  The Commission Directive amending Directive 2001/83/EC introduces a certification scheme for the PMF and VAMF operated by the EMEA. The EMEA is preparing procedural Guidance to support this scheme and intends to publish the draft procedure in the 3rd Quarter of 2003 for consultation. Additionally, technical/scientific CPMP Guidance will also follow.

Mutual Recognition procedure

The CPMP noted the report from the Mutual Recognition Facilitation Group (MRFG) meeting held on 23 June 2003. For further details, please see **Annex 6.**

The 95th plenary meeting of the CPMP will be held from 22 - 24 July 2003.

Noël Wathion
Head of Unit
Post-Authorisation Evaluation of Medicines for Human Use, Tel. (+44-20) 74 18 85 92
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	34	336
Follow-up to Scientific Advice	50	7	57
Protocol Assistance	13	5	18
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	5	16	21	387
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	4	6	10	257[3]
Negative CPMP opinions[4]	1	4	5	1	0	1	6[5]
Marketing authorisations granted by the Commission	88	146	234	1	10	11	245[6]

	1995-2002			2003			Overall Total
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Variations type I	585	1132	1717	72	186	258	1975
Positive opinions, variations type II	405	511	916	74	94	168	1084
Negative opinions, variations type II	1	6	7	0	0	0	7
Extensions (Annex II applications)	44	44	88	1	2	3	91

[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] 3 positive opinion corresponding to 3 Orphan Medicinal Product
[3] 257 positive opinions corresponding to 194 substances
[4] In case of appeal, the opinion will not be counted twice
[5] 6 negative opinions corresponding to 5 substances
[6] 245 marketing authorisations corresponding to 184 substances

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

Invented Name	Forsteo
INN	teriparatide
Marketing Authorisation Holder	Eli Lilly and Company Ltd
ATC code	H05 AA02
Indication	Treatment of established osteoporosis in postmenopausal women. A significant reduction in the incidence of vertebral, but not hip fractures has been demonstrated.
CPMP Opinion date	18/12/2002

Invented Name	Aldurazyme
INN	laronidase
Marketing Authorisation Holder	Genzyme B.V.
ATC code	A16AB
Indication	Long-term replacement therapy in patients with confirmed diagnosis of mucopolysaccharidosis I (MPS I)
CPMP Opinion date	20/02/2003

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

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
22 SPC changes	22 Positive opinions by consensus
4 Quality changes	4 Positive opinions by consensus

Opinions for Annual Re-Assessment applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Trisenox (arsenic trioxide), Cell Therapeutics (UK) Ltd	Positive opinion by consensus	Marketing Authorisation to remain under exceptional circumstances

Opinions for Renewal applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Fortovase (saquinavir) Roche Registration Ltd	Positive opinion by consensus	---

OUTCOME OF THE JUNE 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	Anaemia associated with chronic renal failure	X				X	X	X	
Chemical	Sepsis	X						X	
Biological	Non Hodgkin's lymphoma	X				X	X	X	
Chemical	Non-infectious Uveitis			X				X	
Chemical	Respiratory Syncytial Virus (RSV)-induced Bronchiolitis	X					X	X	
Chemical	Osteoporosis			X				X	
Chemical	Metabolic syndrome	X					X	X	
Chemical	Type 2 diabetes mellitus	X						X	
Chemical	Hepatocellular carcinoma		X				X	X	
Biological	Breast cancer	X				X	X		

SA: Scientific Advice

PA: Protocol Assistance

In May 2003, the above-mentioned 7 Scientific Advice letters, 2 Follow-up Scientific Advice letters and 1 Protocol Assistance letter were adopted. The Committee accepted 4 New Scientific Advice Requests, 1 Follow-up Scientific Advice Request and 3 New Protocol Assistance Requests.

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

SAFETY WORKING PARTY

Reference number	Document	Status
CPMP/SWP/2965/03	Concept Paper on the Development of a CPMP position paper on the contamination of control samples in toxicology studies	**Adopted**

EFFICACY WORKING PARTY

Reference number	Document	Status
CPMP/EWP/1875/03	Points to Consider on the Clinical Requirements of Modified Release Products released as a line extension of an existing Marketing Authorisation	**Released for 3 months consultation**
CPMP/EWP/967/01	Points to Consider on the Clinical development of fibrinolytic medicinal products in the treatment of patients with ST segment elevation acute myocardial infarction (STEMI)	**Adopted**
CPMP/EWP/3020/03/ draft	Note for Guidance on clinical investigation of medicinal products in the treatment of lipid disorders	**Released for 6 months consultation**

AD HOC WORKING GROUPS

Reference number	Document	Status
CPMP/463/00 draft 4	Revision of the Guideline on Excipients in the Package Leaflet	**Adopted**

Report from the meeting held on 23 June 2003

General Issues:

Updated Best Practice Guides published for consultation:

The following MRFG Best Practice Guides have been updated to give detailed procedural guidance on the new Variation Regulation and have been published on the Heads of Agencies website for consultation. Notifications have been sent to the pharmaceutical trade associations EGA, EFPIA and AESGP at time of publication. Any response is kindly requested through the pharmaceutical trade associations and should be forwarded via email to the EMEA/MRFG Secretariat (mrp@emea.eu.int) by the 1 July 2003:

CHAPTER 1
MRFG Best Practice Guide for the allocation of the Mutual Recognition Variation Number for Type I Notifications and Type II Variations
CHAPTER 2
Procedure for the Automatic Validation of Mutual Recognition Procedures for Variations
CHAPTER 3
MRFG Best Practice Guide for the Processing of Type IA Minor Variations (Notifications) in the Mutual Recognition Procedure
CHAPTER 4
MRFG Best Practice Guide for the Processing of Type IB Minor Variations (Notifications) in the Mutual Recognition Procedure
CHAPTER 5
MRFG Best Practice Guide for the handling of Variations in the Mutual Recognition Procedure: Type II Variations
CHAPTER 6
MRFG Standard Operating Procedure: Urgent Safety Restriction

Applications in CTD format in the MRP
Following the publication of Annex I to Dir. 2001/83, MAHs are strongly recommended to submit the new applications in the CTD format after the 1st July 2003, when they request member states to become RMS for MRPs after national approval.
The CTD format is also strongly recommended for MRP variations submitted after the 1st July 2003.

Change in the EU-Presidency
The June 2003 MRFG meeting was the last one under the Greek presidency. Italy will take over the presidency in July 2003. Sylvia Fabiani will be the next MRFG chairperson and she should be contacted in the future in case of any questions regarding the MRP.

Meeting schedule
The next MRFG meeting will be held on 21 July 2003.

Mutual Recognition Monitoring

The MRFG noted that **37** new mutual recognition procedures were finalised during the month of May 2003, as well as **195** type I and **73** type II variations.

The status as of 31st May 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	162	104	968	348	223	287	2 N.A. and 1 Variation

31 new procedures (regarding **74** products) started in May 2003. The categories of these procedures are as follows:

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

21 abridged applications, including **9** multiple applications.

1 Line extension application.

The new procedures started related to **2** full dossiers, **21** generics, **4** bibliographic applications and **4** fixed combinations.

The procedures consisted of **31** chemical substances[1].

28 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 May 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 (8)	4
DK (1)	1
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)	2
NL (3)	5

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
NL (3)	1
NL (1)	3
NO (3)	8
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:

*Pharm. Julia **YOTAKI***
National Organization for Medicines (EOF)
284, Messogeion Avenue
GR 155 62 Holargos
GREECE

Phone: + 30 210 650 7209
Fax: + 30 210 6547 202
e-mail: yotakij@eof.gr

From 1st July 2003:

Dr. Silvia Fabiani
Ministero della Salute
Direzione Generale della Valutazione dei Medicinali e della Farmacovigilanza
Via della Civiltà Romana, 7
00144 – Roma
ITALY

Phone: + 39 06 5994 3495
Fax: + 39 06 5994 3646
e-mail: s.fabiani@sanita.it

*Or you could visit the **MRFG web site** at the EUROPEAN NATIONAL MEDICINES AUTHORITIES WINDOW:*
http://heads.medagencies.org/