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

6 June 2002
EMEA/CPMP/2222/02

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
28-30 MAY 2002 PLENARY MEETING
MONTHLY REPORT

The Committee for Proprietary Medicinal Products (CPMP) held its 82nd plenary meeting from 28 to 30 May 2002.

The CPMP was informed of the nomination of Dr Alex Nicholson as new UK CPMP Member in replacement of Dr Frances Rotblat.

Product related issues

Centralised procedures

The CPMP adopted 5 positive Opinions by consensus on initial marketing authorisation applications:

- For **Ambirix** (Inactivated hepatitis A virus and recombinant hepatitis B surface antigen) (Part A) from GlaxoSmithKline Biologicals S.A., intended for prophylaxis of non-immune children and adolescents from 6 years up to and including 15 years against hepatitis A and hepatitis B infection. (For further details, please see the published Summary of Opinion (CPMP/2052/02)). The active review time was 179 days.
- For **InductOs** (dibotermin alfa) (Part A) from Genetics Institute Europe B.V., intended for the treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary nail fixation (for further details, please see the published Summary of Opinion (CPMP/2228/02)). The active review time was 200 days.
- For **Neulasta** and **Neupopeg** (pegfilgastrim) (Part A) from Amgen Europe, intended for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes), (for further details, please see the published Summaries of Opinion (CPMP/2039/02) and (CPMP/2353/02)). The active review time was 179 days.
- For **Xigris** (recombinant human activated protein C) (Part A) from Eli Lilly Nederland B.V., intended for the treatment of adult patients with severe sepsis with multiple organ failure when added to best standard care (for further details, please see the published Summary of Opinion (CPMP/2273/02)). The active review time was 180 days.

Furthermore, the CPMP revised its opinion of 21 February 2002 for **EVRA** to further address its potential environmental impact. EVRA is a transdermal patch for female contraception containing norelgestromin and ethinyl estradiol, from Janssen-Cilag International NV. The concern relates to the fact that residual amounts of the hormones are present on the patch after use, which may reach the aquatic environment if not properly disposed of. After consultation with the European Commission, the CPMP strengthened the instructions for the safe disposal of the patch after use. In addition, the company will include in the pack a disposal container for used patches.

The Committee also adopted four Lists of Questions (1 Part A and 3 Part B) on initial marketing authorisation applications and two on "line extension" applications (in accordance with Annex II of Commission Regulation (EC) No 542/95 as amended) related to one active substance (2 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 April 2002 is provided in **Annex 2**. The post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 3**.

Referrals

Referral under Article 7(5) of Commission Regulation (EC) No 541/95, as amended

A referral for Arbitration under Article 7(5) of Commission Regulation (EC) No 541/95, as amended was initiated by Sweden on **Norditropin** (somatropin) from Novo Nordisk A/S. The referral relates to an application under mutual recognition procedure for a new indication ("type II variation") for the treatment of children with severe growth failure due to intrauterine growth retardation. A Rapporteur and Co-Rapporteur were appointed and the review procedure has been started.

Referral under Article 29(2) of Directive 2001/83/EC (previously known as Article 10(2) of Council Directive 75/319/EEC, as amended)

A Community-wide review for generic products containing **isotretinoine** from Schering Health Care (Isotretinoin, Scheritonin, Rexidal and Lurantal) has been initiated further to a referral by France under Article 29(2) of Directive 2001/83/EC. The referral relates to public health concerns over the different pregnancy prevention measures proposed for the generic medicinal products in the Member States. A Rapporteur and Co-Rapporteur were appointed and the review procedure has been started.

Referral under Article 30 of Directive 2001/83/EC (previously known as Article 11 of Council Directive 75/319/EEC, as amended)

In view of an European-wide harmonisation of the Summary of Product Characteristics, France initiated a referral under Article 30 of Directive 2001/83/EC for **Roaccutane** (isotretinoine) from Roche Pharmaceuticals in order to avoid disharmony between the pregnancy prevention measures already in place for the brand leader from Roche Pharmaceuticals and those proposed for the generic medicinal products. A Rapporteur and Co-Rapporteur were appointed and the review procedure has been started.

Appeal Procedure under Article 32 (4) of Directive 2001/83/EC (previously known as Article 13(4) of Council Directive 75/319/EEC, as amended)

A final opinion by consensus was adopted by the CPMP for a nationally authorised medicinal product containing **captopril** (Capoten and associated medicinal products invented names), following an appeal to a referral opinion under Article 30 of Directive 2001/83/EC. The CPMP upheld its opinion adopted in March 2002 recommending a European-wide harmonisation of the Summary of Product Characteristics with amendments.

Scientific Advice procedures

The CPMP was informed of the outcome of the discussions of the Scientific Advice Review Group (SciARG) meeting, which was held on Monday 27 May 2002. For further details, please see **Annex 4**.

EMEA PROCEDURAL ANNOUNCEMENT

Companies intending to submit Scientific Advice requests in August 2002 should notify the EMEA Secretariat formally (scientificadvice@emea.eu.int) by 5 July 2002.

Invented Name Review Group

The invented Name Review Group (NRG), held its 29th meeting on Monday 27 May 2002 and the conclusions of the group were subsequently adopted by the CPMP.

Non-product related issues

CPMP Working Parties and Ad Hoc Groups

- The **CPMP Working Parties Chairpersons meeting** chaired by Dr. D. Brasseur was held on 29 May 2002. During the meeting, discussions on coordination of comments on Annex 1 of Directive 2001/83/EEC took place.
- The **Ad hoc group on cell therapy medicinal products** chaired by Dr. P. Kurki met on 29 May 2002.
- The **Vaccine Expert Group (VEG)**, chaired by Dr. R. Dobbelaer met on 30-31 May 2002.

Upcoming meetings:

- The next meeting of the **Ad Hoc Expert Group on Gene Therapy** will be held on 4 July 2002.

Interested Parties meetings:

- The first **EMEA/CPMP workshop with patients' organisations/associations**: "**Evaluation and surveillance of medicinal products in Europe**" was held at the EMEA on 31 May 2002. The EMEA with its Committee for Proprietary Medicinal Products (CPMP) organised this workshop with representatives of seven European Patients' and Consumers Organisations. The objectives of this workshop were to reinforce communication with patients' representatives, to exchange views on information related to medicinal products and to further explore contributions to regulatory activities (for further information, please see meeting Press Release (EMEA/CPMP/2348/02)).

Organisational Matters

- The 13th CPMP ORGAnisational Matters (ORGAM) meeting took place on Monday 27 May 2002, chaired by Dr Daniel Brasseur. During the meeting the following topics were presented/discussed:
  - **Advisory Expert Groups:** The CPMP further discussed the creation, mandate, composition and functioning of the CPMP Therapeutic Advisory Groups.
  - **Clarification meeting with Industry after adoption of the List of Questions (LoQs):** A Guidance document " Guidance to Applicants on meeting with the Rapporteurs on CPMP List of Questions" has been discussed and circulated for comments and is expected to be released shortly for external consultation.
  - **Conduct of trend votes and provision of information to applicants**: Discussions have taken place regarding the timing of trend votes and provision of information on the outcome to applicants.
  - **Templates Day 120 (List of Questions (LoQ)), 150 (Assessment Response to LoQ), 180 (List of Outstanding Issues)**: The EMEA/CPMP is in the process of developing the above-mentioned internal templates to facilitate the centralized procedure review process.

Mutual Recognition procedure

The CPMP noted the report from the MRFG meeting held on 27 May 2002. For further details, please see **Annex 6**.

The 83rd plenary meeting of the CPMP will be held from 25 to 28 June 2002.

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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

	1995-2001			2002			Overall Total
	Part A	Part B	Total	Part A	Part B	Total	
Scientific Advice	88	164	252	3	20	23	275
Follow-up to scientific advice	18	17	35	1	2	3	38
Protocol Assistance	0	2	2	2	0	2	4
Follow-up to Protocol Assistance	2	0	2	1	0	1	3

	1995-2001			2002			
	Part A	Part B	Total	Part A	Part B	Total	
Applications submitted	120	215	335	5	13	18	353
Withdrawals	15	45	60	3	4	7	67
Positive CPMP opinions	77	131	208	14	10	24	232[1]
Negative CPMP opinions[2]	1	4	5	0	0	0	5[3]
Marketing authorisations granted by the Commission	71	123	194	1	13	14	208[4]

	1995-2001			2002			Overall Total
	Part A	Part B	Total	Part A	Part B	Total	
Variations type I	448	806	1254	51	136	187	1441
Positive opinions, variations type II	285	362	647	51	59	110	757
Negative opinions, variations type II	1	6	7	0	0	0	7
Extensions (Annex II applications)	38	36	74	0	3	3	77

[1] 232 positive opinions corresponding to 175 substances
[2] In case of appeal the opinion will not be counted twice
[3] 5 negative opinions corresponding to 4 substances
[4] 208 marketing authorisations corresponding to 159 substances

MEDICINAL PRODUCTS GRANTED A COMMUNITY MARKETING AUTHORISATION UNDER THE CENTRALISED PROCEDURE SINCE APRIL 2002 CPMP MONTHLY REPORT

Invented Name	Ebixa
INN	memantine
Marketing Authorisation Holder	Lundbeck A/S
ATC code	N06DX01
Indication	Treatment of patients with moderately severe to severe Alzheimer's disease
CPMP Opinion date	21/02/2002

Invented Name	Memantine Merz Pharmaceuticals GmbH
INN	memantine
Marketing Authorisation Holder	Merz Pharmaceuticals GmbH
ATC code	N06DX01
Indication	Treatment of patients with moderately severe to severe Alzheimer's disease
CPMP Opinion date	21/02/2001

Invented Name	Tracleer
INN	bosentan
Marketing Authorisation Holder	Actelion Registration Ltd
ATC code	C02KX01
Indication	Treatment of pulmonary arterial hypertension
CPMP Opinion date	21/02/2002

Invented Name	Opatanol
INN	olopatadine
Marketing Authorisation Holder	Alcon Laboratories (UK) Ltd
ATC code	S01GX09
Indication	Treatment of ocular signs and symptoms of seasonal allergic conjunctivitis
CPMP Opinion date	21/02/2002

OUTCOME OF THE MAY 2002 CPMP MEETING IN RELATION TO CENTRALISED APPLICATIONS IN THE POST-AUTHORISATION PHASE

Opinions for Type I Variation applications (following Type II procedure)	
Number of Opinions	**Outcome**
7 changes	Positive opinions by consensus

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
5 Extensions of indication	4 Positive opinions by consensus 1 Positive opinion by majority vote
15 SPC changes	Positive opinions by consensus
15 quality changes	Positive opinions by consensus

Opinions for Renewal applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Neorecormon (epoetin beta), Roche Registration Ltd	Positive opinion by consensus	---
Revasc (desirudin), Aventis	Positive opinion by consensus	---

OUTCOME OF THE MAY 2002 CPMP MEETING IN RELATION TO SCIENTIFIC ADVICE PROCEDURES

Substance	Intended indications(s)	Topic				
		Type of Request		Pharma-ceutical	Pre-Clinical	Clinical
		New	Follow-up			
Chemical	Coronary heart disease	**X**			**X**	
Chemical	Vascular Dementia		**X**			**X**
Chemical	Invasive candidiasis	**X**				**X**
Chemical	Non-small cell lung cancer	**X**		**X**		
Chemical	Borderline Personality Disorder	**X**				**X**
Biological	Fabry disease		**X** (Protocol Assistance)			**X**
Chemical	Hypertension	**X**				**X**
Chemical	Warts	**X**			**X**	

In May 2002, the above-mentioned 7 final Scientific Advice letters and 1 Protocol Assistance letter were adopted. The Committee accepted 8 new Scientific Advice requests, 3 follow-up Scientific Advice requests and 2 requests for Protocol Assistance.

DOCUMENTS PREPARED BY THE CPMP WORKING PARTIES AND AD-HOC GROUPS ADOPTED DURING THE MAY 2002 CPMP MEETING

QUALITY WORKING PARTY

Reference number	Document	Status
CPMP/QWP/158/01	Note for Guidance on Quality of water for pharmaceutical use	Adopted in May 2002

EFFICACY WORKING PARTY

The EWP has considered the need for revision of the following guidelines adopted before 1995;

- Clinical Investigation of Hypnotic Medicinal Products (EudraLex vol. 3C);
- Clinical Investigation of Medicinal Products in the Treatment of Generalised Anxiety Disorder, Panic Disorder and Obsessive-Compulsive Disorder (EudraLex vol. 3C);
- Clinical Investigation of Corticosteroids intended for use on the Skin. (EudraLex vol. 3C).

The requirements of these guidelines were considered still adequate. The update of the guideline on hypnotic medicinal products was not considered to be a priority. Regarding the guidelines on Generalised Anxiety Disorder, Panic Disorder and Obsessive-Compulsive Disorder, and on Corticosteroids intended for use on the Skin, it would be worth to supersede or complete these documents with separate specific disease guidelines. Concept papers will therefore be proposed for adoption by the CPMP. The CPMP adopted these recommendations during its May 2002 plenary meeting.

Reference number	Document	Status
CPMP/EWP/1080/00	Note for Guidance on Clinical investigation of medicinal products in the treatment of diabetes mellitus	Adopted in May 2002
CPMP/EWP/968/00	Concept paper on the Development of a CPMP Points to consider on the evaluation of the pharmacokinetics of medicinal products in the paediatric population	Adopted in May 2002

Report from the meeting held on 27 May 2002

General issues

Communication in the Mutual Recognition Procedure (MRP)

Applicants are reminded that the Reference Member State (RMS) is the main contact point during a MRP. In case of any direct communication between Concerned Member States and local affiliates of the applicant, the RMS should be kept informed.

Handling of medicinal products containing lactose, prepared using calf rennet

With reference to the CPMP statement EMEA/CPMP/571/02, the MRFG agreed that the risk for transmitting animal spongiform encephalopathy by pharmaceutical grade lactose is satisfactorily minimised in accordance with the TSE Note for Guidance (EMEA/410/01 rev. 1). The MRFG therefore decided that for products applied for via the MRP, no further data would be necessary for lactose prepared using calf rennet.
However, the applicant should confirm that

- the lactose is produced only from milk sourced from healthy animals in the same conditions as milk collected for human consumption; and
- the lactose is prepared without the use of other ruminant materials than calf rennet.

The same confirmation should be provided for other excipients/reagents from whey (e.g. lactulose, galactose)

Meeting schedule
The next MRFG meeting will be held on **Monday 24 June 2002**.

The MRFG noted that 21 new mutual recognition procedures were finalised during the month of April 2002, as well as 144 type I and 56 type II variations.

The status as of 30th April 2002 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
2002	118	113	574	270	173	229	2 Var.

38 new procedures (regarding 69 products) started in April 2002. The categories of these procedures are as follows:

6 known active substances (already authorised in at least one member state) including 1 repeat use.

28 abridged applications including **7** multiple applications and **4** repeat use.

4 Line extension applications.

The new procedures started last month relate to 5 full dossiers, 24 generics, 3 bibliographic applications, 2 informed consent applications and 4 for different use, route or dose.

The procedures consisted of 36 chemical substances and 2 biological vaccines[1].

36 of these procedures were prescription-only medicinal products in the reference Member State and 2 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 April 2002

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (1)	4
DE (1)	2
DE (1)	2
DK (2)	1
DK (4)	3
DK (2)	1
DK (4)	15
DK (4)	7
FI (2)	8
FR (2)	1
FR (1)	3
FR (1)	16
FR (1)	3
IR (2)	2
NL (2)	6
NL (2)	1
NL (2)	1
NL (2)	1
NO (2)	7
PT (1)	1
SE (2)	6
SE (1)	4
SE (4)	5
SE (4)	1
SE (1)	11
SE (1)	1
SE (1)	1
SE (1)	1
SE (2)	1

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
SE (1)	1
SE (1)	1
SE (1)	1
UK (3)	1
UK (2)	7
UK (1)	2
UK (1)	16
UK (1)	1
UK (4)	6

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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