European Medicines Agency
Evaluation of Medicines for Human Use

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

The Committee for Medicinal Products for Human Use (CHMP) held its February plenary meeting from 19-22 February 2007.

Centralised procedure

Initial applications for marketing authorisation

The CHMP adopted four positive opinions by consensus on initial marketing authorisation applications at this meeting:

- **Second mock-up pandemic influenza vaccine receives positive opinion**

  The CHMP adopted a positive opinion under exceptional circumstances recommending the granting of a marketing authorisation for **Focetria,** from Novartis Vaccines and Diagnostics S.r.l. Focetria is a mock-up pandemic influenza vaccine, intended for the prevention of influenza during an officially declared pandemic situation, once the pandemic viral strain has been included. It is the second mock-up pandemic influenza vaccine to receive a positive opinion from the Committee. EMEA review began on 31 January 2006 with an active review time of 162 days.
  Mock-up pandemic influenza vaccines are approved only for use in a declared pandemic influenza situation. The objective is to have a marketing authorisation in place that can be changed quickly in the event of a pandemic to include the virus strain responsible, once it has been identified.
  A detailed question and answer document on mock-up pandemic influenza vaccines was published in December 2006 and is available here.

- **Advagraf** (tacrolimus), from Astellas Pharma GmbH, intended for prevention and treatment of transplant rejection. EMEA review began on 1 March 2006, with an active review time of 201 days.

- **Sebivo** (telbivudine), from Novartis Europharm Limited, intended for the treatment of chronic hepatitis B in adult patients with evidence of viral replication and active liver inflammation. EMEA review began on 1 March 2006, with an active review time of 210 days.

- **Toviaz** (fesoterodine), from Schwarz Pharma, intended for the symptomatic treatment of overactive bladder syndrome. EMEA review began on 29 March 2006, with an active review time of 210 days.

Informed consent's applications for marketing authorisation

The CHMP adopted a positive opinion by consensus for a medicinal product for which an "informed consent" application was submitted. This type of application requires that reference is made to an authorised medicinal product and that the marketing authorisation holder of this reference product has given consent to the use of the dossier in the application procedure.

- **Docetaxel Winthrop** (docetaxel), from Aventis Pharma S.A. is recommended for the treatment of breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma and head and neck

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cancer. The reference product for this application is Taxotere, also from Aventis Pharma S.A. EMEA review time was 50 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.

Extensions of indication and other recommendations

The Committee adopted three positive opinions by consensus on the extension of indication of medicinal products that are already authorised in the European Union:

- **Avastin** (bevacizumab), from Roche Registration Ltd, to extend the indication to include Avastin in combination with paclitaxel for the first-line treatment of patients with metastatic breast cancer. Avastin was first authorised in the European Union on 12 January 2005 and is currently authorised for the treatment of patients with metastatic carcinoma of the colon or rectum.

- **Xeloda** (capecitabine), from Roche Registration Ltd, to extend the indication to include first-line treatment of patients with advanced gastric cancer in combination with a platinum-based regimen. Xeloda was first authorised in the European Union on 19 October 2000 and is currently authorised for the treatment of patients with colon cancer, metastatic colorectal cancer and locally advanced or metastatic breast cancer.

- **Prevenar** (pneumococcal conjugate vaccine), from Wyeth-Lederle Vaccines S.A., to extend the indication from active immunisation against bacteraemic pneumonia to active immunisation against pneumonia caused by streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F and 23. Prevenar was first granted a marketing authorisation in the European Union on 2 February 2001 and is currently approved for active immunisation of children from 2 months to 5 years of age against sepsis, meningitis, bacteraemic pneumonia and bacteraemia caused by the same serotypes.

Summaries of opinions for these medicinal products are available and can be found here.

The Committee also adopted two positive opinions by consensus on a “line extension” application (under the optional scope) (in accordance with Annex II of Commission Regulation (EC) No. 1085/2003).

Lists of Questions

The Committee adopted 10 Lists of Questions on initial applications (five under the mandatory scope, and five under the optional scope including two generic applications).

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 January 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 January 2007 CHMP plenary meeting are provided in **Annex 4**.

Referral procedures

Referral procedure concluded

- The Committee concluded a harmonisation referral under Article 30 of the Community code on human medicinal products (Directive 83/2001/EC as amended) for **Xefo** (lornoxicam) and associated names, recommending harmonising the product information across the EU. Xefo is approved in a number of EU Member States for the relief of pain. The procedure was initiated at the request of the marketing authorisation holder, Nycomed Danmark ApS under Article 30 of Directive 2001/83/EC as amended in order to harmonise differences between product information for medicinal products authorised at Member State level.

Referral procedure started

- The Committee started a referral procedure for **Vantas 50 mg implant** (histrelin acetate), from Valera Pharmaceuticals Ltd, Ireland. 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. Vantas is intended for the treatment of advanced prostate cancer.

Referral procedure re-examined

- The Committee concluded the re-examination of its opinion on the referral procedure for **Alendros 70** (alendronate sodium trihydricum), from Zentiva a.s. (treatment of osteoporosis in postmenopausal women). The CHMP confirmed its previous position and recommended the refusal of a marketing authorisation in the concerned Member States and a suspension of the marketing authorisation for Alendros 70 mg tablets in the reference Member State because bioequivalence with the reference product (Fosamax 70 mg tablets) has not been demonstrated. The procedure was initiated under Article 29 of the Community code on human medicinal products (Directive 2001/83/EC as amended) by the Czech Republic because of disagreement among the Member States in the context of the mutual recognition procedure.

Other procedures

- Adequacy of guidance on use of medicinal products in the elderly

The European Commission had requested in September 2006 the CHMP to provide an opinion on the adequacy of guidance on the elderly regarding medicinal products for human use according to the provisions set out in the Regulation (EC) No 726/2004. This review procedure was initiated on the basis of Articles 5(3) and 57(p) of Regulation (EC) No 726/2004 and has now resulted in a CHMP scientific opinion, which will be made publicly accessible shortly.

Mutual Recognition procedure and Decentralised procedures-Human

The CHMP noted the report from the 15th CMD(h) (Co-ordination Group for Mutual Recognition and Decentralised procedures-Human) held on 19-21 February 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 31st January – 2nd February 2007. For further details, please see **Annex 5**.

Documents prepared by the CHMP Working Parties adopted during the February 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 February 2007 CHMP plenary meeting:

- The 31st meeting of the CHMP will be held at the EMEA on 19-22 March 2007.
- The next Invented Name Review Group meeting will be held at the EMEA on 19 March 2007.
- The 16th CMD(h) (Co-ordination Group for Mutual Recognition and Decentralised Procedures) will be held at the EMEA on 19-21 March 2007.
- A SAG Cardiovascular kick off meeting will take place on the 14th March 2007.

Organisational matters

The main topics addressed during the February 2007 CHMP meeting related to:

- Follow-up discussion on models and methods that could be used for assessing the benefit risk of a given medicinal product. The report is being released for 3 months public consultation.
- Discussion on the revised procedure for appointment and replacement of Co-opted members.
- The adoption of the Revised Rules of Procedure for CHMP. The Rules of Procedure will now be submitted to the Management Board and European Commission for agreement prior to publication on the EMEA webpage.
- Preliminary discussion regarding the therapeutic areas in the mandatory scope of the centralised procedure as of 20th May 2008.
- Final discussion regarding the principles to be applied for the deletion of commercially confidential information for the disclosure of EMEA documents.
- Follow-up discussion regarding the Commission Assessment of the Community System of Pharmacovigilance.
- The report on the Open Forum on key issues in Tuberculosis drug development held on 12-13 December 2006. A concept paper will be developed in the near future.
- Follow-up discussion with regards to research areas that could benefit from European Commission funding as part of the 2007 Work Programme for the Health Theme of the 7th Framework Programme.

PROCEDURAL ANNOUNCEMENT

- The EMEA has slightly changed the Paper Dossier requirements for Full and Annex II Applications. Applicants are now being asked to send:
  - For all Modules: One copy for the EMEA
  - Modules 1 + 2: One additional copy for the EMEA

  Further information regarding pre-authorisation and post-authorisation requirements can be found below:

  http://www.emea.europa.eu/htms/human/presub/q23-1.htm

  http://www.emea.europa.eu/htms/human/postguidance/q23.htm

- In line with measures to increase transparency of the EMEA processes, the overview of initial notices for parallel distribution issued by EMEA will now be made publicly available. Further information regarding the initial notices issued in January 2007 can be found here

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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

ANNEX 1 TO CHMP MONTHLY REPORT FEBRUARY 2007

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	2	1	0	0	7	1	1	12	587
Positive opinions	2	1	0	0	1	2	0	6	385
Negative opinions[1]	0	0	0	0	0	0	0	0	12
Withdrawals prior to opinion	0	0	0	0	0	0	0	0	103
Marketing authorisation granted by the Commission	8	0	0	0	1	1	2	12	363

PRE-AUTHORISATION: SCIENTIFIC SERVICES

Activity (submissions)	2007	1995 onwards
Compassionate use applications	0	0
Art. 58 applications	0	3
Consultation for medical devices[2]	0	3
PMF (Click here for a list of PMF certifications)	0	10
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 FEBRUARY 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	N/A	N/A	N/A

ANNEX 2 TO CHMP MONTHLY REPORT FEBRUARY 2007

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)	91	4286
Type II Variations (positive opinions)	160	3022
Type II Variations (negative opinions)	0	8
Annex II Applications (positive opinions)	8	150
Annual Re-assessment (positive opinions)	7	-
Opinion for renewals of conditional MA's (positive opinions)	0	0
5 Year Renewals (positive opinions)	9	-

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
3 Extensions of indication	3 Positive opinions
37 SPC changes	37 Positive opinions
48 Quality changes	48 Positive opinions

Opinions for Annual Re-Assessment applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Xigris (drotrecogin alfa (activated)) Eli Lilly Nederland B.V	Positive Opinion	The CHMP concluded that further to uncertain conclusions of the XPRESS study (investigating the possible interaction between Xigris and heparin) additional clarifications on the benefit/risk balance of Xigris are required. Therefore a placebo-controlled study in patients (who were either on heparin or did not receive any thrombosis prophylaxis) with severe sepsis and documented organ failure should be performed to further clarify the benefit/risk profile of Xigris. The Marketing Authorisation will remain under exceptional circumstances.
Glivec (imatinib mesilate) Novartis Europharm Ltd	Positive Opinion	All specific obligations have now been fulfilled, it was

		agreed that there were no remaining grounds to keep the Marketing Authorisation under exceptional circumstances
Cystagon (mercaptamine) Orphan Europe SARL	Positive Opinion	All specific obligations have now been fulfilled, it was agreed that there were no remaining grounds to keep the Marketing Authorisation under exceptional circumstances
Foscan (temoporfin) Biolitec Pharma Limited	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**
Arixtra (fondaparinux) Glaxo Group	Positive Opinion adopted	unlimited validity
Quixidar (fondaparinux) Glaxo Group	Positive Opinion adopted	unlimited validity
MicardisPlus (telmisartan - hydrochlorothiazide) Boehringer Ingelheim International GmbH	Positive Opinion adopted	unlimited validity
PritorPlus (telmisartan - hydrochlorothiazide) Glaxo Group	Positive Opinion adopted	unlimited validity
Kinzalkomb (telmisartan - hydrochlorothiazide) Bayer AG	Positive Opinion adopted	unlimited validity
Dynastat (parecoxib) Pfizer	Positive Opinion adopted	The Committee agreed that a further 5-year renewal would be required
Dynepo (epoetin delta) Shire Pharmaceutical Contracts Ltd	Positive Opinion adopted	The Committee agreed that a further 5-year renewal would be required

ANNEX 3 TO CHMP MONTHLY REPORT FEBRUARY 2007

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

Invented Name	Cystadane
INN	betaine anhydrous
Marketing Authorisation Holder	Orphan Europe S.A.R.L.
Proposed ATC code	A16A A06
Indication	Adjunctive treatment of homocystinuria, involving deficiencies or defects in: • cystathionine beta-synthase (CBS), • 5,10-methylene-tetrahydrofolate reductase (MTHFR), • cobalamin cofactor metabolism (cbl). Cystadane should be used as supplement to other therapies such as vitamin B6 (pyridoxine), vitamin B12 (cobalamin), folate and a specific diet.
CHMP Opinion date	14.12.2006
Marketing Authorisation Date	15.02.2007

Invented Name	Prezista
INN	darunavir
Marketing Authorisation Holder	Janssen-Cilag International NV
Proposed ATC code	J05AE10
Indication	PREZISTA, co-administered with 100 mg ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in highly pre-treated adult patients who failed more than one regimen containing a protease inhibitor (PI). This indication is based on week-24 analyses of virological and immunological response from 2 controlled dose range finding Phase II trials and additional data from uncontrolled studies (see section 5.1). In deciding to initiate treatment with PREZISTA co-administered with 100 mg ritonavir careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of PREZISTA.
CHMP Opinion date	14.12.2006
Marketing Authorisation Date	12.02.2007

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

Active substance	**Sponsor/applicant**	**EU Designation Number & Date of Orphan Designation**	**Designated Orphan Indication**
N/A[3]	N/A	N/A	N/A

[3] No orphan medicinal product was subject of a centralised application for a marketing authorisation since the January 2007 CHMP meeting.

ANNEX 5 TO CHMP MONTHLY REPORT FEBRUARY 2007

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

	1995 - 2006	2007	Overall Total
Scientific Advice	718	29	747
Follow-up to Scientific Advice	127	6	133
Protocol Assistance	157	6	163
Follow-up to Protocol Assistance	40	4	44
	1042	**45**	**1087**

OUTCOME OF THE FEBRUARY 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 Diabetic Peripheral Neuropathy	X						x	
Chemical	treatment of soft tissue sarcoma and bone sarcoma		x			x			
Biological	treatment of Li Farumeni Syndrome		x			X	X	X	X
Chemical	treatment of leukaemia	X					X	X	
Biological	treatment of non small cell lung cancer	X				X	X	X	
Chemical	treatment of small cell lung cancer	X					X	X	
Chemical	treatment of thrombocytopenia			X				X	
Chemical	treatment of congestive heart failure	X				X		x	
Chemical	treatment of hypertension / proteinuria in children	X						X	
Chemical	treatment of hypertension in children	X						X	

Substance	Intended indications(s)	Type of Request				Topic			
		New		Follow-up		Pharmaceutical	Pre-clinical	Clinical	Significant Benefit
		SA	PA	SA	PA				
Chemical	treatment of hypercholesterolaemia or mixed dyslipedaemia	X						X	
Chemical	treatment of adult attention deficit hyperactivity disorder			X				X	
Biological	Treatment of Alzheimer's disease			X				X	
Chemical	treatment of Parkinson's disease			X		X			
Chemical	treatment of Alzheimer's disease			X			X	X	
Chemical	treatment of cystic fibrosis				X		X	X	
Chemical	treatment of vernal keratoconjunctivitis		X			X	X	X	
Chemical	treatment of congenital adrenal hyperplasia	X					X	X	
Chemical	reduction of mortality in patients in chronic haemodialysis	X						X	
Biological	treatment of anal fistula				X		X		
Biological	treatment of grass pollen rhinitis	X					X	X	

SA: Scientific Advice
PA: Protocol Assistance

The above-mentioned 11 Scientific Advice letters, 3 Protocol Assistance letters, 5 Follow-up Scientific Advice letters and 2 Follow-up Protocol Assistance letters were adopted at the 19-22 February CHMP meeting.

New requests for Scientific Advice Procedures

The Committee accepted 14 new Requests for which the procedure started at the SAWP meeting held on 31 January – 2 February 2007. The new requests are divided as follows: 11 Initial Scientific Advice, 1 Follow-up Scientific Advice, 0 Initial Protocol Assistance and 2 Follow-up Protocol Assistance.

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

BLOOD PRODUCTS WORKING PARTY

Reference number	Document	Status[4]
CHMP/BPWP/123835/ 2006	Report of Expert Meeting on Factor VIII Products and Inhibitor Development	Adopted

GENE THERAPY WORKING PARTY

Reference number	Document	Status[5]
CHMP/GTWP/125491/ 2006	Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products	Adopted for 6 months public consultation.

EFFICACY WORKING PARTY

Reference number	Document	Status[4]
CHMP/EWP/13062/ 2007	Recommendation for Revision of the points to consider on the evaluation of diagnostic agents	Adopted for 3 months public consultation
CHMP/EWP/67522/ 2007	Guideline on the development of new medicinal products for the treatment of Crohn's disease	Adopted for 6 months public consultation
CHMP/EWP/42065/ 2007	Recommendation for revision of the guideline on the clinical development of medicinal products for the treatment of HIV infection (CPMP/EWP/633/02 REV.1)	Adopted for 3 months public consultation
CHMP/EWP/44238/ 2007	Recommendation for revision of the points to consider on orally inhaled products	Adopted for 3 months public consultation

[4] 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").
[5] 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").

ANNEX 7 TO CHMP MONTHLY REPORT FEBRUARY 2007

INVENTED NAME REVIEW GROUP (NRG)

	February 2007			2007	
	Accepted	Rejected	Pending	Accepted	Rejected
Proposed invented names	8	11	29	24	24
Justification for retention of invented name *	3	3	2	6	3

*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.

	February 2007		2007	
	Accepted	Rejected	Accepted	Rejected
Total number of objections raised	26	21	60	37
Criterion - Safety concerns				
Similarity with other Invented name	20	15	46	29
Conveys misleading therapeutic/pharmaceutical connotations	0	0	0	0
Misleading with respect to composition	0	0	0	0
Criterion - INN concerns				
Similarity with INN	1	1	1	1
Inclusion of INN stem	0	2	0	2
Criterion - Other public health concerns				
Unacceptable qualifiers	0	0	0	1
Conveys a promotional message	3	1	8	1
Appears offensive or has a bad connotation	0	2	0	2
Similarity between name of individual active substance and fixed combinations and/or between fixed combinations	2	0	3	0
Similarity between name of prodrug and related active substance	0	0	0	0

See *Guideline on the Acceptability of Invented names for human medicinal products processed through the Centralised procedure (CPMP/328/98)* for detailed explanations of criteria used.