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

30 November 2004
EMEA/CHMP/160431/2004

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

The Committee for Medicinal Products for Human Use (CHMP) held its November plenary meeting from 15 - 18 November 2004.

Centralised procedure

Opinions

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

- **Azilect** (rasagiline), from Teva Pharma GmbH, for the treatment of Parkinson's disease. EMEA review began on 27 October 2003 with an active review time of 208 days.
- **Orfadin** (nitisinone), from Swedish Orphan International AB, for the treatment of hereditary tyrosinemia type 1. EMEA review began on 21 July 2003 with an active review time of 197 days. Orfadin was designated an orphan medicinal product on 29 December 2000 and is the nineteenth orphan medicinal product to receive a positive CHMP opinion.
- **Prialt** (ziconotide), from Elan Pharma International Ltd, for the treatment of severe, chronic pain in patients who require intrathecal analgesia. EMEA review began on 26 May 2003 with an active review time of 196 days. Prialt was designated an orphan medicinal product on 9 July 2001 and is the twentieth orphan medicinal product to receive a positive CHMP opinion.
- **Truvada** (emtricitabine/tenofovir disoproxil) from Gilead Science International Limited, for use in antiretroviral combination therapy for the treatment of Human immunodeficiency virus (HIV-1) infection in adults. Truvada is a fixed dose combination of two antiretroviral agents (emtricitabine and tenofovir disoproxil) to be administered once a day. EMEA review began on 29 March 2004 with an active review time of 182 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 a number of extensions of indication for medicinal products that are already marketed in the European Union:

- **Advate** (octocog alfa), Baxter AG, to include children under the age of 6 in the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Advate was first authorised in the European Union on 2 March 2004.
- **Avandia** (rosiglitazone), GlaxoSmithKline, to extend its use in the treatment of type 2 diabetes mellitus as a triple oral combination treatment, i.e. rosiglitazone in combination with metformin and a sulphonylurea. Avandia was first authorised in the European Union on 11 July 2000.
- **Taxotere** (docetaxel), Aventis, to extend its use in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer and in combination with Herceptin (trastuzumab) for the treatment of patients with metastatic breast cancer whose tumours overexpress HER2. Taxotere was first authorised in the European Union on 27 November 1995.

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The Committee also adopted a positive opinion on a Type II variation for **Norvir** (ritonavir) and **Kaletra** (lopinavir /ritonavir) from Abbott International to include special warnings and precautions and information on the interaction between ritonavir and fluticasone.

List of Questions

The Committee adopted eight Lists of Questions on initial applications, and one List of Questions on a "line extension" application (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 September 2004 is provided in **Annex 2.** The post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 3**.

Applications for marketing authorisation for orphan medicinal products

Details of those Orphan medicinal products that have been subject of a centralised application for marketing authorisation since the October 2004 CHMP are provided in **Annex 4**.

Referrals

- Following the worldwide withdrawl of Vioxx (rofecoxib), the European Medicines Agency (EMEA) has been asked by the European Commission on 22 October 2004, as a precautionary measure, to conduct a review of all licensed COX-2 inhibitor medicines (www.emea.europa.eu/pdfs/human/press/pr/11790804en.pdf). As part of this review exercise, the CHMP formally started the two following procedures at its November 2004 meeting:
  - A Community-wide referral procedure under Article 31 of the Community Code on medicines for human use for medicinal products containing celecoxib, etoricoxib and lumiracoxib.
  - A review procedure under Article 18 of Council Regulation (EEC) 2309/93 for Bextra/Valdyn (valdecoxib), Dynastat/Rayzon (parecoxib) and Onsenal (celecoxib).

- The CHMP initiated a Community-wide referral procedure under Article 29(2) of the Community Code on medicines for human use for Crestor (rosuvastatin) 5 mg from AstraZeneca . The product is already licensed in a number of Member States in dosages ranging from 5 to 40 mg. This referral is made by the United Kingdom and relates to differing views on whether Crestor 5 mg should be the recommended starting dose for patients with predisposing factors to myopathy only, or for all patients. A Rapporteur and a Co-Rapporteur were appointed and the review procedure has started.

CHMP (temporary) Working Parties

The CHMP was informed of the outcome of the discussions of the Scientific Advice Working Group (SAWG) meeting, which was held on 3-4 November 2004. For further details, please see **Annex 5**.

An EMEA workshop on Medicines for the Treatment of Pain in Children was held on 28 October 2004. A Press Release was published on the EMEA website: http://www.emea.eu.int/pdfs/human/press/pr/14943604en.pdf.

Documents prepared by the CHMP Working Parties adopted during the November 2004 CHMP meeting are listed in **Annex 6**.

The CHMP agreed on an overarching guideline on similar biological medicinal products, which describes the EMEA approach to the development and approval of these products. As part of this, the two existing guidelines on comparability of medicinal products containing biotechnology-derived

proteins as drug substance will be revised to give more detailed guidance on the comparability and biosimilarity aspects of the quality, non-clinical and clinical development of biosimilar medicinal products. In addition the Committee agreed on 4 concept papers that will lead to guidelines on the development of biosimilar medicinal products in specific classes. Please see **Annex 6** for further details.

Interested Parties meetings

An EMEA-EFPIA Info day took place at the EMEA on 22 October 2004 during which the result/analysis of the 2004 Performance Indicators exercise on pre- and post-authorisation activities was presented.

The report from the Joint EMEA/Interested Parties Meeting on Invented Names held on 13 September 2004 has now been published on EMEA website.

Upcoming meetings following the November 2004 CHMP plenary meeting:

- The 7th meeting of the CHMP will be held on 13-16 December 2004.
- The next NRG meeting will be held on 13 December 2004.
- A workshop between the EMEA/CHMP Working Group with Patients' Organisations and representatives from all the interested parties who have commented on the recommendations and proposals for action prepared by the Working Group and released for consultation till July 2004, will be held on 3 December 2004 at the EMEA.
- A CHMP Pharmacogenetic Working Party Workshop will be held on 30 November 2004 at the EMEA.
- An EMEA/Gene Therapy Expert Group (GTEG) Training of Assessors in Gene Therapy will be held on 8 December at the EMEA.
- An EMEA/Drug Information Association (DIA) joint meeting on gene therapy and cell therapy products will be held on 9-10 December 2004.

Organisational matters

The main topics addressed during the October 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 CHMP Efficacy Working Party (EWP)
  - The CHMP Safety Working Party (SWP)

  A copy of these documents will be published on the EMEA website.
- The adoption of the new composition for the Paediatric Working Party (PEG), following the adoption of the revised mandate and Rules of Procedure for the PEG at the October 2004 CHMP meeting (http://www.emea.eu.int/pdfs/human/peg/4915404en.pdf). The election of the Chairperson and Vice Chairperson of the PEG will take place at the December 2004 CHMP meeting.
- The election of the Chairperson and Vice Chairperson of the Scientific Advice Working Party (SAWP): **Dr Markku Toivonen** has been re-elected as Chairperson and **Dr Simon Day** was elected as Vice Chairperson. This election follows the adoption of the revised mandate and Rules of Procedure for the SAWP at the September 2004 CHMP meeting (available on the EMEA website: http://www.emea.eu.int/pdfs/human/sciadvice/6968604en.pdf) and the adoption of the new composition for the SAWP at the October 2004 CHMP meeting.
- The 2nd internal CHMP audit was conducted in November 2004. This follows the 1st internal CHMP audit held in June 2003 and the EMEA action plan for improvements of processes in relation to medicines for human use published in January 2004 (http://www.emea.eu.int/htms/hotpress/h088504.htm).

PROCEDURAL ANNOUNCEMENT

Submission of Type IA, Type IB and Type II variations in December 2004

Please note that the EMEA will be closed between 24 December 2004 and 3 January 2004.

Marketing Authorisation Holders are therefore requested not to submit Type IA variation applications to the EMEA between 10 and 23 December 2003 (incl.) because the 14-day timeframe for the Agency to acknowledge the validity of the submitted Type IA variation (see article 4 of Commission Regulation (EC) No 1085/2003) would coincide with the official closure of the EMEA.

Type IA variation applications submitted not later than 10 December 2004 will be finalised before the EMEA Christmas break. Any Type IA variation applications submitted to the EMEA between 11 December 2004 and 3 January of 2005 will start on the 4 January 2005.

Marketing Authorisation Holders intending to apply for Type IB or Type II variations in December 2004 are encouraged to liaise with the EMEA prior to their submission.

Mutual Recognition procedure

The CHMP noted the report from the Mutual Recognition Facilitation Group (MRFG) meeting held on 15 November 2004. For further details, please see **Annex 7.**

The 11th plenary meeting of the CHMP will be held from 13 – 16 December 2004.

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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	63	430
Follow-up to Scientific Advice	60	9	69
Protocol Assistance	30	28	58
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	17	28	45	450
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	23	31	302[3]
Negative opinions[4]	2	5	7	0	0	0	7[5]
Marketing authorisations granted by the Commission	91	164	255	7	25	32	287[6]

	1995-2003			2004			Overall Total
	Part A	**Part B**	**Total**	**Part A**	**Part B**	**Total**	
Variations type I	771	1505	2276	68	395	460	2736
Positive opinions, variations type II	583	697	1280	156	166	322	1602
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] 302 positive opinions corresponding to 233 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] 287 marketing authorisations corresponding to 219 substances

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

Invented Name	Mimpara
INN	cinacalect
Marketing Authorisation Holder	Amgen Europe B.V.
ATC code	H05BX01
Indication	Treatment of secondary hyperparathyroidism (HPT) in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy. Reduction of hypercalcaemia in patients with parathyroid carcinoma.
CPMP Opinion date	29/07/2004
Marketing Authorisation Date	22/10/2004

Invented Name	Parareg
INN	cinacalect
Marketing Authorisation Holder	Amgen Europe B.V.
ATC code	H05BX01
Indication	Treatment of secondary hyperparathyroidism (HPT) in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy. Reduction of hypercalcaemia in patients with parathyroid carcinoma.
CPMP Opinion date	29/07/2004
Marketing Authorisation Date	22/10/2004

Invented Name	Emselex
INN	darifenacin
Marketing Authorisation Holder	Novartis Europharm Ltd
ATC code	G04BD10
Indication	Symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome
CPMP Opinion date	29/07/2004
Marketing Authorisation Date	22/10/2004

OUTCOME OF THE NOVEMBER 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
36 SPC changes	36 Positive opinions
16 Quality changes	16 Positive opinions

Opinions for Annual Re-Assessment applications		
Name of Medicinal Product (INN) **MAH**	**Outcome**	**Comments**
Ventavis (iloprost) Schering AG	Positive Opinion	The Marketing Authorisation will remain under exceptional circumstances

Opinions for Renewal applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Renagel (sevelamer) Genzyme B.V	Positive Opinion	---
Tractocile (atosiban) Ferring AB	Positive Opinion	---

OVERVIEW OF DESIGNATED ORPHAN MEDICINAL PRODUCTS THAT HAVE BEEN THE SUBJECT OF A CENTRALISED APPLICATION FOR MARKETING AUTHORISATION:
UPDATE SINCE THE OCTOBER 2004 CHMP MEETING

Active substance	**Sponsor/applicant**	**EU Designation Number & Date of Orphan Designation**	**Designated Orphan Indication**
Sinapultide, dipalmitoylphosphatidylcholine, palmitoyloleoylphosphatidylglycerol and palmitic acid (Surfaxin)	GMG BioBusiness Ltd.	EU/3/04/216 29/07/2004	Prevention of respiratory distress syndrome in premature neonates of less than 32 weeks of gestational age.
		EU/3/04/217 29/07/2004	Treatment of respiratory distress syndrome in premature neonates of less than 37 weeks of gestational age.
Decitabine (Dacogen)	Eurogen Pharmaceuticals Limited	EU/3/03/135 14/02/2003	Treatment of myelodysplastic syndromes.

OUTCOME OF THE NOVEMBER 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	Tricyclic antidepressant and cocaine poisoning		X				X	X	X
Biological	Anaemias			X				X	
Chemical	Dyslipidemias	X						X	
Biological	Cancer pain management	X					X	X	
Biological	Melanoma		X				X	X	
Chemical	Diabetes	X					X	X	
Chemical	Congestive heart failure			X				X	
Biological	Prostate cancer	X				X	X	X	
Biological	Ascitis	X						X	
Chemical	Myelodysplastic syndromes		X				X	X	
Chemical	Multiple sclerosis	X					X	X	
Chemical	Cystic fibrosis				X			X	
Chemical	Tinnitus	X						X	
Biological	Paroxysmal nocturnal haemoglobinuria		X			X	X	X	
Biological	Neutropenias	X				X	X	X	
Biological	Adjunct in blood cell transplantation		X			X		X	
Chemical	Schizophrenia			X			X	X	
Chemical	Clostridium difficile infection	X						X	
Biological	Ovarian cancer		X				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 1 Follow-up Protocol Assistance were adopted at the 16-18 November 2004 CHMP meeting.

In November 2004, the Committee accepted 5 Initial Scientific Advice Requests, 1 Follow-up Scientific Advice Request and 3 Initial Protocol Assistance Requests.

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

SAFETY WORKING PARTY

Reference number	Document	Status
CHMP/SWP/110421/2004	Concept Paper on the Development of a CHMP guideline on genotoxicity and carcinogenicity evaluation of anti-HIV medicinal products	Released for 2-months consultation
CHMP/SWP/ 110180/2004	Concept paper on the development of a CHMP Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors	Released for 2-months consultation

EFFICACY WORKING PARTY

Reference number	Document	Status
CHMP/EWP/5872/03	Guideline on Data Monitoring Committees	Released for 6-months consultation
CHMP/EWP/139391/2004	Reflexion Paper on the Regulatory Guidance for the Use of Health-Related Quality of Life (HRQL) Measures in the Evaluation of Medicinal Products	Released for 3-months consultation
CHMP/EWP/2454/02	Guideline on Clinical Investigation of Medicinal Products Indicated for the treatment of Psoriasis	adopted
CHMP/EWP/252/03	Guideline on Clinical Investigation of Medicinal Products Intended for the Treatment of Neuropathic Pain	adopted
CHMP/EWP/3635/03	Guideline on Clinical Investigation of Medicinal Products for the Treatment of Social Anxiety Disorder (SAD)	Released for 6-months consultation

AD HOC WORKING GROUP ON COMPARABILITY OF BIOTECHNOLOGY PRODUCTS

Reference number	Document	Status
CHMP/437/04	Guideline on similar biological medicinal products	Released for 3-months consultation
CHMP/Comparability Working Party/146701/04	Concept paper on the development of similar biological medicinal products containing recombinant human granulocyte-colony stimulating factor	Released for 2-months consultation
CHMP/Comparability working party/146710/04	Concept Paper on the Development of similar biological medicinal products containing recombinant human insulin	Released for 2-months consultation

CHMP/Comparability Working Party/146489/04	Concept Paper on the Development of similar biological medicinal products containing recombinant human growth factor Somatropin containing products	Released for 2-months consultation
CHMP/Comparability Working Party/146664/04	Concept Paper on the Development of similar biological medicinal products containing recombinant human erythropoietin.	Released for 2-months consultation

Report from the meeting held on 15 November 2004

General Issues

MRFG Sub-group on Patient information

A sub-group of the MRFG was set up, to discuss the requirements of the new legislation on patient information, and met in the morning prior to the MRFG plenary session.

Abbreviation for the Co-ordination group for Mutual recognition and Decentralised procedure

The MRFG has agreed to use CMD(h) as the abbreviation for the future Co-ordination group for medicinal products for human use, established by Directive 2001/83/EC, as amended.

Questions & Answers on MRP after the EU Enlargement on 1 May 2004
An updated version of the document has been adopted by the group and will be published on the website.

Frequently Asked Questions on MRP

An updated version of the FAQ on MRP document, to include mainly information on bibliographical applications and MRP, has been adopted by the group and will be published on the website.

Triggering of Mutual Recognition by Member States (Article 18 of Directive 2001/83/EC). Member States Standard Operating Procedure

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

It clarifies in the second letter that Applicants should request the RMS to prepare the updated assessment report in order to start a repeat-use procedure.

CTD format in Mutual Recognition Procedure

All Member States have confirmed to accept applications through MRP in the old EU-format until 30 April 2005 (for applications submitted to the RMS in the old EU-format before 1 July 2003).

For further information, please refer to the Notice to Applicants, Volume 2B, Presentation and content of the dossier – Common Technical Document (CTD), Questions and Answers, Updated June 2004 http://pharmacos.eudra.org/F2/eudralex/vol-2/B/CTD-QA-final_june-2004.pdf .

Meeting schedule
The next MRFG meeting will be held on 13 December 2004.

Mutual Recognition Monitoring

The MRFG noted that **64** new mutual recognition procedures were finalised during the month of October, as well as **244** type IA variations, **175** type IB variations and **100** type II variations.

The status as of 31st October 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	598	215	2622	1673	894	2 N.A

52 new procedures (regarding **112** products) started in October 2004. The categories of these procedures are as follows:

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

12 known active substances (already authorised in at least one member state), including **8** repeat use.

32 abridged applications including **6** multiple applications and **4** repeat use.

7 line extension applications, including **3** repeat use.

The new procedures started related to **9** full dossiers, **33** generics, **4** bibliographic applications, **2** fixed combinations and **4** for different use, route or dose.

The procedures consisted of **50** chemical substances, **1** herbal and **1** biological-other[1].

48 of these procedures were prescription-only medicinal products in the reference Member State and **4** 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 October 2004

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (3)	2
DE (3)	5
DE (1)	1
DE (1)	1
DE (2)	26
DK (4)	4
FI (1)	8
FI (1)	1
FI (4)	1
FI (3)	7
FI (1)	4
FI (1)	2
FI (1)	8
FI (1)	3
FI (1)	1
FI (1)	1
FI (1)	3
FI (1)	1

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
FI (5)	8
FI (5)	4
FI (5)	2
FI (5)	1
FI (5)	1
FI (5)	1
FI (1)	1
FI (4)	4
FR (1)	10
FR (1)	9
FR (1)	3
FR (1)	4
FR (1)	12
NL (2)	10
NL (3)	2
NL (4)	13
NL (1)	16
NL (3)	14
NL (4)	15
NL (4)	1
PT (1)	12
SE (1)	2
SE (1)	1
SE (1)	10
UK (1)	1
UK (2)	17
UK (4)	15
UK (1)	1
UK (1)	1
UK (1)	7
UK (1)	7
UK (2)	12
UK (2)	1
UK (1)	4

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