26 November 2010
EMA/CHMP/739938/2010

Monthly Report

Committee for Medicinal Products for Human Use (CHMP)

15 – 19 November 2010

The Committee noted the resignations of Dr Ancuceanu as Romanian CHMP member and of Dr Masseva as Bulgarian CHMP alternate. Replacement nominations are awaited.

Centralised procedure

Initial applications for marketing authorisation

Positive opinion for a new medicine adopted

The Committee adopted a positive opinion by consensus recommending the granting of a marketing authorisation for a new medicine, **Pumarix** [pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted)], from GlaxoSmithKline Biologicals S.A., intended for prophylaxis of influenza in an officially declared pandemic situation. Pumarix is a mock-up vaccine. This means that the current strain can be changed to the pandemic strain once identified. The review for Pumarix began on 6 August 2009 with an active review time of 104 days.

Generic medicinal products

The Committee adopted two positive opinions by consensus recommending the granting of marketing authorisations for:

- **Lamivudine/Zidovudine Teva** (lamivudine/zidovudine), from Teva Pharma B.V., for the antiretroviral combination therapy of Human Immunodeficiency Virus infection. Lamivudine/Zidovudine Teva is a generic of Combivir.
- **Entacapone Teva** (entacapone), from Teva Pharma B.V., for the treatment of Parkinson's disease in combination with levodopa/benserazide or levodopa/carbidopa. Entacapone Teva is a generic of Comtess.

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The summaries of opinion for the above mentioned medicines, including their full indication, can be found here.

Withdrawals

The European Medicines Agency has been formally notified by Schering-Plough Europe of its decision to withdraw its application for a centralised marketing authorisation for the medicine **Zenhale** (mometasone furoate/formoterol fumarate) 50/5, 100/5 or 200/5 mg, pressurised inhalation. This medicine was intended to be used for long-term, twice-daily maintenance treatment of asthma, including reduction of asthma exacerbations, in adults and children aged 12 years or older. The application for the marketing authorisation for Zenhale was submitted to the Agency on 3 August 2009. At the time of the withdrawal it was under review by the CHMP. A separate press release and a question-and-answer document with more information are available.

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:

- **Plavix, Iscover** and **Clopidogrel Winthrop** (clopidogrel), from Sanofi Pharma Bristol-Myers Squibb SNC and Bristol-Myers Squibb Pharma EEIG, to include the prevention of atherothrombotic and thromboembolic events, including stroke, in adult patients with atrial fibrillation who have at least one risk factor for vascular events and who cannot take vitamin K antagonist therapy.

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

Additional safety information

Following the assessment of a follow-up-measure the CHMP adopted amendments to sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) and the respective sections of the package leaflet of **Avastin** (bevacizumab) from Roche with respect to Osteonecrosis of Jaw (ONJ) by consensus. A number of cases of ONJ have been reported in patients treated with Avastin, the majority of whom occurred in patients who had received prior or concomitant treatment with i.v. bisphosphonates, for which ONJ is an identified risk factor. Caution should therefore be exercised when Avastin and i.v. bisphosphonates are used either simultaneously or sequentially.

Following assessment of a follow-up-measure the CHMP adopted amendments to sections 4.4 and 4.8 of the SmPC of **Sutent** (sunitinib) from Pfizer Ltd. with respect to Osteonecrosis of Jaw (ONJ) by consensus. A number of cases of ONJ have been reported in patients treated with Sutent, the majority of whom occurred in patients who had received prior or concomitant treatment with i.v. bisphosphonates, for which ONJ is an identified risk factor. Caution should therefore be exercised when Sutent and i.v. bisphosphonates are used either simultaneously or sequentially. The package leaflet was updated accordingly.

The MAH, Roche Registration Ltd. agreed with the CHMP on a Direct Healthcare Professional Communication informing healthcare professionals that a case of fatal anaphylaxis has been reported in a patient treated with **RoActemra** (tocilizumab). Healthcare professionals must be vigilant for signs of hypersensitivity or anaphylaxis in all patients receiving tocilizumab, both during and following its

administration. Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during treatment with RoActemra. Furthermore the CHMP agreed, on the basis of these finding, to update sections 4.4 and 4.8 of the SmPC. The package leaflet was updated accordingly.

The CHMP adopted a positive opinion by consensus recommending a variation to the terms of the marketing authorisation for the medicinal product **Pradaxa** (dabigatran etexilate) from Boehringer Ingelheim International GmbH. The SmPC was updated in section 4.3 to include a new contraindication regarding concomitant treatment with systemic ketoconazole and removing a contraindication regarding concomitant treatment with quinidine.

Other information on the centralised procedure

Lists of Questions

The Committee adopted four Lists of Questions on initial applications (including two under the mandatory scope, and two under the optional scope as per Regulation (EC) No. 726/2004), together with one List of Questions on a "line extension" application (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 October is provided in **Annex 2**.

Referral procedures

Review of impact of detection of unexpected viral DNA in live attenuated vaccines concluded[1]

The Committee finalised a review of the impact of the detection of unexpected viral DNA fragments from porcine circovirus in some **live attenuated vaccines** using a new testing method. The Committee concluded by consensus that the presence of unexpected viral DNA in these vaccines does not pose a risk to public health, because the type of virus found does not cause disease in humans.

More information about the review of live attenuated vaccines is available in a separate press release and a question-and-answer document on the Agency's website.

Re-examination procedure on modafinil-containing medicines concluded[2]

Finalising a re-examination procedure on **modafinil-containing medicines**, the Committee confirmed its initial opinion by majority vote and recommended 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.

[1] The review of live attenuated vaccines was conducted under Article 5(3) of Regulation (EC) No 726/2004, at the request of the Agency's Executive Director, following the detection, using new testing methods, of endogenous and adventitious viral fragments in manufactured vaccines.
[2] 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 the potential for abuse.

A question-and-answer document with more information about this procedure can be found on the Agency's website.

Re-examination procedure on modified-release oral opioids concluded[3]

Finalising a re-examination procedure on **modified-release oral opioid products** in level III of the World Health Organization (WHO) scale for the management of pain, the Committee confirmed its initial opinion and recommended by majority 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 all modified-release oral opioid medicines with alcohol.

A question-and-answer document with more information about this procedure can be found on the Agency's website.

Review of suppositories containing terpenic derivatives started[4]

The Committee has started reviewing a potential increased risk of neurological disorders such as convulsions in children under three years of age receiving **suppositories containing terpenic derivatives** as adjunctive treatment during benign acute bronchial disorders or oropharyngeal congestive states.

This procedure follows reviews for appropriate use of cough and cold medicines carried out at the level of the Member States throughout Europe.

The CHMP will review all available data to clarify the impact of the potential increased risk of neurological disorders, 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 56th CMDh (Co-ordination Group for Mutual Recognition and Decentralised procedures-Human) held on 15-16 November 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 25-27 October 2010. For further details, please see **Annex 3**.

Documents adopted during the November 2010 CHMP meeting are listed in **Annex 4**.

[3] The review of modified-release oral opioids was conducted under Article 31 of Directive 2001/83/EC, as amended.
[4] The review of suppositories containing terpenic derivatives is being conducted in the context of a formal review, initiated by France under Article 31 of Directive 2001/83/EC, as amended. Terpenic derivatives include camphor, cineole, pine oil, eucalyptus, terpine, niaouli, turpentine, terpineol and wild thyme. The Committee will make recommendations on whether the marketing authorisations for suppositories containing terpenic derivatives should be maintained, changed, suspended or revoked.

Upcoming meetings following the November 2010 CHMP plenary meeting

- The 72nd meeting of the CHMP will be held at the Agency on 13-16 December 2010.
- The Name Review Group meeting will be held at the Agency on 23 November 2010.
- The 57th CMDh (Co-ordination Group for Mutual Recognition and Decentralised Procedures) will be held at the Agency on 13-14 December 2010.

Organisational matters

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

- A discussion on improved processes regarding the assessment of marketing authorisation applications for generic products. The Agency receives an increasing number of applications for generics of centrally authorised medicinal products. In most cases more than one company applies for a generic of the same reference medicine. Furthermore for some active substances generic applications are submitted through national procedures in parallel to the centralised procedure. In order to keep consistency and to optimise the assessment of marketing authorisation applications for generic medicinal products the Agency will set up an internal ad hoc group to assess the current procedures and to develop proposals for improvement.
- A presentation on the progress of the ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) Initiative. A DIA ENCePP Information Day will take place on 26 November 2010 in London. Further information can be found on the ENCePP website (http://www.encepp.eu/).
- The adoption by the CHMP of a reflection paper on 'considerations given to designation of an enantiomer as new active substance in relation to a reference active substance which is a racemic mixture of enantiomers'. The paper is released for 3-month public consultation and can be found here.
- The adoption of the guideline on 'Similar Biological Medicinal Products Containing Monoclonal Antibodies' for release for a five-month public consultation period. This guideline lays down the nonclinical and clinical requirements for monoclonal antibody-containing medicines claiming to be similar to another one already marketed. The guideline will be published on the Agency's website shortly.

Procedural Announcement

Deletion of version number of the detailed description of the pharmacovigilance system (DDPS) from Annex II.B of the Marketing Authorisation

Further to the entry into force of the Variations Regulation (EC) No 1234/2008 and the experience gained with the processing of changes to an existing pharmacovigilance system, as described in the detailed description of the pharmacovigilance system (DDPS), it has been agreed to delete the version number of the DDPS from Annex II.B of the marketing authorisation, in order to reduce the administrative work associated with the update of this version number with every change to the DDPS.

The following change to Annex II.B will be implemented in the next revision of the QRD Templates:

Annex II.B, Conditions of the marketing authorisation, other conditions

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, ~~as described in version {insert version reference}~~ presented in Module 1.8.1 of the Marketing Authorisation ~~<Application>~~, is in place and functioning before and whilst the product is on the market.

Until the revision of the QRD templates the following timeframe should be followed for implementation of the revised Annex II.B for medicinal products with regulatory activity affecting the product information annexes:

- **On-going procedures**

All opinions on **new applications for marketing authorisation, extensions and Type II variations** affecting the annexes adopted as of November 2010 should include the revised annex II.B; the revised annexes in all other languages should be submitted on day +5 after CHMP opinion, as part of the linguistic review process of product information in the centralised procedure.

- **New procedures**

All **new applications for marketing authorisation, extensions and variation applications (Type IA, IB and II)** affecting the annexes submitted as of 1st November 2010 should include the revised annex II.B; this requirement is also applicable if the variation concerns the introduction of a new pharmacovigilance system (C.I.8) or a change to an existing pharmacovigilance system as described in the DDPS (C.I.9)

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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 November 2010

Opinions for annual re-assessment applications		
Name of medicinal product (INN) MAH	**Outcome**	**Comments**
Vedrop (tocofersolan), Orphan Europe	Positive Opinion	Marketing Authorisation remains under exceptional circumstances
Xigris (drotrecogin alfa (activated)), Eli Lilly Nederland B.V.	Positive Opinion	Marketing Authorisation remains under exceptional circumstances

Opinion for renewals of conditional MA's		
Name of medicinal product (INN) MAH	**Outcome**	**Comments**
Arzerra (ofatumumab), Glaxo Group Ltd.	Positive Opinion	Marketing Authorisation remains under conditional approval

Opinions for 5-Year Renewal applications		
Name of medicinal product (INN) MAH	**Outcome**	**Comments**
Rotarix (rotavirus vaccine, live), GlaxoSmithKline Biologicals S.A.	Positive Opinion	Recommending additional renewal
Naglazyme (galsulfase), BioMarin Europe Ltd.	Positive Opinion	Unlimited validity

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Accelerated Assessment Procedures			
Substance	**Intended Indication(s)**	**Accelerated Assessment Requests**	
		Accepted	Rejected
Chemical	Use, in combination with pegylated interferon alpha and ribavirin in adult patients (18 years and older) for the treatment of chronic hepatitis C genotype 1, including patients who are previously untreated or who have failed previous therapy	X	
Chemical	Treatment of chronic Hepatitis C virus infection	X	

Annex 2 to CHMP Monthly Report November2010

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

Invented name	**Ruconest**
INN	conestat alfa
Marketing Authorisation Holder	Pharming Group N.V.
Proposed ATC code	Not yet assigned
Indication	Treatment of acute angioedema attacks in adults with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency
CHMP Opinion date	24.06.2010
Marketing Authorisation Date	28.10.2010

Invented name	**Clopidogrel Teva Generics B.V**
INN	clopidogrel
Marketing Authorisation Holder	Teva Generics B.V.
Proposed ATC code	B01AC-04
Indication	Indicated in adults for the prevention of atherothrombotic events in: • Patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease. • Patients suffering from acute coronary syndrome: - Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA). - ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy.
CHMP Opinion date	22.07.2010
Marketing Authorisation Date	28.10.2010

Invented name	**Clopidogrel HCS**
INN	clopidogrel
Marketing Authorisation Holder	HCS bvba
Proposed ATC code	B01AC-04
Indication	Indicated in adults for the prevention of atherothrombotic events in: • Patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease. • Patients suffering from acute coronary syndrome: - Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA). - ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy.
CHMP Opinion date	22.07.2010
Marketing Authorisation Date	28.10.2010

Annex 3 to CHMP Monthly Report November 2010

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

	1995 - 2009	2010	Overall total
Scientific Advice	1134	210	1344
Follow-up to Scientific Advice	232	82	314
Protocol Assistance	245	47	292
Follow-up to Protocol Assistance	109	23	132
	1720	**362**	**2082**

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 November 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				
Chemical	Treatment of urea cycle disorders.		*x*			*x*	*x*	*x*	*x*
Chemical	Treatment of opioid-induced bowel dysfunction.	*x*					*x*	*x*	
Biological	Treatment of hydradenitis suppurativa.	*x*						*x*	
Chemical	Treatment of acute lymphoblastic leukaemia.	*x*						*x*	
Biological	Treatment of colorectal and head and neck cancer.	*x*				*x*	*x*	*x*	
Chemical	Treatment of castration-resistant prostate cancer.	*x*						*x*	
Biological	Treatment of multiple myeloma.	*x*						*x*	
Chemical	Maintenance therapy in diffuse large B-cell lymphoma.		*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 renal cell carcinoma.		x			x	x	x	
Other innovative	Treatment of graft-versus-host disease.				x			x	x
Biological	Prevention of ischaemia reperfusion injury associated with solid organ transplantation.		x			x			
Chemical	Treatment of soft tissue sarcoma.		x					x	x
Chemical	Treatment of non-small cell lung cancer.	x					x	x	
Biological	Treatment of asthma.	x						x	
Chemical	Treatment of metastatic melanoma.	x						x	
Biological	Treatment of relapsed multiple myeloma.		x					x	
Biological	Treatment of oesophageal cancer.		x			x	x	x	x
Other innovative	Treatment of Crohn's disease.	x						x	
Biological	Treatment of haemophilia A.				x		x	x	
Biological	Treatment of haemophilia B.				x		x	x	
Biological	Treatment of haemophilia A or B.	x				x	x	x	
Biological	Prevention of cardiovascular disease.	x					x	x	
Chemical	Treatment of acute coronary syndrome and coronary artery disease (atherosclerosis).	x						x	
Chemical	Treatment of acute heart failure.			x				x	
Chemical	Treatment of hypertension in children.			x				x	
Chemical	Treatment of Borrelia-infection after tick bite.	x					x	x	
Chemical	Treatment of HCV 1 infection.			x			x	x	
Chemical	Treatment of chronic hepatitis C in adults.			x				x	
Chemical	Prevention of male-to-female sexual transmission of HIV-1.	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 complicated skin and soft-tissue infections.	*x*				*x*	*x*	*x*	
Chemical	Treatment of chronic HCV infection.			*x*			*x*	*x*	
Chemical	Treatment of chronic hyperuricaemia.	*x*				*x*	*x*	*x*	
Biological	Treatment of relapsing multiple sclerosis.	*x*				*x*	*x*	*x*	
Chemical/ Other innovative	Intended for conscious sedation.	*x*				*x*	*x*	*x*	
Chemical/ Other innovative	Intended for conscious sedation in children.	*x*						*x*	
Chemical	Treatment of Friedreich's ataxia.			*x*		*x*	*x*	*x*	
Chemical	Treatment of asthma.			*x*				*x*	
Chemical	Treatment of COPD and asthma.			*x*		*x*			
Chemical	Treatment of COPD and asthma.			*x*			*x*	*x*	
Chemical	Treatment of elevated intra-ocular pressure in open-angle glaucoma or ocular hypertension.	*x*					*x*	*x*	
Chemical	Diagnostic agents used during magnetic resonance imaging or magnetic resonance angiography scans.	*x*						*x*	

SA: scientific advice
PA: protocol assistance

The above-mentioned 22 Scientific Advice letters, 7 Protocol Assistance letters, 9 Follow-up Scientific Advice and 3 Follow-up Protocol Assistance letters were adopted at the 15 - 18 November 2010 CHMP meeting.

New requests for scientific advice procedures

The Committee accepted 28 new requests for which the procedure started at the SAWP meeting held on 25 – 27 October 2010. The new requests are divided as follows: 21 Initial Scientific Advice, 3 Follow-up Scientific Advice, 3 Initial Protocol Assistance and 1 Follow-up Protocol Assistance.

Annex 4 to CHMP Monthly Report November 2010

Documents adopted during the November 2010 CHMP meeting

Biologicals Working Party (BWP)

Reference number	Document	Status[5]
EMA/CHMP/BWP/360133/2010	BWP Work Programme 2011	**adopted**

Biosimilar Medicinal Products Working Party (BMWP)

Reference number	Document	Status[5]
EMA/572297/2010	BMWP Work Programme 2011	**adopted**
EMA/CHMP/BMWP/403543/2010	Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies	**5-month consultation**
EMA/CHMP/BMWP/86289/2010 Rev. 2	Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use	**5-month consultation**

Cardiovascular Working Party

Reference number	Document	Status[5]
EMA/673922/2010	Cardiovascular Working Party Work Programme 2011	**adopted**
EMA/CHMP/217874/2010	Guideline on clinical investigation of medicinal products in the treatment of hypertension • Overview of comments	**adopted**
EMA/215698/2010	Guideline on Lipid Lowering agents	**6-month consultation**

Pharmacovigilance Working Party (PhVWP)

Reference number	Document	Status[5]
EMA/CHMP/PhVWP/295724/2010	PhVWP Work Programme 2011	**adopted**

[5] 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").

Rheumatology/Immunology Working Party

Reference number	Document	Status[5]
EMA/680123/2010	Rheumatology/Immunology Working Party Work Programme 2011	**adopted**

Vaccines Working Party (VWP)

Reference number	Document	Status[5]
EMA/CHMP/VWP/684601/2010	VWP Work Programme 2011	**adopted**

EMA

Reference number	Document	Status[5]
EMA/524982/2010	Briefing note on pilot phase for participation of patients in SAG meetings	**adopted**
EMA/651649/2010	Reflection paper on considerations given to designation of a single stereo isomeric form (enantiomer) as new active substance in relation to a reference active substance which is a racemic mixture of enantiomers	**3-month consultation**