29 July 2010
EMA/CHMP/476111/2010

Monthly Report

Committee for Medicinal Products for Human Use (CHMP)

19-22 July 2010

The Committee re-elected for a further 3 year term Dr Jean-Louis Robert as Co-opted member for the scientific area of Quality (non-biologicals) and Dr Sol Ruiz and Dr Christian Schneider as Co-opted members for the scientific area of Quality and Safety (biological), with expertise in advanced therapies (gene, cell and tissues therapies).

Centralised procedure

Update on the ongoing benefit-risk review of Avandia, Avandamet and Avaglim[1]

The CHMP is currently reviewing the rosiglitazone-containing antidiabetes medicines **Avandia** (rosiglitazone), **Avaglim** (rosiglitazone/glimepiride) and **Avandamet** (rosiglitazone/metformin hydrochloride), from Smithkline Beecham Ltd, to determine the impact of new data, from recent publications on the risk of cardiovascular problems, on the benefit-risk profile of these medicines. While the Committee is reviewing all available data, prescribers in Europe are reminded to strictly follow the recommendations in the product information with respect to patients indicated for treatment, defined contraindications and warnings.

More information about this review is available in a separate press release.

[1] The review of Avandia, Avandamet and Avaglim is being conducted under Article 20 of Regulation (EC) No 726/2004.

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Initial applications for marketing authorisation

New medicinal product

The Committee adopted a positive opinion by majority recommending the granting of a marketing authorisation for **Twynsta** (telmisartan/amlodipine), from Boehringer Ingelheim International GmbH, intended for the treatment of essential hypertension. The review for Twynsta began on 23 September 2009 with an active review time of 210 days.

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

Generic medicinal products

The Committee adopted four positive opinions by consensus recommending the granting of marketing authorisations for the following generic medicines:

- **Clopidogrel Teva Pharma B.V.** (clopidogrel, as hydrobromide), from Teva Pharma B.V., for the prevention of atherothrombotic events. Clopidogrel Teva Pharma B.V. is a generic of Plavix.
- **Clopidogrel HCS** and **Clopidogrel Teva Generics B.V.** (clopidogrel, as hydrochloride), from Teva Pharma B.V. and from HCS bvba, for the prevention of atherothrombotic events. Clopidogrel HCS and Clopidogrel Teva Generics B.V. are generics of Plavix.
- **Myclausen** (mycophenolate mofetil), from Herbert J. Passauer GmbH & Co. KG, for the prophylaxis of acute transplant rejection in combination with ciclosporin and corticosteroids. Myclausen is a generic of Cellcept.

The summary of opinion for all above mentioned medicines, including their 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 extension of the therapeutic indications, adding new treatment options for medicines that are already authorised in the European Union:

- **Arixtra** (fondaparinux sodium), from Glaxo Group Ltd, to include treatment of acute symptomatic spontaneous superficial vein thrombosis of the lower limbs without concomitant deep vein thrombosis.
- **M-M-RVAXPRO** (measles, mumps and rubella vaccine live), from Sanofi Pasteur MSD, SNC, to include vaccination of healthy children from 9 months of age under special circumstances, in accordance with official recommendations or when early protection is considered necessary.
- **Viread** (tenofovir disoproxil), from Gilead Sciences International Ltd, to include treatment of chronic hepatitis B in adults with decompensated liver disease.

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

New paediatric indication for Xalatan[2]

The CHMP recommended by consensus an extension of the therapeutic indications of **Xalatan eye drops** and associated names (latanoprost), from Pfizer group of companies, to include the reduction of elevated intraocular pressure in the treatment of paediatric patients with elevated intraocular pressure and paediatric glaucoma.

The Committee's recommendation was made on the basis of data generated in accordance with an agreed paediatric investigation plan (PIP).

Update on the review of rotavirus vaccines

The CHMP finalised a review of the oral vaccine **Rotarix[3]** (rotavirus vaccine, live) from GlaxoSmithKline Biologicals S.A., following the detection of porcine circovirus 1 (PCV1) DNA in the vaccine. The Committee concluded by consensus that the vaccine continues to have a positive benefit-risk balance and that the presence of a very small amount of viral particles does not present a risk to public health.

The review of the rotavirus vaccine, **Rotateq[4]**, from Sanofi Pasteur MSD, SNC, following the detection of porcine virus in this vaccine is still ongoing and will be considered in September. The CHMP is awaiting further information from the manufacturer on the root cause of the findings and on measures to manufacture the vaccine free of porcine virus. While this review is still ongoing, the Committee confirmed its previous position that there is no need to restrict the use of Rotateq.

More information about the review of Rotarix is available in a separate press release and a question-and-answer document.

Review of topical formulations of ketoprofen concluded[5]

Finalising a review of **topical formulations of ketoprofen**, a non-steroidal anti-inflammatory drug (NSAID), the Committee concluded by majority that the benefits of these medicines continue to outweigh their risks. However, the Committee recommended that doctors should inform patients on how to use these medicines appropriately to prevent the occurrence of serious skin photosensitivity reactions.

More information about this review is available in a separate press release and a question-and-answer document.

Review of modafinil-containing medicines concluded[6]

Finalising a review of **modafinil-containing medicines**, the Committee recommended by consensus restricting the use of these medicines to the treatment of sleepiness associated with narcolepsy. Doctors and patients should no longer use these medicines for the treatment of idiopathic hypersomnia, excessive sleepiness associated with obstructive sleep apnoea or chronic shift work sleep disorder.

[2] The changes to the marketing authorisation for Xalatan were recommended under Article 29 of Regulation (EC) No 1901/2006, the Paediatric Regulation.
[3] The review of Rotarix was conducted under Article 20 of Regulation (EC) No 726/2004.
[4] The review of Rotateq is being conducted under Article 20 of Regulation (EC) No 726/2004.
[5] The review of topical formulations of ketoprofen was conducted under Article 107 of Directive 2001/83/EC, as amended.
[6] The review of modafinil-containing medicines was conducted under Article 31 of Directive 2001/83/EC, as amended.

Modafinil is a wakefulness promoting agent. The review had been initiated because of a number of safety concerns relating to neuropsychiatric disorders, skin and subcutaneous tissue reactions as well as significant off-label use and potential for abuse.

More information about this review is available in a separate press release and a question-and-answer document.

Review of modified-release oral opioids concluded[7]

Finalising a review of **modified-release oral opioid products** in level III of the World Health Organization (WHO) scale for the management of pain, the Committee recommended by consensus the suspension of formulations using polymethacrylate-triethylcitrate controlled release systems because of their interaction with alcohol. The Committee concluded that other formulations had a positive benefit-risk balance, but recommended harmonising existing warnings regarding concomitant use of these medicines with alcohol.

Modified-release oral opioids of the WHO level III scale for the management of pain are strong painkillers used to treat pain that has not been controlled with other medicines.

More information about this review is available in a separate press release and a question-and-answer document.

Harmonisation referral on Daivobet concluded[8]

The Committee recommended by consensus the harmonisation of the prescribing information for **Daivobet** and associated names (calcipotriol/betamethasone), from Leo Pharma and associated companies. The review was initiated because of differences in the summaries of product characteristics, labelling and package leaflets in the countries where the products are marketed. These medicines are authorised to treat psoriasis.

A question-and-answer document with more information about this referral can be found here.

Additional safety information

The CHMP was informed by the MAH (UCB Pharma Ltd) for **Xyrem** (sodium oxybate) of their intention to circulate a Dear Healthcare Professional Communication Letter (DHPC) on potential medication errors with Xyrem. Until November 2008, Xyrem was dispensed with a measuring syringe that displayed a double graduation in grams and millilitres. In order to avoid confusion the syringe was changed to one with a single graduation in grams. Since then there have been cases of medication errors reported in which patients have erroneously dosed in millilitres instead of grams. These have resulted in an administration of double the intended dose. However, since the scale of the syringe is limited to 4.5 grams, and Xyrem is administered in two nightly doses, the maximum recommended daily dose of 9 grams will not be exceeded. The CHMP agreed on the DHPC.

The CHMP adopted amendments to sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) of **Relistor** (methylnaltrexone bromide) from Wyeth Europa Ltd regarding cases of gastrointestinal (GI) perforation that have been reported in the post-authorisation period in patients using Relistor. Although patients had medical conditions that may be associated with localised or diffuse reduction of structural integrity in the wall of the GI tract (e.g., cancer, peptic ulcer, pseudo-obstruction), the use of Relistor may have contributed to these events. Relistor should be used with

[7] The review of modified-release oral opioids was conducted under Article 31 of Directive 2001/83/EC, as amended.
[8] The harmonisation referral on Daivobet was conducted under Article 30 of Directive 2001/83/EC, as amended.

caution in patients with known or suspected lesions of the GI tract. Patients are advised to promptly report severe, persistent, and/or worsening symptoms.

A small number of cases of squamous cell carcinoma (SCC) have been identified during long-term treatment with **Vfend** (voricanazole) in patients with phototoxicity and additional risk factors including immunosuppression. Whereas the contribution of voriconazole to the development of SCC has not been established, the CHMP adopted the amendments to the SmPC (sections 4.2 and 4.4) and Package Leaflet proposed in a type II variation in order to minimise the potential risks for SCC development, with emphasis on the importance of sun-protection measures and recommending that the treatment duration should be as short as possible, taking into account the patient's clinical and mycological response. For long term treatment greater than 6 months, a careful assessment of the benefit-risk balance should be considered.

Other information on the centralised procedure

Lists of Questions

The Committee adopted five Lists of Questions on initial applications (including three under the mandatory scope, and two under the optional scope as per Regulation (EC) No. 726/2004), together with two Lists of Questions on “line extension” applications (in accordance with Annex I of Commission Regulation (EC) No. 1234/2008).

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 June 2010 is provided in **Annex 2**.

Applications for marketing authorisation for orphan medicinal products

Details of those orphan medicinal products that have been subject of a centralised application for marketing authorisation since the June 2010 CHMP plenary meeting are provided in **Annex 3**.

Referral procedures

Review of dexrazoxane-containing medicines started[9]

The Committee has begun looking at the possible risk of acute myelogenous leukaemia (AML), myelodyspastic syndrome (MDS) and solid tumours in paediatric patients taking **dexrazoxane-containing medicines** for the prevention of anthracycline-induced cardiotoxicity. This follows the review of published literature, together with the results of randomised clinical trials, which suggests that these medicines may be linked with a three-fold increased risk of secondary malignancies, especially AML and MDS. At the same time, the available clinical studies show only limited efficacy of these medicines in the prevention of cardiotoxicity, and the alternative treatment options of heart failure have been markedly improved.

[9] The review of dexrazoxane-containing medicines is being conducted in the context of a formal review, initiated by the United Kingdom under Article 31 of Directive 2001/83/EC, as amended.

The CHMP will review all available data thoroughly, including published data, non-clinical and clinical data (including data from clinical trials and epidemiological studies), to clarify the impact of the increased risk of secondary malignancies, coupled with limited data on efficacy, on the balance of risks and benefits of these medicines.

Mutual-recognition and decentralised procedures - Human

The CHMP noted the report from the 53rd CMDh (Co-ordination Group for Mutual Recognition and Decentralised procedures-Human) held on 19-20 July 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 28-30 June 2010. For further details, please see **Annex 4**.

Documents prepared by the CHMP Working Parties adopted during the July 2010 CHMP meeting are listed in **Annex 5**.

Upcoming meetings following the July 2010 CHMP plenary meeting

- The 69th meeting of the CHMP will be held at the Agency on 20-23 September 2010.
- The next Name Review Group meeting will be held at the Agency on 27 July 2010.
- The 54th CMDh (Co-ordination Group for Mutual Recognition and Decentralised Procedures) will be held at the Agency on 20-21 September 2010.

Organisational matters

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

- The adoption of a revised Mandate, Objectives and Rules of Procedure for the EMA Human Scientific Committees Working Party with Patients and Consumers Organisation (PCWP)
- The adoption of new Mandates, Objectives and Rules of Procedure for the Temporary Working Parties (WPs) and Drafting Groups (DGs) and for the Coordination Group. As announced in the May 2010 CHMP Monthly Report a concept was adopted for a restructuring of the Working Parties' system. This includes a partitioning of the Working Parties into Standing and Temporary Working Parties as well as the creation of a Coordination Group. The objective of the Coordination Group is to ensure an integrated management of Scientific Committees and WP/DG operations through the coordination of work programmes among the respective WPs/DGs, avoiding overlaps in their activities and ensuring the efficient integration of common horizontal activities. The new rules will limit the number of members per Temporary Working Party to 10, with possible exceptions. It is foreseen for the Temporary WPs and DGs to schedule face-to-face meetings for up to 3 times per year at the Agency with additional discussions per tele-/videoconference. Drafting Groups will be created on request by CHMP for giving guidance on specific tasks not covered by an existing WP.

- A presentation by EMA on its Research Agenda regarding Drug-Induced Progressive Multifocal Leukoencephalopathy (PML). The aim of this research agenda is to focus and stimulate JC Virus and PML research with the main objective of improving public health by accelerating the delivery of answers to JC Virus and PML knowledge gaps which could impact, on the prevention or treatment of drug induced PML. The project is being developed in collaboration with the U.S. FDA. A workshop will be set up at end of 2010 including representatives from academia, regulatory bodies and stakeholders.

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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 July 2010

Opinions for annual re-assessment applications		
Name of medicinal product (INN) MAH	**Outcome**	**Comments**
Prialt *(ziconotide), Eisai Ltd.*	Positive Opinion	Marketing Authorisation remains 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**
Aptivus *(tipranavir), Boehringer Ingelheim International GmbH*	Positive Opinion	Unlimited validity
DuoTrav *(travoprost / timolol), Alcon Laboratories (UK) Ltd.*	Positive Opinion	Unlimited validity
Kepivance *(palifermin), Biovitrum AB (publ)*	Positive Opinion	Unlimited validity
Panretin *(alitretinoin), Eisai Ltd.*	Positive Opinion	Unlimited validity
Noxafil *(posaconazole), Schering-Plough Europe*	Positive Opinion	Unlimited validity
Revatio *(sildenafil), Pfizer Limited*	Positive Opinion	Unlimited validity
Xyrem *(sodium oxybate), UCB Pharma Ltd.*	Positive Opinion	Recommending additional renewal

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Annex 2 to CHMP Monthly Report July 2010

Medicinal products granted a community marketing authorisation under the centralised procedure since the June 2010 CHMP Monthly Report

Invented name	
INN	roflumilast
Marketing Authorisation Holder	Nycomed GmbH
Proposed ATC code	R03DX07
Indication	Maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (FEV1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment
CHMP Opinion date	22.04.2010
Marketing Authorisation Date	05.07.2010

Annex 3 to CHMP Monthly Report July 2010

Overview of designated orphan medicinal products that have been the subject of a centralised application for marketing authorisation:

Update since the June 2010 CHMP meeting

Active substance	Sponsor/applicant	EU designation number & Date of orphan designation	Designated orphan indication
Recombinant inhibitor of human plasma kallikrein	Dyax s.a. - Belgium	EU/3/02/126	Treatment of angioedema
Mercaptopurine (oral suspension)	Nova Laboratories Limited - UK	EU/3/09/628	Treatment of acute lymphoblastic leukaemia

Annex 4 to CHMP Monthly Report July 2010

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

	1995 - 2009	2010	Overall total
Scientific Advice	1134	149	1283
Follow-up to Scientific Advice	232	60	292
Protocol Assistance	245	35	280
Follow-up to Protocol Assistance	109	16	125
	1720	**260**	**1980**

FDA Parallel Scientific Advice	2006 - 2009	2010	Overall total
Completed	7	2	9
Ongoing	0	1	1
Foreseen	0	1	1
	7	**4**	**11**

Outcome of the July 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				
Advanced therapy	Treatment of Crigler-Najjar syndrome.		*x*			*x*			
Biological	Treatment of exocrine pancreatic insufficiency.	*x*				*x*			
Biological	Treatment of ulcerative colitis.			*x*		*x*	*x*	*x*	
Biological	Treatment of Crohn's disease.	*x*				*x*	*x*	*x*	
Chemical	Treatment of non-invasive bladder cancer.			*x*		*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 Autosomal Dominant Polycystic Kidney Disease (ADPKD).	x						x	
Chemical	Prevention of bronchiolitis obliterans in lung transplant patients.				x		x	x	
Chemical	Treatment of chronic inflammatory demyelinating polyneuropathy (CIDP).		x					x	
Chemical	Treatment of Crohn's disease.	x						x	
Chemical	Treatment of actinic keratosis.	x				x	x	x	
Biological	Treatment of active systemic lupus erythematosus.	x						x	
Biological	Treatment of rheumatoid arthritis.	x					x	x	
Biological	Treatment of non-small cell lung cancer.			x				x	
Biological	Treatment of metastatic melanoma.			x				x	
Chemical	Treatment of neuroblastoma.		x				x		
Biological/ Advanced therapy	Treatment of non-small cell lung cancer.			x		x	x	x	
Chemical	Treatment of prostate carcinoma.	x						x	
Chemical	Treatment of idiopathic thrombocytopenic purpura.	x					x	x	
Biological	Treatment of haemophilia B.		x			x	x	x	
Biological	Treatment of haemophilia B.				x	x	x	x	x
Chemical	Treatment of hypercholesterolaemia	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 palmar-plantar erythrodysesthesia syndrome induced by chemotherapeutic agents.	*x*					*x*	*x*	
Chemical	Treatment of *S. aureus* nasal colonization.	*x*				*x*	*x*	*x*	
Biological	Prophylaxis of influenza.	*x*				*x*	*x*	*x*	
Chemical	Treatment of HIV infection.	*x*					*x*	*x*	
Chemical	Treatment of fungal infections.			*x*			*x*	*x*	
Biological	Active immunisation against *Streptococcus pneumoniae*.	*x*				*x*			
Chemical	Treatment of benign prostatic hyperplasia.	*x*						*x*	
Chemical	Treatment of erectile dysfunction.	*x*						*x*	
Chemical	Treatment of Parkinson's disease.	*x*						*x*	
Chemical	Treatment of painful diabetic neuropathy.	*x*				*x*	*x*	*x*	
Chemical	Treatment of vasomotor symptoms due to menopause.	*x*				*x*	*x*	*x*	
Chemical	Treatment of excessive daytime sleepiness.				*x*			*x*	*x*
Chemical	Treatment of multiple sclerosis.			*x*			*x*	*x*	
Other innovative	Prophylaxis of allergic rhinoconjunctivitis.	*x*				*x*	*x*	*x*	
Chemical	Treatment of sinusitis.			*x*				*x*	
Chemical	Treatment of asthma and COPD.	*x*				*x*			
Chemical	Treatment of open-angle glaucoma and ocular hypertension.	*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 open-angle glaucoma and ocular hypertension.	*x*					*x*	*x*	
Chemical	Treatment of open-angle glaucoma and ocular hypertension.	*x*				*x*	*x*	*x*	
Chemical	New formulation intended for the same indications as oral dexamethasone.	*x*				*x*	*x*	*x*	
Biological	Diagnosis of osteomyelitis.	*x*						*x*	

SA: scientific advice
PA: protocol assistance

The above-mentioned 27 Scientific Advice letters, 4 Protocol Assistance letters, 8 Follow-up Scientific Advice and 3 Follow-up Protocol Assistance letters were adopted at the 19 - 22 July 2010 CHMP meeting.

New requests for scientific advice procedures

The Committee accepted 35 new Requests for which the procedure started at the SAWP meeting held on 28 – 30 June 2010. The new requests are divided as follows: 25 Initial Scientific Advice, 5 Follow-up Scientific Advice, 4 Initial Protocol Assistance and 1 Follow-up Protocol Assistance.

Annex 5 to CHMP Monthly Report July 2010

Documents prepared by the CHMP Working Parties adopted during the July 2010 CHMP meeting

Blood Products Working Party (BPWP)

Reference number	Document	Status [10]
EMA/CHMP/BPWP/9403/ 2007 rev. 2	Guideline on the Clinical Investigation of Human Normal Immunoglobulin for intravenous administration (IVIg) Overview of comments on IVIg guideline (EMA/CHMP/BPWP/604687/2009)	**Adopted**

Vaccine Working Party (VWP)

Reference number	Document	Status [10]
EMA/CHMP/VWP/14169/ 2009	Guideline on Quality, Non-Clinical and Clinical Aspects of Live Recombinant Viral Vectored Vaccines Overview of comments received (EMA/CHMP/VWP/829670/2009)	**Adopted**

Efficacy Working Party (EWP)

Reference number	Document	Status [10]
CPMP/EWP/1776/99 Rev.1	Guideline on Missing Data in Confirmatory Trials	**Adopted**
EMEA/CHMP/EWP/431734/2008	Draft Guideline on the clinical investigation of medicinal products for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) Overview of comments received (EMA/CHMP/EWP/12575/2010)	**Adopted**
CPMP/EP/352438/2008	Addendum to the Guideline on Antiarrhythmics on Atrial Fibrillation and Atrial Flutter	**Adopted**
CPMP/EWP/562/98 rev 1	Revision of the Guideline on Clinical Investigation of Medicinal Products in the Treatment of Chronic Obstructive Pulmonary Disease (COPD)	**Adopted**
EMA/CHMP/EWP/6054/ 2010	Concept Paper on the Need for the Guidance on the Clinical Investigation of Medicinal Products to slow Progression of Renal Insufficiency	**3-month public consultation**
EMA/CHMP/EWP/6054/ 2010	Concept Paper on the Need to Revise the Guideline on the evaluation of Anticancer Medicinal Products in man	**3-month public consultation**

[10] Adopted or release for consultation documents can be found at the European Medicines Agency website (under "Document library-Public Consultations" or under "Regulatory-Human Medicines").

Reference number	Document	Status [10]
CHMP/EWP/566/98 Rev.2/Corr	Corrigendum to the Guideline on Clinical Investigations of Medicinal Products in the Treatment of Epileptic Disorders	**Adopted**