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

London, 28 November 2002
EMEA/CPMP/5857/02

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
NOVEMBER 2002 PLENARY MEETING
MONTHLY REPORT

The Committee for Proprietary Medicinal Products (CPMP) held its 87th plenary meeting from 19 – 21 November 2002.

The CPMP Chairman welcomed Dr Ian Hudson, the new UK CPMP representative who has replaced Dr Alex Nicholson as of November 2002. Dr Nicholson was thanked and congratulated for all the achievements and contributions made during his participation in the CPMP meetings.

Product related issues

Centralised procedures

The CPMP adopted 4 opinions on initial marketing authorisation applications at this meeting:

- A positive opinion by consensus for **Hepsera** (adefovir dipivoxil) (Part B) from Gilead Science International Limited, which is intended for the treatment of chronic hepatitis B in adults (for further details, please see the published Summary of Opinion (CPMP/4495/02)). EMEA review began on 22 April 2002 and the opinion was adopted on 21 November 2002, with an active review time of 152 days.
- Positive opinions for **Levitra** and **Vivanza** (vardenafil) (Part B) from Bayer AG. The products are indicated for the treatment of erectile dysfunction (for further details, please see the published Summary of Opinion (CPMP/5714/02)). EMEA review began respectively on 28 January 2002 and 22 April 2002. The opinions were adopted on 21 November 2002, with an active review time of 180 and 95 days.
- A positive opinion for **Ytracis** (yttrium(Y-90)) (Part B) from CIS bio International. The product is a radiopharmaceutical precursor solution intended for the radio labelling of carrier molecules (for further details, please see the published Summary of Opinion (CPMP/5906/02)). EMEA review began on 22 October 2001 and the opinion was adopted on 21 November 2002, with an active review time of 176 days.

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

The Committee also adopted 2 opinions by consensus on "line extension" applications (2 Part B) and 4 Lists of Questions (1 Part A and 3 Part B). A List of Questions was adopted for a consultation on an ancillary medicinal substance used in a medical device.

The Committee also gave positive opinions for a number of new indications for already authorised medicinal products, including:

- Extension of the indication for **Caspofungin MSD** (caspofungin) (Part B) from Merck Sharp & Dohme to include treatment of invasive candidiasis in non-neutropenic adult patients. Caspofungin MSD was first authorised in the European Union in October 2001.
- Extension of the indication for **Lantus** (insulin glargine) (Part A) from Aventis Pharma Deutschland GmbH to include the treatment in children of 6 years or above with diabetes mellitus. Lantus was first authorised in the European Union in June 2000.

Further information on these extensions will be included in the European Public Assessment Report (EPAR) once the European Commission has granted final approval.

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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 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

The Committee began a Community-wide review for:

- **Mononine** (containing human coagulation factor IX), Aventis Behring Ltd. The product is already licensed in a number of Member States for the treatment and prophylaxis of patients with haemophilia B and the arbitration referral only relates to an application to include a new mode of administration by continuous infusion. The referral is made by Sweden under Article 7(5) of the Variations Regulation (Commission Regulation (EC) No 541/95) and relates to the efficacy of mononine in this new mode of administration only.
- **Laurina** and **associated tradenames** (containing desogestrel and ethinylestradiol), Organon. These combined oral contraceptives are already licensed in a number of Member States. The arbitration referral relates to an application for changes to the wording of the product information, section "Special warnings and precautions for use" concerning the relative risk of acute myocardial infarction in third generation combined oral contraceptives compared with the 1st and 2nd generation COCs. The proposed warning is not in agreement with the September 2001 CPMP position statement on combined oral contraceptives. The referral is made by Germany under Article 7(5) of the Variations Regulation (Commission Regulation (EC) No 541/95).

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

The Committee began a Community-wide review for:

- **Pravachol** (pravastatin) and associated product names from Bristol-Myers Squibb.
- **Zocord** (simvastatin) and associated product names from Merck Sharp & Dohme.

Both of these referrals are part of the first wave of referrals arising from the concerted action by EU regulatory authorities to resolve divergences amongst the nationally authorised SPCs and thus to harmonise its divergent SPCs across Europe. These referrals are made by the European Commission under Article 30 of the Community Code on human medicines (ex-Article 11 of Council Directive 75/319/EEC).

Referral under Article 31 of Directive 2001/83/EC (formerly known as Article 12 of CD 75/319/EEC, as amended)

The Committee concluded its Community-wide reviews for:

- Medicinal products containing **calcitonin**. These products are marketed by a large number of companies throughout the European Union. The CPMP recommended revisions to and harmonisation of the authorised indications of these products. The harmonised indications for the injectable form recommended by the Committee are for the products' use in prevention of acute bone loss due to sudden immobilisation (such as patients with recent bone fractures), Paget's disease (a bone disorder) and hypercalcaemia of malignancy. The harmonised indication for the intranasal form recommended by the Committee is for the products' use in the treatment of established post-menopausal osteoporosis to prevent vertebral fractures. The procedure began in April 2000 following a referral by The Netherlands under Article 31 of the Community Code on human medicines (ex-Article 12 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 November 2002. For further details, please see **Annex 4**.

Non-product related issues

CPMP Working Parties and Ad Hoc Working Groups

The **Working Parties Chairpersons' meeting**, chaired by Dr Daniel Brasseur, was held on 19 November 2002. The Working Parties' work programmes for 2003 were discussed along with organisational matters.

The **CPMP Efficacy Working Party** has considered the need for revision of the "CPMP Note for Guidance on antiarrhythmic" (CPMP/EWP239/95). The content of the guideline was considered still adequate, and the update of the guideline is not a priority. The issue may be reconsidered over 2003.

Within the framework of the **Ad Hoc Expert Group on Oncology**, a report was presented on a series of CPMP initiatives at the margins of the European Society of Medical Oncology (ESMO) conference in Nice in October 2002. Two Oncology Assessor's meetings, and an initial Meeting with Interested Parties on Novel Approaches in Oncology were held on 21 - 22 October 2002. The participants confirmed the interest for this type of interaction among regulators, academia and industry, and expressed hope that the dialogue should continue. A proposal will be presented to CPMP on the establishment of a forum for discussion with Interested Parties.

The CPMP appointed Dr Pekka Kurki as the new Chairperson for the **Ad Hoc Working Group on (pre) clinical comparability of Biotechnology products** in replacement of Dr Markku Toivonen.

The CPMP appointed Prof. Klaus Cichutek as the new Chairperson for the **Ad Hoc Expert Group on Gene Therapy** in replacement of Dr Lincoln Tsang.

Documents prepared by the CPMP Working Parties and Ad-Hoc Groups adopted during the November 2002 CPMP meeting can be seen in **Annex 5.**

Upcoming meetings following the November 2002 CPMP plenary meeting:

The EMEA held a training session for Junior Assessors on human and veterinary medicines procedures on Thursday 21 November 2002 and Friday 20 November 2002.

ICH

For further details of ICH/CPMP documents adopted or released for consultation at this meeting, please see **Annex 5**.

Interested Parties meetings:

The EMEA with EBE, EFPIA, EUROPABIO and EURORDIS will hold their first Joint meeting of all Interested Parties for Orphan Medicinal Products at the Britannia International Hotel, Canary Wharf, London, on 2 and 3 December 2002, on "A Continuity Policy for Orphan Medicines in the EU.

CPMP Organisational Matters

As part of the ongoing discussions on the proposed EMEA Risk Management Strategy, the CPMP had a first discussion on the Agency's proposals for the future handling of safety concerns by the CPMP. The outcome of this first discussion will be reported to the Heads of Agencies as a consultation to the development of a European Risk Management Strategy.

The 17th CPMP Organisational Matters meeting took place on Monday 18 November 2002, chaired by Dr D. Brasseur. During the meeting the following principle topics were presented/discussed:

- **Scientific Advice Working Group (SAWG):** The mandate, the structure and organisation of the SAWG were discussed. The SAWG will be a multidisciplinary group and include 1 Chair, 15 members nominated by CPMP and 2 members nominated by COMP. Dr Markku Toivonen has been confirmed in his position as chair. The SAWG will be a 2 days meeting allowing for up to 8 oral explanations per meeting. These proposals were confirmed and endorsed by CPMP.
- **Therapeutic Advisory Groups (TAGs):** Two TAGs were identified following discussions in October 2002, namely Oncology and Anti-infectives Advisory Groups (see October 2002 CPMP Monthly report (EMEA/CPMP/4979/02)). Based on the forecast of intended submission of centralised applications in 2003, a third TAG was identified on Diagnostic agents. An updated mandate along with the role of the nominated experts was discussed. These proposals were confirmed and endorsed by CPMP. Implementation of TAGs as a pilot phase will take place as of 2003.
- **Feedback from the Informal CPMP/COMP/MRFG meeting held on 24-25 September 2002 in Hillerød, Denmark:** A feedback of this informal CPMP/COMP/MRFG meeting was provided and the Group discussed in particular the scientific and practical challenges of the CPMP in view of the forthcoming EU Enlargement.

PROCEDURAL ANNOUNCEMENTS

- The Group discussed an **update of the number of dossier requirements** (paper/electronic copies) for the CPMP members. This update will be available on the EMEA web site: http://www.emea.eu.intvc.
- **Clarification meeting with applicants after adoption of List of Questions:** A "Guidance on the Rapporteurs' meetings with applicants on the CPMP List of Questions" (EMEA/9947/02) was agreed and this Guidance document will be released on the EMEA web site (http://www.emea.eu.intvc) for 6-months consultation up to April 2003.

The next CPMP Organisational Matters meeting is scheduled to take place on Monday 16 December 2002.

Mutual Recognition procedure

The CPMP noted the report from the Mutual Recognition Facilitation Group (MRFG) meeting held on 18 November 2002. For further details, please see **Annex 6**.

The 88th plenary meeting of the CPMP will be held from 17 – 19 December 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	8	39	47	299
Follow-up to Scientific Advice	18	17	35	5	10	15	50
Protocol Assistance	0	2	2	4	6	10	12
Follow-up to Protocol Assistance	2	0	2	1	1	2	4

	1995-2001			2002			
	Part A	Part B	Total	Part A	Part B	Total	
Applications submitted	120	215	335	7	24	31	366
Consultation for Medical Device[1]	NA	N/A	N/A	0	1	1	1
Withdrawals	15	45	60	5	6	11	71
Positive CPMP opinions	77	131	208	15	23	38	246[2]
Negative CPMP opinions[3]	1	4	5	0	0	0	5[4]
Marketing authorisations granted by the Commission	71	123	194	16	21	37	231[5]

	1995-2001			2002			Overall Total
	Part A	Part B	Total	Part A	Part B	Total	
Variations type I	448	806	1254	137	324	461	1715
Positive opinions, variations type II	285	362	647	108	137	245	892
Negative opinions, variations type II	1	6	7	0	0	0	7
Extensions (Annex II applications)	38	36	74	3	7	10	84

[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] 246 positive opinions corresponding to 184 substances
[3] In case of appeal, the opinion will not be counted twice
[4] 5 negative opinions corresponding to 4 substances
[5] 231 marketing authorisations corresponding to 172 substances

ANNEX 2 to CPMP Monthly Report November 2002

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

Invented Name	Cialis
INN	tadalafil
Marketing Authorisation Holder	Lilly ICOS Limited
ATC code	G04BE
Indication	Treatment of erectile dysfunction
CPMP Opinion date	22/07/2002

Invented Name	Zavesca
INN	miglustat
Marketing Authorisation Holder	Oxford GlycoScience (UK) Ltd
ATC code	A16AX06
Indication	Treatment of mild to moderate type 1 Gaucher disease when enzyme replacement therapy is unsuitable
CPMP Opinion date	25/07/2002

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

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
2 Extensions of indication	2 Positive opinions by consensus
14 SPC changes	14 Positive opinions by consensus
5 Quality changes	5 Positive opinions by consensus

Opinions for Annual re-assessment applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
N/A	N/A	---

Opinions for Renewal applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Viracept (nelfinavir), Roche Registration Ltd	Positive opinion by consensus	---
Viramune (nevirapine), Boehringer Ingelheim International GmbH	Positive opinion by consensus	---

OUTCOME OF THE NOVEMBER 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	Oral Contraceptive	**X**			**X**	
Chemical	Schizophrenia		**X**			**X**
Chemical	Pancreatic cancer	**X**				**X**
Chemica	Cystic fibrosis	**X** (Protocol Assistance/ Significant benefit)			**X**	**X**
Chemical	Parkinson's disease	**X** (Protocol Assistance)			**X**	**X**
Biological	Renal cell carcinoma	**X** (Protocol Assistance/ Significant benefit)				**X**
Chemical	Wegener's granulomatosis	**X** (Protocol Assistance/ Significant benefit)			**X**	**X**
Biological	Diabetes		**X**	**X**	**X**	**X**
Biological	Gliomas	**X** (Protocol Assistance/ Significant benefit)			**X**	**X**
Chemical	Heart failure		**X**			**X**

In November 2002, the above-mentioned 2 final Scientific Advice letters, 5 Protocol Assistance letters and 3 Follow-up Scientific Advice letters were adopted. The Committee accepted 7 new Scientific Advice requests.

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

SAFETY WORKING PARTY

Reference number	Document	Status
CPMP/SWP/799/95	Note for Guidance on the Non-Clinical Documentation of Medicinal Products with Well-Established Use	Released for 6 month consultation

EFFICACY WORKING PARTY

Reference number	Document	Status
CPMP/EWP/4279/02	Concept paper on the development of a CPMP Note for Guidance on clinical investigation of medicinal products for the treatment of obsessive compulsive disorder	Adopted
CPMP/EWP/4280/02	Concept paper on the development of a CPMP Note for Guidance on clinical investigation on medicinal products for the treatment of panic disorder	Adopted
CPMP/EWP/2922/01	Note for Guidance on the clinical investigation of medicinal products in the treatment of asthma	Adopted
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)	Released for 3 month consultation
CPMP/EWP/612/00 rev. 1	Revised Note for Guidance on clinical investigation of medicinal products for treatment of nociceptive pain	Adopted
CPMP/EWP/4914/02	Concept Paper on the Development of a CPMP Note for Guidance on Clinical investigation of medicinal products for the treatment of Generalised Anxiety Disorder	Adopted

BIOTECH WORKING PARTY

Reference number	Document	Status
CPMP/BWP/2879/02	CPMP Position Statement on Creutzfeldt-Jakob Disease and plasma-derived and urine-derived medicinal products	Adopted

AD HOC EXPERT GROUP ON XENOGENIC CELL THERAPY

Reference number	Document	Status
CPMP/1199/02	Points to consider on xenogeneic cell therapy medicinal products	Released for 6 month consultation

AD HOC EXPERT GROUP ON PHARMACOGENETICS

Reference number	Document	Status
CPMP/3070/01	Position paper on terminology in pharmacogenetics	Adopted.

ICH

Reference number	Document	Status
CPMP/ICH/1840/01	ICH M2 – Step 4- Electronic CTD (eCTD) – Specification document	Adopted

Report from the meeting held on 18 November 2002 (Draft. 0)

General issues:

Recommendations to Marketing Authorisation Holders (MAH):

Compliance with Commission Decisions after referral procedures
It is recommended that generic companies after Art. 30 referrals contact their RMS to initiate the harmonisation of SPCs to conform with the Commission Decision. SPC's of recently finalised referrals (domperidone) have been published on the EMEA website. (www.emea.eu.int/htms/human/referral/referral.htm)

When is simplified handling of variations in MRP after a merger acceptable? (press release 9/00)
The MRFG discussed a simplified handling of variations in specific cases and agreed the following: If the MAH in case of a merger wants to change the name of manufacturers and/or the name and address of the MAH in different CMSs for a number of products in different strengths and pharmaceutical forms, it is possible to submit one variation per product including the above mentioned changes due to the merger.

When is simplified handling of variations in MRP not related to a merger acceptable? (press release 11/00)
A simplified handling for certain listed type I variations in MRP - not in connection with a merger - was adopted by the MRFG during the November meeting.

- Change of the brand name (Type I, No.2) where the approved brand name is different in the CMS. If the MAH wants to change the brand name after authorisation in more than one CMS, the submission of only one Type I variation per medicinal product (MA) will cover all different names and all different CMS. If the brand name has to be changed during the MRP, no MR-variation procedure is necessary.

- Change of the name and/or the address of a MAH (Type I, No.3) where the name and/or address is different in the CMS and the change is not to be considered as a transfer. In such cases also the submission of only one type I variation per medicinal product (MA) will cover all different CMS.

It has to be mentioned that fees remain under national considerations.

Validation of applications for the mutual recognition procedure
It is important that companies file their applications in time and in good order to allow the 10 working days for validation in the agencies. This time is needed and if files arrive late, proposed dates for starting the MRP will have to be postponed.

Meeting schedule
The next MRFG meeting will be held on **16 December** 2002.

Annex 1

Joint CPMP/ MRFG working Group on harmonisation of SPC's:
Two referrals have been initiated by the European Commission in November. The WG will initiate pre-referral discussions on four new products.

The MRFG noted that 43 new mutual recognition procedures were finalised during the month of October 2002, as well 200 type I and 41 type II variations.

The status as of 31st October 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	346	103	1713	234	446	252	2 N.A. 7 Var.

34 new procedures (regarding 105 products) started in October 2002. The categories of these procedures are as follows:

3 new active substance (first authorisation in the European Community after RMS approval) classified **2** as repeat use applications and **1** as multiple application.

4 known active substances (already authorised in at least one member state) including **1** multiple application.

26 abridged applications including **7** multiple applications and **1** repeat use .

1 Line extension application.

The new procedures started last month relate to 4 full dossiers, 26 generics, 3 bibliographic applications and 1 for different use, route or dose.

The procedures consisted of 33 chemical substances and 1 biological - other[1].

33 of these procedures were prescription-only medicinal products in the reference Member State and 1 was Non-prescription (including OTC) medicinal product[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 October 2002

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DK (4)	10
DK (4)	1
DK (4)	1
DK (3)	3
FI (3)	1
FI (3)	4
FI (3)	1
IR (3)	1
IR (3)	1
IR (3)	1
IR (3)	3
IR (4)	9

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
IR (4)	1
IR (4)	1
IR (4)	4
NL (7)	3
NL (1)	5
NL (4)	1
NL (4)	12
NL (4)	1
NL (4)	1
SE (1)	1
SE (1)	1
SE (1)	2
SE (4)	1
SE (4)	6
SE (4)	1
SE (4)	3
UK (1)	6
UK (1)	7
UK (2)	4
UK (1)	7
UK (1)	2
UK (4)	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 by the presiding chair of the MRFG:

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http://heads.medagencies.org/

