European Medicines Agency

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
JULY 2005 PLENARY MEETING
MONTHLY REPORT

The Committee for Medicinal Products for Human Use (CHMP) held its July plenary meeting from 25 – 27 July 2005.

Centralised procedure

Initial applications for marketing authorisation

The CHMP adopted opinions on eight initial marketing authorisation applications at this meeting:

- **Aptivus** (tipranavir), from Boehringer Ingelheim International GmbH, co-administered with low dose ritonavir, for the treatment of Human Immunodeficiency Virus (HIV-1) infection in highly pre-treated adult patients with virus that is resistant to multiple protease inhibitors. EMEA review began on 15 November 2004 with an active review time of 204 days.

- **Kepivance** (palifermin), from Amgen Europe B.V., for the prevention and treatment of oral mucositis in patients with haematological (blood and blood-forming tissues) cancers undergoing myoablative therapy, which suppresses bone marrow activity. EMEA review began on 19 July 2004 with an active review time of 217 days.

- **Noxafil** (posaconazole) and **Posaconazole SP** (posaconazole), from SP Europe, for use in the treatment of the following invasive fungal infections in adults (Invasive aspergillosis, Fusariosis, Chromoblastomycosis and mycetoma and Coccidioidomycosis) in patients with disease that is refractory or intolerant to certain commonly used antifungal agents. EMEA review began on 19 July 2004 with an active review time of 219 days.

- **Procoralan** (ivabradine) and **Corlentor** (ivabradine), from Les Laboratoires Servier, for the treatment of chronic stable angina pectoris. EMEA review began on 17 May 2004 with an active review time of 211 days.

- **Revatio** (sildenafil citrate), from Pfizer Limited, for the treatment of pulmonary arterial hypertension. EMEA review began on 20 December 2004 with an active review time of 177 days.
  Revatio is the twenty-second orphan medicinal product to receive a positive CHMP opinion.

- **Xolair** (omalizumab), from Novartis Europharm Ltd., for the treatment of severe persistent allergic asthma. EMEA review began on 19 July 2004 with an active review time of 214 days.

Summaries of opinion for these medicinal products are available on the EMEA website where the complete indications recommended by the CHMP can be found. Further information will be included in the European Public Assessment Report (EPAR) once the European Commission has granted final approval.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 16
E-mail: mail@emea.eu.int http://www.emea.eu.int

Extensions of indication and other recommendations

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

- **Keppra** (levetiracetam), UCB S.A., to extend the indication of adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation to children from 4 years of age with epilepsy. Keppra was first authorised in the European Union on 29 September 2000.

- **Remicade** (infliximab), Centocor B.V., to extend its indication to include treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systematic therapy including cyclosporine, methotrexate or PUVA. Remicade was first authorised in the European Union on 13 August 1999.

The CHMP also adopted an opinion to recommend a new contraindication for **Forsteo** (teriparatide), from Eli Lilly Nederland B.V., to exclude patients with skeletal malignancies or bone metastases from treatment.

Summaries of opinion for these medicinal products are available on the EMEA website. Further information 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 by consensus 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 five Lists of Questions on initial applications (2 Part A and 3 Part B) and one List of Questions on a "line extension" application (Part B) in accordance with Annex II of Commission Regulation (EC) No. 1085/2003).

Application for marketing authorisation for orphan medicinal product

No Orphan medicinal products have been the subject of a centralised application for marketing authorisation since the May 2005 CHMP meeting.

Post-Authorisation follow-up

- After having heard the Steering Committee for the evaluation of metabolic and cardiovascular complications of highly active antiretroviral treatment (HAART), the CHMP adopted conclusions on the long term consequences of HAART in its July meeting. Further information is available on the EMEA website.

- Likewise, in its July meeting and after having heard the Steering Committee on antiretroviral therapy and liver impairment, the CHMP adopted conclusions on main study proposals made. Further information is available on the EMEA website.

- The CHMP reviewed available data on the cardiovascular safety of non-selective NSAIDs. A Press Release and a Questions and Answers document addressing this topic are available on the EMEA website.

Detailed information on the centralised procedure

An overview of centralised procedures since 1995 is given in **Annex 1**. The European Commission has granted no marketing authorisations for medicinal products since the CHMP plenary meeting in June 2005. The post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 2.**

Arbitration procedure

The Committee finalised an arbitration procedure for **Coversyl** 2 and 4 mg (perindopril tertbutylamine salt) and associated trade names from Les Laboratoires Servier, recommending the extension of the indication to include the reduction of risk of cardiac events in patients with stable coronary artery disease with a history of myocardial infarction and/or revascularisation. Coversyl is authorised in a number of EU Member States and is currently indicated for the treatment of hypertension and symptomatic heart failure. The referral was made by the Netherlands under Article 6(12) of Commission Regulation (EC) No 1084/2003.

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 4-6 July 2005. For further details, please see **Annex 3**.

Documents prepared by the CHMP Working Parties adopted during the July CHMP meeting are listed in **Annex 4**.

Upcoming meetings following the July 2005 CHMP plenary meeting:

- The 14th meeting of the CHMP will be held at the EMEA on 12 – 15 September 2005.
- The next Invented Name Review Group meeting will be held at the EMEA on 12 September 2005.
- The next Mutual Recognition Facilitation Group Meeting will be held at the EMEA on 12 – 13 September 2005.
- An EMEA conference on environmental risk assessment for human and veterinary medicinal products will be held at the EMEA on 27 – 28 October 2005.

Organisational matters

The main topic addressed during the July 2005 CHMP related to:

- The adoption for external consultation of the revised procedure for time allowed for applicants to respond to questions and issues raised during the assessment of new marketing authorisation applications in the centralised procedure (to be released on the EMEA website for consultation until end of October 2005).

It should be noted that the following document has been published on the EMEA Website (http://www.emea.eu.int):

- the 2005-2006 Workplan for the EMEA/CHMP Working Group with Patients' Organisations.

PROCEDURAL ANNOUNCEMENT

New QRD Product Information Templates (version 7)

The new QRD Product Information Templates (version 7) have been published on the EMEA website. The EMEA and the Quality Review of Documents Group have updated the Human Product Information templates in line with the new legislation. In addition, the updated templates reflect the revised SPC guideline and recommendations from the EMEA/CHMP Working Group with Patients Organisations.

Three documents are provided:
- A "*Clean Annotated QRD template v.7*
- "*QRD templates v.7* " in all EEA languages
- A "*Highlighted Annotated QRD template* ", which presents all changes made to the current template v.6.1

Guidance on implementation of the new templates can be found via the above EMEA website link.

EMEA implementation of the New EU Pharmaceutical Legislation

The sixth CHMP/EMEA Implementation Task Force (CEITAF) meeting took place on Monday 25 July 2005.

Documents on the following review implementation topics were adopted by the CHMP and will be transmitted to the European Commission:

- Pharmacovigilance risk management system evaluation/procedure
- Cooperation with other bodies in the EU for identification and management of potential conflict over scientific opinions
- Renewals in the centralised procedure
- Coordination between scientific committees of the Agency

In addition, number of other documents on the following review implementation topics will be transmitted to the European Commission

- Actual marketing and cessation
- Sunset clause
- PSUR cycle
- Phasing-in of the new legislation in the centralised procedure

A follow-up discussion took place on the optional scope.

Initial discussions took place on the review implementation topic of an Opinion on any scientific matter.

Mutual Recognition procedure

The CHMP noted the report from the Mutual Recognition Facilitation Group (MRFG) meeting held on 25 – 26 July 2005. For further details, please see **Annex 5**.

Noël Wathion
Head of Unit
Post-Authorisation Evaluation of Medicines for Human Use, Tel. (+44-20) 74 18 85 92
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	65	498
Follow-up to Scientific Advice	71	12	83
Protocol Assistance	59	29	88
Follow-up to Protocol Assistance	12	6	18

	1995-2004			2005			Overall Total
	Part A	Part B	Total	Part A	Part B	Total	
Applications submitted	153	303	456	3	16	19	475
Consultation for Medical Device[1]	0	1	1	0	1	1	2
Withdrawals	22	62	84	0	3	3	87
Positive opinions[2]	107	197	304	2	12	14	318[3]
Negative opinions[4]	2	5	7	0	0	0	7[5]
Marketing authorisations granted by the Commission	98	190	288	3	7	10	298[6]

	1995-2004			2005			Overall Total
	Part A	Part B	Total	Part A	Part B	Total	
Variations type I	863	1937	2800	83	242	325	3125
Positive opinions, variations type II	758	886	1644	162	145	307	1951
Negative opinions, variations type II	1	6	7	0	0	0	7
Extensions (Annex II applications)	53	63	116	5	5	10	126

[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] 20 positive opinion corresponding to 20 Orphan Medicinal Products
[3] 318 positive opinions corresponding to 247 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] 298 marketing authorisations corresponding to 229 substances

OUTCOME OF THE JULY 2005 CHMP 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
28 SPC changes	28 Positive opinions
29 Quality changes	29 Positive opinions

Opinions for Annual Re-Assessment applications		
Name of Medicinal Product (INN)	**Outcome**	**Comments**
Fuzeon (enfuvirtide) Roche Registration Ltd	Positive Opinion	The authorisation will remain under exceptional circumstances

Opinions for Renewal applications		
Name of Medicinal Product (INN)	**Outcome**	**Comments**
Actos (pioglitazone) Takeda Europe R&D Centre Ltd	Positive Opinion	---
Glustin (pioglitazone) Takeda Europe R&D Centre Ltd	Positive Opinion	---
Gonal-f (follitropin alfa) Ares Serono (Europe) Ltd	Positive Opinion	---

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

Substance	Intended indications(s)	Type of Request				Topic			
		New		Follow-up		Pharma ceutical	Pre-clinical	Clinical	Significant Benefit
		SA	PA	SA	PA				
Chemical	Mastocytosis		X			X	X	X	
Chemical	Congenital venous malformations				X			X	
Chemical	HIV-1 infections	X				X	X	X	
Biological	Metachromatic Leukodystrophy		X				X	X	
Chemical	Parkinson's disease	X				X			
Chemical	Opioid-induced bowel dysfunction			X				X	
Biological	Immunisation against Influenza virus	X				X	X	X	
Chemical	Non-small cell lung cancer	X					X	X	
Biological	Non-small cell lung cancer	X					X	X	
Chemical	HIV-1 infections	X					X	X	
Chemical	Hyperlipidaemias			X				X	
Chemical	Non-small cell lung cancer		X					X	X

Substance	Intended indications(s)	Type of Request				Topic			
		New		Follow-up		Pharma ceutical	Pre-clinical	Clinical	Significant Benefit
		SA	PA	SA	PA				
Chemical	Non-small cell lung cancer	X						X	
Chemical	Hyperphenylalaninemia		X			X	X	X	X
Chemical	Cystic fibrosis				X			X	
Chemical	Cystic fibrosis		X				X	X	
Chemical	Obesity, type-2 diabetes and metabolic syndrome	X					X	X	
Chemical	Attention Deficit/Hyperactivity Disorder	X				X	X	X	
Biological	Active immunisation against invasive pneumococcal disease and acute otitis media			X		X		X	
Biological	Hodgkin's lymphoma				X			X	
Biological	Mycosis fungoides		X					X	X

SA: Scientific Advice

PA: Protocol Assistance

The above-mentioned 9 Scientific Advice letters, 3 Follow-up Scientific Advice letters, 6 Protocol Assistance letters and 3 Follow-up Protocol Assistance letters were adopted at the 25- 27 July 2005 CHMP meeting.

The Committee accepted 10 Initial Scientific Advice Requests, 2 Initial Protocol Assistance Requests, and 1 Follow-up Protocol Assistance Request started in July 2005. In addition, the Committee accepted 6 Initial Scientific Advice Requests, 4 Initial Protocol Assistance Requests, and 2 Follow-up Scientific Advice Requests starting in August 2005.

DOCUMENTS PREPARED BY THE CHMP WORKING PARTIES ADOPTED DURING THE JULY 2005 CHMP MEETING

BLOOD PRODUCTS WORKING PARTY

Reference number	Document	Status
CPMP/BPWG/3726/02	Core SPC for human varicella immunoglobulin for intramuscular use	Adopted
CPMP/BPWG/3730/02	Core SPC for human tetanus immunoglobulin for intramuscular use	Adopted
CPMP/BPWG/3732/02	Core SPC for human tick-borne encephalitis immunoglobulin for intramuscular use	Adopted
CPMP/BPWG/3728/02	Core SPC for human rabies immunoglobulin for intramuscular use	Adopted

QUALITY WORKING PARTY

Reference number	Document	Status
CPMP/QWP/2819/00 rev. 1 EMEA/CVMP/814/00 rev. 1	Guideline on quality of herbal medicinal products / traditional herbal medicinal products	Released for 3 months consultation

EFFICACY WORKING PARTY

Reference number	Document	Status
CHMP/89249/04	Guideline on the Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins	Released for 6 months consultation
EMEA/CPMP/EWP/2158/99	Guideline on the Choice of the Non-Inferiority Margin	Adopted
EMEA/CHMP/EWP5872/03	Guideline on Data Monitoring Committees	Adopted
CHMP/EWP/519/98 Rev 1	Guideline on Clinical Investigation of Steroid Contraceptive in Women	Adopted
EMEA/CHMP/EWP/139391/2004	Reflection Paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products	Adopted

PAEDIATRIC WORKING PARTY

Reference number	Document	Status
CHMP/PEG/194605/2005	Concept paper on liver immaturity when investigating medicinal products intended for neonatal use	Released for 6 months consultation
CHMP/194313/2005	Assessment of the Paediatric needs – Rheumatology	Released for 6 months consultation

PHARMACOGILANCE WORKING PARTY

Reference number	Document	Status
CHMP/235910/2005	Guideline on conduct of pharmacovigilance for medicines used by the paediatric population	Released for 6 months consultation

Report from the meeting held on 25 and 26 July 2005

General Issues

Flow Chart of the Decentralised procedure

The MRFG and the VMRFG in collaboration with the Heads of Medicines Agencies have agreed on the flow chart of the decentralised procedure and this is now published on the website, for information to Interested parties.

Detailed procedural guidance to complement the flow chart is under development by the MRFG and VMRFG and will be published for information, when available.

EU Work sharing procedure in the assessment of paediatric data

Following the endorsement by the Heads of Medicines Agencies of the proposal for work sharing in the assessment of paediatric data, the MRFG has agreed on the Best Practice Guide for the EU Work sharing procedure in the assessment of paediatric data and this is now published on the website, for information to Interested parties.

Size limitation for emails

Following a request received from an Interested party concerning the size limitation for emails of 2 MB set in the Best Practice Guide for Mutual Recognition Procedure, the MRFG would like to remind Applicants that the MRFG 'Applicant's response document in Mutual Recognition – Recommended (CTD) format' has been updated recently to include the possibility for applicants to send response documents to National Competent Authorities via Eudralink, in accordance with the national requirements. The size limitation of 2 MB is not applicable to documents sent via Eudralink.

Guideline on the processing of renewals in the mutual recognition and decentralised procedures

The updated guideline on renewals in the mutual recognition and decentralised procedure is being developed alongside the updated guideline on renewals in the centralised procedure and consideration within the Notice to Applicants working group. The guideline is in the process of being finalised and will be published shortly, for information.

MRFG/CMD(h) Concept paper – Achieving harmonised patient information – Consultation procedure

The MRFG is grateful for the comments received on the concept paper and now that the consultation period is complete will consider these carefully when finalising the guidance.

Questions and Answers on the implementation of the new legislation

A Q&A document outlining practical considerations on the implementation of the new legislation to medicinal products for human use authorised or applied for via the mutual recognition procedure or the new decentralised procedure is under development by the MRFG. The Q&A document will be published shortly, for information and further Q&As will be added as they are developed.

Information on MR procedures for new active substances

A mutual recognition procedure for a medicinal product containing (14C) Urea has been finalised on 21 June 2005. Please find below information on the Invented name, INN, MAH, Indication, Procedure number and Day 90.

Invented Name (RMS)	HeliCap
INN	(14C) Urea
Marketing Authorisation Holder	Noster System AB
Indication	For in-vivo diagnosis of Helicobacter pylori infection in the gastrointestinal tract (stomach and duodenum).
Procedure number	SE/H/0521/001
Day 90	21.06.2005

Mutual Recognition Monitoring

The MRFG noted that **135** new mutual recognition procedures were finalised during the month of June 2005, as well as **391** type IA variations, **215** type IB variations and **127** type II variations.

The status as of 30th of June of procedures 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	453	348	1891	910	581	2 Var.

91 new procedures (regarding **149** products) started in June 2005. The categories of these procedures are as follows:

23 known active substances (already authorised in at least one member state), including **4** multiple applications and **5** repeat use.

66 abridged applications including **46** multiple applications and **3** repeat use.

2 line extension applications.

The new procedures started related to **11** full dossiers, **62** generics, **7** bibliographic applications, **7** fixed combinations, **3** informed consent and **1** for different use, route or dose.

The procedures consisted of **89** chemical substances and **2** biological-blood products[1].

90 of these procedures were prescription-only medicinal products in the reference Member State and **1** procedure was 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 June 2005

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
AT (3)	13
BE (1)	6
CZ (3)	6
DE (3)	1
DE (3)	1
DE (3)	4
DE (2)	22
DE (2)	5
DE (2)	23
DK (2)	14
DK (2)	10
DK (2)	15
DK (2)	16
DK (2)	1
DK (2)	9
DK (2)	10
DK (1)	11
DK (1)	4
DK (1)	9
DK (1)	4
DK (2)	12
DK (2)	17

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DK (1)	8
DK (2)	8
FI (1)	3
FI (1)	7
FI (1)	22
FI (1)	2
FI (1)	20
FI (1)	8
FI (1)	2
FI (1)	8
FI (1)	1
FI (1)	1
FI (1)	12
FI (1)	1
FI (1)	1
FI (1)	1
FI (1)	1
FI (1)	1
FI (1)	6
FI (1)	15
FI (1)	18
FI (1)	22
FI (1)	1
FI (1)	4
FI (1)	2
FI (1)	8
FI (1)	4
FI (1)	11
FI (1)	1
FI (1)	3
FI (1)	6
FI (1)	1
FI (1)	15
FI (1)	1
FI (1)	1
FI (1)	20
FI (1)	9
FI (1)	1
FR (1)	15
FR (3)	27
FR (1)	1
HU (4)	5
NL (1)	1
NL (1)	14
NL (1)	1
NL (2)	15
NL (5)	12
NL (5)	13
NL (5)	23
NL (1)	1
NL (1)	8
NL (1)	1
NL (1)	10
NL (1)	1
PT (1)	1
SE (2)	11
SE (1)	13
SE (3)	7
SE (3)	1
SE (3)	5
SE (2)	6
SE (2)	1
SE (2)	3

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
SE (2)	1
SE (2)	5
SE (1)	1
UK (6)	22
UK (1)	14
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 presiding chair of the MRFG:

Ms. Shirley Norton
Medicines and Healthcare products Regulatory Agency
1 Nine Elms Lane – Market Towers
London SW8 5NQ
United Kingdom

Phone: + 44 207084 2390
Fax: + 44 207084 2293
e-mail: Shirley.norton@mhra.gsi.gov.uk

Or you could visit the ***MRFG web site*** *at the EUROPEAN NATIONAL MEDICINES AUTHORITIES WINDOW:*
http://heads.medagencies.org/