European Medicines Agency
Evaluation of Medicines for Human Use

London, 29th March 2007
EMEA/144134/2007

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

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

Centralised procedure

Initial applications for marketing authorisation

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

- **Revlimid** (lenalidomide), from Celgene Europe, intended for the treatment of multiple myeloma. EMEA review began on 29 March 2006, with an active review time of 199 days.
  The active substance of Revlimid, lenalidomide, has a chemical structure that resembles that of thalidomide. More information about Revlimid and the measures taken to minimise any risk of harmful effects to unborn children of patients taking the medicine is available in a separate question and answer document.

- **Altargo** (retapamulin), from Glaxo Group Ltd, intended for the short-term treatment of the following superficial skin infections: impetigo and infected small lacerations, abrasions or sutured wounds. EMEA review began on 19 July 2006, with an active review time of 191 days.

- **Orencia** (abatacept), from Bristol-Myers Squibb Pharma EEIG, intended for the treatment of moderately to severely active rheumatoid arthritis. EMEA review began on 28 December 2005, with an active review time of 204 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 CHMP gave three positive opinions by consensus for applications for extension of indication, adding new treatment options for the following previously approved medicines:

- **Herceptin** (trastuzumab), from Roche Registration Ltd, to extend the indication to include Herceptin in combination with an aromatase inhibitor in the treatment of HER2+ and ER and/or PgR positive metastatic breast cancer. Herceptin was first granted a marketing authorisation in the European Union on 28 August 2000 and is currently indicated, as monotherapy or in combination with paclitaxel or docetaxel, for the treatment of metastatic breast cancer and for the treatment of early breast cancer.

- **Remicade** (infliximab), from Centocor B.V., to extend the indication to include the treatment of paediatric Crohn's disease in children aged 6 to 17 years who have not responded to conventional

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therapy including a corticosteroid, an immunomodulator and primary nutrition therapy or who are intolerant to or have contraindications for such therapies. Remicade was first authorised in the European Union on 13 August 1999. It is currently indicated for the treatment of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, psoriasis and ulcerative colitis.

- **Tracleer** (bosentan), from Actelion Registration Ltd, to extend the indication to include reduction of the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease. Tracleer was first granted a marketing authorisation in the European Union on 15 May 2002. It is currently indicated for the treatment of pulmonary arterial hypertension (PAH) in selected patient populations with grade-III functional status.

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

Withdrawals

The Committee was informed by Eli Lilly Nederland BV of their decision to withdraw their application for a centralised marketing authorisation for the medicinal product **Arxxant** (ruboxistaurin). More information is available in the press release and further details about Arxxant 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/arxxant in the very near future.

Lists of Questions

The Committee adopted 4 Lists of Questions on initial applications (three 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 February 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 February 2007 CHMP plenary meeting are provided in **Annex 4**.

Re-examination procedure concluded

Following the re-examination of the negative opinion adopted on 16 November 2006, the CHMP confirmed its previous position and adopted a final negative opinion 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). A separate question and answer document with more information about the re-examination procedure is available here.

Referral procedures

Referral procedure concluded

The CHMP finalised a review procedure for mifepristone-containing medicines that started in December 2005. The review was triggered by France, following safety and efficacy concerns regarding the use of

the approved dose of 600 mg **mifepristone,** as compared to the use of a 200 mg dose, in the medical termination of developing intra-uterine pregnancy in sequential use with prostaglandin analogue.

The CHMP concluded that the available data support the effectiveness of a 600 mg dose of mifepristone, followed by the use of prostaglandin analogues, for the termination of pregnancy up to 63 days of amenorrhoea (absence of menstrual periods). In pregnancies up to 63 days, comparative studies between 200 mg and 600 mg mifepristone in combination with 1 mg gemeprost delivered vaginally suggest that 200 mg mifepristone may be as effective as 600 mg mifepristone. However, in pregnancies up to 49 days, comparative studies between 200 mg and 600 mg mifepristone in combination with 400 µg misoprostol delivered orally cannot exclude a slightly higher risk of continuing pregnancies with the 200 mg dose. Based on the available published data, the benefit/risk profile of mifepristone in combination with oral misoprostol for pregnancy from 50 to up to 63 days is unfavourable due to poor efficacy.

The CHMP also recommended the addition of new safety information regarding:

- The risk of fatal infections when 200 mg mifepristone is followed by non-authorised vaginal administration of misoprostol tablets for oral use,
- The interactions of mifepristone with other medicines,
- The use of mifepristone and prostaglandin analogues in patients with haemostatic disorders or severe anaemia.

The procedure was carried out in accordance with Article 31 of the Community Code on medicinal products for human use (Directive 2001/83/EC). These types of procedures are initiated to review medicinal products authorised at Member State level, because of public health concerns.

Referral procedures started

The CHMP started a large number of referral procedures under Article 29 of the Community Code on medicinal products for human use (Directive 2001/83/EC). These types of procedures are initiated because of disagreements between the EU Member States in the context of the mutual recognition procedure. The medicines concerned are:

- **Simvastatin Krka** (simvastatin), from Krka Sverige AB,
- **Eformax** (formoterol fumarate), inhalation powder from IVAX Pharmaceuticals UK,
- Fentanyl-containing transdermal patches from STADA Arzneimittel AG (**Fentastad, Fentador, Matripain, Matrigesic** and **Fentrans**).

The CHMP also started three harmonisation referrals under Article 30 of the Community Code on medicinal products for human use. These types of procedures are initiated in order to harmonise the product information of a medicinal product across the European Union. The medicines concerned are:

- **Cozaar** (losartan potassium), from Merck Sharp and Dohme BV,
- **Cozaar Comp** and **Cozaar Comp Forte** (losartan potassium/hydrochlorothiazide), from Merck Sharp and Dohme BV,
- **Lamictal** (lamotrigine), from GlaxoSmithKline.

Mutual Recognition procedure and Decentralised procedures-Human

The CHMP noted the report from the 16th CMD(h) (Co-ordination Group for Mutual Recognition and Decentralised procedures-Human) held on 19-21 March 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 26-28 February 2007. For further details, please see **Annex 5**.

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

- The 32nd meeting of the CHMP will be held at the EMEA on 23-26 April 2007.
- The next Invented Name Review Group meeting will be held at the EMEA on 23rd April 2007.
- The 17th CMD(h) (Co-ordination Group for Mutual Recognition and Decentralised Procedures) will be held at the EMEA on 23-25 April 2007.
- A SAG Cardiovascular meeting will take place on the 17th April 2007.

Organisational matters

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

- The appointment of Dr. Irs, Dr. Maciulaitis, Dr. Ancuceanu, and Dr. Hudson (and their alternates) as CHMP appointed members to the Paediatric Committee. The appointment of a fifth member is still pending.
- First discussion on the Draft "EMEA Fast track procedure for Commmunity Influenza Vaccines annual strain(s) update according to Art. 7 of Commission Regulation 1085/2003". A short external consultation on the proposed procedure is expected to take place in April/May 2007.
- Follow-up discussion regarding the therapeutic areas in the mandatory scope of the centralised procedure as of 20th May 2008.
- Discussion regarding CMD(h) requests to the CHMP.
- Preliminary discussion regarding the agenda for the informal CHMP meeting in Bonn on the 7-8th May 2007.

PROCEDURAL ANNOUNCEMENT

The EMEA has updated its Pre-Submission guidance document in relation to the topic "**Eligibility to the centralised procedure**". Clarifications on the appropriate legal basis for such requests (http://www.emea.europa.eu/htms/human/presub/q01.htm) and details of the procedure, timelines for submission dates of the requests (http://www.emea.europa.eu/htms/human/presub/q02c.htm) and application form for these requests (http://www.emea.europa.eu/htms/human/presub/eligibility_request.doc) are also now available.

Any requests or specific queries related to eligibility to the centralised procedure should be sent to the following mail box: **CPeligibility@emea.europa.eu**

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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 MARCH 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	7	2	0	1	10	1	2	23	598
Positive opinions	3	1	0	0	2	2	1	9	388
Negative opinions[1]	0	0	0	0	0	0	0	0	12
Withdrawals prior to opinion	1	0	0	0	0	0	1	2	105
Marketing authorisation granted by the Commission	8	0	0	0	1	3	2	14	365

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	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 MARCH 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 MARCH 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)	126	4321
Type II Variations (positive opinions)	222	3084
Type II Variations (negative opinions)	0	8
Annex II Applications (positive opinions)	8	150
Annual Re-assessment (positive opinions)	11	-
Opinion for renewals of conditional MA's (positive opinions)	0	0
5 Year Renewals (positive opinions)	14	-

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
3 Extensions of indication	3 Positive opinions
28 SPC changes	28 Positive opinions
31 Quality changes	31 Positive opinions

Opinions for Annual Re-Assessment applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
MabCampath (alemtuzumab) Genzyme B.V	Positive Opinion	The Marketing Authorisation will remain under exceptional circumstances.
Xagrid (anagrelide) Shire Pharmaceutical Contracts Ltd	Positive Opinion	The Marketing Authorisation will remain under exceptional circumstances.
Zavesca (miglustat) Actelion Ltd	Positive Opinion	The Marketing Authorisation will remain under exceptional circumstances.
Zevalin (ibritumomab tiuxetan) Schering AG	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**
Axura (memantine) Merz Pharmaceuticals	Positive Opinion adopted	Unlimited validity
Ebixa (memantine) Lundbeck A/S	Positive Opinion adopted	Unlimited validity
Opatanol (olopatadine) Alcon Laboratories (UK) Ltd	Positive Opinion adopted	Unlimited validity
Tracleer (bosentan) Actelion Registration Ltd	Positive Opinion adopted	The Committee agreed that a further 5-year renewal would be required
Teslascan (mangafodipir) Nycomed Imaging A/S	Positive Opinion adopted	Unlimited validity
Vistide (cidofovir) Pharmacia Enterprise S.A	Positive Opinion adopted	Unlimited validity

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

Invented Name	Januvia
INN	sitagliptin
Marketing Authorisation Holder	Merck Sharp & Dohme Ltd.
Proposed ATC code	A10BH01
Indication	Januvia is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin when diet and exercise, plus metformin do not provide adequate glycaemic control. For patients with type 2 diabetes mellitus in whom use of a PPARγ agonist (i.e. a thiazolidinedione) is appropriate, Januvia is indicated in combination with the PPARγ agonist when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control.
CHMP Opinion date	24.01.2007
Marketing Authorisation Date	21.03.2007

Invented Name	Xelevia
INN	sitagliptin
Marketing Authorisation Holder	Merck Sharp & Dohme Ltd.
Proposed ATC code	A10BH01
Indication	Xelevia is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin when diet and exercise, plus metformin do not provide adequate glycaemic control. For patients with type 2 diabetes mellitus in whom use of a PPARγ agonist (i.e. a thiazolidinedione) is appropriate, Xelevia is indicated in combination with the PPARγ agonist when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control.
CHMP Opinion date	24.01.2007
Marketing Authorisation Date	21.03.2007

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

Active substance	**Sponsor/applicant**	**EU Designation Number & Date of Orphan Designation**	**Designated Orphan Indication**
Thalidomide (Thalidomide Pharmion 50mg Hard Capsules)	Pharmion Ltd	EU/3/01/067 20/11/2001	Treatment of multiple myeloma
2-chloro-9-[2-deoxy-2-fluoro-ß-D-arabinofuranosyl]adenine (Evoltra)	Bioenvision limited	EU/3/03/141 08/05/2003	Treatment of acute myeloid leukaemia

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

	1995 - 2006	2007	Overall Total
Scientific Advice	718	41	759
Follow-up to Scientific Advice	127	8	135
Protocol Assistance	157	11	168
Follow-up to Protocol Assistance	40	6	46
	1042	**2073**	**3115**

OUTCOME OF THE MARCH 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				
Biological	Treatment of Inflammatory Bowel Disease	X					X	X	
Chemical	Treatment of Type 2 Diabete	X						X	
Chemical	Treatment of Wilson's Disease		X				X	X	X
Biological	Treatment of moderate to severe chronic Plaque Psoriasis	X						X	
Chemical	Treatment of Alopecia Universalis		X				X		
Biological	Treatment of Cervical Intra-epithelial Neoplasia	X				X	X	X	
Biological	Treatment of Advanced Non-Small-Cell Lung Cancer	X				X	X	X	
Chemical	Conditioning treatment prior to haematopoietic stem cell transplantation				X			X	
Chemical	Secondary prevention of Acute Coronary Syndrome	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 Febrile Neutropenia			X				X	
Biological	Immunisation for the prevention of invasive disease caused by Neisseria meningitides serogroup B.	X				X		X	
Chemical	Treatment of Overactive Bladder	X					X	X	
Chemical	Treatment of Prostate Cancer	X					X	X	
Biological	Slowing of Dementia of the Alzheimer type			X				X	
Chemical	Treatment of Schizophrenia	X						X	
Chemical	Treatment of Manic episodes	X						X	
Chemical	Treatment of (ischaemic) Perinatal Brain Injury		X				X	X	
Chemical	Prevention of bronchopulmonary dysplasia in premature neonates		X					X	
Chemical	Prevention of rejection for corneal implant		X				X	X	X
Chemical	Treatment of Keratoconjunctivits Sicca	X				X		X	
Chemical	Treatment of Adrenal Insufficiency				X			X	X

SA: Scientific Advice
PA: Protocol Assistance

The above-mentioned 12 Scientific Advice letters, 5 Protocol Assistance letters, 2 Follow-up Scientific Advice letters and 2 Follow-up Protocol Assistance letters were adopted at the 19-22 March CHMP meeting.

New requests for Scientific Advice Procedures

The Committee accepted 24 new Requests for which the procedure started at the SAWP meeting held on 26-28 February 2007. The new requests are divided as follows: 11 Initial Scientific Advice, 4 Follow-up Scientific Advice, 7 Initial Protocol Assistance and 2 Follow-up Protocol Assistance.

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

BIOLOGICS WORKING PARTY (BWP)

Reference number	Document	Status[3]
CHMP/BWP/108182/2007	EU recommendations for the seasonal Influenza Vaccine Composition for the Season 2007/2008	Adopted

SAFETY WORKING PARTY (SWP)

Reference number	Document	Status[3]
CHMP/SWP/28367/2007	Guideline on requirements for First-in-Man Clinical Trials for potential high-risk medicinal products	Adopted for 2 months public consultation

EFFICACY WORKING PARTY

Reference number	Document	Status[3]
CPMP/EWP/563/95 Rev. 1	Guideline on clinical investigation of medicinal products in the treatment of Parkinson's Disease	Adopted for 6 months public consultation
CHMP/EWP/110542/2007	Guideline on the development of medicinal substances contained in drug-eluting (medicinal substance-eluting) coronary stents	Adopted for 6 months public consultation
CHMP/EWP/81927/2007	Concept Paper on the need for a Guideline on the development of new medicinal products intended for the management and treatment of Cystic Fibrosis	Adopted for 3 months public consultation
CPMP/EWP/555/95 Rev. 1 CHMP/EWP/506296/2006	▪ Guideline on clinical trials with haemopoietic growth factors for the prophylaxis of infection following myelosuppressive or myeloablative therapy ▪ Overview of Comments received on Guideline on clinical trials with haemopoietic growth factors	Adopted. 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").

ANNEX 7 TO CHMP MONTHLY REPORT MARCH 2007

INVENTED NAME REVIEW GROUP (NRG)

	March 2007		2007	
	Accepted	Rejected	Accepted	Rejected
Proposed invented names	14	15	38	39
Justification for retention of invented name *	0	2	6	5

*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.

	March 2007		2007	
	Accepted	Rejected	Accepted	Rejected
Total number of objections raised	22	37	82	74
Criterion - Safety concerns				
Similarity with other Invented name	21	28	67	57
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	0	1	1
Inclusion of INN stem	0	0	0	2
Criterion - Other public health concerns				
Unacceptable qualifiers	0	0	0	1
Conveys a promotional message	0	8	8	9
Appears offensive or has a bad connotation	0	0	0	2
Similarity between name of individual active substance and fixed combinations and/or between fixed combinations	0	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.