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

24 October 2002
EMEA/CPMP/4979/02

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
15 – 17 OCTOBER 2002 PLENARY MEETING
MONTHLY REPORT

The Committee for Proprietary Medicinal Products (CPMP) held its 86th plenary meeting from 15 to 17 October 2002.

Product related issues

Centralised procedures

The CPMP adopted 1 opinion on an initial marketing authorisation application at this meeting:

- A positive opinion by consensus for **Carbaglu** (N-carbamoyl-L-glutamic acid), (Part B) from Orphan Europe, which is indicated for the treatment of hyperammonemia associated with N-acetyl-glutamate synthase (NAGS) deficiency (for further details, please see the published Summary of Opinion (EMEA/CPMP/4796/02)). The EMEA review began on 22 October 2001 and the opinion was adopted on 17 October 2002, with an active review time of 148 days.

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

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

The Committee also gave a positive opinion on a new indication for an already authorised medicinal product:

- Extension of the indications for **Caelyx** (doxorubicin hydrochloride) from Schering-Plough Europe to include monotherapy treatment for patients with metastatic breast cancer, where there is an increased cardiac risk. Caelyx was first authorised in the European Union in June 1996.

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

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 September 2002 is provided in **Annex 2.** The post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 3**.

Referrals

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

- The CPMP initiated a referral procedure under Article 29(2) of Directive 2001/83/EC for **Botox (**clostridium botulinum type A neurotoxin complex) from Allergan Pharmaceuticals. The product is already licensed in a number of Member States and the arbitration referral only relates to an application for a new indication for the treatment of primary axillary hyperhidrosis (excessive sweating). This referral is made by Germany and Italy under Article 29(2) of Directive 2001/83/EC and relates to safety and efficacy concerns of Botox in this new

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indication only. A Rapporteur and a Co-Rapporteur were appointed and the review procedure has started.

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

- The CPMP adopted an opinion on **Beriate P** (human coagulation Factor VIII) from Aventis Behring GmbH. The CPMP recommended that the summary of product characteristics, in particular the warning on transmissible agents, is brought in line with the June 2000 core SPC for human plasma derived factor VIII products (CPMP/BPWG/1619/99, 29 June 2000). The procedure began in September 2001, following a referral by the marketing authorisation holder under Article 31 of Directive 2001/83/EC.

Referral under Article 36(1) of Directive 2001/83/EC (formerly known as Article 15a of CD 75/319/EEC, as amended)

- The CPMP recommended the revocation of national authorisations granted through the mutual recognition procedure for a number of generic medicines containing **felodipine**. This follows a GCP inspection that identified irregularities in the conduct and reporting of clinical trials supporting these authorisations. The review began in September 2002, following a referral by Germany under Article 36 of Directive 2001/83/EC. The recommendation does not relate to originator (non-generic) products containing felodipine.

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 14 October 2002. For further details, please see **Annex 4**.

Invented Name Review Group

The invented Name Review Group, held its 33rd meeting on Monday 14 October 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 **Paediatric Expert Group (PEG)** meeting, chaired by Dr D. Brasseur, was held on 20 September 2002. The Group discussed amongst other topics, the maturation of the immune system (consequences for the evaluation of medicinal products in children), the paediatric needs and assessment of existing paediatric medicinal products by therapeutic classes and the evaluation of medicinal products in neonates.

- The **Ad Hoc Expert Group on Pharmacogenetics** meeting, chaired by Dr E. Abadie, was held on 30 September 2002. The Group discussed amongst other topics, a Position paper on terminology in Pharmacogenetics (layout, general principles and detailed wording).

- The **Ad Hoc Working Group on (pre) – clinical comparability of Biotechnology medicinal products** meeting, chaired by Dr M.Toivonen, was held on 2 October 2002. The Group discussed amongst other topics, the Guidance document "Comparability of biotechnology products: preclinical and clinical issues" and Criteria for the definition of biosimilar medicinal products: Annex I to Directive 2001/83/EC.

Upcoming meetings following the October 2002 CPMP plenary meeting:

- A **Workshop on Methodology of Clinical trials for Efficacy Evaluation in small populations** was held on 22 October 2002 at the EMEA. This meeting was co-chaired by Prof. Josep Torrent-Farnell and Dr Daniel Brasseur. FDA colleagues joined the Workshop by videoconference.
- The **Ad Hoc Expert Group on Oncology** chaired by Dr B. Jonsson, held its assessors' meeting as well as a meeting with interested parties on novel approaches in oncology (ESMO) on 21 and 22 October 2002 in Nice.

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.

Organisational Matters

The 16^{h} CPMP Organsational Matters meeting took place on Monday 14 October 2002, chaired by Dr D. Brasseur. During the meeting the following principle topics were presented/discussed:

- **Follow-up on the schedule and organisation of the Scientific Advice Review Group (SciARG)**. Changes in the schedule and organisation of SciARG have been agreed and will be implemented in early 2003.
- **Therapeutic Advisory Groups:** Following discussion on how to optimise the use of clinical expertise in the CPMP review process, two groups were identified, namely Oncology and Anti-infectives Advisory Groups. Implementation as a pilot phase will take place as of 2003.
- **Follow-up of the Management Board (MB) meeting held on 03 October 2002**: The EMEA transparency policy proposals were presented to the group. For more information please refer to the MB press release which can be found together with other information about the work of the EMEA on the EMEA web site at the following location: http://www.emea.eu.int.

The next CPMP Organsational Matters meeting is scheduled to take place on Monday 18 November 2002.

PROCEDURAL ANNOUNCEMENT

As announced to the Management Board during its meeting held on Wednesday 3 October 2002, the number of applications for Marketing Authorisations submitted to the EMEA in 2002 has been below the number forecasted in the EMEA Work programme. As a consequence, the EMEA had to revise its 2002 budget and a contingency plan has been introduced for all types of expenditures for internal and external activities.

The following meetings related to CPMP activities have been cancelled and postponed for the remaining of 2002:

- Invented Name Review Group
- Vaccine Expert Group
- Paediatric Expert Group
- Efficacy Working Party and related drafting groups
- Workshop on Viral Safety
- Ad-Hoc Group on Plasma Master File
- Ad-Hoc Group on manufacturing changes
- Quality Review of Documents

Mutual Recognition procedure

The CPMP noted the report from the Mutual Recognition Facilitation Group (MRFG) meeting held on 14 October 2002. For further details, please see **Annex 5.**

The 87th plenary meeting of the CPMP will be held from 19 – 21 November 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	37	45	297
Follow-up to Scientific Advice	18	17	35	4	8	12	47
Protocol Assistance	0	2	2	2	3	5	7
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	6	22	28	363
Consultation for Medical Device[1]	NA	N/A	N/A	0	1	1	1
Withdrawals	15	45	60	4	5	9	69
Positive CPMP opinions	77	131	208	15	19	34	242[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	109	254	363	1617
Positive opinions, variations type II	285	362	647	102	122	224	871
Negative opinions, variations type II	1	6	7	0	0	0	7
Extensions (Annex II applications)	38	36	74	2	6	8	82

[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] 242 positive opinions corresponding to 181 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

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

Invented Name	Actrapid
INN	insulin human
Marketing Authorisation Holder	Novo Nordisk
ATC code	A10AB01
Indication	Treatment of diabetes mellitus
CPMP Opinion date	25/04/2002

Invented Name	Velosulin
INN	insulin human
Marketing Authorisation Holder	Novo Nordisk
ATC code	A10AB01
Indication	Treatment of diabetes mellitus
CPMP Opinion date	25/04/2002

Invented Name	Monotard
INN	insulin human
Marketing Authorisation Holder	Novo Nordisk
ATC code	A10AB01
Indication	Treatment of diabetes mellitus
CPMP Opinion date	25/04/2002

Invented Name	Insulatard
INN	insulin human
Marketing Authorisation Holder	Novo Nordisk
ATC code	A10AB01
Indication	Treatment of diabetes mellitus
CPMP Opinion date	25/04/2002

Invented Name	Protaphane
INN	insulin human
Marketing Authorisation Holder	Novo Nordisk
ATC code	A10AB01
Indication	Treatment of diabetes mellitus
CPMP Opinion date	25/04/2002

Invented Name	Mixtard
INN	insulin human
Marketing Authorisation Holder	Novo Nordisk
ATC code	A10AB01
Indication	Treatment of diabetes mellitus
CPMP Opinion date	25/04/2002

Invented Name	Actraphane
INN	insulin human
Marketing Authorisation Holder	Novo Nordisk
ATC code	A10AB01
Indication	Treatment of diabetes mellitus
CPMP Opinion date	25/04/2002

Invented Name	Ultratard
INN	insulin human
Marketing Authorisation Holder	Novo Nordisk
ATC code	A10AB01
Indication	Treatment of diabetes mellitus
CPMP Opinion date	25/04/2002

Invented Name	InductOs
INN	dibotermin alfa
Marketing Authorisation Holder	Genetics Institute of Europe B.V.
ATC code	M06A
Indication	Treatment of acute tibia fractures in adults, as an adjunct to standard care
CPMP Opinion date	30/05/2002

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

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
1 Extensions of indication	1 Positive opinions by consensus
5 SPC changes	5 Positive opinions by consensus
12 Quality changes	12 Positive opinions by consensus

Opinions for Annual re-assessment applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Fabrazyme (agalsidase beta), Genzyme B.V.	Positive opinion by consensus	Marketing Authorisation to remain under exceptional circumstances
Replagal (agalsidase alfa), TKT Europe 5S AB	Positive opinion by consensus	Marketing Authorisation to remain under exceptional circumstances

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

OUTCOME OF THE OCTOBER 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			
Biological	Crohn's disease and Multiple Sclerosis	**X**				**X**
Chemical	Attention Deficit Hyperactivity Disorder (ADHD)		**X**			**X**
Chemical	Ovarian cancer	**X** (Protocol Assistance/ Significant benefit)			**X**	**X**
Chemical	Alzheimer's disease	**X**				**X**
Chemical	Non-Hodgkin's Lymphoma	**X**				**X**
Chemical	Restless Legs Syndrome	**X**				**X**
Chemical	Neuropathic pain due to diabetic neuropathy	**X**				**X**
Biological	Severe sepsis with multiple organ failure		**X**			**X**

In October 2002, the above-mentioned 5 final Scientific Advice letters, 1 Protocol Assistance letter and 2 Follow-up Scientific Advice letters were adopted. The Committee accepted 4 new Scientific Advice requests and 1 Follow-up Scientific Advice request.

Report from the meeting held on 14 October 2002

General issues

Publications on the MRFG Website (http://www.medagencies.org):

The core SPC on HRT products had been reviewed by an MRFG expert group in September. The updated proposal will be published on the MRFG website. Comments should be forwarded to the chair of the MRFG no later than 4 November 2002.

The following MRFG publication was adopted and will be published on the MRFG website:

"Guidance on submission dates for applicants of the MRP"

Recommendations to Marketing Authorisation Holders (MAH):

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

- Changes to Drug Master Files (DMF)
  Changes to DMFs which are part of marketing authorisations after undergoing the MRP are only acceptable if submitted to the RMS as variation applications for mutual recognition.
  Only changes to the content of DMF which are part of purely national marketing authorisations should be introduced to the competent authorities by means of national variation applications through the MAH. It is recommended for MAHs to inform DMF holders that the DMF is part of the marketing authoristation and that any changes to the DMF are changes to the MA itself.

- Notifications to CPMP

  Notifications in the Mutual Recognition Procedure as mentioned in the Notice to Applicants, Chapter 2 should be adressed to the Human Post-Authorisation Unit, MRFG secretariat at the EMEA, preferably in electronic format to the following email address mrp@emea.eu.int.

Representation of the European Commission at MRFG meetings:

Birka Lehmann was introduced and welcomed as the new European Commission representative.

Meeting schedule

The next MRFG meeting will be held on 18 November 2002.

ANNEX 1

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

No meeting of the WG was held in October.

The MRFG noted that 39 new mutual recognition procedures were finalised during the month of September 2002, as well as 221 type I and 29 type II variations.

The status as of 30th September 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	303	114	1513	261	405	200	2 N.A. 5 Var.

41 new procedures (regarding 96 products) started in September 2002. The categories of these procedures are as follows:

6 new active substance (first authorisation in the European Community after RMS approval) including **4** repeat use applications and **1** multiple application.

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

19 abridged applications including **1** multiple application.

8 Line extension applications including **3** multiple applications and **1** repeat use application.

The new procedures started last month relate to 15 full dossiers, 15 generics, 5 bibliographic applications, 1 fixed combination and 5 for different use, route or dose.

The procedures consisted of 41 chemical substances[1].

39 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 September 2002

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (4)	3
DE (2)	2
DE (4)	5
DK (4)	3
DK (1)	3
DK (4)	14
DK (4)	14
DK (4)	4

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DK (4)	4
DK (4)	3
DK (3)	1
DK (4)	3
DK (4)	8
FI (1)	13
FI (3)	11
FI (1)	1
FI (1)	8
FI (1)	3
FR (1)	1
SE (4)	1
SE (1)	13
SE (1)	1
SE (1)	1
SE (1)	1
SE (4)	5
SE (4)	4
SE (4)	3
SE (2)	3
SE (1)	16
SE (1)	15
SE (1)	3
UK (2)	10
UK (1)	4
UK (1)	8
UK (3)	1
UK (1)	10
UK (1)	7
UK (1)	1
UK (2)	1
UK (4)	11
UK (1)	10

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/

