European Medicines Agency
Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
MAY 2007 PLENARY MEETING
MONTHLY REPORT

The European Medicines Agency's (EMEA) Committee for Medicinal Products for Human Use (CHMP) held its May plenary meeting from 21-24 May 2007.

This May plenary meeting was the last one chaired by Daniel Brasseur who is stepping down as chairman of the Committee after two terms of office. Dr. Brasseur has been a leading and emblematic figure for the Committee, and will be missed by both CHMP members and EMEA colleagues alike. The election of the next CHMP Chair and Vice Chair will take place at the June meeting.

Centralised procedure

Initial applications for marketing authorisation

The CHMP has adopted five positive opinions by consensus recommending the granting of a marketing authorisation for the following medicinal products:

- **Aerinaze** (desloratadine 2.5 mg/pseudoephedrine sulphate 120 mg), from Schering-Plough Europe, for the symptomatic treatment of seasonal allergic rhinitis, accompanied by nasal congestion. EMEA review began on 26 July 2006 with an active review time of 196 days.

- **Increlex** (mecasermin), from Tercica Europe Ltd, for the long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor-1 deficiency. Increlex is the **39th orphan medicinal product** to receive a positive opinion. The CHMP recommended the granting of a marketing authorisation under exceptional circumstances. Such authorisations are permissible for medicinal products for which the applicant can demonstrate that comprehensive data cannot be provided, for example because of the rarity of the condition, as long as it can be demonstrated on a regular basis that the benefits outweigh the risks. EMEA review began on 28 December 2005 with an active review time of 208 days.

- **Mircera** (methoxy polyethylene glycol-epoetin beta), from Roche Registration Ltd, for the treatment of anaemia associated with chronic kidney disease. EMEA review began on 24 May 2006 with an active review time of 176 days.

- **Optimark** (gadoversetamide), from Tyco Healthcare Deutschland GmbH, for use in magnetic resonance imaging. EMEA review began on 24 May 2006 with an active review time of 196 days.

- **Orlistat GSK** (orlistat), from Glaxo Group Ltd, for the treatment of obese patients and overweight patients with associated risk factors. The application for marketing authorisation for Orlistat GSK was made as an 'informed consent' application to Xenical, from Roche Registration Ltd. This type of application requires that reference be made to an authorised medicinal product and that the marketing authorisation holder of this reference product gives consent to the use of the dossier in the

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application procedure. EMEA review began on 25 March 2007 with an active review time of 60 days.

Summaries of opinion for these medicinal products are available on the EMEA website http://www.emea.europa.eu/htms/human/opinion/opinion.htm. Further information will be included in the European Public Assessment Report (EPAR) once the European Commission has granted final approval.

Negative opinions

The CHMP adopted a negative opinion by consensus recommending the refusal of a marketing authorisation for **Vectibix** (panitumumab), from Amgen Europe B.V., intended for the treatment of metastatic carcinoma of the colon or rectum after failure of oxaliplatin- and/or irinotecan- containing chemotherapy regimens.

A separate question-and-answer document explaining the grounds for the negative opinion for Vectibix is available on the EMEA website.

Extensions of indication and other recommendations

The CHMP gave three positive opinions by consensus for applications for extensions of indication, adding new treatment options for the following previously approved medicines:

- **Forsteo** (teriparatide), from Eli Lilly Nederland B.V., to extend the indication to include treatment of osteoporosis in men. Furthermore, the indication has been revised to osteoporosis in postmenopausal women "at increased risk of fracture" and to include a statement on reduction in non-vertebral fractures in women. Forsteo is currently authorised for the treatment of established osteoporosis in postmenopausal women.

- **Plavix** (clopidogrel), from Sanofi Pharma Bristol Myers Squibb SNC, and **Iscover** (clopidogrel), from Bristol-Myers Squibb Pharma EEIG, to clarify its indication (in combination with acetylsalicylic acid) in the prevention of atherothrombotic events in patients suffering from non-ST segment elevation acute coronary syndromes, to include patients to be managed with a stent following a percutaneous coronary intervention procedure. Plavix is currently authorised for prevention of atherothrombotic events in patients suffering from myocardial infarction, ischaemic stroke or established peripheral arterial disease and, in combination with acetylsalicylic acid, for the treatment of patients suffering from non-ST segment elevation acute coronary syndromes (unstable angina or non-Q-wave myocardial infarction) and of patients suffering from ST segment elevation acute myocardial infarction who are eligible for thrombolytic therapy.

Changes to contraindications

The CHMP recommended the removal of the contraindication regarding the concurrent administration of **Sustiva** (efavirenz), from Bristol Myers Squibb Pharma EEIG, and **Stocrin** (efavirenz), from Merck Sharp & Dohme, with voriconazole. The recommendation to remove the contraindication was made in the context of dose adjustments agreed by the CHMP. Sustiva and Stocrin are currently authorised for antiviral combination treatment of HIV-1 infected patients.

Summaries of opinion for all mentioned products, including their full indication, can be found here.

Withdrawals

The Committee was informed by ISTA Pharma Ltd of its decision to withdraw their application for a centralised marketing authorisation for the medicinal product **Vitragan** (hyaluronidase [ovine]), 1020 IU/ml, powder for solution for injection. More information is available in a separate press release and further details about Vitragan and its current state of scientific assessment at the time of withdrawal will be made available in a question and answer document. This document, together with the withdrawal

letter from the company, will be published on the EMEA website http://www.emea.europa.eu/humandocs/Humans/EPAR/vitragan/vitraganW.htm in the very near future.

The Committee was informed by Protherics PLC of its decision to withdraw their application for a centralised marketing authorisation for the medicinal product **Voraxaze** (glucarpidase) powder for solution for injection. More information will be available in a separate press release and further details about Voraxaze and its current state of scientific assessment at the time of withdrawal will be made available in a question and answer document. These documents, together with the withdrawal letter from the company, will be published on the EMEA website http://www.emea.europa.eu/humandocs/Humans/EPAR/voraxaze/voraxazeW.htm in due course.

Lists of Questions

The Committee adopted three Lists of Questions on initial applications (two under the mandatory scope, and one under the optional scope).

Detailed information on the centralised procedure

An overview of centralised procedures since 1995 is given in **Annex 1**. The post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 2**. The list of medicinal products for which marketing authorisations have been granted by the European Commission since the CHMP plenary meeting in April 2007 is provided 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 April 2007 CHMP plenary meeting are provided in **Annex 4**.

Referral procedures

Referral procedures concluded

Finalising a review of the safety and efficacy of **bicalutamide 150 mg**-containing medicinal products in the treatment of locally advanced prostate cancer, the CHMP concluded that the benefits of these products outweigh their risks, but only in those patients who are at high risk of their disease getting worse.
This referral procedure was initiated by Belgium because of efficacy and safety concerns, in particular concerns over heart problems, regarding the use of the medicinal product in the treatment of early prostate cancer.
The legal basis for this procedure was Article 31 of the Community code on human medicinal products (Directive 2001/83/EC as amended). A separate question and answer document with more detailed information on the referral is available here.

The CHMP finalised a referral procedure for **Vantas 50 mg implant** (histrelin acetate), from Valera Pharmaceuticals Ltd, Ireland, concluding that the benefits of Vantas outweigh its risks in the palliative treatment of advanced prostate cancer. The procedure was initiated under Article 29 of Directive 2001/83/EC as amended because of disagreement between the Member States in the context of the mutual recognition procedure regarding the safety and efficacy of the medicinal product.

Referral procedures started

The CHMP started a referral for **Belara** and **Balanca** (30 micrograms ethinyl estradiol + 2 mg chlormadinone acetate), from Grünenthal GmbH, because of differences among Member States on whether the indication of these two products should be extended to include the treatment of women suffering from moderate acne.

Belara and Balanca are currently authorised in a number of Member States as oral contraceptives.
The referral procedure was initiated under Article 6(12) of Commission Regulation (EC) No 1084/2003. This type of procedure is initiated in cases where Member States disagree on a variation to the marketing authorisation of a product under the mutual recognition procedure.

The CHMP started harmonisation referrals for **Efexor** and associated names (venlafaxine) and **Efexor Depot** and associated names (venlafaxine), both from Wyeth, on the request of the European Commission. The procedure was initiated under Article 30 of the Community code on human medicinal products (Directive 2001/83/EC as amended). This type of procedure is initiated with a view to harmonising product information for medicinal products authorised at Member State level.

Other procedures

The CHMP started a review of systemic formulation of **nimesulide**-containing medicinal products due to concerns over serious liver problems. This follows the suspension of the marketing authorisations in Ireland for all nimesulide-containing products by the Irish Medicines Board on 15 May 2007.
Products containing nimesulide are approved in a number of Member States for the treatment of acute (short-term) pain, symptomatic treatment of painful osteoarthritis and primary dysmenorrhoea (period pains).
The CHMP is now looking at the available scientific data on nimesulide to reach a scientific opinion in July 2007 on whether the marketing authorisations for nimesulide should be maintained, changed, suspended or revoked in the Member States where it is marketed. The review was initiated under Article 107 (2) of Directive 2001/83/EC as amended.

Re-examination procedure under Article 9(2) of Regulation (EC) No. 726/2004

- The European Medicines Agency has been formally requested by Ark Therapeutics Ltd to re-examine the negative opinion for **Cerepro** (adenovirus-mediated *Herpes simplex* virus-thymidine kinase gene) adopted during the CHMP meeting that took place on 23-26 April 2007.
- The European Medicines Agency has been formally requested by Genta Development Ltd to re-examine the negative opinion for **Genasense** (oblimersen) adopted during the CHMP meeting that took place on 23-26 April 2007.

Review of a Publication in the New England Journal of Medicine regarding rosiglitazone.

An article published in the New England Journal of Medicine (NEJM) has raised concern about a small increased risk of myocardial infarction and cardiovascular death in patients with type 2 diabetes treated with rosiglitazone (Avandia, Avandamet, Avaglim). More information is available in a separate press release.

Mutual Recognition procedure and Decentralised procedures-Human

The CHMP noted the report from the 18th CMD(h) (Co-ordination Group for Mutual Recognition and Decentralised procedures-Human) held on 21-23 May 2007. For further details, please see the relevant press release on the CMD(h) website under the heading Press Releases: http://www.hma.eu/

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 2-4 May 2007. For further details, please see **Annex 5**.

Documents prepared by the CHMP Working Parties adopted during the May 2007 CHMP meeting are listed in **Annex 6**.

Name Review Group (NRG)

Statistical information on the outcome of the checking of acceptability of proposed invented names for medicinal products processed through the centralised procedure is provided in **Annex 7**.

Upcoming meetings following the May 2007 CHMP plenary meeting:

- The 34th meeting of the CHMP will be held at the EMEA on 18-21 June 2007.
- The next Invented Name Review Group meeting will be held at the EMEA on 18th June 2007.
- The 19th CMD(h) (Co-ordination Group for Mutual Recognition and Decentralised Procedures) will be held at the EMEA on 18-19 June 2007.
- A SAG Oncology meeting will take place on the 2nd July 2007.

Organisational matters

The main topics addressed during the May 2007 CHMP meeting are summarised below:

- Preliminary discussion regarding the qualification of (pre-clinical) toxicity genomic biomarkers.
- The appointment of experts to attend the European Partnership for Alternative Approaches to Animal testing Workshop on Regulatory Acceptance of 3R methods scheduled in Brussels on 18 -19 June 2007.
- Follow-up discussion on the SCENIHR preliminary report on the appropriateness of the EU Technical Guidance Documents for chemicals as regards to nanomaterials.
- Discussion with regard to setting up a multi-disciplinary CHMP ad hoc group for HIV prophylactic vaccines. A draft mandate, objectives and composition for such group was adopted by the Committee.
- Discussion with regards to the support of the continued development of the EU Regulatory Framework and the support required for the CHMP.

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

PRE-AUTHORISATION: MARKETING AUTHORISATION APPLICATIONS

Activity	2007								1995 onwards
	Optional Scope				Mandatory scope			Total	Overall total
	NAS	Significant innovation	Interest of Patients	Generics	Biotech	Indications	Orphans		
Applications for MA submitted	14	3	0	1	12	4	2	36	611
Positive opinions	9	1	0	1	6	2	1	20	399
Negative opinions[1]	0	0	0	0	2	1	0	3	15
Withdrawals prior to opinion	3	1	0	0	2	0	1	7	110
Marketing authorisation granted by the Commission	9	1	0	0	3	4	2	19	384

PRE-AUTHORISATION: SCIENTIFIC SERVICES

Activity (submissions)	2007	1995 onwards
Compassionate use applications	0	0
Art. 58 applications	1	4
Consultation for medical devices[2]	1	3
PMF (Click here for a list of PMF certifications)	0	11
VAMF	0	0

[1] In case of Re-examination under Art. 9(2) of Regulation (EC) No. 726/2004, the opinion will not be counted twice.
[2] 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 derivates of human blood or plasma and Directive 2001/104/EC

OUTCOME OF THE MAY 2007 CHMP MEETING IN RELATION TO ACCELERATED ASSESMENT PROCEDURES

Substance	Intended indications(s)	Accelerated Assessment Requests	
		Accepted	Rejected
Biological	N/A	N/A	N/A
Chemical	Reversal of neuromuscular blockade induced by rocuronium or vecuronium.		X

POST-AUTHORISATION: TYPE I AND II VARIATIONS, ANNEX II, RENEWALS AND ANNUAL RE-ASSESSMENT APPLICATIONS

Activity	2007	Overall total 1995 onwards
Type I Variations (positive notifications)	343	4538
Type II Variations (positive opinions)	333	3195
Type II Variations (negative opinions)	0	8
Annex II Applications (positive opinions)	12	154
Annual Re-assessment (positive opinions)	16	-
Opinion for renewals of conditional MA's (positive opinions)	0	0
5 Year Renewals (positive opinions)	23	-

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
2 Extensions of indication	2 Positive opinions
32 SPC changes	32 Positive opinions
20 Quality changes	20 Positive opinions

Opinions for Annual Re-Assessment applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Prialt (ziconotide) Eisai Pharma International Ltd	Positive Opinion	The Marketing Authorisation will remain under exceptional circumstances.
Trisenox (arsenic trioxide) Cell Therapeutics (UK)	Positive Opinion	The Marketing Authorisation will remain under exceptional circumstances.
Reyataz (atazanavir sulphate) Bristol Myers Squibb Pharma EEIG	Positive Opinion	The Marketing Authorisation will remain under exceptional circumstances.
Onsenal (celecoxib) Pharmacia-Pfizer EEIG	Positive Opinion	The Marketing Authorisation will remain under exceptional circumstances.

Opinion for renewals of conditional MA's		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
N/A	N/A	N/A

Opinions for 5-Year Renewal applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Neulasta (pegfilgrastim) Amgen Europe	Positive Opinion adopted	Unlimited validity
Neupopeg (pegfilgrastim) Dompé Biotec S.p.A	Positive Opinion adopted	Unlimited validity
Xigris (drotrecogin alfa (activated)) Eli Lilly Nederland B.V	Positive Opinion adopted	The Committee agreed that a further 5-year renewal would be required
Benefix (nonacog alfa) Wyeth Europe Ltd	Positive Opinion adopted	The Committee agreed that a further 5-year renewal would be required

MEDICINAL PRODUCTS GRANTED A COMMUNITY MARKETING AUTHORISATION UNDER THE CENTRALISED PROCEDURE SINCE THE APRIL 2007 CHMP MONTHLY REPORT

Invented Name	Focetria
INN	A/Viet Nam/1194/2004 (H5N1) virus surface inactivated antigen
Marketing Authorisation Holder	Novartis Vaccines and Diagnostics S.r.l
Proposed ATC code	J07BB02
Indication	Prophylaxis of influenza in an officially declared pandemic situation. Pandemic influenza vaccine should be used in accordance with Official Guidance.
CHMP Opinion date	22.02.2007
Marketing Authorisation Date	02.05.2007

OVERVIEW OF DESIGNATED ORPHAN MEDICINAL PRODUCTS THAT HAVE BEEN THE SUBJECT OF A CENTRALISED APPLICATION FOR MARKETING AUTHORISATION: UPDATE SINCE THE APRIL 2007 CHMP MEETING

Active substance	**Sponsor/applicant**	**EU Designation Number & Date of Orphan Designation**	**Designated Orphan Indication**
N/A	N/A	N/A	N/A

PRE-AUTHORISATION: SCIENTIFIC ADVICE AND PROTOCOL ASSISTANCE EMEA CENTRALISED PROCEDURES

	1995 - 2006	2007	Overall Total
Scientific Advice	718	55	773
Follow-up to Scientific Advice	127	16	143
Protocol Assistance	157	20	177
Follow-up to Protocol Assistance	40	9	49
	1042	**100**	**1142**

OUTCOME OF THE MAY 2007 CHMP MEETING IN RELATION TO SCIENTIFIC ADVICE PROCEDURES

Final 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	Treatment of Nonalcoholic steatohepatitis (NASH)	X						X	
Innovative product	Prevention of oral mucositis		X				X	X	
Biological	Treatment of chronic plaque psoriasis	X				X		X	
Chemical	Treatment of soft tissue sarcoma and bone sarcoma				X			X	
Chemical	Treatment of advanced-stage soft tissue sarcoma	X						X	
Biological	Treatment of multiple sclerosis			X				X	
Chemical	Treatment of advanced hepatocellular carcinoma	X						X	

Substance	Intended indications(s)	Type of Request				Topic			
		New		Follow-up		Pharmaceutical	Pre-clinical	Clinical	Significant Benefit
		SA	PA	SA	PA				
Biological	Treatment of Systemic Juvenile Idiopathic Arthritis	X						X	
Biological	Treatment of thrombocytopenia	X						X	
Biological	Treatment of idiopathic thrombocytopenic purpura (ITP).	X				X			
Biological	Treatment of Critical Limb Ischemia			X		X	X		
Innovative product	Treatment of adult chronic diabetic leg and foot ulcers	X					X	X	
Biological	Treatment of pneumonia		X				X	X	X
Chemical	Treatment of Influenza	X						X	
Chemical	Treatment of vasomotor symptoms	X				X	X	X	
Chemical	Treatment of acute migraine			X				X	
Chemical	Treatment of acromegalic patients	X						X	

SA: Scientific Advice
PA: Protocol Assistance

The above-mentioned 9 Scientific Advice letters, 3 Protocol Assistance letters, 4 Follow-up Scientific Advice letters and 1 Follow-up Protocol Assistance letters were adopted at the 21-24 May CHMP meeting.

New requests for Scientific Advice Procedures

The Committee accepted 32 new Requests for which the procedure started at the SAWP meeting held on 2-4 May 2007. The new requests are divided as follows: 14 Initial Scientific Advice, 6 Follow-up Scientific Advice, 7 Protocol Assistance and 1 Follow-up Protocol Assistance.

DOCUMENTS PREPARED BY THE CHMP WORKING PARTIES ADOPTED DURING THE MAY 2007 CHMP MEETING

BIOLOGICS WORKING PARTY (BWP)

Reference number	Document	Status[3]
CHMP/BWP/157653/2007	Draft guideline on production and quality control of monoclonal antibodies and related substances	Adopted for 6-month public consultation
CHMP/166042/2007	Concept paper on the revision of the Guideline on dossier structure and content for pandemic influenza vaccine	Adopted for 3-month public consultation
CHMP/BWP/99698/2007	EMEA Procedural document on fast track procedure for community human influenza vaccines annual strain(s) update according to Art. 7 of Commission Regulation 1085/2003	Adopted for 4-month public consultation
CHMP/165085/2007	Concept paper on the revision of the points to consider on xenogeneic cell therapy medicinal products	Adopted for 3-month public consultation

GENE WORKING PARTY (GTWP)

Reference number	Document	Status[3]
CHMP/GTWP/405681/ 2006	Concept paper on the development of a guideline on the quality, preclinical and clinical aspects of medicinal products containing genetically modified cells	Adopted for 3-month public consultation

CHMP PHARMACOGENETICS WORKING PARTY (PgWP)

Reference number	Document	Status[3]
EMEA/128517/2006	Reflection paper on the use of phamacogenetics in the pharmacokinetic evaluation of medicinal products	Adopted
EMEA/19720/2007	Overview of comments received on draft reflection paper on the use of phamacogenetics in the pharmacokinetic evaluation of medicinal products	Adopted

[3] Adopted or release for consultation documents can be found at the EMEA website (under "What's new-recent publications" or under Human Medicines-Guidance documents").

EFFICACY WORKING PARTY (EWP)

Reference number	Document	Status[3]
CHMP/EWP/200943/2007	Recommendation for Revision of (CHMP) - NfG Guidance on the investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98	Adopted.
CHMP/EWP/213035/2007	Concept Paper on Biopharmaceutics Classification System-based Biowaiver	Adopted.
CHMP/EWP/213122/2007	Draft guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases	Adopted for 6-month public consultation

INVENTED NAME REVIEW GROUP (NRG)

	May 2007		2007	
	Accepted	Rejected	Accepted	Rejected
Proposed invented names [1]	10	15	55	61
Justification for retention of invented name *	1	2	8	11

*In case of objections to the proposed invented name(s), the applicant may justify the retention of the proposed invented name using the relevant justification form available on the EMEA website.
[1]Five proposed invented name requests have been postponed from the April NRG meeting