European Medicines Agency
Evaluation of Medicines for Human Use

18 October 2004
EMEA/CHMP/1214/04/corr.*

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
JULY 2004 PLENARY MEETING
MONTHLY REPORT

The Committee for Medicinal Products for Human Use (CHMP) held its 3rd plenary meeting from 27-29 July 2004.

Product related issues

Centralised procedures

The Committee adopted three positive opinions on the initial marketing authorisation applications for:

- **Emselex** (darifenacin), from Novartis Europharm Limited, for the symptomatic treatment of patients with overactive bladder syndrome. EMEA review began on 23 June 2003 and the opinion was adopted on 29 July 2004, with an active review time of 181 days.
- **Mimpara and Parareg** (cinacalect), from Amgen Europe B.V., for the treatment of secondary hyperparathyroidism in patients with chronic renal disease, and for reduction of hypercalcaemia in patients with parathyroid carcinoma. EMEA review began on 27 October 2003 and the opinion was adopted on 29 July 2004, with an active review time of 196 days.

Summaries of these opinions, including the full indications for each product, are available on the EMEA web site: http://www.emea.eu.int.

The Committee also adopted four Lists of Questions on initial Marketing Authorisation Applications.

The CHMP also revised its opinion of 24 July 2003 for **Xagrid** (anagrelide), from Shire Pharmaceutical Contracts Limited, recommending the granting of a marketing authorisation under exceptional circumstances. Based on new clinical data becoming available as part of the post-authorisation obligations, the Committee revised the assessment report, product information and post-authorisation commitments and concluded that the benefit/risk profile remains positive. Xagrid was designated as an orphan medicinal product on 29 December 2000 and is indicated for the reduction of elevated platelet counts in at risk essential thrombocythaemia patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy.

The CHMP completed its safety review of the benefit/risk balance of **SonoVue** (sulphur hexafluoride), from Bracco International B.V., and decided to reinstate the echocardiography indication, to extend the contraindications to patients with recent acute coronary syndrome or clinically unstable ischaemic cardiac disease, and to add several warnings and precautions. This follows the urgent safety restriction

* The correction relates to the reference number of the "Process Validation Guideline - Annex II- Non standard processes" in Annex 5 to the July CHMP Monthly Report published on 05th August 2004.

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

introduced in May 2004. The revised information for healthcare professionals and patients will be published on the EMEA web site once the final decision has been taken by the European Commission and a Dear Healthcare Professional letter will be issued.

The CHMP recommended the addition of safety precautions to the Summary of Product Characteristics and Package leaflet of **InductOs** regarding potential serious adverse events during the off label use of InductOs in cervical spine fusion. The CHMP agreed with the proposals of the MAH to release a Dear Healthcare Professional letter in this respect. The "off label" use of InductOs for cervical spine fusion has been associated with an increased risk of localised oedema swelling, in some cases resulting in breathing difficulties, which can be very serious. Although InductOs is not approved in the EU for use in any form of spine fusion, a proportion of its use in the EU has been for spine fusion procedures. InductOs is indicated for the treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary nail fixation.

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

- **Arixtra and Quixidar** (fondaparinux), Sanofi Synthelabo, to include the treatment of acute deep vein thrombosis and the treatment of acute pulmonary embolism except in haemodynamically unstable patients or patients who require thrombolysis or pulmonary embolectomy. Arixtra and Quixidar were first authorised in the European Union on 21 March 2002.

- **Enbrel** (etanercept), Wyeth Europe Ltd, to extend its use to the treatment of adult patients with moderate to severe plaque psoriasis. Enbrel was first authorised in the European Union on 3 February 2000.

- **Remicade** (infliximab), Centocor B.V., to extend its use to the treatment of patients with active and progressive psoriatic arthritis. Remicade was first authorised in the European Union on 13 August 1999.

Further information on these extensions will be included in the public assessment report (EPAR) once the European Commission has granted final approval.

The Committee also adopted two opinions 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 June 2004 is provided in **Annex 2.** The post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 3**.

Non-product related issues

CHMP Working Parties and Ad Hoc Groups

The CHMP was informed of the outcome of the discussions of the Scientific Advice Working Group (SAWG) meeting, which was held on 5-6 July 2004. For further details, please see **Annex 4**.

Documents prepared by the CHMP Working Parties and Ad Hoc Groups adopted during the July 2004 CHMP meeting are listed in **Annex 5**.

Organisational Matters

The CHMP elected five new members to join the Committee as of September 2004, adding specific areas of complementary expertise in the fields of blood products and vaccines; quality - chemical

substances; quality and safety – biotech substances, cell therapy and gene therapy; pharmacovigilance and pharmacoepidemiology. The possibility of co-opting five additional members is part of the new legislation that came into force in May 2004. The CHMP now has 32 members, including one from each of the 25 Member States, one each from Iceland and Norway.

The five co-opted members are:

- Manfred Haase
- Pekka Kurki
- Ingemar Persson
- Jean-Louis Robert
- Frances Rotblat

The 2nd CHMP Organisational Matters (ORGAM) meeting took place on Monday 26 July 2004, chaired by Dr D. Brasseur. Following discussions held at the 22-23 June 2004 ORGAM meeting, it was decided that the ORGAM meeting will be integrated into the CHMP plenary meeting from September 2004 onwards. Such integration will lead to plenary CHMP meetings starting on Mondays at 13.00 with discussions on organisational matters / ongoing Working Party activities.

The main topics addressed during the July 2004 ORGAM meeting related to:

- CHMP Rules of Procedures
- A discussion on the establishment of Scientific Advisory Groups and Working Parties in the framework of Regulation (EC) 726/2004
- A discussion on the draft European Regulation (EC) on conditional marketing authorisation for medicinal products falling within the scope of Regulation No 726/2004 of the European Parliament and the Council of 31 March 2004

Upcoming meetings following the July 2004 CHMP plenary meeting:

- The 4th meeting of the CHMP will be held on 13-16 September 2004.
- An EMEA Interested Parties meeting on the Invented Names procedure will take place on 13 September 2004.
- The next NRG meeting will be held on 13 September 2004.

PROCEDURAL ANNOUNCEMENTS

- **The CHMP agreed to replace the August 2004 plenary meeting by written procedures to be established for certain ongoing applications.**

- **New dates for the Scientific Advice Working Party (SWAP) October 2004 meeting**

Due to the informal CHMP/COMP meeting taking place on 4 and 5 October 2004, the October SAWP meeting will be held on 11-12 October 2004. However, the deadline for submission of new requests remains on 20 September 2004.

PROCEDURAL ANNOUNCEMENTS (cont'd)

- **Publication of INN of Orphan Medicinal Products for new Marketing Authorisation Application**

The Management Board at its June meeting endorsed the EMEA's proposal to publish the International Nonproprietary Name (INN) of Orphan Medicinal Products when a Marketing Authorisation Application is submitted, in line with Article D.1.4 of the Commission Communication on Orphan Medicinal Products (C 178/8 of 29.7.2003). It has been agreed that the INN of the product, the designated orphan indication and the name of the sponsor will be made public.

- **Annex A to CHMP/CVMP Opinions Templates**

Templates for the Annex A to CHMP/CVMP Opinions, listing all product presentations, are now available on the EMEA website in all EU languages:
http://www.emea.eu.int/htms/human/qrd/qrdtemplate.htm
http://www.emea.eu.int/htms/vet/qrd/qrdtemplate.htm

These templates are to be used when providing translations of the revised Annex A as part of a Variation or Extension application amending Annex A. In addition MAHs will be asked to provide the Annex A translations of authorised products in the 8 new languages, in the context of the next EPAR update.

Mutual Recognition procedure

The CHMP noted the report from the Mutual Recognition Facilitation Group (MRFG) meeting held on 26 July 2004. For further details, please see **Annex 6.**

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 - 2003	2004	Overall Total
Scientific Advice	367	39	406
Follow-up to Scientific Advice	60	3	63
Protocol Assistance	30	17	47
Follow-up to Protocol Assistance	9	2	11

	1995-2003			2004			
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Applications submitted	134	271	405	12	16	28	433
Consultation for Medical Device[1]	0	1	1	0	0	0	1
Withdrawals	22	55	77	0	4	4	81
Positive opinions[2]	99	172	271	5	16	21	292[3]
Negative opinions[4]	2	5	7	0	0	0	7[5]
Marketing authorisations granted by the Commission	91	164	255	6	13	19	274[6]

	1995-2003			2004			Overall Total
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Variations type I	771	1505	2276	42	277	319	2595
Positive opinions, variations type II	583	697	1280	103	80	183	1463
Negative opinions, variations type II	1	6	7	0	0	0	7
Extensions (Annex II applications)	49	56	105	4	5	9	114

[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] 17 positive opinion corresponding to 17 Orphan Medicinal Products
[3] 292 positive opinions corresponding to 224 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] 274 marketing authorisations corresponding to 209 substances

MEDICINAL PRODUCTS GRANTED A COMMUNITY MARKETING AUTHORISATION UNDER THE CENTRALISED PROCEDURE SINCE 22- 23 JUNE 2004 CHMP MONTHLY REPORT

Invented Name	Erbitux
INN	cetuximab
Marketing Authorisation Holder	Merck KGaA
ATC code	L01XC06
Indication	Erbitux in combination with irinotecan is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy
CPMP Opinion date	24.03.2004

Invented Name	Lyrica
INN	Pregabalin
Marketing Authorisation Holder	Pfizer Ltd
ATC code	N03A (proposed)
Indication	Neuropathic pain Lyrica is indicated for the treatment of peripheral neuropathic pain in adults. Epilepsy Lyrica is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.
CPMP Opinion date	24.03.2004

Invented Name	Pedea
INN	Ibuprofen
Marketing Authorisation Holder	Orphan Europe S.A.R.L.
ATC code	C01 EB16
Indication	Treatment of a haemodynamically significant patent ductus arteriosus in preterm newborn infants less than 34 weeks of gestational age.
CPMP Opinion date	22.04.2004

OUTCOME OF THE 27-29 JULY 2004 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
21 SPC changes	21 Positive opinions
24 Quality changes	24 Positive opinions

Opinions for Annual Re-Assessment applications		
Name of Medicinal Product (INN) **MAH**	**Outcome**	**Comments**
Fuzeon (enfuvirtide) Roche Registration	Positive Opinion	The Marketing Authorisation will remain under exceptional circumstances N/A

Opinions for Renewal applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Arava (leflunomide) Aventis	Positive opinion	---
Novorapid (insulin aspart) Novo Nordisk	Positive opinion	---
Paxene (paclitaxel) Norton HealthCare	Positive opinion	---
Zyprexa velotab (olanzapine) Eli Lilly and Company Ltd	Positive opinion	---
Zeffix (lamivudine) GlaxoSmithKline	Positive opinion	---

OUTCOME OF THE 27-29 JULY 2004
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				
Chemical	Schizophrenia	X						X	
Chemical	Bipolar type I disorder	X						X	
Chemical	Rhinitis	X						X	
Chemical	Parkinson's disease	X						X	
Chemical	Breast Cancer	X					X		
Chemical	Fybromyalgia	X						X	
Chemical	Postherpetic neuralgia	X						X	
Chemical	Multiple sclerosis, rheumathoid arthritis and various tumors	X					X		
Chemical	Metabolic Syndrome	X						X	
Chemical	Myopia	X				X	X	X	
Chemical	Keratoconjunctivitis		X			X	X	X	X
Chemical	Gastrointestinal Stroma Tumors		X					X	
Chemical	Hereditary angioedema				X			X	X
Biological	Peripheral arterial disease	X					X		
Biological	Pancreatic cancer		X					X	
Biological	Mucopolysaccharidosis		X			X	X		
Biological	Melanoma			X		X			

SA: Scientific Advice

PA: Protocol Assistance

The above-mentioned 11 Scientific Advice letters, 4 Protocol Assistance letters, 1 Follow-up Scientific Advice letter and 1 Follow-up Protocol Assistance letter were adopted at the 27-29 July CHMP meeting.

The Committee accepted 9 Initial Scientific Advice Requests, and 2 Initial Protocol Assistance Requests.

DOCUMENTS PREPARED BY THE CHMP WORKING PARTIES AND AD HOC GROUPS ADOPTED DURING THE JULY 2004 CHMP MEETING

QUALITY WORKING PARTY

Reference number	Document	Status
CPMP/QWP/450/03	Guideline on Residual solvents: ▪ Annex I Specifications for class 1 and class 2 residual solvents in active substances ▪ Annex II residues of solvents used in the manufacture of finished products	Adopted
CPMP/QWP/2054/03	Process Validation Guideline - Annex II- Non standard processes	Adopted

EFFICACY WORKING PARTY

Reference number	Document	Status
CPMP/EWP/2986/03	Note for Guidance on clinical investigation of medicinal products for the treatment of cardiac failure – addendum on acute cardiac failure	Adopted
CPMP/EWP/3020/03	Note for Guidance on clinical investigation of medicinal products in the treatment of lipid disorders	Adopted
CHMP/EWP/1068/04	Recommendation on the need for Revision of the Note for Guidance on Evaluation of Anticancer Medicinal Products in Man	Adopted

BLOOD PRODUCTS WORKING GROUP

Reference number	Document	Status
CPMP/BPWG/1089/00	Guideline on the clinical investigation of plasma derived fibrin sealant/haemostatic products	Adopted
CPMP/BPWG/859/95 rev 2	Core SPC for Human normal immunoglobulin for intravenous administration (IVIg)	Adopted
CPMP/BPWG/153/00	Core SPC for plasma derived fibrin sealant/haemostatic products	Adopted
CPMP/BPWG/2048/04	Core SPC for human plasma coagulation factor VII products	Adopted

Report from the meeting held on 26 July 2004

General Issues

MRFG Guidance on submission dates for Applicants of the Mutual Recognition Procedure

An updated version of the Annex, to include dates for submissions of new applications for mutual recognition for 2005, has been adopted by the group and will be published on the website.

Communication between Companies and MRFG

Companies are reminded that they are not expected to send items for discussion or questions directly to all MRFG members, but they need to contact a Member State that will be responsible for bringing the question to the MRFG.

E-mails to MRFG contact points

Companies are reminded that they should not send e-mails in relation with on going mutual recognition procedures directly to MRFG members, but they should follow national policies.
For further information, please refer to the MRFG Guidance document on National Administrative Processes in the MRP http://heads.medagencies.org/mrfg/docs/general/nationaladminprocess.pdf

Meeting schedule

The next MRFG meeting will be held on 13 September 2004.

Mutual Recognition Monitoring

The MRFG noted that **126** new mutual recognition procedures were finalised during the month of June 2004, as well as **307** type IA variations, **160** type IB variations and **151** type II variations.

The status as of 30th June 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 IA variations finalised	Procedures from Type IB variations finalised	Procedures from Type II variations finalised	Arbitrations referred to CPMP
2004	343	204	43	1449	994	519	1 N.A

80 new procedures (regarding **161** products) started in June 2004. The categories of these procedures are as follows:

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

13 known active substances (already authorised in at least one member state), including **1** multiple application and **7** repeat use.

56 abridged applications including **29** multiple applications and **2** repeat use.

7 extension applications including **2** multiple applications.

The new procedures started related to **14** full dossiers, **59** generics, **4** bibliographic applications, **2** informed consent applications and **1** for different use, route or dose.

The procedures consisted of **77** chemical substances, **2** herbal medicinal products and **1** biological-other[1].

78 of these procedures were prescription-only medicinal products in the reference Member State and **2** 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 June 2004

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

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DK (2)	5
DK (2)	1
DK (2)	5
DK (2)	1
DK (2)	1
DK (2)	1
DK (2)	1
DK (2)	1
FI (1)	10
FI (1)	1
FI (1)	1
FI (1)	2
FI (1)	9
FI (2)	8
FI (2)	1
FI (2)	1
FI (2)	2
FI (2)	1
FI (2)	1
FI (2)	1
FI (2)	16
FI (3)	12
FI (2)	1
IE (1)	13
NL (3)	9
NL (1)	9
NL (1)	3
NL (2)	6
NL (2)	1
NL (3)	7
NL (3)	5
NL (3)	1
NL (3)	11
SE (3)	7
SE (4)	16
SE (1)	8
SE (1)	4
SE (2)	26
SE (2)	1
SE (2)	6
SE (2)	1
SE (2)	1
SE (2)	6
SE (2)	3
SE (2)	3
SE (2)	10
SE (2)	1
SE (2)	9
SE (2)	1
SE (2)	1
UK (1)	9
UK (4)	2
UK (4)	2
UK (2)	12
UK (3)	2
UK (3)	2
UK (3)	2
UK (1)	10
UK (4)	13
UK (3)	6
UK (1)	7
UK (3)	2
UK (3)	11

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
UK (3)	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:

Mrs. Truus Janse-de Hoog
College ter Beoordeling van Geneesmiddelen
Kalvermarkt 53
NL – 2500 Den Haag
The Netherlands

Phone: + 31 70 356 74 08
Fax: + 31 70 356 75 15
e-mail: gm.janse@cbg-meb.nl

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