European Medicines Agency
Evaluation of Medicines for Human Use

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

The Committee for Medicinal Products for Human Use (CHMP) held its December plenary meeting from 11-14 December 2006.

Centralised procedure

Initial applications for marketing authorisation

The CHMP gave three 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:

- The CHMP recommended the granting of a marketing authorisation for **Cystadane** (betaine anhydrous), from Orphan Europe SARL, intended for the adjunctive treatment of homocystinuria, a rare metabolic disorder caused by an enzyme deficiency. EMEA review began on 17 August 2005 with an active review time of 194 days. Cystadane is the **35th orphan medicinal product** to receive a positive CHMP opinion.
- The CHMP recommended the granting of a conditional marketing authorisation for **Prezista** (Darunavir), from Jansen-Cilag International NV, intended for the treatment of Human Immunodeficiency Virus (HIV-1) infected adult patients with advanced disease and limited treatment options. Conditional marketing authorisations are granted for medicines that are likely to have a significant benefit for patients, before all of the formal studies into its efficacy and safety have been completed. EMEA review began on 1 February 2006 with an active review time of 204 days.
- The CHMP recommended the granting of a marketing authorisation under exceptional circumstances for **Daronrix** (whole virion adjuvanted influenza vaccine of A/Viet Nam/1194/2004 (H5N1)), from GlaxoSmithKline Biologicals s.a., intended for the prevention of influenza during an officially declared pandemic situation. Marketing authorisations under exceptional circumstances are granted subject to certain specific obligations to be reviewed annually. Daronrix is the first mock-up pandemic influenza vaccine to receive a positive opinion. A mock-up pandemic influenza vaccine is not intended for use or stockpiling. Based on the mock-up, a final vaccine can be prepared quickly in the event of a pandemic outbreak, once the responsible strain has been identified. EMEA review began on 1 February 2006 with an active review time of 142 days.

  More information is available in a press release and a question and answer document.

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.

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Extensions of indication and other recommendations

The Committee adopted one positive opinion by consensus on the extension of indication of a medicinal product that is already authorised in the European Union in the area of diabetes:

- The Committee gave a positive opinion to extend the marketing authorisation for **Actos** (pioglitazone), from Takeda Global R&D Centre (Europe) Ltd. The CHMP recommended including combination therapy with insulin in type-2 diabetes mellitus patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance. Actos was first granted a marketing authorisation in the European Union on 13 October 2000. It is currently authorised for the treatment of type-2 diabetes mellitus, either as mono, dual or triple oral therapy.

Change to contraindications

- The Committee recommended the addition of a contraindication for **Actos**, saying that Actos must not be used in patients with diabetic ketoacidosis, and recommended the removal of the contraindication for use in combination with insulin (see 'Extension of indication' above).

- The Committee recommended the removal of a contraindication for **Avandamet** (rosiglitazone/metformin) from SmithKline Beecham plc, for use in combination with insulin. Avandamet was first authorised in the European Union on 20 October 2003. It is currently authorised for the treatment of type-2 diabetes mellitus as dual combination therapy and as triple combination therapy with sulphonylurea.

Summaries of opinions for these products, including more detailed information on the new indication and the contraindications is available and can be found here.

The Committee also adopted a positive opinion by consensus on a "line extension" application (under the mandatory scope) (in accordance with Annex II of Commission Regulation (EC) No. 1085/2003).

Re-examination procedure concluded

- Following a re-examination procedure the Committee adopted a final positive opinion by majority for **Tarceva** (erlotinib), from Roche Registration Limited, recommending the extension of the marketing authorisation to add treatment of metastatic pancreatic cancer, in combination with gemcitabine.

A summary of opinion and question and answer document with more detailed information about the re-examination procedure are available.

Withdrawals

The Committee was informed by Fournier Laboratories Ireland Ltd of their decision to withdraw their application for a centralised marketing authorisation for the medicinal product **Synordia** (fenofibrate/metformin hydrochloride).

More information is available in a press release and further details about Synordia 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/synordia/synordiaW.htm in the very near future.

Lists of Questions

The Committee adopted five Lists of Questions on initial applications (three under the mandatory scope and two 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 November 2006 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 November 2006 CHMP plenary meeting are provided in **Annex 4**.

Referral procedures

Referral procedures concluded

- The Committee concluded a referral procedure for **Metoprolol/Felodipine** containing medicinal products (metoprolol tartrate and felodipine). The medicinal products concerned were **Metoprolol/felodipine YES** (and associated names) and **Mefelosan** (and associated names) from "YES" Pharmaceuticals Development Services GmbH, **Mefelor** (and associated names) and **Mefecomb** (and associated names) from Ratiopharm GmbH, **Mefecur** (and associated names) from Sandoz Pharmaceuticals GmbH, and **Mefesan** (and associated names) from CT Arzneimittel GmbH, intended for the treatment of arterial hypertension. The CHMP recommended by consensus the refusal of a marketing authorisation in the concerned Member States and a suspension of the marketing authorisation for Metoprolol/Felodipine containing medicinal products in the reference Member State because equivalence with the reference medicinal product (Mobloc/Logimax) 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) due to the lack of bioequivalence studies performed in accordance with the *NfG on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98).*

- The Committee finalised referral procedures for **Gadovist/Gadograf** (gadobutrol) from Schering AG, recommending by consensus to extend the marketing authorization to contrast enhanced magnetic resonance imaging (MRI) of liver or kidneys in patients over 18 years of age with high suspicion or evidence of having focal lesions to classify these lesions as benign or malignant. The referrals were triggered by Spain in accordance with Article 36(1) of the Community code on human medicinal products (Directive 83/2001/EC as amended), with a view to restrict the indication applied for by the marketing authorization holder in the context of the mutual recognition procedure. The scope of the application for extension of indication originally applied for was contrast-enhanced MRI of liver and kidneys.

Referral procedures started

- The CHMP started a referral procedure for **Lansoprazole** 15 & 30mg Gastro-resistant Capsules (lansoprazole), from Teva UK Ltd, indicated for the treatment of gastro oesophageal reflux disease, ulcers, acid-related dyspepsia and as an adjuvant in the eradication of Helicobacter pylori. The referral was initiated under Article 29 of the Community code on human medicinal products (Directive 2001/83/EC as amended) because of disagreement among the Member States in the context of the mutual recognition procedure regarding bioequivalence with the originator product.

Referral re-examination application withdrawn

The Committee was informed by BMM Pharma Ab of their decision to withdraw their application for re-examination of the negative opinion adopted on the 18 October 2006 in the context of a referral procedure under Article 36 of the Community code on human medicinal products (Directive 2001/83/EC as amended) for **Simvastatine** (simvastatine).

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

The European Medicines Agency has been formally requested by NeuTec Pharma Plc to re-examine the negative opinion for **Mycograb** (efungumab) adopted during the CHMP meeting that took place on 13-16 November 2006.

Other procedures

- **Review of the adequacy of guidance on the elderly regarding medicinal products for human use**

The European Medicines Agency has concluded that most of the current efficacy guidelines are in compliance with ICH E7. Those that are not are currently being reviewed or planned for review in 2007/2008. This review procedure has been initiated by the European Commission under Article 5(3) and 57(1)p of Regulation (EC) N° 726/2004 and has resulted in a CHMP scientific opinion, which will be available on the EMEA website http://www.emea.europa.eu in the very near future.

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 11-12 December 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 27-29 November 2006. For further details, please see **Annex 5**.

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

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 7.**

Upcoming meetings following the December 2006 CHMP plenary meeting:

- The 29th meeting of the CHMP will be held at the EMEA on 22-25 January 2007.
- The next Invented Name Review Group meeting will be held at the EMEA on 22 January 2007.
- The 14th CMD(h) (Co-ordination Group for Mutual Recognition and Decentralised Procedures) will be held at the EMEA on 22-23 January 2007.

Organisational matters

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

- The proposal for an expert meeting on CJD and VCJD risks and urine-derived medicinal products in the 1st sememster of 2007.
- The draft programme for an assessor training on EMEA Pandemic Influenza Plan to be held on the 29th-30th January 2007.
- Discussions on the revision of the Variations Regulations.
- Feedback on the outcome of the discussions on the first EMEA CHMP Health-Care Professionals Working Group (HCP WG) held on 17 November 2007. The HCP WG has been created to develop a

framework of interaction between EMEA, its Scientific Committees and HCPs and to make recommendations and proposals for actions.

- Feedback on the outcome of the discussions on the first EMEA Human Scientific Committees Working Party with Patients' and Consumers' Organisations (PCWP) held on 8 December 2007. The PCWP supersedes the former EMEA CHMP Working group with Patients' and Consumers' Organisations which participated in the preparation of the framework of interaction between EMEA and Patients and Consumers' organisations
- The appointment of Dr. Seitz and Dr. Ljunberg as Chair and Vice-Chair of the Blood Products Working Party.
- The nomination of Dr. Dahl as a new member of the Pharmacogenetics Working Party.
- The nomination of Dr. Sancho as a new member of the Cell-Based Products Working Party.
- The appointment of Dr. Bannister and Dr. Van Dissel as Chair and Vice-Chair of the SAG Anti-Infectives.
- The appointment of Dr. Gale and Dr. Kiess as Chair and Vice-Chair of the SAG Diabetes and Endocrinology.

EMEA Implementation of the New EU Pharmaceutical Legislation

The following Guideline was adopted by the CHMP and will be published on the EMEA website for 3 months external consultation:

- Guideline on the Scientific Application and the Practical Arrangements necessary to implement Commission Regulations EC N° 507/2006 on the Conditional Marketing Authorisation for Medicinal Products for Human Use falling within the Scope of Regulation (EC) N°726/2004.

PROCEDURAL ANNOUNCEMENT

We would like to inform MAHs that the Excel sheet table to provide the agency with the marketing status data of their product(s) has been updated with the two new EU Member States (Bulgaria and Romania). This updated sheet which will be available in the very near future, can be downloaded from the "*Questions and answers on notification to the EMEA of actual marketing and cessation of placing on the market for centrally authorised products*" sections 5.2.1 and 5.3 and also in the *Post-Authorisation Guidance, section "Marketing and cessation notification*", questions 4 and 6.

Please note that this Excel sheet table should be used to report Marketing status data to the Agency.

Furthermore, we would like to remind MAHs of the requirement to notify the Agency within 30 days of the initial placing on the market of the product within the Community. Thereafter, any subsequent placing on the market or change in the marketing status should be reported through updates provided following the PSUR-cycle timelines and after renewal, annually in accordance with anniversary of the Commission Decision date. The reporting table should be attached to the cover letter of the PSUR and the electronic version of the table should be sent to the PTL by e-mail.

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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 DECEMBER 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	27	8	0	4	15	10	17	81	571
Positive opinions	23	2	0	0	9	1	10	45	373
Negative opinions[2]	3	0	0	0	2	0	1	6	13
Withdrawals prior to opinion	2	1	0	0	1	1	4	9	104
Marketing authorisation granted by the Commission	20	1	0	0	10	1	8	40	351

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)	3	12
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

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

Substance	Intended indications(s)	Accelerated Assessment Requests	
		Accepted	Rejected
Biological	Prophylaxis of pandemic influenza caused by the H5N1 strain.	X	--
Chemical	Treatment of HIV-1 infections	X	--

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)	704	4189
Type II Variations (positive opinions)	680	2862
Type II Variations (negative opinions)	1	8
Annex II Applications (positive opinions)	15	142
Annual Re-assessment (positive opinions)	22	-
Opinion for renewals of conditional MA's (positive opinions)	0	0
5 Year Renewals (positive opinions)	52	-

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
3 Extensions of indication	3 Positive opinions
47 SPC changes	47 Positive opinions
6 Quality changes	6 Positive opinions

Opinions for Annual Re-Assessment applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Benefix (nonacog alfa) Wyeth Europe Ltd	Positive Opinion	The Marketing Authorisation will remain under exceptional circumstances.
Replagal (agalsidase alfa) TKT Europe-5S AB	Positive Opinion	The Marketing Authorisation will remain under exceptional circumstances.
Fabrazyme (agalsidase beta) 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**
Avonex (interferon beta-1a) Biogen France S.A	Positive Opinion adopted	Unlimited validity
Leukoscan (sulesomab) Immunomedics B.V	Positive Opinion adopted	Unlimited validity
Lumigan (bimatoprost) Allergan Pharmaceuticals (Ireland) Ltd.	Positive Opinion adopted	Unlimited validity
Refludan (lepirudin) Pharmion Ltd,	Positive Opinion adopted	Unlimited validity
Trisenox (arsenic trioxide) Cell Therapeutics (UK) Ltd	Positive Opinion adopted	Unlimited validity

ANNEX 3 TO CHMP MONTHLY REPORT DECEMBER 2006

MEDICINAL PRODUCTS GRANTED A COMMUNITY MARKETING AUTHORISATION UNDER THE CENTRALISED PROCEDURE SINCE THE NOVEMBER 2006 CHMP MONTHLY REPORT

Invented Name	Sprycel
INN	Dasatinib
Marketing Authorisation Holder	Bristol-Myers Squibb Pharma EEIG
Proposed ATC code	L01XE06
Indication	SPRYCEL is indicated for the treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate. SPRYCEL is also indicated for the treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy
CHMP Opinion date	21.09.2006
Marketing Authorisation Date	20.11.2006

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

Active substance	**Sponsor/applicant**	**EU Designation Number & Date of Orphan Designation**	**Designated Orphan Indication**
Beclomethasone 17, 21-dipropionate (Orbec)	Voisin Consulting S.A.R.L.	EU/3/02/093 13/03/2002	Treatment of intestinal graft-versus-host disease
Muramyl Tripeptide Phosphatidyl Ethanolamine (Mepact)	Immunodesigned Molecules SA	EU/3/04/206 21/06/2004	Treatment of osteosarcoma

ANNEX 5 TO CHMP MONTHLY REPORT DECEMBER 2006

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

	1995 - 2005	2006	Overall Total
Scientific Advice	558	160	718
Follow-up to Scientific Advice	94	33	127
Protocol Assistance	107	50	157
Follow-up to Protocol Assistance	26	14	40
	785	**257**	**1042**

OUTCOME OF THE DECEMBER 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				
Biological	Treatment of thrombocytopenia associated with immune (idiopathic) thrombocytopenic purpura (ITP)				X			X	
Biological	Treatment of irritable bowel syndrome	X				X	X	X	
Chemical	Treatment of type 2 diabetes mellitus	X				X			
Biological	Treatment of hepatitis C	X				X	X	X	
Biological	Treatment of melanoma	X				X			
Biological	Treatment of non-small cell lung cancer	X				X	X	X	
Chemical	Treatment of renal cell carcinoma		X					X	X
Chemical	Treatment of hypertension in children			X				X	
Biological	Treatment of psoriasis	X						X	
Chemical	Treatment of psoriasis	X					X		

Substance	Intended indications(s)	Type of Request				Topic			
		New		Follow-up		Pharmaceutical	Pre-clinical	Clinical	Significant Benefit
		SA	PA	SA	PA				
Biological	Neisseria meningitidis vaccine	X				X	X	X	
Biological	Cholera vaccine	X				X	X	X	
Biological	Pseudomonas aeruginosa vaccine	X				X	X	X	
Chemical	Treatment of bacterial infections in children	X						X	
Chemical	Treatment of osteoporosis			X				X	
Chemical	Treatment of osteoarthritis	X					X	X	
Chemical	Treatment of Duchenne muscular dystrophy		X				X	X	
Chemical	Treatment of epilepsy	X						X	
Chemical	Treatment of acute migraine	X					X	X	
Chemical	Treatment of primary insomnia	X					X	X	
Chemical	Treatment of allergic rhinitis	X				X	X	X	
Biological	Treatment of growth hormone deficiency	X				X	X	X	

SA: Scientific Advice
PA: Protocol Assistance

The above-mentioned 17 Scientific Advice letters, 2 Protocol Assistance letters, 2 Follow-up Scientific Advice letters and 1 Follow-up Protocol Assistance letter were adopted at the 11-14 December CHMP meeting.

New requests for Scientific Advice Procedures

The Committee accepted 25 new Requests for which the procedure started at the SAWP meeting held on 27-29 November 2006. The new requests are divided as follows: 20 Initial Scientific Advice, 2 Follow-up Scientific Advice and 3 Initial Protocol Assistance.

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

BIOLOGICS WORKING PARTY

Reference number	Document	Status[4]
EMEA/CHMP/427732/ 2006	Overview of comments on guideline on the Scientific Data Requirements for a Plasma Master File	Adopted
EMEA/CHMP/BWP/ 473191/2006	Draft Guideline on Environmental Risk Assessments for Medicinal Products Consisting of, or Containing, Genetically Modified Organisms (GMOs)	Adopted
EMEA/CHMP/BWP/ 480303/2006	Overview of comments received on Draft Guideline on Environmental Risk Assessments for Medicinal Products Consisting of, or Containing, Genetically Modified Organisms (GMOs)	Adopted
EMEA/CHMP/BWP/ 495530/2006	Concept paper on revision of the Guideline on plasma-derived medicinal products	Adopted

CHMP Pharmacogenetics Working Party

Reference number	Document	Status
EMEA/CHMP/PGxWP/27 8789/2006	Reflection paper on the use of genomics in cardiovascular clinical trials	Released for 3 months consultation

EFFICACY WORKING PARTY

Reference number	Document	Status
CPMP/EWP/4937/03	Guideline on Non-Clinical and Clinical development of Medicinal Products for the Prevention of Nausea and Vomiting Associated with Cancer Chemotherapy	Adopted
CHMP/EWP/438/04	Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis	Adopted
EMEA/CHMP/EWP/ 498145/2006	Reflection Paper on Gender Differences in Cardiovascular Diseases	Released for 3 months consultation

CHMP Working Group with Health Care Professionals

Reference number	Document	Status
EMEA/CHMP/421182/ 2006	Health Care Professionals Working Group Mandate and Rules of Procedure	Adopted

[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").

ANNEX 7 TO CHMP MONTHLY REPORT DECEMBER 2006

INVENTED NAME REVIEW GROUP (NRG)

	December 2006			2006	
	Accepted	Rejected	Pending	Accepted	Rejected
Proposed invented names	6	8	28	153	152
Justification for retention of invented name *	0	1	4	17	26

*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.