European Medicines Agency
Evaluation of Medicines for Human Use

London, 27th March 2008
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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
MARCH 2008 PLENARY MEETING
MONTHLY REPORT

The Committee for Medicinal Products for Human Use (CHMP) held its March plenary meeting from 17-19 March 2008.

CENTRALISED PROCEDURE

Initial applications for marketing authorisation

The CHMP adopted one positive opinion by consensus for **Extavia** (interferon beta-1b), from Novartis Europharm Limited. Extavia is intended for the treatment of patients with multiple sclerosis.

Extavia was assessed as an informed consent application. 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. In the case of Extavia the reference product is Betaferon. EMEA review began on 14 October 2007 with an active review time of 77 days.

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

Negative opinion

The CHMP adopted a negative opinion by majority recommending the refusal of a marketing authorisation for **Ceplene** (histamine dihydrochloride), from EpiCept GmbH. Ceplene, a designated orphan medicine, was intended to be used in combination with interleukin-2 for the maintenance of remission in patients with acute myeloid leukaemia in first remission. EMEA review began on 25 October 2006 with an active review time of 202 days.

A separate question-and-answer document with more detailed information about the negative opinion is available here.

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

Following the re-examination of the negative opinion adopted on 13 December 2007, the CHMP confirmed its previous position and adopted a final negative opinion by majority for **Rhucin** (recombinant human C1 inhibitor), from Pharming Group N.V. Rhucin, a designated orphan medicine, was intended to treat sudden attacks of angioedema (swelling of the blood vessels).

A separate question and answer document with more information about the re-examination procedure is available here.

The CHMP concluded the re-examination of the negative opinion adopted on 16 November 2007 for **Cimzia** (certolizumab pegol), from UCB S.A. The CHMP confirmed its previous position and adopted a final negative opinion by consensus. Cimzia was intended to be used for reducing signs and symptoms and maintaining clinical response in patients with active Crohn's disease.

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A separate question and answer document with more information about the re-examination procedure is available here.

Withdrawal

The EMEA has been formally notified by Neurochem of its decision to withdraw its application for a marketing authorisation application for **Kiacta** (eprodisate disodium) capsules. Kiacta was expected to be used for the treatment of amyloid A amyloidosis, a rare, life threatening disease that occurs in patients with long lasting inflammation, most commonly due to rheumatoid arthritis. A separate press release with more information and a question-and-answer document are available.

The EMEA has been formally notified by Wyeth Europa Ltd of its decision to withdraw its application for a marketing authorisation application for **Pristiqs** (desvenlafaxine) 50mg and 100mg prolonged release tablets. Pristiqs was expected to be used for the treatment of vasomotor symptoms associated with menopause. A separate press release with more information and a question-and-answer document are available.

Post-authorisation procedures

Extensions of indication and other recommendations

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

- **Viread** (tenofovir disoproxil fumarate), from Gilead Science International Limited, to extend the indication to include the treatment of patients with chronic hepatitis B. Viread is currently authorised, in combination with other antiretroviral medicines, for the treatment of HIV-1 infected adults over 18 years of age.

- **Zevalin** (ibritumomab tiuxetan), from Schering AG, to extend the indication to the consolidation therapy after remission induction in previously untreated patients with follicular lymphoma. Zevalin is currently authorised for the treatment of adult patients with relapsed or refractory follicular B-cell non-Hodgkin's lymphoma, in combination with rituximab.

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

Withdrawal

The EMEA has been formally notified by Bioenvision Limited of its decision to withdraw the application for an extension of indication for the centrally authorised medicine **Evoltra** (clofarabine). Evoltra was expected to be used for the treatment of acute myeloid leukaemia (AML) in elderly patients. A separate press release with more information is available. The question-and-answer document will be available following the CHMP's April 2008 meeting.

New contraindications

The CHMP recommended the addition of a new contraindication for **Velcade** (bortezomib), from Janssen-Cilag International NV, stating that Velcade should not be used in multiple myeloma patients who are diagnosed with acute diffuse infiltrative pulmonary and pericardial disease.

A separate press release and a question-and-answer document with more detailed information are available.

Updated Safety information

The CHMP concluded that warnings about liver injury should be added to the product information for **Tysabri** (natalizumab). Tysabri is used to treat relapsing-remitting multiple sclerosis (MS) in patients

with high disease activity despite treatment with a beta-interferon or whose disease is severe and evolving rapidly.

A separate press release and a question-and-answer document with more detailed information are available.

OTHER INFORMATION ON THE CENTRALISED PROCEDURE

Lists of Questions

The Committee adopted six Lists of Questions on initial applications (including three under the mandatory scope, and three under the optional scope) and one List of Questions on a "line extension" application (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**. 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 2008 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 2008 CHMP plenary meeting are provided in **Annex 4**.

REFERRAL PROCEDURES

Referral procedure concluded

The CHMP finalised two referral procedures under article 29 of the Community code on human medicinal products (Directive 2001/83/EC, as amended) for:

- **Alvesco and associated names**, 40, 80, 160 micrograms, inhaler (ciclesonide), from Altana Pharma AG, for the treatment of obstructive airway disease. The CHMP concluded by consensus that the benefits of the medicine outweigh the risks and recommended the granting of a marketing authorisation for Alvesco, subject to certain conditions considered essential for the safe and the effective use of the medicine, including changes in the SPC. The procedure was initiated by the United Kingdom due to efficacy and safety concerns on the use of higher doses of the medicine in the treatment of severe asthmatics.

- **Pulairmax**, 100, 200, 400 micrograms/dose, inhalation powder (budesonide), from IVAX Pharmaceuticals UK, for the treatment of asthma. The CHMP concluded by consensus that the application did not satisfy the criteria for authorisation in respect of safety and therapeutic equivalence with the reference product, Pulmicort Turbuhaler, and recommended the suspension of the granted marketing authorisation and the refusal of the marketing authorisation, where appropriate. The procedure was initiated by Denmark due to bioequivalence and safety concerns and to the lack of pharmacodynamic and clinical data.

Arbitrations under article 29 of Directive 2001/83/EC are initiated by one or more Member States in cases where an agreement cannot be reached in the context of the mutual recognition procedure.

The CHMP finalised a referral procedure by consensus under article 6(12) of Regulation (EC) 1084/2003 for **Actira, Avalox, Octegra and associated invented names** (400 mg moxifloxacin as hydrochloride), from Bayer Healthcare AG and Bayer Vital GmbH, recommending the granting of an extension of indication to include treatment of mild to moderate pelvic inflammatory disease without an associated

tubo-ovarian or pelvic abscess. The data submitted were considered sufficient to demonstrate that the benefits of the medicines outweigh the risks in the indication applied for. Actira, Avalox, Octegra and associated invented names are not recommended for use in monotherapy of mild to moderate pelvic inflammatory disease, unless infection with moxifloxacin-resistant *Neisseria gonorrhoeae* can be excluded. Actira, Avalox, Octegra and associated invented names are currently authorised in a number of Member States as antibiotics.

Procedures under article 6(12) are initiated in cases of disagreement between Member States in the context of the mutual recognition procedure in relation to applications to change the marketing authorisation.

The CHMP noted that the referral procedure under article 36 of the Community code on human medicinal products (Directive 2001/83/EC, as amended) for **Menomune**, (Meningococcal Polysaccharide Vaccine**,** Groups A, C, Y and W-135 combined), from Sanofi Pasteur MSD, indicated for prophylaxis of meningitis caused by the meningococcal bacteria groups A, C, Y and W-135 was no longer required. The procedure was initiated by Italy under article 36 of Directive 2001/83/EC, as amended because of manufacturing concerns, however, the Marketing Authorisation Holder has since notified the EMEA of the withdrawal of the National Marketing Authorisations, therefore the referral has been stopped.

Arbitrations under article 36 of Directive 2001/83/EC are initiated by one or more Member States in cases where potential public health concerns have been identified.

Re-examination of opinion on referral

The CHMP concluded by majority a referral re-examination under Article 29 of the Community code on human medicinal products (Directive 2001/83/EC, as amended) for **Fentanyl-containing transdermal patches** (Fentastad, Fentador, Fentrans, Matrigesic, Matripain), from STADA Arzneimittel AG, for the treatment of patients with severe chronic pain. The procedure was initiated by a number of Member States in relation to efficacy, safety and bioequivalence concerns. The CHMP confirmed its previous negative opinion adopted on 16 November 2007 and concluded that the product failed to show adequate characteristics which are key requirements for a product of this type in order to guarantee its safety and efficacy. Therefore the CHMP recommended the refusal of the granting of the marketing authorisations and the suspension of the granted marketing authorisation where appropriate.

Referral procedures started

The CHMP started referral procedures under article 29 of Directive 2001/83/EC for:

- **Sabumalin & Sanohex**, 100µg/dose, pressurised inhalation suspension, (salbutamol), from Hexal AG, indicated for the symptomatic treatment of reversible bronchoconstriction due to bronchial asthma and chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema**.**
- **Activelle**, 0.5mg/0.1mg, film-coated tablets, (estradiol/norethisterone acetate), from Novo Nordisk A/S, indicated for Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in women more than one year after menopause and for the prevention of osteoporosis in postmenopausal women at high risk of future fractures.

MUTUAL RECOGNITION AND DECENTRALISED PROCEDURES - HUMAN

The CHMP noted the report from the 27th CMD(h) (Co-ordination Group for Mutual Recognition and Decentralised procedures-Human) held on 17-18 March 2008. 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 25 - 27 February 2008. For further details, please see **Annex 5**.

UPCOMING MEETINGS FOLLOWING THE MARCH 2008 CHMP PLENARY MEETING

- The 43rd meeting of the CHMP will be held at the EMEA on 21-24 April 2008.
- The next Name Review Group meeting will be held at the EMEA on 1st April 2008.
- The 28th CMD(h) (Co-ordination Group for Mutual Recognition and Decentralised Procedures) will be held at the EMEA on 21-22 April 2008.

ORGANISATIONAL MATTERS

Due to a 3-day plenary meeting because of the Easter 2008 EMEA holiday, only a limited number of organisational topics were addressed during the March 2008 CHMP meeting. These related to:

- The endorsement of the EU recommendations for the seasonal influenza vaccine composition for the season 2008/2009 (EMEA/CHMP/BWP/133836/2008).
- The adoption of ICH Topic S2 (R1) Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use (EMEA/CHMP/ICH/126642/2008).
- The adoption of Appendix 1 (Paediatrics) of the guideline on the requirements for clinical documentation for orally inhaled products (CPMP/EWP/4151/00 Rev. 1), which will now be released for a 2-month public consultation.
- Finalisation and adoption of the Reflection Paper on Benefit-Risk Assessment Methods in the Context of the Evaluation of Marketing Authorisation Applications of Medicinal Products for Human Use (EMEA/CHMP/15404/2007). The reflection paper will be published on the EMEA website in the very near future.
- Discussion regarding the European Commission's public consultation in preparation of a legal proposal to combat counterfeit medicines for human use. The CHMP agreed to provide comments by the required 9th May 2008 deadline.
- Preliminary discussion with regard to future interactions foreseen between the CHMP and the Committee for Advanced Therapies (CAT).
- Preliminary discussion on the Guideline on Safety and Efficacy Follow-up - Risk Management of Advanced Therapy Medicinal Products.
- Discussion regarding the EMEA's reply to the WHO regarding Biosimilars INN naming convention.

PROCEDURAL ANNOUNCEMENT

- Fee regulation update

The European Commission will adopt a new Regulation to reflect the increase of the inflation rates for 2006-2007. Applicants/MAHs are being made aware that a fee increase will be foreseen from the 1st April 2008. The EMEA fee webpage will be updated accordingly in the very near future.

- EMEA out of office hours cover

Applicants/MAHs are informed that the EMEA has revised its procedure on out of office hours cover including EMEA holidays.

The EMEA can be contacted on the following Product Emergency Hotline number: + 44 207 523 7600. This number is for use **only** to inform the EMEA about a potentially serious problem with a centrally authorised medicinal product, excluding product defects and recalls (see below).

The number is for use **only** outside of business hours including EMEA holidays. During business hours (Monday to Friday, 9:00-17:30h), please contact the main switchboard: +44 207 418 8400.

Please note there will no longer be permanence for any EMEA holiday and the above contact number is for emergencies only.

It should, however, be reminded that in case of product defects and recalls, dedicated procedures are in place. For further information, please consult the EMEA website (http://www.emea.europa.eu/Inspections/Defects.html). The following telephone number should be used for product defects and recalls outside business hours including EMEA holidays: +44 7880 550697.

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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 2008

PRE-AUTHORISATION: MARKETING AUTHORISATION APPLICATIONS

Activity	2008								1995 onwards
	Optional Scope				Mandatory scope			Total	Overall total
	NAS	Significant innovation	Interest of Patients	Generics	Biotech	Indications	Orphans		
Applications for MA submitted	10	1	0	0	4	3	3	21	689
Positive opinions	3	2	0	0	7	0	2	14	444
Negative opinions[1]	0	0	0	0	0	0	2	2	20
Withdrawals prior to opinion	1	0	0	0	3	0	1	5	121
Marketing authorisation granted by the Commission	3	1	0	2	0	0	0	6	423

PRE-AUTHORISATION: SCIENTIFIC SERVICES

Activity (submissions)	2008	1995 onwards
Compassionate use applications	0	0
Art. 58 applications	0	4
Consultation for medical devices[2]	1	5
PMF (Click here for a list of PMF certifications)	0	11
VAMF	0	0

[1] In case of Re-examination under Art. 9(2) of Regulation (EC) No. 726/2004, the opinion will not be counted twice.
[2] Consultation in accordance with Council Directive 93/42/EEC concerning medical devices as amended by Directive 2000/70/EC as regards medical devices incorporating stable derivates of human blood or plasma and Directive 2001/104/EC

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OUTCOME OF THE MARCH 2008 CHMP MEETING IN RELATION TO ACCELERATED ASSESMENT PROCEDURES

Substance	Intended indications(s)	Accelerated Assessment Requests	
		Accepted	Rejected
Chemical	Treatment of prostate cancer		X
Biological	N/A	N/A	N/A

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

Activity	2008	Overall total 1995 onwards
Type I Variations (positive notifications)	241	5443
Type II Variations (positive opinions)	55	3844
Type II Variations (negative opinions)	0	10
Annex II Applications (positive opinions)	15	184
Annual Re-assessment (positive opinions)	8	-
Opinion for renewals of conditional MA's (positive opinions)	0	2
5 Year Renewals (positive opinions)	10	-

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
2 Extensions of indication	2 Positive opinion
31 SPC changes	31 Positive opinions
22 Quality changes	22 Positive opinions

Opinions for Annual Re-Assessment applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Xagrid (anagrelide) Shire Pharmaceutical Contracts Ltd	Positive Opinion adopted	remaining under exceptional circumstances
Zavesca (miglustat) Actelion Ltd	Positive Opinion adopted	remaining under exceptional circumstances
Onsenal (celecoxib) Pfizer Limited	Positive Opinion adopted	remaining under exceptional circumstances
Foscan (temoporfin) Biolitec Pharma Limited	Positive Opinion adopted	recommending lifting exceptional circumstances
Zevalin (ibritumomab tiuxetan) Schering AG	Positive Opinion adopted	recommending lifting exceptional circumstances

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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**
Aldurazyme (laronidase) Genzyme B.V	Positive Opinion adopted	unlimited validity
Exelon (rivastigmine) Novartis Europharm Ltd	Positive Opinion adopted	unlimited validity
Prometax (rivastigmine) Novartis Europharm Ltd	Positive Opinion adopted	unlimited validity
Fuzeon (enfuvirtide) Roche Registration Ltd,	Positive Opinion adopted	unlimited validity
Rebif (interferon beta-1a) Serono Europe Ltd	Positive Opinion adopted	unlimited validity
Mabthera (rituximab) Roche Registration Ltd,	Positive Opinion adopted	unlimited validity
Forsteo (teriparatide) Eli Lilly and Company Ltd	Positive Opinion adopted	recommending additional renewal
Optison (perfultren) GE Healthcare	Positive Opinion adopted	recommending additional renewal

MEDICINAL PRODUCTS GRANTED A COMMUNITY MARKETING AUTHORISATION UNDER THE CENTRALISED PROCEDURE SINCE THE FEBRUARY 2008 CHMP MONTHLY REPORT

Invented Name	Mycophenolate mofetil Teva
INN	mycophenolate mofetil
Marketing Authorisation Holder	Teva Pharma B.V
Proposed ATC code	LO4A A06
Indication	Mycophenolate mofetil Teva is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.
CHMP Opinion date	13.12.2007
Marketing Authorisation Date	21.02.2008

Invented Name	Myfenax
INN	mycophenolate mofetil
Marketing Authorisation Holder	Teva Pharma B.V
Proposed ATC code	LO4A A06
Indication	Myfenax is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.
CHMP Opinion date	13.12.2007
Marketing Authorisation Date	21.02.2008

OVERVIEW OF DESIGNATED ORPHAN MEDICINAL PRODUCTS THAT HAVE BEEN THE SUBJECT OF A CENTRALISED APPLICATION FOR MARKETING AUTHORISATION: UPDATE SINCE THE FEBRUARY 2008 CHMP MEETING

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

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ANNEX 5 TO CHMP MONTHLY REPORT FEBRUARY 2008

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

	1995 - 2007	2008	Overall Total
Scientific Advice	887	48	935
Follow-up to Scientific Advice	171	8	179
Protocol Assistance	198	13	211
Follow-up to Protocol Assistance	90	5	95
	1346	**74**	**1420**

OUTCOME OF THE FEBRUARY 2008 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 Graft-versus-Host disease		X					X	
Chemical	Treatment for type 2 diabetes	X					X		
Chemical	Treatment of type 2 diabetes	X					X	X	
Chemical	Treatment of retinopathy	X						X	
Chemical	Treatment of sensorimotor neuropathy	X						X	
Biological	Prevention of necrotizing enterocolitis		X			X	X	X	
Chemical	Prevention of organ rejection in solid organ transplant	X						X	

Substance	Intended indications(s)	Type of Request				Topic			
		New		Follow-up		Pharmaceutical	Pre-clinical	Clinical	Significant Benefit
		SA	PA	SA	PA				
Biological	Treatment of hormone independent prostate cancer	X				X		X	
Chemical	Treatment of non-small cell lung cancer.			X				X	
Chemical	Treatment of cancer	X						X	
Biological	Treatment of renal cell carcinoma				X	X			
Chemical	Treatment of soft tissue sarcoma		X					X	
Chemical	Prevention of hepatic veno-occlusive disease		X					X	
Biological	Prevention of thromboembolic disorders	X				X		X	
Chemical	Treatment of ventricular arrhythmias	X				X	X	X	
Chemical	Treatment of hypercholesterola-mia or dyslipidaemia.	X					X	X	
Chemical	Treatment of congestive heart failure	X						X	
Biological	Prevention of influenza	X					X		
Chemical	Treatment of severe sepsis	X					X		
Biological	Prevention of hip fracture in high risk osteoporosis	X						X	
Chemical	Treatment of bronchiectasis	X						X	
Chemical	Prevention of corneal graft rejection		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 HIV-associated abdominal fat accumulation	X				X	X	X	
Chemical	Treatment of hyperphosphataemia	X				X	X		
Chemical and Biological	Broader advice	X				X			
Chemical	Diagnosis of Alzheimer's Disease	X					X	X	

SA: Scientific Advice
PA: Protocol Assistance

The above-mentioned 19 Scientific Advice letters, 5 Protocol Assistance letters, 1 Follow-up Scientific Advice and 1 Follow-up Protocol Assistance letters were adopted at the 17-19 March CHMP meeting.

New requests for Scientific Advice Procedures

The Committee accepted 27 new Requests for which the procedure started at the SAWP meeting held on 25-27 February. The new requests are divided as follows: 16 Initial Scientific Advice, 5 Follow-up Scientific Advice, 5 Initial Protocol Assistance and 1 Follow-up Protocol Assistance.