European Medicines Agency
Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
JUNE 2008 PLENARY MEETING
MONTHLY REPORT

The Committee for Medicinal Products for Human Use (CHMP) held its June plenary meeting from 23-26 June 2008.

CENTRALISED PROCEDURE

Initial applications for marketing authorisation

The CHMP adopted three positive opinions by consensus on initial marketing authorisations, including one for a generic medicine, recommending the granting of a marketing authorisation:

- **Intelence** (etravirine), from Janssen-Cilag International NV, for use in combination with a boosted protease inhibitor and other antiretroviral medicines for the treatment of human immunodeficiency virus (HIV-1) infection in antiretroviral treatment-experienced adult patients. EMEA review began on 15 August 2007 with an active review time of 178 days. This positive opinion concerns the recommendation for granting a conditional marketing authorisation.

- **Oprymea** (pramipexole), from Krka D.D., for the treatment of the signs and symptoms of idiopathic Parkinson's disease in monotherapy or combination therapy. The reference product for Oprymea is Sifrol, from Boehringer Ingelheim International GmbH, which is already authorised in the European Union (EU), in the applied indication. EMEA review began on 21 November 2007 with an active review time of 177 days.

- **Vimpat** (lacosamide), from UCB Pharma S.A., for use as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older. EMEA review began on 23 May 2007 with an active review time of 209 days.

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

Negative opinion

The CHMP adopted a negative opinion recommending the refusal of a marketing authorisation for **Opgenra** (recombinant human osteogenic protein-1/eptotermin), from Howmedica International S. de R.L. Opgenra was intended to be used for posterolateral lumbar spinal fusion in adult patients with spondylolisthesis where autograft has failed, is not feasible or is unlikely to be efficacious. EMEA review began on 21 February 2007 with an active review time of 202 days.

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 16
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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

The EMEA has been formally requested by Takeda Global Research & Development Centre (Europe) LTD, to re-examine the negative opinion for **Ramelteon** (ramelteon), intended to be used for the treatment of primary insomnia in patients aged 18 years or older, adopted during the CHMP meeting on 27-30 May 2008.

Withdrawals

The EMEA has been formally notified by Euro Nippon Kayaku GmbH of its decision to withdraw its application for a marketing authorisation application for **Spanidin** (gusperimus). Spanidin was to be used for induction of remission in adult patients suffering from clinically refractory Wegener's granulomatosis, where standard treatment with cyclophosphamide and glucocorticoids failed to induce or maintain remission. A separate press release with more information and a question-and-answer document are available.

The EMEA has been formally notified by Novartis Vaccines and Diagnostics S.r.l. of its decision to withdraw its application for a marketing authorisation application for pre-pandemic vaccine **Aflunov** (A/VietNam/1194/2004 (H5N1) virus surface inactivated antigen). Aflunov was expected to be used for active pre-pandemic immunisation against H5N1 subtype of the influenza A virus. A separate press release with more information and a question-and-answer document are available.

The EMEA has been formally notified by Celgene Europe Limited of its decision to withdraw its application for a marketing authorisation application for **Lenalidomide Celgene Europe** (lenalidomide). Lenalidomide Celgene Europe was intended to be used for the treatment of anaemia due to myelodysplastic syndromes. 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:

- **Cymbalta** (duloxetine), from Eli Lilly Nederland B. V., and **Xeristar** (duloxetine), from Boehringer Ingelheim International GmbH, to extend the indication to include the treatment of generalised anxiety disorder. Cymbalta and Xeristar are currently indicated for the treatment of major depressive episodes and diabetic peripheral neuropathic pain in adults.

- **Tracleer** (bosentan), from Actelion Registration Ltd, to extend the indication to include that some improvements have also been shown in patients with Pulmonary Arterial Hypertension (PAH) functional class II. Tracleer is currently indicated for the treatment of PAH to improve exercise capacity and symptoms in patients with functional class III. Tracleer is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

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

New safety information

The CHMP has recommended a new warning for **epoetin-containing medicines**. These medicines are indicated for the treatment of anaemia in patients with non-myeloid tumours receiving chemotherapy and in patients with chronic renal failure. A separate press release and a question-and-answer document with more detailed information are available on the EMEA website.

Updated safety information

In the context of a wider discussion on **Champix** (varenicline), a medicine indicated for smoking cessation in adults, that took place at the May 2008 PhVWP and CHMP meetings, a review of spontaneous reporting data on Suicide-Related Events (SRE) was presented and discussed. As a result of the discussion on Suicide-Related Events, the CHMP considered that updates to section 4.4 of the SPC (and section 4 of the Package Leaflet) were required to strengthen the existing warnings with regards to SRE. In particular, mention of the fact that not all patients experiencing depression and suicidal thoughts had a previous history of psychiatric illness or had stopped smoking was added to the SPC. Moreover, instructions on stopping Champix and contacting doctors when patients develop agitation, depressed mood, changes in behaviour or suicidal thoughts were added to the Product Information.

The CHMP recommended updating the product information of **Exjade** (deferasinox) from Novartis Europham Ltd following results from the 4th PSUR. These results showed that cases of hepatic failure, sometimes fatal have been reported with Exjade. Most of these reports involved patients with significant comorbidities, including liver cirrhosis and multi-organ failure. However, the role of Exjade as a contributing or aggravating factor cannot be excluded. Consequently, monitoring of hepatic function before initiation of treatment and during treatment has been introduced. In addition, cases of upper gastrointestinal ulceration and haemorrhage and renal tubulopathy have been reported in patients taking Exjade. The CHMP and the MAH agreed on a Direct Healthcare Professional Communication concerning these safety signals.

Following assessment of new information on psychiatric adverse events with **Acomplia** (rimonabant), from Sanofi-Aventis, the CHMP concluded that depression may occur as a side effect of Acomplia in patients who have no obvious risk factors, apart from obesity itself. More than half of the patients who develop such side effects do so within one month of starting treatment, and approximately 80% do so within three months. Consequently, the CHMP recommended updating the product information to reflect this new information and to advise prescribers to monitor patients for signs and symptoms of psychiatric disorders, particularly depression, after the start of treatment. The CHMP and the MAH (Sanofi-Aventis) agreed on a Direct Healthcare Professional Communication concerning this updated information on psychiatric adverse events with Acomplia. The CHMP will continue to monitor the efficacy and safety of Acomplia.

The CHMP recommended updating the product information of **Humira** (adalimumab) from Abbott Abbott Laboratories Ltd, with information on hepatosplenic T-cell lymphoma, a rare aggressive form of non-Hodgkin lymphoma with a poor prognosis that occurs most commonly in adolescent and young adult males. Three cases were identified. Some of the patients were also receiving azathioprine or 6-mercaptopurine for the treatment of inflammatory bowel disease. Based on the data presented a causal relationship of hepatosplenic T-cell lymphoma and adalimumab therapy cannot be excluded. The CHMP and MAH agreed on a Direct Healthcare Professional Communication concerning these issues.

OTHER INFORMATION ON THE CENTRALISED PROCEDURE

Lists of Questions

The Committee adopted five Lists of Questions on initial applications (including one under the mandatory scope, and four under the optional scope).

Detailed information on the centralised procedure

An overview of centralised procedures since 1995 is given in **Annex 1**. The post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 2**. The list of medicinal products for which marketing authorisations have been granted by the European Commission since the CHMP plenary meeting in May 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 May 2008 CHMP plenary meeting are provided in **Annex 4**.

REFERRAL PROCEDURES

Referral procedure concluded

The CHMP concluded a referral procedure for **ergot-derived dopamine agonists**, a class of medicines that is primarily used for the treatment of Parkinson's disease. A separate press release and a question-and-answer document with more detailed information are available on the EMEA website.

The CHMP concluded referral procedures for **etoricoxib-containing medicines,** intended for the treatment of osteoarthritis, rheumatoid arthritis and acute gouty arthritis. A separate press release and a question-and-answer document with more detailed information are available on the EMEA website.

The CHMP concluded a referral procedure for **Activelle,** 0.5 mg/0.1 mg, film-coated tablets (estradiol/norethisterone acetate), from Novo Nordisk A/S, indicated for Hormone Replacement Therapy 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. The Committee concluded that the benefits of the medicines outweigh their risks and, therefore, recommended the granting of a marketing authorisation. The procedure was initiated under Article 29(4) of Directive 2001/83/EC, as amended, because of concerns over the endometrial safety of Activelle 0.5 mg/0.1 mg.

The CHMP concluded a referral procedure for **Rapinyl** 50, 100, 200, 300, 400, 600 and 800 microgram (fentanyl citrate), from ProStrakan Ltd, indicated for the treatment of breakthrough pain in patients using opioid therapy for chronic cancer pain. The CHMP concluded that the benefits of the medicine outweigh the risks and, therefore, recommended the granting of a marketing authorisation subject to changes in the product information and follow-up measures. The procedure was initiated under Article 29(4) of Directive 2001/83/EC, as amended, because of a disagreement among some Member States whether additional data demonstrating efficacy and safety of Rapinyl in the management of breakthrough pain is required.

Procedures under Article 29(4) are initiated in cases where no agreement can be reached in the context of the mutual recognition procedure or the decentralised procedure.

The CHMP concluded two harmonisation referrals for:

- **Gemzar** (gemcitabine), from Lilly, indicated for the treatment of bladder cancer, advanced non- small cell lung cancer, advanced pancreatic cancer, breast cancer and ovarian cancer.

- **Remeron** (mirtazapine), from Organon N.V., indicated for the treatment of episodes of major depression.

The CHMP recommended the harmonisation of the product information across the European Union for both products. The procedure was initiated under Article 30 of Directive 2001/83/EC, as amended, with a view to harmonising the product information across the EU for medicinal products authorised at the level of the Member States.

Referral procedures started

The CHMP started a harmonisation referral procedure under Article 30 of Directive 2001/83/EC for **Diovan comp and associated names** (valsartan/hydrochlorothiazide), from Novartis group of companies and associated companies, intended for the treatment of hypertension.

Referral procedures withdrawn

The EMEA has been formally notified by Sandoz B.V. of its decision to withdraw its application for five medicines containing atorvastatin calcium from the concerned Member State markets. In December 2007, the CHMP had initiated referral procedures under Article 29 of Directive 2001/83/EC as amended for five medicines containing atorvastatin calcium, namely **Atorvatyrol**, (10, 20, 40, 80 mg) from Sandoz GmbH Austria , **Atorvac** (10, 20, 40, 80 mg) and **Atorvastatin Hexal**,(30, 60 mg) both from Hexal Pharma GmbH Austria, **Atorvis** (10, 20, 40, 80 mg)**,** from Sandoz GmbH Austria and **Atorvapharm** (10, 20, 40, 80 mg**),** from 1A Pharma GmbH Austria, because of concerns that bioequivalence with the reference medicine has not been demonstrated sufficiently. The medicines were intended for the treatment of hypercholesterolaemia and prevention of cardiovascular disease.

Review procedures under Article 107

The CHMP is reviewing **moxifloxacin-containing medicines**, intended for the treatment of acute exacerbation of chronic bronchitis, community acquired pneumonia and acute bacterial sinusitis. The procedure was triggered by the United Kingdom under Article 107 of Directive 2001/83/EC, due to new safety data which raise concerns that the benefits of the medicines do not outweigh their risks in the treatment of acute bacterial sinusitis and acute exacerbation of chronic bronchitis.
This type of procedure is initiated in cases where a Member State considers that, as a result of the evaluation of pharmacovigilance data, a medicine's marketing authorisation should be withdrawn, suspended or changed. It provides for a harmonised European approach because the CHMP is asked to prepare an opinion on whether or not the regulatory actions should be implemented throughout the European Union.

MUTUAL RECOGNITION AND DECENTRALISED PROCEDURES - HUMAN

The CHMP noted the report from the 30th CMD(h) (Co-ordination Group for Mutual Recognition and Decentralised procedures-Human) held on 23-24 June 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 2-4 June 2008. For further details, please see **Annex 5**.

Documents prepared by the CHMP Working Parties adopted during the June 2008 CHMP meeting are listed in **Annex 6**.

UPCOMING MEETINGS FOLLOWING THE JUNE 2008 CHMP PLENARY MEETING

- The 46th meeting of the CHMP will be held at the EMEA on 21-24 July 2008.
- The next Name Review Group meeting will be held at the EMEA on 29th July 2008.
- The 31st CMD(h) (Co-ordination Group for Mutual Recognition and Decentralised Procedures) will be held at the EMEA on 21-22 July 2008.

ORGANISATIONAL MATTERS

The main topics addressed during the June 2008 CHMP meeting related to:

- The election of Dr. Weise as Vice- Chair of the Working Party on Similar Biological Medicinal Products.
- The publication of the CHMP scientific Article 5(3) opinion on the potential risks of carcinogens, mutagens and substance toxins to reproduction when these substances are used as excipients of medicinal products for human use.

- Preliminary discussion regarding interactions between the CHMP and PhVWP on class reviews initiated by the PhVWP.
- Discussion regarding the application of the Global Marketing Authorisation concept in the context of Regulation 1901/2006 on medicinal products for paediatric use (see Procedural Announcement).
- Preliminary discussion regarding the creation of a methodological Annex for the Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No. 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004.
- The adoption of internal procedure and templates for producing assessement reports when handling submissions for centrally authorised products in relation to Art 45 and Art 46 of the Paediatric Regulation 1901/2006, as amended.
- The adoption of a revision regarding the guidance document on the Voting in the Framework of Discussion and Adoption of CHMP Opinions and Recommendations (CHMP/3137/01 Rev 1.1) which will now be published on the EMEA website.
- The adoption of the guideline on the use of statistical signal detection methods in the Eudravigilance date analysis system (EMEA/106464/2006 rev. 1) and the overview of comments received following the public consultation (EMEA/252216/2007).
- Information regarding updated dossier requirements for pre- and post-authorisation electronic submissions (see Procedural Announcement).
- Follow-up discussion regarding proposal for standardisation of timelines for submission of written responses at Day 120 and Day 180. The guideline will be revised shortly and published on the EMEA website.
- Preliminary discussion regarding the pilot phase regarding Benefit-Risk assessment in the context of the evaluation of marketing authorisation applications of medicinal products for human use. An action plan for the pilot phase using the new Benefit-Risk assessment template and the list of products that will be concerned by this pilot was agreed upon.
- Preliminary discussion regarding the re-examination procedure for Advanced Therapies Medicinal Products including the involvement of the future Committee for Advanced Therapies.
- An update regarding the report on the progress of the interaction with patients' and consumers' organisations and assessment of performances indicators (MB/81204/2008). The report showed the good progress made by the EMEA in 2007 with regard to interaction with patients' and consumers' organisations.
- The update of the Committee regarding the last ICH meeting held in Portland (USA) on 1-5 June 2008. The Committee adopted the E2F Step 3 Note for Guidance on Development Safety Update Report (EMEA/CHMP/ICH/309348/2008) and also noted the E14 questions-and-answer document on the Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (EMEA/CHMP/ICH/310133/2008) and the Q10 Step 4 Pharmaceutical Quality System (EMEA/CHMP/ICH/214732/2007).

PROCEDURAL ANNOUNCEMENT

- **Electronic submissions**

  Applicants are reminded that from 1st July 2008, the EMEA will accept electronic-only submissions, either in eCTD format or non-eCTD format (eCTD is the recommended electronic format), with no additional requirement for paper copies. This will apply to all applications (new and existing) and all types of submissions to the EMEA in the context of the centralised procedure (e.g. new applications, supplementary information, variations, and renewals). Rapporteurs and CHMP members may, however, still have paper-copy requirements at this point.

  More details can be found in the following announcement and question-and-answer documents:

  http://www.emea.europa.eu/pdfs/human/regaffair/56336607en.pdf

  http://www.emea.europa.eu/pdfs/human/regaffair/59687007en.pdf

  http://www.emea.europa.eu/pdfs/human/regaffair/59688107en.pdf

  Updated EMEA and CHMP dossier requirements can be found in the following documents:

  http://www.emea.europa.eu/htms/human/presub/dossierrequirements.pdf

  http://www.emea.europa.eu/pdfs/human/regaffair/30033908en.pdf

  The Pre-Submission and Post-Authorisation Procedural Advice documents, published on the EMEA website, are currently being updated to reflect these revised dossier requirements.

- **Procedural guidance on the application of the paediatric Regulation requirements**

➢ Application requirements

The EMEA would like to remind Applicants/Marketing Authorisation Holders that the paediatric requirements of Article 7 of Regulation (EC) No 1901/2006 will apply:

- as of **26th July 2008** to new Marketing Authorisation Applications for a medicinal product not authorised in the EEA on 26th July 2008, as set out in Article 7 of Regulation (EC) No 1901/2006.

- as of **26th January 2009** to applications for new indications, new routes of administration, and/or new pharmaceutical forms for an authorised medicinal product which is protected either by a supplementary protection certificate under Regulation (EEC) No 1768/92, or by a patent which qualifies for the granting of the supplementary protection certificate, as set out in Article 8 of Regulation (EC) No 1901/2006.
  This requirement applies irrespective of the type of application submitted for such a change(s) i.e. variation, extension or new marketing authorisation application and irrespective of whether the change is related to adult or paediatric use.

The requirements will apply to applications submitted as from the above-mentioned dates (i.e. submission date, not validation date).

As a consequence, at the time of submission, such application must include one or more of the following in order for the application to be considered "valid":

- The results of all studies performed and details of all information collected in compliance with an agreed Paediatric Investigation Plan (PIP)

- A decision of the EMEA on a PIP including any deferral granted
- A decision of the EMEA granting a product-specific waiver
- A decision of the EMEA granting a class waiver on condition

This information is to be included in Module 1.10 of the application dossier – NTA (Vol 2B): http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol2_en.htm#2b

The following types of application are exempted from the application of Articles 7 and 8:

- Generics (Art 10(1) of Directive 2001/83/EC)
- Hybrid medicinal products (Art 10(3) of Directive 2001/83/EC)
- Similar biological medicinal products (Art 10(4) of Directive 2001/83/EC)
- Medicinal products containing active substance(s) of well-established medicinal use (Art 10a of Directive 2001/83/EC)
- Homeopathic medicinal products (Art 13-16 of Directive 2001/83/EC)
- Traditional herbal medicinal products (Art 16a-16i of Directive 2001/83/EC)

➢ Application of Global Marketing Authorisation in the context of Article 7 and 8 of the Paediatric Regulation

Articles 7 and 8 refer respectively to **"**a medicinal product for human use which is not authorised in the Community" and to an "authorised medicinal product". At the time of submitting a new stand-alone application it is necessary to establish whether the product applied for is considered or not **"**a medicinal product for human use which is not authorised in the Community". In this context, the Global Marketing Authorisation concept, as defined in Article 6(1), 2nd subparagraph of Directive 2001/83/EC, as amended, applies. The notion of Global Marketing Authorisation applies to products belonging to the same marketing authorisation holder. "Same marketing authorisation holder" is defined in the Commission Communication on the Community marketing authorisation procedures for medicinal products (98/C 299/03) as applicants belonging to the same mother company or group of company, or which are "licensees".

The Global Marketing Authorisation concept covers both orphan and non-orphan marketing authorisations held by the same marketing authorisation holder.

The impact of the application of the notion of Global Marketing Authorisation together with the concept of 'same marketing authorisation holder' is explained further in the Procedural Advice question-and-answer document available under "Medicines for children" on the EMEA website.

The Global Marketing Authorisation approach applies to PIP or Waiver applications as well as to variations, extension and new marketing authorisation applications falling under the requirements of Article 7 and 8. It implies that Global Marketing Authorisation concept applies to such applications as of 26 July 2008. Where relevant, applicants should also consider whether any modification to an agreed or ongoing PIP/Waiver decision may be required in case the GMA concept had not been applied, in order to avoid difficulties at validation of the subsequent regulatory submission.

➢ Compliance check

When planning the submission of an application falling under the requirements of Article 7 or 8, applicants have to take into account the need for a compliance check of the Paediatric Investigation Plan (PIP), or relevant parts of it. The compliance check for applications to the Centralised Procedure will be performed by the Paediatric Committee, following a 30 or 60-day procedure.
Applicants can choose to apply for the compliance check directly to the Paediatric Committee before the submission of their application and to include the opinion of the Paediatric Committee on compliance, as part of the submission package. This approach is strongly recommended, otherwise, at the validation stage, the EMEA will request the compliance check by the Paediatric Committee, with the consequence that validation will be suspended until the Paediatric Committee compliance opinion is available. Further information on compliance check will soon be released by the EMEA.

Applicants and Marketing authorisation Holders are therefore strongly encouraged to request the opinion of the Paediatric Committee on compliance before the submission of their application, in order not to delay its validation.

Please note that updated application forms for new marketing authorisations/extensions and variations including the above requirements are now available on the European Commission website and have to be used for any upcoming submission of applications:
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol2_en.htm

- **CHMP August 2008 written procedure**

  The CHMP agreed to replace the August 2008 plenary meeting by written procedures to be established for certain ongoing applications.

Noël Wathion
Head of Unit
Post-Authorisation Evaluation of Medicines for Human Use, Tel. (+44-20) 74 18 85 92

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

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	16	4	0	3	9	4	6	42	710
Positive opinions	11	2	0	1	7	4	3	28	457
Negative opinions[1]	1	0	0	0	1	0	1	3	21
Withdrawals prior to opinion	4	0	0	0	4	0	4	12	128
Marketing authorisation granted by the Commission	6	3	0	2	3	1	2	17	434

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)	1	12
VAMF	0	0

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

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

Substance	Intended indications(s)	Accelerated Assessment Requests	
		Accepted	Rejected
Chemical	N/A	N/A	N/A
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)	603	5805
Type II Variations (positive opinions)	301	4145
Type II Variations (negative opinions)	1	11
Annex II Applications (positive opinions)	21	190
Annual Re-assessment (positive opinions)	16	-
Opinion for renewals of conditional MA's (positive opinions)	0	2
5 Year Renewals (positive opinions)	27	-

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
5 Extensions of indication	5 Positive opinions
46 SPC changes	46 Positive opinions
25 Quality changes	25 Positive opinions

Opinions for Annual Re-Assessment applications		
Name of Medicinal Product (INN) MAH	**Outcome**	**Comments**
Elaprase (idursulfase) Shire Human Genetic Therapies	Positive Opinion adopted	remaining under exceptional circumstances
Orfadin (nitisinone) Swedish Orphan International AB	Positive Opinion adopted	remaining 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**
Aldara (imiquimod) Laboratories 3M Sante	Positive Opinion adopted	unlimited validity
Humira (adalimumab) Abbott Laboratories	Positive Opinion adopted	unlimited validity
Comtess (entacapone) Orion Corporation	Positive Opinion adopted	unlimited validity
Comtan (entacapone) Novartis Europharm Ltd	Positive Opinion adopted	unlimited validity
Viagra (sildenafil) Pfizer Limited	Positive Opinion adopted	unlimited validity
Ventavis (iloprost) Bayer Schering Pharma AG	Positive Opinion adopted	requiring 2nd Renewal

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

Invented Name	Tyverb
INN	Lapatinib
Marketing Authorisation Holder	Glaxo Group Limited
Proposed ATC code	L01XE07
Indication	Tyverb, in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress ErbB2 (HER2). Patients should have progressive disease following prior therapy which must include anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting.
CHMP Opinion date	24.04.2008
Marketing Authorisation Date	10.06.2008

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

Active substance	Sponsor/applicant	EU Designation Number	Designated Orphan Indication
Caffeine citrate	Chiesi Farmaceutici S.P.A.	EU/3/03/132	Treatment of primary apnoea of premature newborns

ANNEX 6 TO CHMP MONTHLY REPORT JUNE 2008

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

	1995 - 2007	2008	Overall Total
Scientific Advice	887	109	996
Follow-up to Scientific Advice	171	30	201
Protocol Assistance	198	26	224
Follow-up to Protocol Assistance	90	9	99
	1346	**174**	**1520**

OUTCOME OF THE JUNE 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 hyperlipidemia	X					X	X	
Chemical	Treatment of gastro oesophageal reflux disease	X						X	
Chemical	Treatment of Type 2 diabetes mellitus	X					X	X	
Chemical	Treatment of diabetes mellitus			X				X	
Chemical	Treatment of Type 2 diabetes mellitus			X				X	
Chemical	Treatment of gastro oesophageal reflux disease			X			X	X	
Biological	Treatment of Type 1 diabetes			X				X	
Chemical	Treatment of prostate cancer	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 multiple sclerosis	X					X	X	
Biological	Treatment of neutropenias			X				X	
Biological	Treatment of neutropenias	X				X	X	X	
Biological	Treatment of non-Hodgkin lymphoma			X				X	
Biological	Treatment of non-Hodgkin lymphoma	X				X			
Chemical	Treatment of acute lymphoblastic leukaemia		X			X	X	X	
Chemical	Treatment of acute lymphoblastic leukaemia		X			X	X	X	
Innovative product	Treatment of chronic Graft-versus-Host disease		X					X	X
Chemical	Treatment of metastatic breast cancer			X				X	
Chemical	Treatment of systemic lupus erythematosus	X					X	X	
Biological	Treatment of neutropenias	X				X	X	X	
Biological	Treatment of emphysema				X			X	
Biological	Treatment of acute ischaemic stroke	X				X		X	
Chemical	Secondary prevention of cardiovascular events and slowing the progression of atherosclerosis	X				X			
Chemical	Prevention of acute coronary syndrome			X				X	

Substance	Intended indications(s)	Type of Request				Topic			
		New		Follow-up		Pharmaceutical	Pre-clinical	Clinical	Significant Benefit
		SA	PA	SA	PA				
Biological	Prophylaxis of scarring of wound margins			X		X		X	
Chemical	Treatment of *Staphylococcus Aureus* Bacteraemia	X						X	
Biological	Prevention of cervical cancer and cervical, vulvar and vaginal dysplasia and genital warts	X						X	
Chemical	Treatment of HIV-1 infection	X						X	
Chemical	Treatment of *Pseudomonas aeruginosa* lung infection in cystic fibrosis				X	X	X	X	X
Chemical	Treatment of urge incontinence and/or increase urinary frequency and urgency	X					X	X	
Chemical	Treatment of penile erectile dysfunction	X						X	
Chemical	Treatment of osteoporosis	X						X	
Biological	Treatment of osteoarthritis and/or chronic pain	X				X	X		
Chemical	Treatment of transthyretin amyloidosis		X			X	X	X	
Chemical	Treatment of cancer pain	X						X	
Chemical	Treatment of cognitive dysfunction in schizophrenia	X						X	
Chemical	Treatment of Alzheimer's disease	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 Alzheimer's disease	X						X	
Chemical	Treatment of Alzheimer's disease and other neurodegenerative disorders	X				X	X	X	
Chemical	Treatment of schizophrenia	X					X	X	
Biological	Treatment of severe asthma			X				X	
Chemical	Treatment of acanthamoeba keratitis		X				X	X	
Chemical	Treatment of acromegaly	X					X	X	
Chemical	Treatment of chronic iron overload in thalassemia		X					X	X
Chemical	Prevention of recurrent painful vaso-occlusive crises in Sickle Cell Syndrome		X					X	
Chemical	Treatment of Lupus nephritis	X				X	X	X	

SA: Scientific Advice
PA: Protocol Assistance

The above-mentioned 26 Scientific Advice letters, 10 Protocol Assistance letters, 7 Follow-up Scientific Advice and 2 Follow-up Protocol Assistance letters were adopted at the 23-26 June 2008 CHMP meeting.

New requests for Scientific Advice Procedures

The Committee accepted 25 new Requests for which the procedure started at the SAWP meeting held on 2-5 June 2008. The new requests are divided as follows: 19 Initial Scientific Advice, 2 Follow-up Scientific Advice, 2 Initial Protocol Assistance and 2 Follow-up Protocol Assistance.

DOCUMENTS PREPARED BY THE CHMP WORKING PARTIES ADOPTED DURING THE JUNE 2008 CHMP MEETING

WORKING PARTY ON SIMILAR BIOLOGICAL (BIOSIMILAR) MEDICINAL PRODUCTS (BMWP)

Reference number	Document	Status[3]
EMEA/CHMP/BMWP/ 170734/2008	Concept paper on the revision of the guidance on similar biological medicinal products containing recombinant erythropoietins	Adopted for 3-month public consultation

QUALITY WORKING PARTY (QWP)

Reference number	Document	Status[3]
EMEA/CHMP/CVMP/ QWP/321287/2008	Questions & Answers document on glycerol contamination	Adopted
EMEA/CHMP/QWP/ 321315/2008	Safety Annex to the Quality Medicinal Gases Guideline	Adopted
EMEA/CHMP/QWP/ 321351/2008	Questions & Answers document on Investigational Medicinal Products in clinical trials	Adopted
EMEA/CHMP/CVMP/ QWP/321388/2008	Questions & Answers document on Calculation of Expiry Dates	Adopted
EMEA/CHMP/CVMP/ QWP/321422/2008	Questions & Answers document on Uniformity of Dosage Units	Adopted

SAFETY WORKING PARTY (SWP)

Reference number	Document	Status[3]
EMEA/CHMP/SWP/ 431994/2007	Revised Question & Answers document on the CHMP Guideline on the Limits of Genotoxic Impurities	Adopted
EMEA/CHMP/SWP/ 67006/2008	CHMP SWP Report to CHMP on the use of Red2G as colouring matter in medicinal products	Adopted
EMEA/CHMP/SWP/ 302413/2008	Concept Paper on Single Dose/Acute Toxicity	Adopted for 3-month public consultation

EFFICACY WORKING PARTY (EWP)

Reference number	Document	Status[3]
CPMP/EWP/1119/98 Rev 1	Guideline on Clinical Evaluation of Diagnostic Agents	Adopted for 6-month public consultation

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

Reference number	Document	Status[3]
EMEA/CHMP/EWP/ 321066/2008	Appendix 1 to the Guideline on Clinical Evaluation of Diagnostic Agents (CPMP/EWP/1119/98 Rev 1) on imaging agents.	Adopted for 6-month public consultation.

CHMP Working group with Health Care Professionals (HCPWG)

Reference number	Document	Status[3]
EMEA/185036/2008	Draft Recommendations for the future interaction between the EMEA and healthcare professionals' organisations	Adopted for 3-month public consultation.