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

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EMEA/CPMP/8204/02/Corr

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

The Committee for Proprietary Medicinal Products (CPMP) held its 81st plenary meeting from 23 to 25 April 2002.

Product related issues

Centralised procedures

The CPMP adopted 8 positive Opinions on initial marketing authorisation applications:

- For **Actraphane, Mixtard, Actrapid, Insulatard, Protaphane, Monotard, Ultratard** and **Velosulin** (recombinant human insulin) (Part A) from Novo Nordisk A/S. indicated for the treatment of diabetes mellitus (for further details, please see the published Summaries of Opinion (CPMP/3424/02, CPMP/3430/02, CPMP/3377/02, CPMP/3420/02, CPMP/3422/02, CPMP/3400/02, CPMP/3418/02, CPMP/3397/02). The opinions were adopted by consensus, with an active review time of 181 and 184 days.

The Committee also adopted two Lists of Questions (2 Part B) on initial marketing authorisation applications and three 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 A and 1 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 March 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 Ireland on medicinal products containing the fixed combination **salmeterol/fluticasone** (Seretide Diskus, Viani Diskus and associated invented names). The referral relates to two applications under the mutual recognition procedure for a new indication ('type II variation') for chronic obstructive pulmonary disease. 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)

The CPMP adopted one positive opinion by consensus for **Dacarbazine Faulding** (dacarbazine) from Faulding Pharmaceutical plc. The CPMP concluded that concerns raised in relation to the quality of the product had been resolved and that harmonised national marketing authorisations could be issued. The arbitration referral procedure was referred to the EMEA under the mutual recognition procedure by France in November 2001. The CPMP opinion will now be forwarded to the Commission.

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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 in March 2001 under Article 30, the CPMP adopted by consensus an opinion for a nationally authorised medicinal product containing the fixed combination captopril/ hydrochlorothiazide (**ECAZIDE** and associated invented names), leading to a EU-wide harmonised SPC. The referral was initiated because of divergences in the disease indications and dosage information for prescribers (summary of product characteristics) in the different Member States.

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

The CPMP began during its plenary meeting, four Community level reviews of the benefit/risk for the following medicinal products:

- **nimesulide** containing medicinal products (Aulin, Mesulide, Nimed and associated invented names), due to safety concerns. The referral procedure was initiated by Finland.
- **gatifloxacin** containing medicinal products (Bonoq, Crispin, Urobonoq, Urocrispin and associated invented names) due to safety and efficacy concerns. The referral procedure was initiated by Belgium.
- **loratadine** and **desloratadine** containing medicinal products (Clarityn, Azomyr and other associated invented names) due to a potential safety issue. These referral procedures were initiated by Sweden.

For all these referral procedures, Rapporteurs and Co-Rapporteurs were appointed.

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 April 2002. For further details, please see **Annex 4**.

Invented Name Review Group

The invented Name Review Group (NRG), held its 28th meeting on Monday 22 April 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 23 April 2002. During the meeting, proposals for training of Assessors from regulatory authorities in the EEA for 2002-2003 were presented and proposals for streamlining information on Interested Parties/ CPMP Working Parties interactions were discussed.
- The **Vaccine Expert Group (VEG)**, chaired by Dr. R. Dobbelaer met on 17 April 2002. The next meeting is scheduled to take place on 30-31 May 2002.

ICH

The ICH Maintenance Document (CPMP/ICH/1507/02) for the **ICH Q3C** Note for Guidance on Impurities: Residual Solvents was endorsed by the CPMP and will be published on the EMEA web site (see also **Annex 5**). The CPMP noted that the ICH Q3C Expert Working Group on Residual Solvents had evaluated a request to increase the Permissible Daily Exposure (PDE) of ethylene glycol. The group concluded that, in the case discussed, ethylene glycol is characterised as an impurity and thus falls within the scope of the Q3A Guideline on Impurities in New Drug Substances. An increase in a residual solvent/impurity level is supported by the Q3 guidelines, if appropriately justified. This position was endorsed by the ICH Steering Committee in February 2002.

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

Upcoming meetings:

- The first **EMEA/CPMP workshop with patients' organisations/associations**: "**Evaluation and surveillance of medicinal products in Europe**" will be held at the EMEA on 31 May 2002.
- A meeting of the **Ad hoc working group on (pre)-clinical comparability of biotechnology products** will be held on 13 May 2002.

Organisational Matters

- The 12th CPMP ORGAnisational Matters (ORGAM) meeting took place on Monday 22 April 2002, chaired by Dr Daniel Brasseur. During the meeting the following topics were presented/discussed:
  - Advisory Expert Groups: updated proposals for such groups were presented and discussion will continue at the informal CPMP meeting in Spain on 7-8 May 2002.
  - Clarification meeting with Industry after adoption of List of Questions: following comments from CPMP Members and applicants, it was felt that a guidance document would facilitate such meetings and add transparency to this aspect of the centralized procedure.
  - Consultation procedure for ancillary medicinal substances in medical devices: The group discussed the general principles of data requirements for such type of combination and agreed that further detailed proposals will be produced and circulated for consultation to the CPMP Working Parties.
  - Well-established use (WEU) medicinal product applications: A draft guidance document for Applicants providing information on how to prepare a "well-established use" justification (to be included in applications filed under the legal basis of Article 10 (1)(a)(ii) of Directive 2001/83/EC (previously known as Article 4.8 a)ii) of Council Directive 65/65/EEC)) was discussed. It was also highlighted that data requirements for such medicinal products' applications would need to be further developed in form of a multidisciplinary Note for Guidance by CPMP Working Parties.

EMEA PROCEDURAL ANNOUNCEMENT

Applicants are reminded that after the 1st July 2003, it will be mandatory to submit all applications in the EEA using the new European Common Technical Document (CTD) format. Applicants are therefore **strongly encouraged** to start using the new EU-CTD format for new applications (even if only for the quality data), in order to facilitate the handling of variations and line-extensions after July 2003.

The EU-CTD format details are available in the Notice To Applicants, vol. 2B (edition 2001) at the following European Commission Website: http://pharmacos.eudra.org/F2/eudralex/vol-2/B/ctdoct01.pdf.

Mutual Recognition procedure

The CPMP noted the report from the MRFG meeting held on 22 April 2002. For further details, please see **Annex 6**.

The joint CPMP/MRFG working group on harmonisation of Summary Products of Characteristics (SPCs), met on Monday 22 April 2002. Annex 1 of the enclosed MRFG Press Release provides information on the aim and timelines of this SPC prospective harmonisation exercise and also information discussed during the meeting.

The 82nd plenary meeting of the CPMP will be held from 28 to 30 May 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	14	17	269
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	5	11	16	351
Withdrawals	15	45	60	1	3	4	64
Positive CPMP opinions	77	131	208	9	10	19	227[1]
Negative CPMP opinions[2]	1	4	5	0	0	0	5[3]
Marketing authorisations granted by the Commission	71	123	194	1	9	10	204[4]

	1995-2001			2002			Overall Total
	Part A	Part B	Total	Part A	Part B	Total	
Variations type I	448	806	1254	36	80	116	1370
Positive opinions, variations type II	285	362	647	34	41	75	722
Negative opinions, variations type II	1	6	7	0	0	0	7
Extensions (Annex II applications)	38	36	74	0	1	1	75

[1] 227 positive opinions corresponding to 171 substances
[2] In case of appeal the opinion will not be counted twice
[3] 5 negative opinions corresponding to 4 substances
[4] 204 marketing authorisations corresponding to 156 substances

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

Invented Name	Invanz
INN	ertapenem
Marketing Authorisation Holder	Merck Sharp & Dohme
ATC code	J01DHXX
Indication	Treatment of moderate to severe infections caused by susceptible strains
CPMP Opinion date	17.01.2002
Date of Commission Decision	18.04.2002

Invented Name	MicardisPlus
INN	telmisartan - hydrochlorothiazide
Marketing Authorisation Holder	Boehringer Ingelheim International GmbH
ATC code	C09DA
Indication	Treatment of essential hypertension
CPMP Opinion date	17.01.2002
Date of Commission Decision	19.04.2002

Invented Name	BolusacPlus
INN	telmisartan - hydrochlorothiazide
Marketing Authorisation Holder	Boehringer Ingelheim International GmbH
ATC code	C09DA
Indication	Treatment of essential hypertension
CPMP Opinion date	17.01.2002
Date of Commission Decision	19.04.2002

Invented Name	PritorPlus
INN	telmisartan - hydrochlorothiazide
Marketing Authorisation Holder	Glaxo Group Ltd
ATC code	C09DA
Indication	Treatment of essential hypertension
CPMP Opinion date	17.01.2002
Date of Commission Decision	22.04.2002

OUTCOME OF THE APRIL 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**
6 changes	Positive opinions by consensus

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
13 SPC changes	Positive opinions by consensus
7 quality changes	Positive opinions by consensus

Opinions for Annual re-assessment applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Neurobloc (botulinum toxin type B), Elan Pharma International Ltd	Positive opinion by consensus	Marketing Authorisation to remain under exceptional circumstances
Renagel (sevelamer), Genzyme B.V.	Positive opinion by consensus	Marketing Authorisation to remain under exceptional circumstances
Viramune (nevirapine), Boehringer Ingelheim International GmbH	Positive opinion by consensus	Marketing Authorisation no longer to remain under exceptional circumstances

Opinions for Renewal applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Vistide (cidofovir), Pharmacia Enterprises S.A	Positive opinion by consensus	---

OUTCOME OF THE APRIL 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	Chronic neuropathic pain	**X**			**X**	**X**
Chemical	Diabetic peripheral neuropathy	**X**				**X**
Chemical	Idiopathic restless leg syndrome	**X**				**X**
Chemical	Non small cell lung cancer	**X**			**X**	**X**
Chemical	Diagnosis in Magnetic Resonance Imaging	**X**				**X**
Chemical	Prostate cancer	**X**				**X**

In April 2002, the above-mentioned 6 final Scientific Advice letters were adopted. The Committee accepted 5 new Scientific Advice requests, 3 follow-up Scientific Advice requests and one follow-up request for Protocol Assistance.

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

BIOTECHNOLOGY WORKING PARTY

Reference number	Document	Status
CPMP/BWP/1571/02	CPMP Position Statement on the Quality of water used in the production of vaccines for parenteral use	Adopted in April 2002
CPMP/BWP/1412/02	Position Paper on Testing for SV40 in Poliovirus vaccines	Adopted in April 2002
CPMP/BWP/6622/02	Concept paper on the Development of a CPMP Note for Guidance on Requirements for the evaluation of new adjuvants in vaccines	Released in April 2002 for 3 month consultation
CPMP/BWP/764/02	Points to consider on Quality aspects of medicinal products containing active substances produced by stable transgene expression in higher plants	Released in April 2002 for 6 month consultation
CPMP/BWP/1793/02	Note for Guidance on the Use of bovine serum in the manufacture of human biological medicinal products	Released in April 2002 for 6 month consultation

EFFICACY WORKING PARTY

Reference number	Document	Status
CPMP/EWP/518/97 rev. 1	Note for Guidance on Clinical investigation of medicinal products in the treatment of depression	Adopted in April 2002
CPMP/EWP/714/98 rev. 1	Note for Guidance on Clinical investigation of medicinal products for the treatment of peripheral arterial occlusive disease	Adopted in April 2002
CPMP/EWP/785/97	Points to consider on the Evaluation of medicinal products for the treatment of irritable bowel syndrome	Released in April 2002 for 3 month consultation

ICH

Reference number	**Document**	**Status**
CPMP/ICH/1507/02	ICH Topic Q3C (M) Maintenance of document for Guidance on Impurities: residual solvents	Adopted in April 2002

Report from the meeting held on 22 April 2002

General issues

Implementation of the Common Technical Document (CTD) in the MRP after July 2003.

The Group discussed the handling of MR applications after July 2003 when the new EU-CTD format (NTA, Vol. 2B, edition 2001) will be mandatory, based on a draft proposal from the NTA Group.

The agreed approach will be included in the list of new NTA "Questions and Answers", and published on the WebSite of the European Commission (http://pharmacos.eudra.org).

Applicants are **strongly encouraged** to start using the new NTA format for new applications (even if only for the quality data), in order to facilitate the handling of variations and MR procedures after July 2003.

Terfenadine containing medicinal products

Medicinal products with terfenadine as active substance have been the subject in 1998 of a Commission Decision on a referral under article 31 of Directive 2001/83/EC, resulting in a harmonised SPC for all Marketing Authorisations of terfenadine-containing medicinal products in the European Community.

Recently, a safety- related Type II variation application has been approved for one of the Marketing Authorisation Holders (MAH), adding a new interaction between terfenadine and carbamazepine in the SPC as follows:

Section 4.4

"Terfenadine should be used cautiously in patients of epilepsy under treatment of carbamazepine (see section 4.5)."

Section 4.5

"A drug interaction between terfenadine and carbamazepine has been reported. It is characterised by increased serum carbamazepine concentrations with possible clinical symptoms of carbamazepine overdosage. Data suggest, that the mechanism is linked to inhibition of hepatic metabolism of carbamazepine (inhibition of CYP3A4 enzyme). Consequently, especially for patients under long-term concomitant treatment, clinical and laboratory monitoring is recommended."

In order to maintain a harmonised SPC and to ensure that the same safety-related information is given, all other MAHs of terfenadine-containing medicinal products are hereby requested to apply for an identical change to their SPC. The corresponding variation application should be submitted **not later than 15 July 2002** to the national competent authorities.

MAHs are reminded that for medicinal products, which have been subject of an article 31 referral, a change to the Marketing Authorisation should be submitted via a MR procedure as outlined in Commission Regulation (EC) 541/95, as amended. Therefore, and in order to be able to submit a variation application, the MAH has to choose a Member State as RMS. The RMS will then issue the MR-number to the MAH and assign, where applicable, the CMS(s) for this procedure.

The MRFG will review the situation at their meeting of 22 July 2002 and will consider, in case of a possible non-compliance with this request, whether a new referral procedure should be triggered.

Meeting schedule

The next MRFG meeting will be held on **Monday 27 May 2002** and not on Tuesday 28 May 2002 as previously scheduled.

ANNEX 1

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

The Joint CPMP/MRFG Working group on harmonisation of SPCs met on Monday 22nd April, 2002 at the offices of the EMEA. The following was discussed and concluded.

- The requested pre-submission information has been received from the large majority of the MAHs. Dossiers remaining to be sent are expected in the near future.
- CPMP "co-ordinators" during the pre-referral phase were assigned during the April CPMP meeting.
- The co-ordinators are to assess divergences in the currently existing SPCs in the Member States, and Norway and Iceland. This assessment will be based on the pre-submission information submitted by the MAHs and the report produced by the MRFG sub-group on SPC harmonisation last year.

Furthermore, the EMEA has met with a number of MAHs. Based on questions raised during these meetings the Working Group saw a value in repeating the following information relevant to the selection of the candidates for a prospective harmonisation.

- The Heads of Agencies asked MRFG in December 2000 to investigate the possibility of a prospective harmonisation. The MRFG understood that this would possibly be applicable for products in general use that were soon expected to lose patent protection/exclusivity protection
- National Agencies in all MS were invited to suggest candidate medicinal products
- A list of 36 possible candidates was compiled
- Based on information provided by the MAHs the products were prioritised considering the following factors: differences in the core parts of the SPC (Sections 4.1-4.4), exclusivity/patent expiry dates, extent of use of the product, number of Member States where the product was approved
- The Heads of Agencies decided in November 2001 that a pre-referral discussion should be initiated with a limited number of MAHs
- From the products with highest priority the Working Group decided to initiate a pre-referral dialogue with 7 MAHs relating to the products in question
- Following appointment of co-ordinators during the April CPMP plenary, it is anticipated that the 7 MAHs concerned will meet with the co-ordinators during May/early June in order to (a) be informed of the outcome of the report produced by the MRFG sub-group on SPC harmonisation last year, (b) review the existing divergences amongst the approved SPCs and (c) to enable the co-ordinator to prepare a review for discussion in June (joint CPMP/MRFG Working group meeting/CPMP).
- Thereafter, a report will be prepared for the Heads of Agencies meeting 4-5 July, 2002.

Report from the MRFG meeting held in April 2002

The MRFG noted that 37 new mutual recognition procedures were finalised during the month of March 2002, as well as 166 type I and 54 type II variations.

The status as of 31st March 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	97	98	430	199	117	236	1 Var.

46 new procedures (regarding 108 products) started in March 2002. The categories of these procedures are as follows:

8 new active substances, including **3** multiple applications and **3** repeat use.

10 known active substances (already authorised in at least one member state) including **2** multiple applications and **2** repeat use.

23 abridged applications including **4** multiple applications.

5 Line extension applications including **1** multiple application.

The new procedures started last month relate to 14 full dossiers, 21 generics, 3 bibliographic applications, 6 fixed combinations and 2 for different use, route or dose.

The procedures consisted of 43 chemical substances, 2 biological vaccines and 1 biological blood product[1].

42 of these procedures were prescription-only medicinal products in the reference Member State and 4 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 March 2002

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
AT (1)	6
AT (2)	5
AT (2)	5
DE (1)	1
DE (2)	15
DE (1)	16
DE (8)	2
DE (1)	6
DE (4)	7
DK (1)	2
DK (2)	3
DK (1)	1
ES (1)	7

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
ES (1)	7
FI (3)	10
FI (3)	12
FI (3)	5
FI (3)	1
FI (3)	1
FI (3)	1
FR (2)	16
FR (2)	16
IR (4)	6
IR (4)	4
IR (4)	13
IR (4)	6
NL (1)	12
NL (1)	10
SE (5)	1
SE (2)	2
SE (1)	15
SE (5)	1
SE (1)	1
SE (1)	5
SE (1)	7
UK (4)	6
UK (1)	1
UK (1)	12
UK (1)	9
UK (1)	6
UK (3)	4
UK (3)	16
UK (3)	5
UK (3)	3
UK (3)	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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