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

1 March 2002
CPMP/590/02

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
19-21 FEBRUARY 2002 PLENARY MEETING
MONTHLY REPORT

The Committee for Proprietary Medicinal Products (CPMP) held its 79th plenary meeting from 19 to 21 February 2002.

CPMP Members were informed of Mrs. Antonia Pantouvaki and Dr Else Høibraaten's resignations. The CPMP Chairman thanked them on behalf of the Committee for their contributions and welcomed the new Greek CPMP representative, Prof. Nikolaus Drakoulis.

Product related issues

Centralised procedures

The CPMP adopted five positive Opinions on initial marketing authorisation applications:

- For **EVRA** (norelgestromin – ethinyl estradiol), Part B, from Janssen Cilag International N. V. presented as a transdermal patch intended for women of fertile age. The EMEA assessment review began on 27 March 2001 and the opinion was adopted by consensus on 21 February 2002, with an active review time of 175 days. For further details, please see the published Summary of Opinion (CPMP/499/02).
- For **Tracleer** (bosentan), Part B, from Actelion Registration Ltd indicated for the treatment of pulmonary arterial hypertension to improve exercise capacity and symptoms in patients with grade III functional status. The EMEA review assessment began on 27 February 2001 and the opinion was adopted under exceptional circumstances by consensus on 21 February 2002, with an active review time of 173 days. Tracleer was designated an orphan medicinal product on 14 February 2001. This is the 5th orphan medicinal product to receive a positive opinion for marketing authorisation from the CPMP. For further details, please see the published Summary of Opinion (CPMP/531/01).
- For the double application **Memantine Merz Pharmaceuticals GmbH** (memantine hydrochloride) from Merz Pharmaceuticals GmbH, and **Ebixa** (memantine hydrochloride) from Lundbeck A/S indicated for the treatment of patients with moderately severe to severe Alzheimer's disease. The EMEA assessment review for Memantine Merz Pharmaceuticals GmbH began on 26 September 2000 and for Ebixa on 22 October 2001. The opinion was adopted by majority votes on 21 February 2002, with an active review time of 208 and 62 days respectively. For further details, please see the published Summaries of Opinion (CPMP/446/02) and (CPMP/553/02).
- For **Opatanol** (olopatadine) from Alcon Laboratories (UK) Ltd., indicated for the treatment of ocular signs and symptoms of seasonal allergic conjunctivitis. The EMEA assessment review began on 27 March 2001 and the opinion was adopted by majority votes on 21 February 2002, with an active review time of 218 days. For further details, please see the published Summary of Opinion (CPMP/3852/01).

The CPMP also gave a positive opinion for a new indication for **Glivec** (imatinib mesylate) from Novartis Europharm Ltd. for the treatment of adult patients with unresectable and/or metastatic gastrointestinal stromal tumours (GIST)**.** Glivec was first authorised in the European Union on 7 November 2001 and orphan medicinal product designation for GIST was granted on 20 November 2001. The EMEA review began on 14 December 2001.

Furthermore, the CPMP adopted one positive opinion by consensus on "line extension" applications (in accordance with Annex II of Commission Regulation (EC) No 542/95 as amended) related to one active substance (Part B).

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

Referrals

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

Following a referral initiated by France under Article 11, the CPMP adopted by consensus an opinion for a nationally authorised medicinal product containing midazolam (Hypnovel, Ipnovel, Dormicum), leading to a EU-wide harmonised SPC.

Referral under Article 36 of Directive 2001/83/EC (previously known as Article 15a of Council Directive 75/319/EEC, as amended)

The CPMP initiated a Community review on the risk-benefit of bupropion containing medicinal products (Corzen, Quomem, Zyban, Zyntabac) authorised under the mutual recognition procedure, following a referral by Germany under Article 36 of the Community Code on human medicines (ex-Article 15a of Council Directive 75/319/EEC).

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 18 February 2002. For further details, please see **Annex 4**.

Non-product related issues

CPMP Working Parties and Ad Hoc Groups

- The CPMP and its Biotechnology Working Party (BWP) have conducted a risk assessment of lactose prepared using calf rennet. The CPMP adopted a public statement entitled "Lactose prepared using calf rennet: risk assessment in relationship to bovine spongiform encephalopathies (BSE) (EMEA/CPMP/571/02)" which will be published on the EMEA Website.
- The CPMP and its Pharmacovigilance Working Party (PhVWP) have conducted a class review of dopaminergic substances and sudden sleep onset. The CPMP adopted a position statement (CPMP/578/02) with recommendations on the ability to drive and use machines for the Summary of Product Characteristics and Package Leaflets, which will be published on the EMEA Website.
- The Ad Hoc Expert Group on comparability of Biotechnology products: pre-clinical and clinical aspects, chaired by Dr. M. Toivonen was held on 18 January 2002. Progress was made in the preparation of the Pre-clinical and clinical Annex to the Biotech quality guidance document.
- The meeting of the Ad Hoc Expert Group on Xenogeneic cell therapy medicinal products, Chaired by Dr. P. Kurki was held on 5 February 2002. During this meeting the experts reviewed current scientific and regulatory approaches and experience in this field. The focus of the session was on safety aspects, methods available to minimise viral risks, special methodological aspects to be considered for clinical efficacy, post exposure safety monitoring and surveillance.
- The 3rd meeting of the Paediatric Expert Group (PEG), chaired by Dr D. Brasseur, Chairman of the CPMP was held on 22 February 2002. Part of the meeting was held in conjunction with the International Federation of Associations of Pharmaceutical Physicians, and addressed issues of clinical studies at extreme of age, i.e. in children and elderly.
- The meeting of the Ad Hoc Expert Group on Gene Therapy, chaired by Dr L. Tsang, was held on 11 February 2002 during which adenoviral vector shedding, assays for control testing of onco-retroviral vectors and Lentiviral vectors were discussed. The report from the previous meeting held on 12 October 2001 (CPMP/EMEA/27917/01) will be published shortly on the EMEA Website.

- An updated Guidance document on use of medicinal products for treatment and prophylaxis of biological agents that might be used as weapons of bioterrorism was adopted by CPMP and will be published on the EMEA Website.
- The 2d meeting of the Vaccines Expert Group (VEG), chaired by Dr. R. Dobbelaer was held on 22 February 2002. The next meeting is scheduled to take place on 21-22 March 2002.
- A revised Blood Product Working Group 2002-2003 work programme (CPMP/BPWG/2648/01) was adopted by the CPMP and will be published on the EMEA Website.

An overview of guidance documents adopted during the meeting or released for consultation to Interested Parties is attached as **Annex 5**.

Organisational Matters

- The NRG held its 26th meeting on Monday 18 February 2002 and the conclusions of the group were subsequently adopted by the CPMP.
- The following documents were adopted and will be published on the EMEA Website (please see Annex 5):
  - Guidance to applicants on CPMP oral explanations in relation to Centralised applications (CPMP/ CPMP/2390/01 rev.2).
  - Guidance document on voting in the framework of the discussion and adoption of CPMP opinions (EMEA/CPMP/3137/01 rev.0).

PROCEDURAL ANNOUNCEMENT

The CPMP adopted the CPMP meetings calendar meeting dates for 2005

Calendar for CPMP meetings in 2005	
Month	CPMP Dates
January	18, 19, 20
February	15, 16, 17
March	15, 16, 17
April	19. 20, 21
May	24, 25, 26
June	21, 22, 23
July	26, 27, 28
August[1)]	*23, 24, 25*
September	13, 14, 15
October	11, 12, 13
November	15, 16, 17
December	13, 14, 15

[1)]dates for August are tentative

Mutual Recognition procedure

The CPMP noted the report from the MRFG, which was held on 18 February 2002. (for further details, please see **Annex 6**).
The Chairman of the working group on harmonisation of SPCs, which consists of members from the EMEA/CPMP/MRFG and European Commission, reported the outcome of their meeting of 18 February 2002 to the CPMP, with particular emphasis on candidate medicinal products for pre-referral discussions. The CPMP agreed with the list of medicinal products as presented and the timetable for future actions in support of this process (for further information, please see Annex 1 of the enclosed MRFG Press Release).

The 80th plenary meeting of the CPMP will be held from 19 to 21 March 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	0	5	5	257
Follow-up to scientific advice	18	17	35	1	1	2	37
Protocol Assistance	0	2	2	2	0	2	4
Follow-up to Protocol Assistance	2	0	2	0	0	0	2

	1995-2001			2002			
	Part A	Part B	Total	Part A	Part B	Total	
Applications submitted	120	215	335	1	3	4	339
Withdrawals	15	45	60	0	2	2	62
Positive CPMP opinions	77	131	208	0	9	9	217[1]
Negative CPMP opinions[2]	1	4	5	0	0	0	5[3]
Marketing authorisations granted by the Commission	71	123	194	0	1	1	195[4]

	1995-2001			2002			Overall Total
	Part A	Part B	Total	Part A	Part B	Total	
Variations type I	448	806	1254	13	43	56	1310
Positive opinions, variations type II	285	362	647	19	25	44	691
Negative opinions, variations type II	1	6	7	0	0	0	7
Extensions (Annex II applications)	38	36	74	0	1	1	75

[1] 217 positive opinions corresponding to 168 substances
[2] In case of appeal the opinion will not be counted twice
[3] 5 negative opinions corresponding to 4 substances
[4] 195 marketing authorisations corresponding to 150 substances

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

Brand name	Viread
INN	Tenofovir
Marketing Authorisation Holder	Gilead Science International Ltd.
ATC code	J05A
Indication	Treatment of HIV infected patients with early virological failure in combination with other anti-HIV products.
CPMP Opinion date	18/10/01
Date of Commission Decision	05/02/02

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

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
9 extension indications	Positive opinions (2 by majority votes and 7 by consensus)
7 SPC changes	Positive opinions by consensus
9 quality changes	Positive opinions by consensus

Opinion for Annual Re-Assessment applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Ammonaps (phenylbutyrate), Orphan Europe SARL	Positive opinion by consensus	Marketing Authorisation to remain under exceptional circumstances
Agenerase (amprenavir), GlaxoSmithKline	Positive opinion by consensus	Marketing Authorisation to remain under exceptional circumstances

Opinions for Renewal applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Leukoscan (sulesomab), Immunomedics B.V	Positive opinion by consensus	---

OUTCOME OF THE FEBRUARY 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	Management of Pain	X				X
Chemical	Parkinson's disease	X				X
Biological	Acute Stroke		X	X	X	X

In February 2002, the above-mentioned three final Scientific Advice letters were adopted. The Committee accepted six new requests and one follow-up request for Scientific Advice.

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

QUALITY WORKING PARTY

Reference number	Document	Status
CPMP/QWP/227/02	Revised Note for Guidance on the European Drug Master File procedure	Released in February 2002 for 6 month consultation
CPMP/QWP/122/02	Note for Guidance on Stability testing: stability testing of existing active substances and related finished products	Released in February 2002 for 6 month consultation

BIOTECHNOLOGY WORKING GROUP

Reference number	Document	Status
EMEA/CPMP/571/02	Lactose prepared using calf rennet: risk assessment in relationship to bovine spongiform encephalopathies (BSE).	Adopted in February 2002

EFFICAY WORKING GROUP

Reference number	Document	Status
CPMP/EWP/49/01	Appendix to the NfG on the Clinical investigation of medicinal products in the treatment of schizophrenia (CPMP/EWP/559/95) – Methodology of clinical trials concerning the development of depot preparations of approved medicinal products in schizophrenia	Released in February 2002 for 6 month consultation

ICH

Reference number	Document	Status
CPMP/ICH/4104/00	ICH Q1D – Note for Guidance on bracketing and matrixing designs for stability testing of drug substances and drug products	Adopted in February 2002
CPMP/ICH/2737/99	ICH Topic Q3A ® – Note for Guidance on impurities testing: Impurities in new drug substances (revision of CPMP/ICH/142/95)	Adopted in February 2002
CPMP/ICH/1840/01	ICH M2 – The Step 2eCTD – Specification document	Released in February 2002 for 5 month consultation
CPMP/ICH/420/02	ICH Q1E – Note for Guidance on evaluation of stability data	Released in February 2002 for 6 month consultation
CPMP/ICH/421/02	ICH Q1F – Note for Guidance on stability data package for registration in climatic zones III and IV	Released in February 2002 for 6 month consultation
CPMP/ICH/423/02	ICH S7B – Note for Guidance on safety pharmacology studies for assessing the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals	Released in February 2002 for 6 month consultation

ORGANISATIONAL MATTERS

Reference number	Document	Status
CPMP/2390/01 rev. 2	Guidance to applicants on CPMP Oral Explanations in relation to Centralised Applications	Adopted in February 2002
CPMP/3137/01 rev. 0	Guidance Document on voting in the framework of the discussion and adoption of CPMP Opinions	Adopted in February 2002

Report from the meeting held on 18 February 2002

General issues

A medicinal product used as comparison for bioequivalence study

With reference to Chapter 1 of the NTA it was confirmed that a medicinal product used as comparison for bioequivalence study, where a bioequivalence study is applicable, must be a version of the original medicinal product that is *authorised within the Community*. This medicinal product is normally the same as the reference medicinal product. Bioequivalence studies performed with a product not authorised within the EEA will consequently not be considered acceptable.

TSE and Milk Derivatives - Risk on regulatory assessment of lactose prepared using calf rennet

The MRFG heard a report from the BWP on the risk assessment of lactose prepared using calf rennet in relationship to bovine spongiform encephalopathies (BSE). This report will be presented to the CPMP for adoption at the February 2002 meeting. Further information can be found in the public statement (EMEA/CPMP/571/02) which will be published on the EMEA Website.

Core-SPC for Hormone Replacement Therapy products

The MRFG adopted the above core-SPC, which will soon be published on the Heads of Agencies Website.

Meeting schedule

The next MRFG meeting will be held on **18 March 2002**.

ANNEX 1

Joint CPMP / MRFG Working Group on harmonisation of SPCs

At the February, 2002 meeting of the working group on harmonisation of SPCs, consisting of members from the EMEA/CPMP/MRFG and European Commission, the future of the prospective Article 30 referral harmonisation was discussed.

The following points summarise the main outcomes of the meeting:

- The prospective harmonisation of SPCs through Article 30 referrals will continue in 2002.
- 7 medicinal products, selected from several different classes, have been identified for which pre-referral discussion will be initiated.
- Within the next two weeks, the MAHs of these 7 medicinal products will receive a request for information relating to the product, including a copy of all latest approved SPCs, a description of the divergences across those SPCs and a proposal for a harmonised SPC, and various other background information.
- This information should be submitted to the EMEA by 10th April, 2002.
- Rapporteurs and Co-Rapporteurs for those seven products will be assigned at the plenary meeting of the March CPMP.
- Pre-referral discussions should be finalised before the plenary meeting of the CPMP in June 2002.
- Once the outcome of the pre-referral discussions is known, discussions between the working group and the CPMP will be conducted with the aim of presenting their findings to the Heads of Agencies at the May and/or July meetings.

The MAHs that receive notifications relating to the Article 30 referrals concerning their products will be invited to a preparatory meeting at the offices of the EMEA.

The MRFG noted that 40 new mutual recognition procedures were finalised during the month of January 2002, as well as 99 type I and 35 type II variations.

The status as of 31 January 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	40	76	99	170	35	219	--

20 new procedures (regarding 33 products) started in January 2002. The categories of these procedures are as follows:

7 new active substances, including **5** multiple applications.

2 known active substances (already authorised in at least one member state) classified as repeat use.

11 abridged applications including **2** repeat use.

The new procedures started last month relate to 8 full dossiers, 11 generics and 1 informed consent.

The procedures consisted of 20chemical substances[1].

18 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 January 2002

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
AT (3)	8
AT (2)	1
DE (2)	16
DE (2)	16
DE (2)	16
DE (2)	16
DE (4)	2
DK (2)	2
DK (1)	3
FI (1)	8
NL (1)	1
NL (1)	1
NL (1)	16
NL (1)	16
SE (1)	6
SE (1)	1
SE (1)	1
UK (2)	6
UK (1)	11
UK (1)	11

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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