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

31 July 2002
EMEA/CPMP/3473/02

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
23-25 JULY 2002 PLENARY MEETING
MONTHLY REPORT

The Committee for Proprietary Medicinal Products (CPMP) held its 84th plenary meeting from 23 to 25 July 2002.

The Committee was informed of the resignation of Pharm. Geert De Greef as Belgian CPMP Member. On behalf of the Committee, the CPMP Chairman thanked him for all his contributions to the CPMP.

Product related issues

Centralised procedures

The Agency's scientific committee, the CPMP, adopted 8 opinions on initial marketing authorisation applications at this meeting, including opinions for 2 orphan medicines:

- A positive opinion by consensus for **Somavert** (pegvisomant) (Part B) from Pharmacia Enterprises S.A. intended for the treatment of acromegaly (for further details, please see the published Summary of Opinion (CPMP/3627/02)). EMEA review began on 29 March 2001 and the opinion was adopted on 25 July 2002, with an active review time of 195 days.

  Somavert was designated an orphan medicinal product on 14 February 2001 and is the sixth orphan medicinal product to receive a positive opinion for marketing authorisation from the CPMP.

- A positive opinion by majority vote for **Zavesca** (miglustat) (Part B) from Oxford GlycoScience (UK) Ltd. intended for the treatment of mild to moderate type 1 Gaucher disease (for further details, please see the published Summary of Opinion (CPMP/3247/01)). EMEA review began on 17 July 2001 and the opinion was adopted on 25 July 2002, with an active review time of 198 days.

  Zavesca was designated an orphan medicinal product on 18 October 2000 and is the seventh orphan medicinal product to receive a positive opinion for marketing authorisation from the CPMP.

- A positive opinion by consensus for **Cialis** (tadalafil) (Part B) from Lilly ICOS Limited intended for the treatment of erectile dysfunction (for further details, please see the published Summary of Opinion (CPMP/277/01)). EMEA review began on 17 July 2001 and the opinion was adopted on 25 July 2002, with an active review time of 202 days.

- Five positive opinions by consensus for multiple applications for the following products containing valdecoxib (5 Part B): **Bextra** (Pharmacia-Pfizer EEIG), **Valdyn** (Pharmacia Europe EEIG), **Valdecoxib Pfizer Ltd** (Pfizer Limited), **Kudeq** (Pfizer Limited) and **Valdecoxib Pharmacia Europe EEIG** (Pharmacia Europe EEIG). The medicinal product is intended for symptomatic relief in the treatment of osteoarthritis or rheumatoid arthritis and treatment of primary dysmenorrhoea (for further details, please see the published Summaries of Opinion (CPMP/3404/02, CPMP/3663/02, CPMP/3664/02, CPMP/3665/02 and CPMP/3666/02)). EMEA review began on 17 July 2001 and the opinions were adopted on 25 July 2002, with an active review time of 204 days.

The Committee also adopted one opinion by consensus on a "line extension" application (Part B) (in accordance with Annex II of Commission Regulation (EC) No. 542/95, as amended) and eight Lists of Questions (3 Part A and 5 Part B) on initial marketing authorisation applications.

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The CPMP noted the withdrawal for commercial reasons of the Marketing Authorisation for **ZARTRA** (Imiquimod), indicated for topical treatment of external genital and perianal warts (condyloma acuminata) in adult patients from Laboratoires 3M Santé. **ZARTRA** has never been marketed in the European Union. **ALDARA** (Imiquimod), a second application from the same Marketing Authorisation Holder is marketed in all European Member States and will continue to be available (for further details, please see Public Statement (EMEA/12594/02)).

An overview of centralised procedures since 1995 is given in **Annex 1**. The post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 2**. No Commission Decision was granted since the June 2002 CPMP plenary meeting.

Referrals

Referral under Article 7(5) of Commission Regulation (EC) No. 541/95

A referral for Arbitration under Article 7(5) of Commission Regulation (EC) No 541/95, as amended was initiated by The Netherlands on medicinal products containing lisinopril (**Cardiostad** and associated invented names). The referral relates to a variation application for a generic medicinal product under the mutual recognition procedure for a new indication (treatment of incipient nephropathy in diabetes characterized by microalbuminuria). A Rapporteur and a Co-Rapporteur were appointed and the review procedure has been started.

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

Furthermore, in parallel to the referral for Arbitration under Article 7(5) of Commission Regulation (EC) No 541/95, as amended for medicinal products containing lisinopril (**Cardiostad** and associated invented names), The Netherlands initiated a referral under Article 30 of Directive 2001/83/EC (formally known as Article 11 of Council Directive 75/319/EEC, as amended) for harmonising the product information in all Member States for the original product **Zestril** and associated product names (lisinopril) against which essentially similarity was claimed. A Rapporteur and a Co-Rapporteur were appointed and the review procedure has been started.

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

A Community-wide review for all medicinal products containing **celecoxib**, **etoricoxib**, **parecoxib**, **rofecoxib** and **valdecoxib** has been initiated following a referral by France under Article 31 of Directive 2001/83/EC (formally known as Article 12 of Council Directive 75/319/EEC, as amended). The review was initiated because of safety concerns relating to the frequency of gastrointestinal and cardiovascular adverse events. A Rapporteur and Co-Rapporteurs were appointed and the review procedure has been started.

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

The CPMP adopted a positive opinion by majority vote for bupropion containing medicinal products (**Corzen**, **Quomem**, **Zyban**, **Zyntabac**) authorised under the mutual recognition procedure. The Committee considered that the balance of risks and benefits of bupropion remains favourable for the current indication (i.e.: "as an aid to smoking cessation in combination with motivational support in nicotine-dependent patients") and recommended the maintenance of the Marketing Authorisations with amendments to the Summary of Product Characteristics. The Committee recommended also that bupropion should be used in accordance with smoking cessation guidelines. The Member States competent authorities will continue to keep the product under regular review, including follow-up measures to be submitted in the next Periodic Safety Update Report by September 2002. The referral under Article 36 of Directive 2001/83/EC (formaly known as Article 15a of Council Directive 75/319/EEC, as amended) was initiated by Germany in February 2002.

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 22 July 2002. For further details, please see **Annex 3**.

Invented Name Review Group

The invented Name Review Group (NRG) held its 31st meeting on Monday 22 July 2002 and the conclusions of the group were subsequently adopted by the CPMP.

Non-product related issues

CPMP Working Parties and Ad Hoc Groups

*All the documents prepared by the CPMP working parties and ad-hoc groups adopted during the July 2002 CPMP meeting are listed in **Annex 4** and will be published on the EMEA Web site.*

- The **CPMP Working Parties Chairpersons** meeting chaired by Dr. D. Brasseur was held on 23 July 2002 to discuss the EC report on status of Annex I to Directive 2001/83/EC and the EMEA/CPMP contributions to the next ICH meeting in Washington from 9 to 12 September 2002.
- The CPMP adopted the **Note for Guidance on the development of vaccinia virus based vaccines against smallpox** (CPMP/1100/02) developed by the Vaccine Expert Group, which is available on the EMEA website (http://www.emea.eu.int/pdfs/human/veg/110002en.pdf). This Note for Guidance is also available through the European Commission website.
- The CPMP has adopted for release for six months consultation the "Note for Guidance on Comparability of medicinal products containing biotechnology-derived proteins as drug substance – Annex on Non-clinical and clinical considerations (CPMP/3097/02)" elaborated by **Ad Hoc working group on (pre) clinical comparability of biotechnology medicinal products** chaired by Dr M. Toivonen (see also **Annex 4**).
- The CPMP heard the report from **Ad Hoc Expert group on Gene Therapy** meeting which was held on 4 July 2002 and chaired by Dr L. Tsang where topics for the development of joint ICH recommendations on gene therapy have been identified. Such recommendations will be put forward as European proposals at the upcoming ICH meeting in September 2002.
- The CPMP adopted the revised EMEA/CPMP **Guidance document on use of medicinal products for treatment and prophylaxis of biological agents that might be used as weapons of bio terrorism** (CPMP/4048/01 rev.3). This revised Guidance document will be published on the EMEA website.

Upcoming meetings:

- A Workshop on methodological aspects of clinical trials for efficacy evaluation in small populations will be held at the EMEA on 22 October 2002.

Interested Parties meetings:

- The EMEA held a meeting with representatives of the EFPIA on 19 July 2002 to discuss preliminary results of the Centralised Procedure Performance Indicators 2001/2002 exercise.

Organisational Matters

The 14th CPMP ORGAnisational Matters (ORGAM) meeting took place on Monday 22 July 2002, chaired by Dr Daniel Brasseur. During the meeting the following topics were presented/discussed:

- **EMEA Risk Management Strategy**
- **Scientific Advice Group meetings**
- **Therapeutic Advisory Groups (TAGs) and the current CPMP Ad Hoc Expert groups**
- **Summary Product of Characteristics Guideline**
- **Templates Day 120 (List of Questions (LoQ)), 150 (Assessment Response to LoQ), 180 (List of Outstanding Issues)**: The CPMP adopted the above-mentioned internal templates to facilitate the centralized procedure review process.

PROCEDURAL ANNOUNCEMENTS

The CPMP agreed to replace the August 2002 plenary meeting by written procedures to be established for certain ongoing applications.

As part of the implementation of the EMEA Risk Management Strategy, the CPMP agreed that, as of January 2003, the Pharmacovigilance Working Party meetings will be rescheduled to be held in parallel with CPMP plenary meetings.

Mutual Recognition procedure

The CPMP noted the report from the MRFG meeting held on 22 July 2002. The July 2002 MRFG meeting was the first under the Danish Presidency. Denmark will maintain the Chairmanship for 6 Months until 31 December 2002. The chair Mrs Joan Boye or her co-chair Mrs Pia Næsborg Andersen should be contacted in future in case of any questions regarding the Mutual Recognition Procedure.

This report includes information on recommendations made by the Joint CPMP / MRFG Working Group on harmonisation of SPC's which met on Monday 22 July 2002:

- Referrals should be initiated for the 6 products where pre-referral discussions have been concluded during Spring 2002. Two to four of these referrals should be initiated during this year with the remaining in the beginning of 2003.
- The European Commission would be the most appropriate body to initiate these referrals.
- Additional pre-referral discussions should be initiated for other products during Autumn 2002.

The Working Group should continue to evaluate the project and report to the Head of Agencies. For further details, please see **Annex 5.**

The 85th plenary meeting of the CPMP will be held from 17 to 19 September 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	6	30	36	288
Follow-up to scientific advice	18	17	35	3	6	9	44
Protocol Assistance	0	2	2	2	1	3	5
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	5	17	22	357
Withdrawals	15	45	60	4	4	8	68
Positive CPMP opinions	77	131	208	15	17	32	240[1]
Negative CPMP opinions[2]	1	4	5	0	0	0	5[3]
Marketing authorisations granted by the Commission	71	123	194	3	20	23	217[4]

	1995-2001			2002			Overall Total
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Variations type I	448	806	1254	80	199	279	1533
Positive opinions, variations type II	285	362	647	71	98	169	816
Negative opinions, variations type II	1	6	7	0	0	0	7
Extensions (Annex II applications)	38	36	74	0	5	5	79

[1] 240 positive opinions corresponding to 179 substances
[2] In case of appeal the opinion will not be counted twice
[3] 5 negative opinions corresponding to 4 substances
[4] 217 marketing authorisations corresponding to 166 substances

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

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
1 Extension of indication	1 Positive opinion by consensus
15 SPC changes	15 Positive opinions by consensus
11 quality changes	11 Positive opinions by consensus

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

Opinions for Renewal applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Aprovel (irbesartan) Sanofi Pharma Bristol Myers Squibb SNC	Positive opinion by consensus	---
Karvea (irbesartan) Bristol Myers Squibb Pharma EEIG	Positive opinion by consensus	---
Infanrix HepB (DTPa-HepB vaccine), GlaxoSmithKline Biologicals S.A.,	Positive opinion by consensus	---
Sifrol (pramipexole), Boehringer Ingelheim International GmbH	Positive opinion by consensus	---
Mirapexin (pramipexole), Pharmacia & Upjohn S.A.	Positive opinion by consensus	---
Daquiran (pramipexole), Boehringer Ingelheim Pharma KG	Positive opinion by consensus	---

OUTCOME OF THE JULY 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	Postmenopausal osteoporosis	**X**			**X**	**X**
Chemical	Colorectal cancer	**X**				**X**
Biological	Protein C deficiency		**X**			**X**
Chemical	Oral contraception	**X**				**X**
Chemical	Insomnia	**X**				**X**
Chemical	Chronic iron overload	**X** (Protocol Assistance)			**X**	**X**
Biological	Sepsis	**X**		**X**	**X**	**X**
Chemical	Hyperlipidaemias	**X**			**X**	**X**
Chemical	Migraine	**X**				**X**
Chemical	Colorectal cancer	**X**				**X**
Biological	Acute lung failure		**X**		**X**	**X**
Biological	Allergic asthma	**X**				**X**
Chemical	Colorectal cancer		**X**			**X**
Chemical	Squamous cell carcinoma of the head and neck	**X**				**X**
Chemical	Functional dyspepsia		**X**			**X**
Chemical	Irritable Bowel Syndrome (IBS)		**X**			**X**

In July 2002, the 16 above-mentioned final Scientific Advice letters were adopted. The Committee accepted 5 new Scientific Advice requests, 2 follow-up Scientific Advice requests and 5 requests for Protocol Assistance.

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

BIOTECHNOLOGY WORKING PARTY

Reference number	Document	Status
CPMP/BWP/2758/02	Guidance on Pharmaceutical aspects of the Product Literature for Human Vaccines	Released in July 2002 for 3 month consultation
CPMP/BWP/2712/02	Note for Guidance on Production and quality control of animal immunoglobulins and immunosera for human use	Adopted in July 2002

SAFETY WORKING PARTY

Reference number	Document	Status
CPMP/SWP/2877/00	Note for Guidance on Carcinogenic potential	Adopted in July 2002

EFFICACY WORKING PARTY

Reference number	Document	Status
CPMP/EWP/2455/02	Concept paper on the Development of a CPMP Points to consider on Allergic rhino-conjunctivitis	Adopted in July 2002
CPMP/EWP/282/02	Position paper on the Regulatory requirements for the authorisation of low-dose modified release ASA formulations in the secondary prevention of cardiovascular events	Adopted in July 2002
CPMP/EWP/2454/02	Concept paper on the Development of a CPMP Note for Guidance on Clinical investigation of medicinal products for the treatment of psoriasis	Adopted in July 2002
CPMP/EWP/2459/02	Concept Paper on the Development of a CPMP Points to Consider on methodological issues in confirmatory clinical trials with flexible design and analysis plan	Adopted in July 2002
CPMP/EWP/2339/02	Concept paper on the Development of a CPMP Note for Guidance on the evaluation of the pharmacokinetics of medicinal products in patients with hepatic impairment	Adopted in July 2002
CPMP/EWP/556/95 rev. 1	Points to consider on Clinical investigation of medicinal products for treatment of rheumatoid arthritis	Released in July 2002 for 3 month consultation

EFFICACY WORKING PARTY (cont'd)

Reference number	Document	Status
CPMP/EWP/633/02 draft 5	Note for Guidance on the Clinical development of medicinal products for the treatment of HIV infection	Released in July 2002 for 3 month consultation
CPMP/EWP/1343/01	Points to consider on the Evaluation of new anti-fungal agents for invasive fungal infections	Released in July 2002 for 6 month consultation

BLOOD PRODUCT WORKING GROUP

Reference number	Document	Status
CPMP/BPWG/282/00	Core SPC for Human Normal immunoglobulin for subcutaneous and intramuscular use	Adopted in July 2002
CPMP/BPWG/283/00	Note for Guidance on the Clinical investigation of human normal immunoglobulin for subcutaneous and intramuscular use	Adopted in July 2002

AD HOC EXPERT GROUP on (PRE-) CLINICAL COMPARABILITY of BIOTECHNOLOGY MEDICINAL PRODUCTS

Reference number	Document	Status
CPMP/3097/02	Note for Guidance on Comparability of medicinal products containing biotechnology-derived proteins as drug substance – Annex on Non-clinical and clinical considerations	Released in July 2002 for 6 month consultation

Report from the meeting held on 22 July 2002

General issues

Update of MRFG Documents:

The following MRFG publications have been updated to reflect Directive 2001/83/EC and will be published on the MRFG website:

- Simultaneous applications (Article 17 paragraph 2 of Directive 2001/83/EC) - Member States Standard Operating Procedure
- Triggering of Mutual Recognition by Member States (Article 18 of Directive 2001/83/EC) - Member States Standard Operating Procedure
- Informed consent applications in Mutual Recognition Procedures - Recommendations
- Recommendations on Multiple applications in Mutual Recognition Procedures
- Applications under Annex II of Regulation (EC) No 541/95 in Mutual Recognition procedures - Member States Recommendation
- Recommendation for Mutual Recognition Procedure after finalisation of an arbitration procedure with a positive opinion by the CPMP and a positive decision by the EU-Commission
- Updated list of MRP contact points

Legal basis for an application under Article 10 a) iii 1st or 2nd paragraph when the strength or pharmaceutical form of the Reference product differs between RMS/CMS(s)

The recommendation regarding the legal basis of Article 10.1 a) iii applications, as mentioned in the June press release, will be published as a new document on the MRFG website.

Change in the EU-Presidency

The July MRFG meeting was the first under the Danish Presidency. Denmark will maintain the Chairmanship for 6 Months as until 31 December 2002. The chair Mrs Joan Boye or her co-chair Mrs Pia Næsborg Andersen should be contacted in future in case of any questions regarding the MRP.

Meeting schedule

The next MRFG meeting will be held on **16 September 2002**.

ANNEX 1
Joint CPMP / MRFG Working Group on harmonisation of SPC's

At it's meeting of the 4th of July 2002 in Denmark, The Heads of Agencies (HoA) supported the recommendation from the Joint CPMP/MRFG Working Group on Harmonisations of SPC's (WG). These recommendations were:

- Referrals should be initiated for the 6 products where pre-referral discussions have been concluded during Spring 2002. Two to four of these referrals should be initiated during this year with the remaining in the beginning of 2003.
- The European Commission would be the most appropriate body to initiate these referrals.
- Additional pre-referral discussions should be initiated for other products during Autumn 2002.
- The WG should continue to evaluate the project and report to the HoA

At it's meeting of the 22 July the WG identified the steps needed to allow the first referrals to start at the end of September. The exact timing of the 6 referrals will be further discussed at the WG meeting in September but ultimately this will depend on the referring body and the CPMP.

During it's meeting, the WG also discussed the issue of "vertical" harmonisation (i.e. harmonisation of generic SPCs according to the harmonised SPC of the original product within the same Member State). Furthermore, the WG will invite the EGA to discuss ways of monitoring how generic companies voluntarily follow the outcome of Article 30 referrals of the brand leader.

The MRFG noted that 38 new mutual recognition procedures were finalised during the month of June 2002, as well as 129 type I and 46 type II variations.

The status as of 30th June 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	194	108	891	239	279	192	1 N.A. 3 Var.

39 new procedures (regarding 70 products) started in June 2002. The categories of these procedures are as follows:

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

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

28 abridged applications including **16** multiple applications.

4 Line extension applications including **1** repeat use.

The new procedures started last month relate to 10 full dossiers, 28 generics and 1 fixed combination.

The procedures consisted of 37 chemical substances and 2 biological - other[1].

36 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 June 2002

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (4)	4
DK (1)	1
DK (1)	6
DK (1)	7
DK (2)	3
DK (1)	8
DK (1)	5
DK (1)	7
DK (1)	1
DK (4)	1
DK (4)	10
DK (4)	1
DK (3)	2
DK (4)	1
DK (1)	1
DK (1)	1
ES (1)	6
ES (1)	5
FI (1)	3
FI (3)	5
FI (2)	1
FI (1)	3

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
FI (2)	1
FI (3)	1
FI (3)	4
IR (1)	13
NL (1)	6
NL (1)	4
NL (1)	1
NL (1)	4
NL (1)	4
NL (1)	16
SE (2)	1
UK (1)	9
UK (1)	2
UK (1)	8
UK (3)	16
UK (1)	1
UK (1)	3

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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