European Medicines Agency
Evaluation of Medicines for Human Use

London, 29 November 2006
EMEA/484273/2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
NOVEMBER 2006 PLENARY MEETING
MONTHLY REPORT

The Committee for Medicinal Products for Human Use (CHMP) held its November plenary meeting from 13-16 November 2006.

Centralised procedure

Initial applications for marketing authorisation

The CHMP gave positive opinions by consensus on initial marketing authorisation applications, including one opinion for a medicinal product that is intended for the treatment of patients suffering from rare diseases:

- **Exforge**, **Dafiro**, **Copalia** and **Imprida** (amlodipin besylate/valsartan), from Novartis Europharm Ltd, are intended for the treatment of essential hypertension. EMEA review time for Exforge was 173 days and 80 days for Dafiro, Copalia and Imprida.

- **Inovelon** (rufinamide), from Eisai Ltd, is intended for the treatment of seizures associated with Lennox-Gastaut syndrome, one of the most severe forms of childhood epilepsy. EMEA review time was 208 days. Inovelon is the 34th orphan medicinal product to receive a positive CHMP opinion.

- **Lucentis** (ranibizumab), from Novartis Europharm Ltd, for the treatment of neovascular (wet) age-related macular degeneration (AMD), which causes damage to the retina by abnormal blood vessels growing and leaking into the eye. EMEA review time was 195 days.

The Committee adopted a negative opinion by consensus for **Mycograb** (efungumab), from NeuTec Pharma Plc. Mycograb, an orphan medicinal product, was intended to be used for the treatment of invasive candidiasis, in combination with amphotericin B (including lipid-associated formulations). EMEA review time was 207 days.

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

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'Informed consent' applications

The Agency adopted positive opinions by consensus for a number of medicinal products for which 'informed consent' applications were 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.

- **Insulin Human Winthrop** (insulin human), from Sanofi-Aventis Deutschland GmbH, is recommended for the treatment of diabetes mellitus where treatment with insulin is required. The reference product for this application is Insuman, also from Sanofi-Aventis Deutschland GmbH. EMEA review time was 110 days.

- **Irbesartan Hydrochlorothiazide BMS** (irbesartan/hydrochlorothiazide), from Bristol-Myers Squibb Pharma EEIG, is intended for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone. The reference product for this application is Karvezide, also from Bristol-Myers Squibb Pharma EEIG. EMEA review time was 50 days.

- **Irbesartan Hydrochlorothiazide Winthrop** (irbesartan/hydrochlorothiazide), from Sanofi Pharma Bristol-Myers Squibb SNC, is recommended for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone. The reference product for this application is CoAprovel, also from Sanofi Pharma Bristol-Myers Squibb SNC. EMEA review time was 50 days.

- **Irbesartan BMS** (irbesartan), from Bristol-Myers Squibb Pharma EEIG, is recommended for treatment of essential hypertension and treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an anti-hypertensive regimen. The reference product for this application is Karvea, also from Bristol-Myers Squibb Pharma EEIG. EMEA review time was 50 days.

- **Irbesartan Winthrop** (irbesartan), from Sanofi Pharma Bristol-Myers Squibb SNC, is recommended for the treatment of essential hypertension and treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an anti-hypertensive regimen. The reference product for this application is Aprovel, also from Sanofi Pharma Bristol-Myers Squibb SNC. EMEA review time was 50 days.

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

Extensions of indication

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

- **Keppra** (levetiracetam), from UCB S.A., to include the treatment of primary generalised tonic-clonic seizures as adjunctive therapy in adults and adolescents from 12 years of age with idiopathic generalised epilepsy. Keppra was first granted a marketing authorisation in the European Union on 29 September 2000 and is currently indicated to treat partial onset seizures and myoclonic seizures in patients with epilepsy.

- **Neupro** (rotigotine), from Schwarz Pharma Ltd, to include the treatment of the signs and symptoms of advanced-stage idiopathic Parkinson's disease in combination with levodopa. Neupro was first granted a marketing authorisation in the European Union on 15 February 2006 and is currently indicated to treat signs and symptoms of early stage idiopathic Parkinson's disease.

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

New contraindications

The Committee recommended adding a contraindication for **Ketek and Levviax** (telithromycin), from Aventis Pharma S.A., saying that Ketek or Levviax must not be used in patients with previous history of hepatitis and/or jaundice associated with the use of telithromycin. Ketek and Levviax were first granted marketing authorisation on 9 July 2001 and are currently authorised for a number of respiratory-tract infections.

Summaries of opinions, including more detailed information on the new indications or contraindications for all products mentioned above are available and can be found here.

Safety update

Update on Tamiflu

Following recent media interest, the CHMP reaffirmed its position of 15 December 2005 that there is no new safety signal relating to psychiatric disorders while taking Tamiflu and therefore no need to change the current prescribing advice to doctors in the EU.

The Agency has been aware of incidents of psychiatric disorders associated with the use of Tamiflu since its approval. No causal relationship has been identified between use of Tamiflu and these incidents. The Agency has required Roche to follow closely all reports of such behaviour since the launch of Tamiflu in Europe in February 2003.

Tamiflu, from Roche, was approved in the European Union in June 2002 and is currently indicated for prevention and treatment of influenza in adults and children aged one year or above.

Withdrawals

Re-examination application withdrawn

The Committee was informed by Les Laboratoires Servier of their decision to withdraw the application for re-examination of the negative opinion for **Valdoxan** and **Thymanax** (agomelatine), adopted by the Committee on 27 July 2006.

A question and answer document explaining the grounds for the negative opinion and the next steps in the procedure can be found here.

Lists of Questions

The Committee adopted three Lists of Questions on initial applications (two under the mandatory scope and one under the optional scope), and five Lists of Questions on "line extensions" applications (in accordance with Annex II of Commission Regulation (EC) No. 1085/2003.

Detailed information on the centralised procedure

An overview of centralised procedures since 1995 is given in **Annex 1**. No medicinal products have been granted marketing authorisations by the European Commission since the CHMP plenary meeting in October 2006. The post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 2**.

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 2006 CHMP plenary meeting are provided in **Annex 3**.

Referral procedures

The Committee concluded two referral procedures, one for **Ciprofloxacin Nycomed** 2mg/ml solution for infusion (ciprofloxacin), from Nycomed Denmark APS, and one for **Ciprofloxacine Kabi** (ciprofloxacin hydrogen sulphate), from Fresenius Kabi Nederland B.V. The Committee recommended the harmonisation of the dosing recommendation for the treatment of complicated urinary tract infections, and of the maximum daily dose for adults in approved indications, across the European Union. The procedures were initiated under Article 29 of Directive 2001/83/EC as amended because of disagreement in the context of the mutual recognition procedure.

Mutual Recognition procedure and Decentralised procedures-Human

The CHMP noted the report from the 12th CMD(h) (Co-ordination Group for Mutual Recognition and Decentralised procedures-Human) held on 13-14 November 2006. For further details, please see the relevant press release on the CMD(h) website under the heading Press Releases: http://heads.medagencies.org/

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 24-26 October 2006. For further details, please see **Annex 4**.

Documents prepared by the CHMP Working Parties adopted during the November 2006 CHMP meeting are listed in **Annex 5**.

Invented 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 6.**

Upcoming meetings following the November 2006 CHMP plenary meeting:

- The 28th meeting of the CHMP will be held at the EMEA on 12-15 December 2006.
- The next Invented Name Review Group meeting will be held at the EMEA on 12 December 2006.
- The 13th CMD(h) (Co-ordination Group for Mutual Recognition and Decentralised Procedures-Human) will be held at the EMEA on 12-15 December 2006.

Organisational matters

The main topics addressed during the November 2006 CHMP meeting related to:

- Assessment of the Community System of Pharmacovigilance and a discussion on the European Commission public consultation and the next steps.
- Draft Report on the quality and completeness of the EU Risk Management Plans submitted in support of centralised applications.
- Draft report on the CHMP strategy on preparation of guidance in respect of first-in-man Phase I clinical trials.

- Preparation of a proposal to the European Commission for the extension of the mandatory scope of the centralised procedure foreseen in 2008.

PROCEDURAL ANNOUNCEMENTS

Submission of Type IA and Type IB variations in December 2006

Please note that the EMEA will be closed between 25 December 2006 and 2 January 2007.

Marketing Authorisation Holders are therefore requested not to submit Type IA variations applications to the EMEA between 8-22 December 2006 (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 variations applications submitted not later than 7 December 2006 will be finalised before the EMEA Christmas break. Any type IA variation applications submitted to the EMEA between 8 December 2006 and 2 January 2007 will start on 3 January 2007.

Marketing Authorisation Holders intending to apply for Type IB variations in December 2006 are encouraged to liaise with the EMEA prior to their submission.

EMEA changes of the payment method

As you are aware the EMEA has changed the method for payment of fees for all dossiers submitted and validated on or after the 1st December 2005. An invoice will be sent to the billing address indicated by the applicant.

To facilitate this operation Applicants/Marketing authorisation Holders who are demanding a Purchase Order Number on the EMEA invoice are now requested to indicate this Number clearly on the cover letter of a given application. The EMEA will no longer accept separate notifications of Purchase Order numbers, not associated with the dossier. The Applicants/Marketing authorisation Holders must state the following sentence on the Cover letter of each application:

Please quote Purchase Order Number …….. on the invoice.

If the Applicants/Marketing authorisation Holders do not require a Purchase Order Number on the EMEA invoice, this should also be clearly stated in the cover letter.

Linguistic Review Process of Maltese Product Information in Preparation of the Expiry of Derogation Measures

On 1 May 2007 the temporary derogation measures relating to translations in Maltese, as laid down in Council Regulation (EC) No 930/2004, are expected to cease to apply.
Marketing Authorisation Holders (MAHs) will therefore be legally obliged to provide translations of product information in Maltese as of the expiry date of the derogation (01/05/07).

To this end the EMEA in cooperation with the Maltese National Authorities, will conduct a linguistic check in the period between December 2006 and September 2007 in order to facilitate the phasing in of Commission Decisions related to the EU centralised procedure in the Maltese language after the end of the derogation, and to prevent the provision of sub-standard quality translations.

MAHs are invited to submit translations of product information in Maltese for linguistic check as of 1 December 2006. For detailed guidance and timelines please refer to "Linguistic Review Process of Maltese Product Information in Preparation of the Expiry of Derogation Measures" published on the EMEA website. Additional guidance on the phasing-in of Commission Decision Annexes in Maltese will be published at the beginning of 2007.

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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 NOVEMBER 2006

PRE-AUTHORISATION: MARKETING AUTHORISATION APPLICATIONS

Activity	Dec 2005/2006[1]								1995 onwards
	Optional Scope				Mandatory scope			Total	Overall total
	NAS	Significant innovation	Interest of Patients	Generics	Biotech	Indications	Orphans		
Applications for MA submitted	26	7	0	2	15	8	16	74	564[5]
Positive opinions	23	2	0	0	8	0	9	42	370[6]
Negative opinions[2]	3	0	0		2	0	1	6	13
Withdrawals prior to opinion	2	1	0		1	0	4	8	103[7]
Marketing authorisation granted by the Commission	20	1	0		10	0	8	39	350

PRE-AUTHORISATION: SCIENTIFIC SERVICES

Activity (submissions)	Dec 2005/2006	1995 onwards
Compassionate use applications	0	0
Art. 58 applications	1	3
Consultation for medical devices[3]	1	5
PMF (click here for a list of PMF certifications)	2	11
VAMF	0	0

[1] Starting point for operation of the new eligibility criteria to the centralised procedure
[2] In case of Re-examination under Art. 9(2) of Regulation (EC) No. 726/2004, the opinion will not be counted twice.
[3] 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
[5]From the September 2006 CHMP Monthly Report there was a small numerical error in the number of overall total applications for MA submitted
(596 instead of the correct number 551), which was carried over in the Annex I of the October 2006 CHMP Monthly Report. This error is rectified in this Monthly Report.
[6] From the December 2005 CHMP Monthly Report there was a small numerical error in the number of overall total positive opinions (328 instead of the correct number 330) which was carried over in the Annex I of the subsequent CHMP Monthly Reports in 2006. This error is rectified in this Monthly Report.
[7] From the January 2006 CHMP Monthly Report there was a small numerical error in the number of overall total withdrawals prior to opinion (100 instead of the correct number 96), which was carried over in Annex I of the subsequent CHMP Monthly Reports in 2006. This error is rectified in this Monthly Report.

OUTCOME OF THE NOVEMBER 2006 CHMP MEETING IN RELATION TO ACCELERATED ASSESMENT PROCEDURES

Substance	Intended indications(s)	Accelerated Assessment Requests	
		Accepted	Rejected
Chemical	Treatment of gastrointestinal Graft-versus-Host disease (GvHD)	--	X

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ANNEX 2 TO CHMP MONTHLY REPORT NOVEMBER 2006

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

Activity	2006	Overall total 1995 onwards
Type I Variations (positive notifications)	623	4063
Type II Variations (positive opinions)	624	2806
Type II Variations (negative opinions)	1	8
Annex II Applications (positive opinions)	14	141
Annual Re-assessment (positive opinions)	19	-
Opinion for renewals of conditional MA's (positive opinions)	0	0
5 Year Renewals (positive opinions)	47	-

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
4 Extensions of indication	4 Positive opinions
31 SPC changes	31 Positive opinions
39 Quality changes	39 Positive opinions

Opinions for Annual Re-Assessment applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Aldurazyme (laronidase) Genzyme B.V.	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**
Insuman (human insulin) Sanofi-Aventis Deutschland GmbH	Positive Opinion adopted	Unlimited validity

OVERVIEW OF DESIGNATED ORPHAN MEDICINAL PRODUCTS THAT HAVE BEEN THE SUBJECT OF A CENTRALISED APPLICATION FOR MARKETING AUTHORISATION: UPDATE SINCE THE OCTOBER 2006 CHMP MEETING

Active substance	**Sponsor/applicant**	**EU Designation Number & Date of Orphan Designation**	**Designated Orphan Indication**
Eculizumab (Soliris)	Alexion Europe SAS	EU/3/03/166 17/10/2003	Treatment of paroxysmal nocturnal haemoglobinemia
Histamine dihydrochloride (Ceplene)	EpiCept GmbH	EU/3/05/272 11/04/2005	Treatment of acute myeloid leukaemia
Nilotinib (Tasigna)	Novartis Europharm Limited - UK	EU/3/06/375 22/05/2006	Treatment of chronic myeloid leukaemia
Temsirolimus (Torisel)	Wyeth Europa Limited - United Kingdom	EU/3/06/365 06/04/2006	Treatment of renal cell carcinoma

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

	1995 - 2005	2006	Overall Total
Scientific Advice	558	143	701
Follow-up to Scientific Advice	94	31	125
Protocol Assistance	107	48	155
Follow-up to Protocol Assistance	26	13	39
	785	**235**	**1020**

OUTCOME OF THE NOVEMBER 2006 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 opioid-induced constipation and post-operative ileus	X				X		X	
Biological	Treatment of neutropenias	X				X	X	X	
Chemical	Treatment and prevention of graft rejection after lung transplantation		X				X	X	X
Biological	Treatment of Neutropenias	X				X	X	X	
Biological	Treatment of Neutropenias	X					X	X	
Chemical	Treatment of endometrial cancer	X					X	X	
Chemical	Treatment of paediatric tumours	X						X	
Biological	Treatment of glioma		X					X	X

Substance	Intended indications(s)	Type of Request				Topic			
		New		Follow-up		Pharmaceutical	Pre-clinical	Clinical	Significant Benefit
		SA	PA	SA	PA				
Chemical	Prophylaxis of transplant rejection in paediatric solid organ transplant recipients	X						X	
Chemical	Treatment of Ovarian, breast and lung cancer, Kaposi's sarcoma	X				X	X	X	
Biological	Primary prevention of venous tromboembolic events	X					X		
Biological	Treatment of myocardial infarction	X						X	
Chemical	Treatment of visceral leishmaniasis	X					X	X	
Biological	Treatment of severe sepsis and septic shock	X				X	X	X	
Biological	Treatment of solitary bone cysts		X			X	X	X	
Chemical	Treatment of Multiple Sclerosis	X						X	
Chemical	Treatment of Parkinson's Disease	X					X	X	
Chemical	Treatment of keratoconjunctivitis secca	X					X	X	

SA: Scientific Advice
PA: Protocol Assistance

The above-mentioned 15 Scientific Advice letters, 3 Protocol Assistance letters were adopted at the 13-16 November CHMP meeting.

New requests for Scientific Advice Procedures

The Committee accepted 28 new Requests for which the procedure started at the SAWP meeting held on 24-26 October. The new requests are divided as follows: 19 Initial Scientific Advice, 3 Follow-up Scientific Advice, 4 Initial Protocol Assistance and 2 Follow-up Protocol Assistance.

DOCUMENTS PREPARED BY THE CHMP WORKING PARTIES ADOPTED DURING THE NOVEMBER 2006 CHMP MEETING

BIOLOGICS WORKING PARTY

Reference number	Document	Status[4]
CHMP/BWP/271475/2006	Draft Guideline on potency testing of cell based immunotherapy medicinal products for the treatment of cancer	Adopted for release for 6 months consultation

GENE THERAPY WORKING PARTY

Reference number	Document	Status
EMEA/273974/2005	Guideline on the quality, preclinical and clinical aspects of gene transfer medicinal products - Annex on non-clinical testing for inadvertent germline transmission of gene transfer vectors	Adopted
EMEA/484273/2006	Overview of comments received on the Guideline on the quality, preclinical and clinical aspects of gene transfer medicinal products - Annex on non-clinical testing for inadvertent germline transmission of gene transfer vectors	Adopted

PAEDIATRIC WORKING PARTY

Reference number	Document	Status
EMEA/405166/2006	List of paediatric needs Anaesthesiology	Adopted for release for 6 months consultation
EMEA/484273/2006	List of paediatric needs Obstructive Lung disease	Adopted for release for 6 months consultation
EMEA/439649/2006 EMEA/404310/2006	List of paediatric needs Cardiovascular: • List of Paediatric needs – Cardiovascular • Overview of comments received on list of paediatric needs Cardiovascular	Adopted for release for 6 months consultation
EMEA/435350/2006	List of paediatric needs Anti-infectious therapy	Adopted for release for 6 months 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").

PHARMACOGENETICS WORKING PARTY

Reference number	Document	Status
EMEA/201914/2006	Reflection paper on pharmacogenomic Samples, Testing and Data handling	Released for 3 months consultation

EFFICACY WORKING PARTY

Reference number	Document	Status
CPMP/EWP/561/98 Rev. 1	Guideline on the clinical investigation of medicinal products for the treatment of Multiple Sclerosis	Adopted
CHMP/EWP/18463/2006	Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis	Released for 6 months consultation
CHMP/EWP/21441/2006	Q&A on Guideline on Clinical investigation of Corticosteroids intended for use on the Skin	Adopted
CPMP/EWP/552/95 Rev. 2	Guideline on the evaluation of medicinal products in the treatment of Primary Osteoporosis	Adopted
CPMP/EWP/707/98 Rev. 1	Guideline on clinical investigation of medicinal products for Prophylaxis of high Intra- and Post-operative Venous Thromboembolic Risk	Released for 6 months consultation

ICH

Reference number	Document	Status
CHMP/ICH/437986/2006	ICH Topic E15 - Note for guidance on establishing definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories	Released for 3 months consultation

PHARMACOVIGILANCE RELATED ISSUES

Reference number	Document	Status
EMEA/CHMP/PhVWP/460186/2006	Recommendations for the core Pharmacovigilance Plan for Pandemic Influenza Vaccines	Adopted
EMEA/106464/2006	Draft Guideline on the use of statistical signal detection methods in the EV data analysis system	Released for 6 months consultation

ANNEX 6 TO CHMP MONTHLY REPORT NOVEMBER 2006

INVENTED NAME REVIEW GROUP (NRG)

	November 2006			2006	
	Accepted	Rejected	Pending	Accepted	Rejected
Proposed invented names	11	10	14	147	144
Justification for retention of invented name *	1	2	1	17	25

*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.