European Medicines Agency
Evaluation of Medicines for Human Use

25 February 2005

CHMP/45462/2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
FEBRUARY PLENARY MEETING
MONTHLY REPORT

The Committee for Medicinal Products for Human Use (CHMP) held its February plenary meeting from 14 - 17 February 2005.

Centralised procedure

Opinions

The CHMP adopted one positive opinion on an initial marketing authorisation application for:

- **Duloxetine Lilly** (duloxetine), Eli Lilly Nederland B.V., for the treatment of diabetic peripheral neuropathic pain. The EMEA review began on 17 May 2004, with an active review time of 210 days.
  A summary of this opinion, including the full indication for the product, is available on the EMEA web site: http://www.emea.eu.int

The Committee also adopted four positive opinions on extension of indication for medicinal products that are already authorised in the EU:

- **Paxene** (paclitaxel), Norton HealthCare Ltd, to extend its use in combination with cisplatin to the treatment of advanced ovarian cancer and also to extend its use to the treatment of non-small cell lung cancer. Paxene was first authorised in the European Union on 19 July 1999.

- **InductOs** (dibotermin alfa), Wyeth Europa Ltd, to extend its use to include single-level (L4 - S1) anterior lumbar spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease who have had at least 6 months of non-operative treatment for this condition. InductOs was first authorised in the European Union on 9 September 2002.

- **Xeloda** (capecitabine), Roche Registration Ltd, to extend its use to the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer. Xeloda was first authorized in the European Union on 2 February 2001.

Summaries of opinion for Paxene, InductOs and Xeloda are available on the EMEA web site: http://www.emea.eu.int.

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In addition the Committee adopted two positive opinions on extension of posology for medicinal products that are already authorised in the EU:

- **Levemir** (insulin detemir), Novo Nordisk, to extend its use for treatment in children and adolescents of 6-17 years of age. Levemir was first authorised in the European Union on 1 June2004.

- **NovoRapid** (insulin aspart), Novo Nordisk, to extend its use for treatment of children of 2-6 years of age. Novorapid was authorised in the European Union on 7 September 1999.

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

The Committee also adopted a positive opinion on a safety variation for **Abilify** (aripiprazole), Otsuka Pharmaceuticals Europe Ltd, in order to include a warning concerning cerebrovascular adverse events in elderly patients with psychosis associated with Alzheimer's disease. A Dear Doctor Letter was communicated to the European Health Care Professionals.

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

The Committee also adopted a position opinion on a "line extension" application (Part B) (in accordance with Annex II of Commission Regulation (EC) No. 1085/2003).

Lists of Questions

The Committee adopted seven Lists of Questions on initial applications and nine Lists of Questions on "line extension" applications (in accordance with Annex II of Commission Regulation (EC) No. 1085/2003).

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 CHMP plenary meeting in January 2005 is provided in **Annex 2.** The post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 3**.

Application for marketing authorisation for orphan medicinal product

There was no centralised application for marketing authorisation for orphan medicinal products since the January 2005 CHMP meeting.

Plasma Master File Certification product

The CHMP adopted at its February 2005 CHMP meeting the Plasma Master File (PMF) Evaluation Report recommending the Bayer AG PMF certification. This is the second PMF Certificate issued by the EMEA. More information on the PMF Certification scheme is available on the EMEA website: http://www.emea.eu.int.

Referrals

- The Committee agreed on a number of urgent regulatory actions as part of its ongoing review of **COX-2 inhibitors**. A separate statement is available on the EMEA web site that details the contraindications and warnings introduced by the Committee (please see: http://www.emea.eu.int.

- The CHMP began a formal review procedure under Article 18 of Council Regulation (EEC) No 2309/93 for **Hexavac**, from Aventis Pasteur MSD. The review was initiated following a request from Germany to the European Commission (EC). The EC has requested the CHMP to review the safety of the centrally authorised vaccine and to give an opinion whether a regulatory action is warranted at this time. The Committee already completed a review in December 2003 on hexavalent vaccines and had previously concluded that there was no need to introduce changes to the conditions of use.

CHMP Working Parties

The CHMP was informed of the outcome of the discussions of the Scientific Advice Working Party (SAWP) meeting, which was held on 31 January - 02 February 2005.

The SAWP Rules of Procedures (Article 1: SAWP composition and Article 2: Appointment of Chairperson, Vice-Chairperson and SAWP members) have been revised at the February 2005 CHMP meeting in order to bring them in line with the CHMP Rules of Procedure. As a consequence, the SAWP now includes one additional member, (i.e. total of 22 Members including the SAWP Chairperson), which was appointed by the Committee this month.
The revised SAWP Rules of Procedures are available on the EMEA web site: http://www.emea.eu.int.

The CHMP noted the resignation of Dr Markku Toivonen (CHMP Member and Chairman of the SAWP). The CHMP Chairman, on behalf of the Committee, thanked Dr M. Toivonen for his valuable contribution to the Committee. The election of the new SAWP Chairperson, in replacement of Dr M. Toivonen, will take place at the March 2005 CHMP meeting.

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

Documents prepared by the CHMP Working Parties adopted during the February 2005 CHMP meeting are listed in **Annex 5**.

Upcoming meetings following the February 2005 CHMP plenary meeting:

- The 10th meeting of the CHMP will be held at the EMEA on 14-17 March 2005.
- The next Invented Name Review Group will be held at the EMEA on 14 March 2005.

- A Training Session for the new Assessors will be held at the EMEA on 21–22 February 2005.
- The Paediatric Pharmacovigilance Specialised Experts meeting will be held at the EMEA on 22 February 2005.
- A Training Session Workshop on PMF Evaluation will be held at the EMEA on 10-11 March 2005.
- The CHMP Ad-hoc Experts meeting on Metabolic Syndrome will be held at the EMEA on 30 March 2005.

Organisational matters

The main topics addressed during the February 2005 CHMP related to:

- The adoption of the Mandate, Objectives and Rules of Procedure for the:

  CHMP Biologics Working Party (BWP), Blood Products Working Party (BPWP), Vaccine Working Party (VWP), Gene Therapy Working Party (GTWP), Working Party on Similar Biological (Biosimilar) Medicinal Products (BMWP), Pharmacogenetics Working Party (PGWP), Working Party on Cell-Based Products (CPWP).
  The adopted Mandate, Objectives and Rules of Procedure of the above CHMP Working Parties will available on the EMEA web site: http://www.emea.eu.int.

- The adoption of the Composition of the Human/Veterinary Quality Working Party, and the CHMP Safety Working Party (SWP) and CHMP Efficacy Working Part (EWP).
- The Establishment of the EMEA Bio Co-ordination Group (BCG). The Committee adopted the Roles and tasks of the BCG.
- The Revision 1 of the Guideline on Summary Product Characteristics. This revised Guideline will be released on the EMEA website (http://www.emea.eu.int) for 3 months external consultation and the deadline for comments is 31 May 2005. Please see also **Annex 5**.
- The first CHMP/EMEA Implementation Task Force (CEITAF) meeting took place on Monday 14th February 2005. Initial discussions on the following review implementation topics took place:
  - Main principles of the mandatory scope of the centralised procedure
  - Main principles of the Compassionate Use procedure
  - Article 58 of regulation (EC) 726/2004: Scientific opinion in collaboration with World Health Organisation (WHO).
    As soon as draft Guidelines on the above topics will be available, the EMEA will release them for consultation. To that effect, the EMEA will dedicate a specific section in its external webpage to facilitate the future external consultation.

PROCEDURAL ANNOUNCEMENTS

Request for Eligibility to the Centralised Procedure in 2005/2006

In accordance with Article 90 of Regulation (EC) 726/2004, the access to the centralised procedure in relation to the mandatory scope (as defined in Article 3(1) in connection with the Annex to Regulation (EC) No 726/2004) and the optional scope as per Article 3(2) of Regulation (EC) 726/2004, will be applicable as of 20 November 2005.

Until that date, the Annex to Council Regulation (EEC) 2309/93 applies.

Applicants are recommended to submit their requests to confirm the eligibility to the centralised procedure 18 months in advance of the intended submission date.

Taking into account the above:

- Applicants intending to submit an application before 20th November 2005 should do so in accordance with the Annex to Council Regulation 2309/93.
- Applicants intending to submit an application after 20th November 2005 and requesting confirmation of the eligibility to the centralised procedure before that date, should send such a request to the EMEA justifying their eligibility in accordance with the criteria set out in Regulation (EC) 726/2004. Further to the consideration of the justifications for eligibility, the EMEA will inform the applicants on the CHMP opinion as to the access of their application to the centralised procedure. After 20 November 2005, this position will need to be officially re-confirmed by the EMEA following the December 2005 CHMP meeting

Detailed guidance with regard to the optional criteria for centralised procedure eligibility are currently being developed and discussed with CHMP (as part of the CHMP/EMEA Implementation Task Force (CEITAF) meetings), and will be released for external consultation in 2Q2005.

In case further clarifications are requested, applicants are advised to contact the EMEA Regulatory Affairs Sector.

Mutual Recognition procedure

The CHMP noted the report from the Mutual Recognition Facilitation Group (MRFG) meeting held on 14 February 205. For further details, please see **Annex 6.**

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This CHMP Monthly Report and other documents are available on the Internet at the following address:
http://www.emea.eu.int

EMEA CENTRALISED PROCEDURES

	1995 - 2004	2005	Overall Total
Scientific Advice	433	18	451
Follow-up to Scientific Advice	71	1	72
Protocol Assistance	59	8	67
Follow-up to Protocol Assistance	12	1	13

	1995-2004			2005			
	Part A	Part B	Total	Part A	Part B	Total	
Applications submitted	153	303	456	2	2	4	460
Consultation for Medical Device[1]	0	1	1	0	1	1	2
Withdrawals	22	62	84	0	2	2	86
Positive opinions[2]	107	197	304	0	2	2	306[3]
Negative opinions[4]	2	5	7	0	0	0	7[5]
Marketing authorisations granted by the Commission	98	190	288	2	2	4	292[6]

	1995-2004			2005			Overall Total
	Part A	Part B	Total	Part A	Part B	Total	
Variations type I	863	1937	2800	14	55	69	2869
Positive opinions, variations type II	758	886	1644	43	41	84	1728
Negative opinions, variations type II	1	6	7	0	0	0	7
Extensions (Annex II applications)	53	63	116	1	1	2	118

[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] 19 positive opinion corresponding to 19 Orphan Medicinal Products
[3] 306 positive opinions corresponding to 237 substances
[4] In case of appeal, the opinion will not be counted twice
[5] 7 negative opinions corresponding to 6 substances (2 of these negative opinions correspond to 2 Orphan Medicinal Products)
[6] 292 marketing authorisations corresponding to 223 substances

MEDICINAL PRODUCTS GRANTED A COMMUNITY MARKETING AUTHORISATION UNDER THE CENTRALISED PROCEDURE SINCE THE JANUARY 2005 CHMP MONTHLY REPORT

Invented Name	Fendrix
INN	Hepatitis B surface antigen 1, 2, 3 - 20 micrograms 1 adjuvanted by AS04C containing: -3-O-desacyl-4'- monophosphoryl lipid A (MPL) 2 - 50 micrograms 2 adsorbed on aluminium phosphate (0.5 milligrams Al3+ in total) 3 produced in yeast cells (Saccharomyces cerevisiae) by recombinant DNA technology.
Marketing Authorisation Holder	GlaxoSmithKline Biologicals s.a
Proposed ATC code	JO7AP
Indication	For active immunisation against hepatitis B virus infection (HBV) caused by all known subtypes for patients with renal insufficiency (including pre-haemodialysis and haemodialysis patients), from the age of 15 years onwards
CPMP Opinion date	21/10/2004
Marketing Authorisation Date	02/02/2005

OUTCOME OF THE FEBRUARY 2005 CHMP MEETING IN RELATION TO CENTRALISED APPLICATIONS IN THE POST-AUTHORISATION PHASE

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
4 Extensions of indication	4 Positive opinions
22 SPC changes	22 Positive opinions
26 Quality changes	26 Positive opinions

Opinions for Annual Re-Assessment applications		
Name of Medicinal Product (INN) **MAH**	**Outcome**	**Comments**
Cancidas (caspofungin) Merck Sharp & Dohme	Positive Opinion	The Marketing Authorisation will remain under exceptional circumstances.

Opinions for Renewal applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Intron A (interferon alfa-2b) SP Europe	Positive Opinion.	---
Viraferon (interferon alfa-2b) SP Europe	Positive Opinion.	---

OUTCOME OF THE FEBRUARY 2005 CHMP MEETING IN RELATION TO SCIENTIFIC ADVICE PROCEDURES

Substance	Intended indications(s)	Type of Request				Topic			
		New		Follow-up		Pharmaceutical	Pre-clinical	Clinical	Significant Benefit
		SA	PA	SA	PA				
Biological	Prophylaxis of organ rejection in patients receiving allogeneic renal transplant	X					X	X	
Chemical	Major depressive disorder and vasomotor symptoms associated with menopause	X				X			
Chemical	Systemic secondary Amyloidosis				X		X	X	
Chemical	Diabetic neuropathy	X					X	X	
Chemical	Acute Lynphoblastic Leukemia	X						X	
Biological	Systemic lupus erythematosus	X					X	X	
Biological	Angioedema		X			X	X	X	
Chemical	Restless legs syndrome	X						X	
Chemical	Conditioning treatment prior to haematopoietic progenitor cell transplantation		X			X	X	X	X
Chemical	Diabetic nephropathy	X				X	X	X	
Chemical	Soft tissue sarcoma		X					X	X
Biological	Neutropenia	X				X	X	X	
Chemical	Asthma and COPD	X					X	X	
Biological	Hodgkin's lymphoma		X					X	
Chemical	Cholangiocarcinoma		X					X	
Chemical	Hypertension and dyslipidaemia	X				X	X	X	
Chemical	Metastatic colorectal cancer	X				X			

SA: Scientific Advice

PA: Protocol Assistance

In February 2005, the above-mentioned 11 Scientific Advice letters, 5 Protocol Assistance letters and 1 Follow-up Protocol Assistance letter were adopted.

The Committee accepted 5 new Scientific Advice requests and 2 new Protocol Assistance requests.

ANNEX 5 to CHMP Monthly Report February 2005

DOCUMENTS PREPARED BY THE CHMP AND CHMP WORKING PARTIES ADOPTED DURING THE FEBRUARY CHMP MEETING

QUALITY WORKING PARTY

Reference number	Document	Status
CHMP/QWP/178621/04	Guideline on the suitability of the graduation of delivery devices for liquid dosage forms	Released for 6 months consultation

EFFICACY WORKING PARTY

Reference number	Document	Status
CHMP/EWP/4937/03	Guideline on non-clinical and clinical development of medicinal products for the treatment of nausea and vomiting associated with cancer chemotherapy	Released for 6 months consultation
CHMP/EWP/6172/03	Guideline on the evaluation of medicinal products intended for treatment of Hepatitis B	Released for 6 months consultation
CHMP/EWP/633/02 rev. 1	Guideline on the clinical development of medicinal products for the treatment of HIV infection	Released ease for 3 months consultation
CPMP/EWP/2339/02	Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired Hepatic function	Adopted
CHMP/EWP/147013/04	Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population	Released for 6 months consultation

CHMP Review of the Guideline on Summary Product Characteristics

Reference number	Document	Status
EMEA/CHMP/64302/2005	Revision 1 of the Guideline on Summary Product Characteristics.	Released for 3 months consultation. Deadline for for comments is 31 May 2005.

Report from the meeting held on 14 February 2005

General Issues

MRFG Sub-group meeting on Article 17 and 18 procedures

The MRFG Sub-group on Article 17 and 18 procedures held its third meeting in the morning following the MRFG plenary session to continue the discussions on the national pending applications in the new Member States, following the enlargement of the EU on 1 May 2004.

Applicants are reminded that the CTD format will be compulsory for mutual recognition and repeat-use procedures as of 1 May 2005 and therefore should contact the respective(s) National Competent Authority(ies) in order to start mutual recognition or repeat-use procedures as soon as possible.

Variation sub-group meeting

The Variation sub-group held its third meeting on 15 February 2005 to continue discussions on an harmonized approach in the assessment of variations, submitted in accordance with the Commission Regulation (EC) No 1084/2003.

Best Practice Guide for Mutual Recognition Procedure

An updated version of the document has been adopted by the group and will be published on the website.

Template for CMS comments in the MRP

The MRFG has agreed on the template for CMS comments in the Mutual Recognition Procedure. The template will be published on the website as an annex to the Best Practice Guide for Mutual Recognition Procedure.

Position paper on repeat use of the Mutual Recognition Procedure

An updated version of the document, mainly with regard to the deadline for submission of mutual recognition applications in the 'old' NTA format (for applications submitted to the RMS in the old EU-format before 1 July 2003) and to include reference to the common renewal date (as agreed at the completion of the initial MRP) in the updated Assessment Report, has been adopted by the group and will be published on the website.

Contact points for advice on MRP

The MRFG has updated the list of contact points for advice on the Mutual Recognition Procedure.

The MRFG has agreed that the purpose of the list is to assist Companies identifying a contact point in each MS that can be approached for general questions regarding the MRP but should not be approached for questions on particular applications.

Applications for marketing authorisation for Orphan medicinal products

Please find below the information on the active substance, the sponsor/applicant and the designated orphan indication for the following medicinal product subject to a repeat-use mutual recognition procedure for marketing authorization, started on 22.12.2004.

Active Substance	*Sponsor*	*Designated Orphan Indication & Date of Orphan Designation/EU Designation Number*	*Information on the MRP*
Levodopa/Carbidopa (Gastroenteral use) (Duodopa intestinal gel)	NeoPharma AB, Sweden	Treatment of advanced idiopathic Parkinson's disease with severe motor fluctuations and not responding to oral treatment. 10/05/2001 - EU/3/01/035	SE/H/0415/001/E001 RMS: SE CMS: BE, EL, IE, IT, UK Day 90: 22.03.2005

Meeting schedule

The next MRFG meeting will be held on 14 March 2005.

Mutual Recognition Monitoring

The MRFG noted that 51 new mutual recognition procedures were finalised during the month of January 2005, as well as 163 type IA variations, 112 type IB variations and 73 type II variations.

The status as of 31st January of procedures and for the whole year under mutual recognition is as follows:

Year	Procedures from New applications finalised	Procedures from New applications in process	Procedures from Type IA variations finalised	Procedures from Type IB variations finalised	Procedures from Type II variations finalised	Arbitrations referred to CHMP
2005	51	222	163	112	73	--

48 new procedures (regarding 111 products) started in January 2005. The categories of these procedures are as follows:

4 new active substances (first authorisation in the European Community after RMS approval), including 2 multiple applications and 1 repeat use.

9 known active substances (already authorised in at least one member state), including 1 repeat use.

29 abridged applications including 10 multiple applications and 2 repeat use.

6 line extension applications including 1 repeat use.

The new procedures started related to 13 full dossiers, 25 generics, 5 bibliographic applications and 5 for different use, route or dose.

The procedures consisted of 47 chemical substances and 1 biological-vaccine[1].

45 of these procedures were prescription-only medicinal products in the reference Member State and 3 procedures were classified as a 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 January 2005

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
CZ (3)	5
DE (2)	5
DE (1)	7
DE (1)	15
DE (1)	9
DE (1)	5
DE (1)	6
DE (1)	5
DE (1)	12
DE (1)	13
DK (1)	**2**

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DK (3)	9
DK (3)	4
DK (1)	4
DK (2)	8
FI (1)	2
FI (4)	11
FR (1)	6
FR (1)	10
FR (3)	26
FR (3)	2
IT (1)	9
IT (1)	5
IT (1)	2
IT (1)	6
NL (2)	15
NL (1)	7
NL (2)	10
NO (3)	8
NO (2)	7
PT (1)	1
PT (2)	1
SE (1)	1
SE (3)	5
SE (4)	9
SE (4)	2
SE (4)	8
SE (1)	3
SE (6)	10
SE (6)	2
SE (6)	8
SE (6)	2
SE (6)	1
SE (6)	1
SE (1)	1
UK (1)	9
UK (2)	5
UK (1)	1

All documents mentioned in this press release can be found at the MRFG website at the European Medicines Authorities Windows under the heading MRFG Guidance.

Information on the above mentioned issues can be obtained from the chair of the MRFG on behalf of the Luxembourg Presidency:

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http://heads.medagencies.org/