28 May 2010
EMA/CHMP/330906/2010

Monthly Report

Committee for Medicinal Products for Human Use (CHMP)

17-20 May 2010

The Committee noted the following changes in the membership of the CHMP:

Dr Ondřej Slanař, (previously alternate from Czech Republic) replaces Dr Martin Votava as CHMP member.

Dr Daniela Melchiorri (previously Italian alternate), replaces Prof Guiseppe Nisticó as CHMP member.

Dr Luca Pani replaces Dr Melchiorri as the new Italian alternate.

Mrs Emilia Mavrokordatou replaces Dr Panayiota Kokkinou as the new Cyprus alternate.

Dr Karsten Bruins Slot replaces Dr Liv Mathiesen as the new Norway alternate.

CENTRALISED PROCEDURE

Initial applications for marketing authorisation

New medicinal product

The Committee adopted a positive opinion by consensus recommending the granting of a marketing authorisation for **Ozurdex** (dexamethasone), from Allergan Pharmaceuticals Ireland, intended for the treatment of macular oedema. The review for Ozurdex began on 25 March 2009 with an active review time of 210 days.

The summary of opinion for this medicine, including the full indication, can be found here.

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Generic medicinal product

The Committee adopted a positive opinion by consensus recommending the granting of a marketing authorisation for the generic medicine **Leflunomide medac** (leflunomide), from medac GmbH, for the treatment of active rheumatoid arthritis. Leflunomide medac is a generic of Arava.

The summary of opinion for this medicine, including the full indication, can be found here.

Post-authorisation procedures

Extensions of indications and other recommendations

The Committee gave three positive opinions by consensus for applications for extensions of the therapeutic indications, adding new treatment options for medicines that are already authorised in the European Union, for:

- **Orencia** (abatacept), from Bristol-Myers Squibb Pharma EEIG, to include treatment of moderate to severe active rheumatoid arthritis in patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs including methotrexate or a TNF alfa inhibitor.
- **Taxotere** and **Docetaxel Winthrop** (docetaxel), from Aventis Pharma S.A., to include adjuvant treatment, in combination with doxorubicin and cyclophosphamide, of patients with operable node-negative breast cancer eligible to receive chemotherapy according to internationally established criteria for primary therapy of early breast cancer.

Summaries of opinion for all mentioned medicines, including their full indication, can be found here.

Restriction of indication for Zeffix adopted

The Committee recommended changes to the product information of **Zeffix** (lamivudine), from Glaxo Group Ltd, to restrict its therapeutic indication in chronic hepatitis B, due to the high risk of resistance to lamivudine, stating that treatment with lamivudine should only be initiated in patients with compensated liver disease when the use of an alternative antiviral agent with a higher genetic barrier to resistance is not available or appropriate. In addition, in patients with decompensated liver disease, lamivudine should always be used in combination with a second antiviral agent without cross-resistance to lamivudine.

The summary of opinion for this medicine, including the full indication, can be found here.

Update on Genzyme's manufacturing quality assurance system

The CHMP heard a presentation given by Genzyme on its manufacturing and quality assurance systems, following a series of manufacturing and quality problems with several of its medicines, including **Cerezyme**, **Fabrazyme** and **Myozyme**. Whilst the Committee acknowledged that these products remain safe for patients and that Genzyme has taken actions to rectify these problems, the CHMP remains concerned about this issue and has requested that Genzyme implement a robust programme of measures to prevent similar manufacturing and quality problems in the future.

In this regard, the CHMP has now requested that Genzyme carry out a risk assessment of its manufacturing processes and use this to prepare a detailed plan for improvement. The plan should aim at proactive identification of potential risks and continuous assurance of quality and supply of Genzyme's medicines. Genzyme has also been requested to provide regular progress reports on the implementation of this plan to the CHMP. The Committee will continue to monitor the situation closely.

Further inspections of the manufacturing sites in the USA have been scheduled and will start as of June 2010, as requested by the Committee earlier this year.

Over the past two years, Genzyme has reported several product quality defects, which have led to the ongoing supply shortages for Cerezyme and Fabrazyme, which are used by patients suffering from rare, inherited enzyme-deficiency disorders, and for which no or only limited alternative treatments exist. As a result, the CHMP issued temporary treatment recommendations to ensure that these medicines continue to be available to European patients at greatest need of treatment.

For more information on the temporary treatment recommendations for Cerezyme and Fabrazyme see the Agency's April press release.

No need to restrict use of rotavirus vaccines

The Committee confirmed that there is no evidence that the unexpected presence of porcine circovirus (PCV) in batches of the oral rotavirus live vaccines, **Rotarix** and **Rotateq**, presents a risk to public health. PCV is not known to cause disease in humans.

In the framework of an ongoing formal review of Rotarix, from GlaxoSmithKline Biologicals S.A., initiated in March 2010, the CHMP discussed available data, including new laboratory results, that further clarify and characterise the nature of the presence of PCV in this rotavirus vaccine. Investigations are still ongoing, but the CHMP confirmed its previous position that there is no need to restrict the use of Rotarix. For more information see also the Agency's March 2010 press release.

The Committee is now also reviewing Rotateq, based on information received from the manufacturer (Sanofi Pasteur MSD SNC) that batches of this centrally authorised rotavirus vaccine contained low amounts of PCV DNA fragments. As with Rotarix, there is no need to restrict the use of this vaccine.

The CHMP is awaiting further information from the manufacturers on the root cause of the findings and on measures to manufacture the vaccines free of porcine circoviruses. The CHMP will be reviewing all new data on an ongoing basis. The Committee will consider the need for further recommendations in its meeting in July 2010, as further data emerge. [1]

Additional safety information

The CHMP adopted amendments to section 4.8 of the Summary of Product Characteristics (SmPC) of **Viagra** (Sildenafil) from Pfizer Ltd. Section 4.8 of the SmPC was amended to include severe cutaneous adverse drug reactions (i.e. Stevens Johnson syndrome and Toxic epidermal necrolysis) as an undesirable effect of not known frequency. The package leaflet is updated accordingly. This variation application was submitted at the CHMP request further to the evaluation of an extensive cumulative review of serious cutaneous reactions in the post marketing experience data as a result of which the CHMP concluded that there were 6 cases for which a possible relation can be identified between the occurrence of SCAR and the use of sildenafil. Hence, considering the potentially serious nature of these events, the MAH was requested to update the section 4.8 of the SmPC. The Marketing Authorisation Holder submitted this extensive cumulative review as a follow up measure further to the evaluation of the renewal application during which cases of severe cutaneous reactions were reported in the post marketing experience data.

[1] The review of Rotateq and Rotarix are being conducted in the context of a formal review, initiated by the European Commission under Article 20 of Regulation (EC) No 726/2004/EC. The Committee will make recommendations on whether the marketing authorisation for Rotateq should be maintained, changed, suspended or revoked.

OTHER INFORMATION ON THE CENTRALISED PROCEDURE

Lists of Questions

The Committee adopted seven Lists of Questions on initial applications (including three under the mandatory scope, and four under the optional scope) as per Regulation (EC) No. 726/2004, together with three List of Questions on "line extension" applications (in accordance with Annex II of Commission Regulation (EC) No. 1085/2003).

Detailed information on the centralised procedure

Monthly figures related to the centralised procedure activities are published independently on the Agency's website within two weeks following the end of the CHMP meeting and can be found here. The overview of opinions for annual re-assessments and renewals is provided in **Annex 1**. The list of medicinal products for which marketing authorisations have been granted by the European Commission since the CHMP plenary meeting in April 2010 is provided in **Annex 2.**

REFERRAL PROCEDURES

Arbitration procedures started

The Committee started two arbitration procedures under Article 29(4) of Directive 2001/83/EC **for Fortipan Combi D** (Procter & Gamble Pharmaceuticals) and **Norsed Combi D** (sanofi-aventis AB). Both products contain **risedronate sodium**, **calcium carbonate** and **cholecalciferol** as active substance.

The CHMP was requested to assess whether the submitted clinical supporting evidence is sufficient and if the combination of the three active substances can be considered an exceptional case as defined by the CHMP Guideline for fixed combination medicinal products. Furthermore the Committee is asked to make a recommendation on whether the public health benefit as well as an improved patient compliance can be demonstrated for the combination products.

Re-examination procedure concluded

The CHMP concluded a re-examination procedure for **valproic acid/valproate containing medicinal products**, under Article 32(4) of Directive 2001/83/EC confirming its previous opinion of 17 December 2009 by consensus. The re-examination procedure started on 14 April 2010 on request by various Marketing Authorisation Holders to re-examine the opinion recommending a variation of the Marketing Authorisations to include the treatment of manic episodes in bipolar disorders when lithium is contraindicated or not tolerated.

Question-and-answer documents with more information about these referrals can be found here

MUTUAL-RECOGNITION AND DECENTRALISED PROCEDURES - HUMAN

The CHMP noted the report from the 51st CMDh (Co-ordination Group for Mutual Recognition and Decentralised procedures-Human) held on 17-18 May 2010. For further details, please see the relevant press release on the CMDh 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 April 2010. For further details, please see **Annex 3**.

Documents prepared by the CHMP Working Parties adopted during the May 2010 CHMP meeting are listed in **Annex 4**.

UPCOMING MEETINGS FOLLOWING THE MAY 2010 CHMP PLENARY MEETING

- The 67th meeting of the CHMP will be held at the Agency on 21-24 June 2010.
- The next Name Review Group meeting was held at the Agency on 25 May 2010.
- The 52nd CMDh (Co-ordination Group for Mutual Recognition and Decentralised Procedures) will be held at the Agency on 21-22 June 2010.

ORGANISATIONAL MATTERS

The main topics addressed during the May 2010 CHMP meeting related to:

- The adoption of a reflection paper regarding Working Parties (WPs) restructure. In the light of an increased workload and complexity of the system over the past years a review of the current WP system became necessary in order to facilitate the WPs' role in providing high quality scientific and regulatory input and to increase their efficiency. The main changes will affect the partition of the current groups into Standing and Temporary Working Parties. Whereas for the Standing WPs (BWP, SWP and QWP)[2] no major changes are foreseen, the other WPs will be restructured as Temporary WPs in order to strengthen their efficiency. This will affect the BPWP, BMWP, PgWP and VWP and those resulting from the current EWP which will be transformed in Pharmacokinetics WP, Biostatistics WP and a number of therapeutic WPs. Finally in light of the creation of the Committee for Advanced Therapies, it has been agreed that the Gene Therapy and the Cell-based WPs will be discontinued. The review has also proposed the creation of a Coordinator Group (incorporating the chairs of all WPs and relevant Committees, to meet once a month by TC) and the Consistency Group (composed by few senior CHMP and EMA members in order to provide scientific and regulatory consistency to guidelines). Furthermore, a new system to better plan production of guidelines has been set up. The implementation of this restructuring is intended towards September 2010.
- A discussion of a revision of the Key Principles on the handling of Conflicts of Interest which will be presented to the EMA Management Board in June 2010. The aim of the revision is to further increase the efficiency, robustness and transparency of the process for the handling of conflicts of interest of Scientific Committees' members and experts.
- The adoption of the revised policy on scientific publication and representation for European Medicines Agency's Scientific Committees and their members. The policy was revised in order to

[2] BWP: Biologics Working Party, SWP: Safety Working Party, QWP: Quality Working Party, BPWP: Blood Products Working Party, BMWP: Similar Biological (Biosimilar) Medicinal Products Working Party, PgWP: Pharmacogenomics Working Party, VWP: Vaccine Working Party, EWP: Efficacy Working Party.

harmonise the section on scientific publication with the internal EMA publication policy. It will be adopted by all EMA Scientific Committees and subsequently published on the EMA website.

- Follow-up discussion on a workshop held at EMA 4th – 5th February 2010 on radiopharmaceuticals – "Current Use and Future Needs of Radiopharmaceuticals labelled with Radionuclides produced in Reactors and Possible Alternatives". The conclusions of the workshop will be published on the EMA website in the near future.

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This CHMP Monthly Report and other documents are available on the Internet at the following address: http://www.ema.europa.eu

ANNEX 1 TO CHMP MONTHLY REPORT MAY 2010

Opinions for annual re-assessment applications		
Name of medicinal product (INN) MAH	**Outcome**	**Comments**
Naglazyme ***(galsulfase), BioMarin Pharmaceutical Inc***	Positive Opinion	Marketing Authorisation remains under exceptional circumstances
Trisenox ***(arsenic trioxide), Cephalon Europe***	Positive Opinion	no remaining grounds for the Marketing Authorisations to 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**
Fosavance ***(alendronate sodium / colecalciferol), Merck Sharp & Dohme Ltd.***	Positive Opinion	Recommending additional renewal
GONAL-f ***(follitropin alfa), Merck Serono Europe Ltd.***	Positive Opinion	Unlimited validity
Herceptin ***(trastuzumab), Roche Registration Ltd.***	Positive Opinion	Unlimited validity
DaTSCAN ***(ioflupane (123I)), GE Healthcare Limited***	Positive Opinion	Unlimited validity

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ANNEX 2 TO CHMP MONTHLY REPORT MAY 2010

Medicinal products granted a community marketing authorisation under the centralised procedure since the April 2010 CHMP monthly report

Invented name	Docefrez
INN	docetaxel
Marketing Authorisation Holder	Sun Pharmaceutical Industries Europe B.V.
Proposed ATC code	L01CD02
Indication	<u>Breast cancer</u> Docetaxel in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer. Docetaxel in combination with doxorubicin is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition. Docetaxel monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy. Previous chemotherapy should have included an anthracycline or an alkylating agent. Docetaxel in combination with trastuzumab is indicated for the treatment of patients with metastatic breast cancer whose tumours over express HER2 and who previously have not received chemotherapy for metastatic disease. Docetaxel in combination with capecitabine is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. <u>Non-small cell lung cancer</u> Docetaxel is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy. Docetaxel in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer, in patients who have not previously received chemotherapy for this condition. <u>Prostate cancer</u> Docetaxel in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer. <u>Gastric adenocarcinoma</u> Docetaxel in combination with cisplatin and 5-fluorouracil is indicated for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior

Invented name	Docefrez
	chemotherapy for metastatic disease. Head and neck cancer Docetaxel in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck.
CHMP Opinion date	18.02.2010
Marketing Authorisation Date	10.05.2010

Invented name	Raloxifene Teva
INN	raloxifene
Marketing Authorisation Holder	Teva Pharma B.V.
Proposed ATC code	G03XC01
Indication	Treatment and prevention of osteoporosis in postmenopausal women. A significant reduction in the incidence of vertebral, but not hip fractures has been demonstrated. When determining the choice of raloxifene or other therapies, including oestrogens, for an individual postmenopausal woman, consideration should be given to menopausal symptoms, effects on uterine and breast tissues, and cardiovascular risks and benefits
CHMP Opinion date	18.02.2010
Marketing Authorisation Date	29.04.2010

ANNEX 3 TO CHMP MONTHLY REPORT MAY 2010

Pre-authorisation: scientific advice and protocol assistance EMA centralised procedures

	1995 - 2009	2010	Overall total
Scientific Advice	1134	90	1224
Follow-up to Scientific Advice	232	40	272
Protocol Assistance	245	23	268
Follow-up to Protocol Assistance	109	12	121
	1720	**165**	**1885**

Outcome of the May 2010 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 Hunter syndrome.		*x*					*x*	
Chemical	Treatment of hepatocellular carcinoma.				*x*			*x*	
Biological	Prevention of urate lowering therapy induced flares in patients with gouty arthritis.			*x*		*x*		*x*	
Chemical	Treatment of non-small cell lung cancer.			*x*				*x*	
Biological	Treatment of systemic lupus erythematosus.			*x*			*x*	*x*	
Biological	Treatment of systemic lupus eryhtematosus.	*x*				*x*			
Chemical/ Biological	Treatment of breast cancer.	*x*					*x*	*x*	

Substance	Intended indications(s)	Type of request				Topic			
		New		Follow-up		Pharmaceutical	Pre-clinical	Clinical	Significant Benefit
		SA	PA	SA	PA				
Biological	Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy.			x				x	
Biological	Treatment of metastatic colorectal carcinoma.	x						x	
Biological	Treatment of metastatic gastric cancer.	x						x	
Biological	Treatment of gout.	x				x		x	
Chemical/ Biological	Treatment of Hodgkin's Lymphoma.				x	x			
Biological	Prophylaxis and treatment of bleeding episodes in patients with haemophilia A.			x		x		x	
Chemical	Treatment of acute myeloid leukemia.	x				x	x	x	
Chemical	Treatment of pulmonary arterial hypertension.				x			x	
Chemical	Treatment of primary hypercholesterolaemia or mixed dyslipidaemia.			x			x	x	
Chemical	Reduction of cardiovascular events in patients with permanent atrial fibrillation.	x						x	
Chemical	Treatment of dyslipidaemia.	x				x			
Chemical	Treatment of chronic plaque psoriasis.	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	Treatment of chronic hepatitis C.	x				x	x		
Biological	Prevention of various infectious diseases.	x				x			
Biological	Treatment of *P. aeruginosa* pulmonary infection in cystic fibrosis patients.				x			x	
Chemical	Treatment of HIV infection.			x				x	
Biological	Post-exposure prophylaxis of inhalation anthrax.		x			x	x	x	
Biological	Treatment of inhalation anthrax.		x			x	x	x	
Biological	Treatment of chronic inflammatory demyelinating polyneuropathy.	x						x	
Advanced Therapy	Treatment of Duchenne's muscular dystrophy.		x			x	x		
Chemical	Treatment of fragile X syndrome.	x					x	x	
Biological	Treatment of chronic inflammatory demyelinating polyneuropathy.	x						x	
Biological	Treatment of myasthenia gravis.	x						x	
Biological	Treatment of multifocal motor neuropathy.	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 chronic inflammatory demyelinating polyneuropathy.	x						x	
Chemical	Treatment of chronic obstructive pulmonary disease.	x				x	x	x	
Chemical	Treatment of cystic fibrosis.		x			x	x	x	
Chemical	Treatment of chronic obstructive pulmonarydisease.	x						x	
Biological	Treatment of *P. aeruginosa* infections in cystic fibrosis patients.		x				x	x	x
Biological	Prevention of the ischemia/reperfusion injury associated with solid organ transplantation.		x				x	x	
Chemical	Treatment of Friedreich's ataxia.	x				x	x	x	
Chemical	Detection of structural abnormalities in pancreatitis.			x				x	
Chemical	Treatment of Alzheimer's disease.			x		x	x	x	

SA: scientific advice
PA: protocol assistance

The above-mentioned 20 Scientific Advice letters, 7 Protocol Assistance letters, 9 Follow-up Scientific Advice and 4 Follow-up Protocol Assistance letters were adopted at the 17 - 20 May 2010 CHMP meeting.

New requests for scientific advice procedures

The Committee accepted 58 new requests for which the procedure started at the SAWP meeting held on 26 - 28 April 2010. The new requests are divided as follows: 36 Initial Scientific Advice, 14 Follow-up Scientific Advice, 6 Initial Protocol Assistance and 2 Follow-up Protocol Assistance.

ANNEX 4 TO CHMP MONTHLY REPORT MAY 2010

DOCUMENTS PREPARED BY THE CHMP WORKING PARTIES ADOPTED DURING THE MAY 2010 CHMP MEETING

BIOLOGICS WORKING PARTY

Reference number	Document	Status [3]
EMA/CHMP/BWP/68803/2010	Guidance document on Quality Aspects on the Isolation of Candidate Influenza Vaccine Viruses in Cell Culture	**Adopted for 3-month public consultation**
EMA/CHMP/BWP/99698/2007/ Rev 1	Revision of the procedural advice on the Submission of Variations for Annual Update of Human Influenza Inactivated Vaccines Applications in the Centralised Procedure	**Adopted for 3-month public consultation**

GENE THERAPY WORKING PARTY

Reference number	Document	Status [3]
EMA/CHMP/GTWP/671639/2008	Draft Guideline on Genetically-Modified Cells	**Adopted for 6-month public consultation**

QUALITY WORKING PARTY

Reference number	Document	Status [3]
	Question-and-Answer document on GMP compliance documentation that should be submitted in case of sterilisation of an active substance	**Adopted**

EFFICACY WORKING PARTY

Reference number	Document	Status [3]
EMA/CHMP/EWP/203111/2010	Concept Paper on the Need for a Guideline on Thrombocytopenia	**Adopted for 3-month public consultation**
EMA/CHMP/EWP/1303/2010	Concept Paper on the Need for Revision of the Note for Guidance on Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic and Clinical Evaluation)	**Adopted for 3-month public consultation**
EMA/CHMP/EWP/607022	Guideline on the treatment of Premenstrual Dysphoric	**Adopted for 6-**

[3] Adopted or release for consultation documents can be found at the European Medicines Agency website (under "What's new-recent publications" or under Human Medicines-Guidance documents").

Reference number	Document	Status [3]
/2009	Disorder (PMDD)	**month public consultation**
EMA/CHMP/EWP/213972 /2010	Paediatric Addendum for the Pulmonary Arterial Hypertension (PAH) Guideline	**Adopted for 6-month public consultation**
EMA/CHMP/EWP/215701 /2010	Concept paper on the Need for Revision of the Addendum on Acute Cardiac Failure of the Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Cardiac Failure CPMP/EWP/2986/03	**Adopted for 3-month public consultation**