European Medicines Agency
Post-Authorisation Evaluation of Medicines for Human Use

06 January 2005
CHMP/203834/2004

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

The Committee for Medicinal Products for Human Use (CHMP) held its December plenary meeting from 13 - 15 December 2004.

Centralised procedure

Opinions

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

- **Aloxi** (palonosetron), from Helsinn Birex Pharmaceuticals Ltd, for the prevention of nausea and vomiting associated with cancer chemotherapy. EMEA review began on 18 August 2003 with an active review time of 206 days.

- **Zonegran** (zonisamide), from Eisai Ltd, for the adjunctive therapy of partial seizures in epilepsy. EMEA review began on 24 November 2003 with an active review time of 202 days.

More information about these products can be obtained in the summaries of opinions available on the EMEA web site: http://www.emea.eu.int

The Committee also adopted positive opinions on extensions of indication for medicinal products that are already marketed in the European Union:

- **Arixtra** (fondaparinux), Sanofi Synthelabo, and **Quixidar** (fondaparinux), N.V. Organon, to extend its use to the prevention of Venous Thromboembolic Events (VTE) in medical patients who are judged to be at high risk of thromboembolic complications due to acute illness such as cardiac insufficiency, and/or acute respiratory disorders, and/or acute infectious or inflammatory disease. Arixtra and Quixidar were both first authorised in the European Union on 21 March 2002.

- **Pegasys** (peginterferon alfa-2a), Roche Registration Ltd, to extend its use in combination therapy with Ribavirin for the treatment of chronic hepatitis C in patients co-infected with HIV. Pegasys was first authorised in the European Union on 20 June 2002.

List of Questions

The Committee adopted two Lists of Questions on initial applications, and two 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 November 2004 is provided in **Annex 2.** The post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 3**.

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Applications for marketing authorisation for orphan medicinal products

There was no centralised application for marketing authorisation for orphan medicinal products authorisation since the November 2004 CHMP.

Referrals

- Following the extraordinary CHMP meeting held on 18 December 2004 on SSRIs, the European Medicines Agency (EMEA) received on 17 December 2004 a letter from the European Commission requesting the review of the risk of suicidal behaviour, including suicide attempts and suicidal ideation and/or related behaviour like self-harm, hostility and mood liability related to the use of SSRIs in children and adolescents. Therefore, the two following procedures will be started at the January 2005 CHMP meeting:
    - A Community-wide referral procedure under Article 31 of the Community Code on medicines for human use for medicinal products containing atomoxatine, citalopram, escitalopram, fluoxetine, fluvoxamine, mianserine, milnacepran, mirtazapine, paroxetine, reboxetine, sertraline and venlafaxine.
    - A review procedure under Article 18 of Council Regulation (EEC) 2309/93 for medicinal products containing duloxetine.
- The Committee finalised an EU-wide referral for arbitration for **Artirem** (Gadoteric acid) from Guerbet. Artirem is a contrast agent for arthrography using magnetic resonance imaging (MRI) for certain joints and diseases. The referral was initiated by Germany under Article 29 of the Community Code on human medicines in March 2004 based on unsolved safety and efficacy objections. After reviewing all available data the Committee concluded that the safety and efficacy for Artirem are sufficiently proven and that a marketing authorisation can be granted in the context of the mutual recognition procedure.
- The CHMP began a Community referral under Article 29(2) of Directive 2001/83/EC as amended, for the medicinal product **Adartrel** (ropinirole) from Laboratoires GlaxoSmithKline. The referral was initiated by Spain and the Netherlands because of concerns regarding the efficacy and long-term safety of the medicinal product for the symptomatic treatment of moderate to severe idiopatic restless legs syndrome.

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 1-2 December 2004. For further details, please see **Annex 4**.

Documents prepared by the CHMP Working Parties adopted during the December 2004 CHMP meeting are listed in **Annex 5**.

Please also refer to the section "Organisational matters" for information on Working Parties' organisational related aspects.

Upcoming meetings following the December 2004 CHMP plenary meeting:

- The 8th meeting of the CHMP will be held on 17-20 January 2005.
- The next NRG meeting will be held on 17 January 2004.

Organisational matters

The main topics addressed during the December 2004 CHMP related to:

- The adoption, by the CHMP, of the revised Mandate and Rules of Procedures in the framework of Regulation (EC) 726/2004 for the Scientific Advisory Groups (SAGs) on Oncology, Anti-Infectives and Diagnostics. A copy of these documents will be published on the EMEA website. The adoption of the new composition of these SAGs will take place at the February 2005 CHMP meeting. Chairpersons' elections are expected to take place the following month.
- The establishment over 2005 and 2006 of the future SAGs, namely HIV/Viral diseases, Endocrinology/Diabetes, CNS/Psychiatry and Cardiology. Further information will be made available in the near future.
- The election of the Chairperson and Vice Chairperson of the Paediatric Working Party (PEG): **Dr Daniel Brasseur** has been elected as Chairperson and **Dr Kalle Hoppu** was elected as Vice Chairperson. This election follows the adoption of the revised Mandate and Rules of Procedure for the PEG at the October 2004 CHMP meeting (available on the EMEA website: (http://www.emea.eu.int/pdfs/human/peg/4915404en.pdf) and the adoption of the new composition for the PEG at the November 2004 CHMP meeting.
- The adoption, by the CHMP, of the Work Programmes 2005 for:
  - The CHMP Efficacy Working Party (EWP)
  - The CHMP Safety Working Party (SWP)
  - The CHMP Paediatric Working Party (PEG)
  - The CHMP Blood Product Working Party (BPWP)
  - The CHMP Pharmacogenetics Working Party
  - The CHMP Pharmacovigilance Working Party (PhVWP)

  A copy of these documents will be published on the EMEA website.

PROCEDURAL ANNOUNCEMENT

As part of the improvement of the EMEA Transparency policy towards the life cycle of the medicinal product, the EMEA will be publishing, summaries of opinions for certain post-authorisation applications over 2005, and this will be done in a stepwise approach.

There will be, after the **January 2005 CHMP meeting**, publication of post-authorisation summaries of opinion (positive/negative opinions) for:

- All Type II variations related to extension and deletion of the therapeutic indication(s) (section 4.1 SPC) and
- All Type II variations related to changes to contra-indications (section 4.3 SPC).

Such implementation of the extension of the EMEA Transparency policy will be monitored in 2/3 Q2005 and changes made, as appropriate. An updated publication policy of CHMP summaries of opinion will be made available in January 2005 together with the procedure and templates.

Mutual Recognition procedure

The CHMP noted the report from the Mutual Recognition Facilitation Group (MRFG) meeting held on 13 December 2004. 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 - 2003	2004	Overall Total
Scientific Advice	367	66	433
Follow-up to Scientific Advice	60	11	71
Protocol Assistance	30	29	59
Follow-up to Protocol Assistance	9	3	12

	1995-2003			2004			
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Applications submitted	134	271	405	19	32	51	456
Consultation for Medical Device[1]	0	1	1	0	0	0	1
Withdrawals	22	55	77	0	7	7	84
Positive opinions[2]	99	172	271	8	25	33	304[3]
Negative opinions[4]	2	5	7	0	0	0	7[5]
Marketing authorisations granted by the Commission	91	164	255	7	26	33	288[6]

	1995-2003			2004			Overall Total
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Variations type I	771	1505	2276	92	432	524	2800
Positive opinions, variations type II	583	697	1280	175	189	364	1644
Negative opinions, variations type II	1	6	7	0	0	0	7
Extensions (Annex II applications)	49	56	105	4	7	11	116

[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] 304 positive opinions corresponding to 235 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] 288 marketing authorisations corresponding to 220 substances

MEDICINAL PRODUCTS GRANTED A COMMUNITY MARKETING AUTHORISATION UNDER THE CENTRALISED PROCEDURE SINCE THE NOVEMBER 2004 CHMP MONTHLY REPORT

Invented Name	Xagrid
INN	anagrelide
Marketing Authorisation Holder	Shire Pharmaceutical Contracts Ltd.
ATC code	B01AC14
Indication	Reduction of elevated platelet counts in at risk essential thrombocythaemia patients who are intolerant to or not satisfactorily treated with their current therapy.
CPMP Opinion date	29.07.2004
Marketing Authorisation Date	16.11.2004

OUTCOME OF THE DECEMBER 2004 CHMP MEETING IN RELATION TO CENTRALISED APPLICATIONS IN THE POST-AUTHORISATION PHASE

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
3 Extensions of indication	3 Positive opinions
20 SPC changes	20 Positive opinions
19 Quality changes	19 Positive opinions

Opinions for Annual Re-Assessment applications		
Name of Medicinal Product (INN) **MAH**	**Outcome**	**Comments**
Ceprotin (protein C) Baxter AG	Positive Opinion.	The Marketing Authorisation will remain under exceptional circumstances.
Fabrazyme (agalsidase beta) Genzyme B.V.	Positive Opinion.	The Marketing Authorisation will remain under exceptional circumstances.
Replagal (agalsidase alfa) TKT Europe-5S AB	Positive Opinion.	The Marketing Authorisation will remain under exceptional circumstances.

Opinions for Renewal applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Ammonaps (phenylbutyrate) Orphan Europe SARL	Positive Opinion	---
Enbrel (etanercept) Wyeth Europe Ltd	Positive Opinion	
Orgalutran (ganirelix) N.V. Organon,	Positive Opinion	
Thyrogen (thyrotrophin alfa) Genzyme B.V	Positive Opinion	

OUTCOME OF THE DECEMBER 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				
Biological	Anaemias			X		X	X	X	
Chemical	Osteoporosis in men	X						X	
Biological	Dermatomyositis		X				X	X	
Biological	Wound cleansing	X				X	X	X	
Chemical	Complicated skin and skin structure infections	X				X	X	X	
Biological	Neutropenias			X				X	

SA: Scientific Advice

PA: Protocol Assistance

The above-mentioned 3 Scientific Advice letters, 2 Follow-up Scientific Advice letters, and 1 Protocol Assistance letters were adopted at the 13-15 December 2004 CHMP meeting.

In December 2004, the Committee accepted 14 Initial Scientific Advice Requests, 5 Initial Protocol Assistance Requests and 1Follow-up Protocol Assistance Request.

DOCUMENTS PREPARED BY THE CHMP (TEMPORARY) WORKING PARTIES ADOPTED DURING THE DECEMBER 2004 CHMP MEETING

QUALITY WORKING PARTY

Reference number	Document	Status
CHMP/QWP/185401/2004	Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials	Adopted

BIOTECHNOLOGY WORKING PARTY

Reference number	Document	Status
CHMP/BWP/124447/2004	Concept Paper on the development of a Guideline on Viral Safety Evaluation of Biotechnological Products to be used in Clinical Trials	Adopted

SAFETY WORKING PARTY

Reference number	Document	Status
EMEA/26387/01	CHMP Safety Working Party (SWP) Work Programme 2005	Adopted

EFFICACY WORKING PARTY

Reference number	Document	Status
CHMP/EWP/145749/2004	CHMP Efficacy Working Party (EWP) Work Programme 2005 and 2006 dates	Adopted

PHARMACOGENETICS WORKING PARTY

Reference number	Document	Status
CHMP/186179/2004	CHMP Pharmacogenetics Working Party Work Programme 2005	Adopted

BLOOD PRODUCTS WORKING PARTY

Reference number	Document	Status
CHMP/BPWG/7/04	CHMP Blood Product Working Party (BPWP) Work Programme 2005 and dates for 2006	Adopted
CHMP/BPWG/134068/2004	BPWP Concept Paper for a revision of the Notes for Guidance on the Clinical Investigation of Human Plasma Derived and Recombinant Factor VIII and IX products and the corresponding core SPCs	Released for 3 months consultation
CPMP/BPWG/220/02	BPWP Guideline on the Clinical Investigation of Human Plasma Derived von Willebrand Factor Products	Re-released for 2 months consultation

ICH

Reference number	Document	Status
CHMP/167068/2004-ICH	ICH Q8 Pharmaceutical Development – Note for Guidance on Pharmaceutical Development (Step 2)	Released for 6 months consultation
CPMP/ICH/5721/03	ICH Q5E Comparability of Biotechnical/Biological Products – Note for Guidance on Biotechnical/Biological Products Subject to changes in their manufacturing process (Step 4)	Adopted
CHMP/167235/2004-ICH	ICH S8 Immunotoxicity studies for Human Pharmaceuticals – Note for Guidance on Immunotoxicity Studies for Human Pharmaceuticals (Step 2)	Released for 4 months consultation
CPMP/ICH/5716/03	E2E Pharmacovigilance Planning (PVP) – Note for Guidance on Planning Pharmacovigilance Activities (Step 4)	Adopted

PAEDIATRIC WORKING PARTY

Reference number	Document	Status
CPMP/PEG/35132/03	Discussion Paper on the Impact of Renal Immaturity when investigating Medicinal Products intended for Paediatric Use	Adopted
CHMP/PEG/178964/2004	Paediatric Working Party (PEG) Work Programme 2005-2006	Adopted

Report from the meeting held on 13 December 2004

General Issues

MRFG meeting with Interested parties on issues arising from Enlargement of the EU

A meeting between MRFG members and representatives from interested parties (EFPIA, EGA and AESGP) was held in the morning prior to the MRFG plenary session to share the experience gained so far with the use of the Mutual Recognition Procedure and, particularly, with the Repeat-use procedure in new Member States.

MRFG Sub-group meeting on Article 17 and 18 procedures

The MRFG Sub-group on Article 17 and 18 procedures held its second meeting in the morning following the MRFG plenary session.

Applicants are reminded to respond to the request of National Competent Authorities regarding Article 17(2) and 18 procedures within the given timeframes, because Competent Authorities will trigger Article 17 (2) and 18 procedures.

No response to required update of documentation can invalidate pending applications.

For further information, please refer to the MRFG documents 'Simultaneous applications (Article 17 paragraph 2 of Directive 2001/83/EC). Member States Standard Operating Procedure' http://heads.medagencies.org/mrfg/docs/sops/sim_application.pdf and 'Triggering of Mutual Recognition by Member States (Article 18 of Directive 2001/83/EC). Member States Standard Operating Procedure' http://heads.medagencies.org/mrfg/docs/rec/trig_mrp.pdf

Questions & Answers list for the submission of Variations according to Commission Regulation (EC) 1084/2003

The MRFG has agreed on a Questions & Answers document to reflect a harmonised interpretation of the Commission Regulation (EC) No 1084/2003 and of the conditions to be fulfilled for Type IA and IB variations. The Q&A document will be published on the website**.**

Notifications to the EMEA/CHMP in the Mutual Recognition Procedure

Applicants are reminded to limit the documentation to be submitted to the EMEA in relation to Mutual Recognition Procedure to notifications of marketing authorisation applications and to the full dossier, only in case of arbitrations, in accordance with the document "Notifications to the EMEA/CHMP in the Mutual Recognition Procedure (MRP)", currently available on the Heads of Agencies website http://heads.medagencies.org/mrfg/docs/prod/notifications.pdf

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 mutual recognition application for marketing authorisation after July 2003.

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 RMS: SE CMS: AT, DE, DK, ES, FI, FR, NL, NO, PT Day 90: 08.06.2004

Change in the EU-Presidency

The December 2004 MRFG meeting was the last one under the Dutch presidency. Nevertheless, The Netherlands will continue to chair the MRFG meetings during the Luxembourg presidency and Truus Janse-de Hoog should be contacted in case of any questions regarding the MRP.

Meeting schedule

The next MRFG meeting will be held on 17 January 2005.

Mutual Recognition Monitoring

The MRFG noted that **46** new mutual recognition procedures were finalised during the month of November, as well as **326** type IA variations, **151** type IB variations and **102** type II variations. **1** arbitration related to a new application has been referred to the CHMP.

The status as of 30th November 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
2004	644	298	2948	1824	996	3 N.A

62 new procedures (regarding **123** products) started in November 2004. The categories of these procedures are as follows:

5 new active substances (first authorisation in the European Community after RMS approval), classified as repeat use.

6 known active substances (already authorised in at least one member state), including **4** repeat use.

50 abridged applications including **20** multiple applications and **8** repeat use.

1 line extension application.

The new procedures started related to **8** full dossiers, **48** generics, **2** bibliographic applications, **1** fixed combination and **3** for different use, route or dose.

The procedures consisted of **61** chemical substances and **1** biological-vaccine[1].

60 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 November 2004

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
BE (1)	14
DE (1)	10
DE (1)	4
DE (1)	11
DK (1)	1
DK (1)	1
DK (4)	6
DK (2)	4
DK (3)	3
DK (4)	8
DK (1)	2
FI (1)	1
FI (4)	5
FI (1)	1
FI (1)	1
FI (1)	1
FI (1)	1
FI (1)	2
FI (1)	10
FI (1)	2
FI (1)	1
FI (1)	2
FI (1)	2
FI (1)	5
FI (1)	2
FI (1)	1
FI (2)	2
FR (2)	9
NL (1)	6
NL (4)	1
NL (1)	1
NL (1)	9
NL (4)	6
NL (2)	3
NL (2)	9
NL (2)	8
NL (4)	2
NL (4)	1
NL (4)	1
NL (4)	1
NL (4)	7
NL (3)	2
NO (2)	3
PT (2)	6
SE (1)	10
UK (1)	7
UK (2)	7
UK (1)	13
UK (1)	2
UK (3)	4
UK (2)	13

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
UK (1)	1
UK (3)	16
UK (1)	2
UK (2)	5
UK (2)	3
UK (3)	1
UK (3)	1
UK (3)	1
UK (3)	11
UK (3)	1
UK (2)	18

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:

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http://heads.medagencies.org/