



## **Report from the CMD(h) meeting held on 11<sup>th</sup> and 12<sup>th</sup> December 2006**

### Requests for advice from the CMD(h)

The CMD(h) has agreed a questions and answers document which addresses the procedure and criteria for acceptance of requests for advice submitted by Companies or EEA Member States, as foreseen in Article 10 of the CMD(h) Rules of Procedure.

The CMD(h) will provide procedural and regulatory advice in the framework of the mutual recognition and decentralised procedures, when the question submitted is not addressed in CMD(h) documents/Q&As. Applicants are advised to request first advice from NCA(s), which should bring the issue to the attention of the CMD(h) if there is a need to have an EU view.

Any comments on the questions and answers document should be sent to the attention of the CMD(h) secretariat ([sonia.ribeiro@emea.europa.eu](mailto:sonia.ribeiro@emea.europa.eu)) by 20 February 2006.

### Enlargement of the European Union – 1<sup>st</sup> January 2007

The CMD(h) has agreed a revised 'Questions and Answers on MRP&DCP after the EU Enlargement', to consider, where appropriate, the accession of Romania and Bulgaria to the EU on 1<sup>st</sup> January 2007.

Romania and Bulgaria can be included in a mutual recognition or decentralised procedure, as RMS or CMS, as of 1<sup>st</sup> January 2007.

### New Question and Answer on CMD(h) SOP – Disagreement in Procedures – Referral to CMD(h)

The CMD(h) has agreed a new Q&A to address the product information (SPC, package leaflet and labelling) to be included in the marketing authorisations granted in accordance with Article 29(6) of Directive 2001/83/EC, as amended, i.e. where the CMD(h) failed to reach an agreement within the 60 day period.

### Application of Sunset clause in the framework of the mutual recognition and decentralised procedures

The CMD(h) has agreed a paper to consider the sunset clause and, in particular, its application for duplicate(s) in the framework of the mutual recognition and decentralised procedures.

However, the CMD(h) acknowledges that the application of the sunset clause is a national decision to be made by each concerned member state.

### Guidance on submission dates for Applicants of the Decentralised Procedure

The CMD(h) has agreed an updated Guidance on submission dates for Applicants of the Decentralised Procedure, to include the submission dates for 2007.

The Guidance on submission dates has also been updated to include, under assessment step II, Day 106 of the procedure.

### Core SPC for trivalent influenza vaccines

The CMD(h) has agreed a revised core SPC for trivalent influenza vaccines that will be published on the website.

### Change in the EU-Presidency

The December 2006 CMD(h) meeting was the last one under the Finnish presidency of the EU. Germany will take over the presidency in January 2007. Mr. Peter Bachmann will be the Vice-Chairperson of the CMD(h), for the German presidency of the Council of the European Union.

Information on MR procedures for new active substances

A mutual recognition procedure for a medicinal product containing human coagulation factor VIII and human von Willebrand factor has been finalised on 27.11.2006. Please find below information on the Invented name, INN, MAH, Indication, Procedure number and Day 90.

<b>Invented Name (RMS)</b>	Wilate 450/900
<b>INN</b>	Human coagulation factor VIII and human von Willebrand factor (VWF)
<b>Marketing Authorisation Holder</b>	Octapharma GmbH
<b>Indication</b>	<p><u>Von Willebrand disease (VWD)</u></p> <p>Treatment and prophylaxis of bleeding in patients with VWD due to a quantitative and/or qualitative deficiency in VWF, when DDAVP (1-deamino-8-D-arginine vasopressin/desmopressin) treatment is ineffective or contra-indicated. The major indications are:</p> <ul style="list-style-type: none"> <li>- the prevention and treatment of bleeding episodes and</li> <li>- the prevention and treatment of bleeding in minor surgeries.</li> </ul> <p><u>Haemophilia A</u></p> <p>Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital FVIII deficiency) and for the prevention and treatment of bleeding in minor surgical procedures.</p> <p>Controlled clinical trials to evaluate the safety and efficacy of Wilate in major surgeries are ongoing in both VWD and haemophilia A patients. Therefore, limited data are presently available on which to evaluate or to base dosing recommendations in either of these settings. Thus, in the case of major surgical interventions, a precise monitoring of the substitution therapy by means of coagulation analysis (FVIII:C and possibly VWF:RCo) is indispensable.</p>
<b>Procedure number</b>	DE/H/0471/001-2/MR
<b>Day 90</b>	27.11.2006

Information on applications referred to the CMD(h) in accordance with Article 29(1) of Directive 2001/83/EC, as amended

Please find below information on the Name of the products in the RMS, active substances, pharmaceutical forms, procedure numbers, CMS, legal basis, grounds for referral to CMD(h), Day 60 and outcome of the procedures, for the referrals to the CMD(h) finalised on 20.11.2006 and 23.11.2006.

<b>Name of the product in the RMS</b>	Oxaliplatin Medac	Oxaliplatin Ratiopharm	Oxali	Oxamed
<b>Active substance</b>	oxaliplatin			
<b>Pharmaceutical form</b>	Powder for solution for infusion			
<b>Procedure number</b>	FI/H/584/01/MR	FI/H/585/01/MR	FI/H/587/01/MR	FI/H/589/01/MR
<b>CMS</b>	AT, BE, CY, CZ, DE, DK, EE, ES, FR, HU, IE, LT, NO, PL, PT, SE, SK, UK	AT, BE, CZ, DE, DK, ES, FR, HU, IT, NO, PL, PT, SE, SK, UK	AT, BE, CY, CZ, DE, DK, EE, ES, HU, IE, IT, LT, LU, NO, PL, PT, SE, SK, UK	AT, BE, DE, UK
<b>Legal basis</b>	Article 10a, Directive 2001/83/EC - Bibliographic			
<b>Grounds for referral to CMD(h)</b>	The bibliographic application of oxaliplatin was accepted by all member states except one involved in this procedure. According to the disagreeing MS non-clinical and clinical data were considered insufficient to provide adequate evidence of safety and efficacy.			

<b>Day 60</b>	23.11.06
<b>Outcome</b>	<p>After the responses by the Applicant and the final discussion in CMD(h), it was concluded that the well-established use of oxaliplatin has been demonstrated and that the bibliography of this application is both extensive and of high quality. Thus, the application fulfils the requirements for a well established use and no potential serious public health concern exists.</p> <p>Following the CMD(h) meeting at EMEA on 14 November 2006, the disagreeing MS concurred with the majority view of the other 17 Concerned Member States in these procedures and the view of the RMS that the dossier submitted under “well-established use” comprised data that demonstrated systematic, documented and extensive evidence of use over a period of 10-years. Agreement was reached.</p>

<b>Name of the product in the RMS</b>	Lansoprazole Teva 15, 30mg
<b>Active substance</b>	lansoprazole
<b>Pharmaceutical form</b>	Capsule
<b>Procedure number</b>	UK/H/884/01-02/MR
<b>CMS</b>	AT, BE, CZ, DE, DK, ES, FI, FR, HU, IE, NL, NO, PL, PT, SE, SK
<b>Legal basis</b>	Art 10.1, Directive 2001/83/EC - Generic
<b>Grounds for referral to CMD(h)</b>	A serious public health concern was raised by three Member States who considered that bioequivalence in the fed state had not been established for registration in the national market concerned. Bioequivalence had been demonstrated only under fasting conditions.
<b>Day 60</b>	23.11.06
<b>Outcome</b>	<p>At the CMD(h) meeting the RMS presented its view and the applicant’s written and oral explanation were discussed.</p> <p>The Company explained the absence of any potential risk to public health resulting from the findings of the fed study (90% CI for AUCinf. 78-110%). Lansoprazole’s bioavailability is not only markedly reduced (by approx. 70%) when taken with food, but its absorption, in the presence of food, can be quite erratic as shown by the large intra-subject variability (70-82%). This is particularly so following a high fat high calorie meal as is the case with the applicant’s fed study.</p> <p>The SPC and PIL are amended to make it clear that the product should be administered on an empty stomach. The final proposed wording was: The capsules are swallowed whole with liquid. The capsules may be emptied, but the contents may not be chewed or ground. Concomitantly taken food slows down and reduces the absorption of lansoprazole. This medicine has the best effect when taken into empty stomach.</p> <p>This is consistent with the outcome of the Article 29 referral for generic lansoprazoles (which was converted to Commission Decision on 21 February 2006).</p> <p>However, the proposal was not acceptable to the CMS and the application was therefore referred to CHMP for arbitration.</p>

<b>Name of the product in the RMS</b>	Ondansetron 2mg/ml solution for injection
<b>Active substance</b>	ondansetron
<b>Pharmaceutical form</b>	Solution for injection
<b>Procedure number</b>	UK/H/850/01/MR

<b>CMS</b>	AT, BE, CZ, DK, EE, ES, LT, LV, PL, PT, SE, SI, SK
<b>Legal basis</b>	Art 10.1, Directive 2001/83/EC - Generic
<b>Grounds for referral to CMD(h)</b>	A serious public health concern was raised by a Member State regarding the lack of concomitant therapy with dexamethasone in protecting against delayed or prolonged emesis in section 4.2 of the SPC.
<b>Day 60</b>	20.11.06
<b>Outcome</b>	<p>The RMS gave a presentation on the procedure.</p> <p>The RMS was of the view that the changes to the posology section would have implications on other ondansetron SPCs, including oral and suppository formulations and did not consider it appropriate to substitute the current text with a recommendation to combine dexamethasone with ondansetron, since evidence for this particular combination had not been formally assessed.</p> <p>However, the RMS acknowledged that important issues had been raised and that the text under discussion could be improved and proposed to include the following under section 4.2:          “Prescribers intending to use ondansetron in the prevention of delayed nausea and vomiting associated with chemotherapy or radiotherapy in adults, adolescents or children should take into consideration current practice and appropriate guidelines”.</p> <p>This proposal was accepted by all CMS. Agreement was therefore reached.</p>

Name of the product in the RMS	Ramipril HCT 2.5/12.5mg tablets	Ramipril HCT 5/25mg tablets
Active substance	ramipril/hydrochlorothiazide	
Pharmaceutical form	Tablet	
Procedure number	NL/H/721/01-02/MR	NL/H/723/01-02/MR
CMS	DE, IT	AT, DK, FI, SE
Legal basis	Art 10.1, Directive 2001/83/EC - Generic	
Grounds for referral to CMD(h)	Two member states have the opinion that, due to the lack of an add-on study in non-responders to HCT, the add-on indication for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on HCT alone cannot be granted.	
Day 60	23.11.06	
Outcome	<p>All Concerned Member States are in agreement that the add-on effects of ramipril to non-responders to HCT have been adequately demonstrated by results from appropriately designed parallel group comparative studies of the combination with the individual components.</p> <p>The CMD(h) forwarded a request for further discussion of the CHMP NfG hypertension (CPMP/EWP/2238/95 Rev 2) to the cardiovascular group of EWP, in relation to the statements in section 7.2.1 and addendum, section 3.3 which could be regarded as slightly contradictory. Therefore the following two questions were posed to the EWP for clarification regarding the assessment of combination medicinal products:          Is it possible to further specify when one pivotal add-on study is sufficient?          Should omission of the add-on trial on the second component be the exception or the rule?</p> <p>Agreement reached.</p>	

<b>Name of the product in the RMS</b>	Sertraline 50, 100mg tablets
<b>Active substance</b>	sertraline
<b>Pharmaceutical form</b>	Tablet
<b>Procedure number</b>	UK/H/863/01-02/MR
<b>CMS</b>	AT, BE, CZ, DE, DK, EL, ES, FI, FR, HU, IE, IT, NL, NO, PL, PT, SE
<b>Legal basis</b>	Art 10.1, Directive 2001/83/EC - Generic
<b>Grounds for referral to CMD(h)</b>	<p>A serious public health concern was raised by a Member State who considered that bioequivalence of the application product to an adequate comparator had not been established for registration in the national market concerned.</p> <p>Bioequivalence had been demonstrated between the applicant's sertraline tablets and Lustral 100mg tablets (the reference product authorised in the RMS).</p> <p>A biostudy was requested with the relevant 100mg capsule formulation of the reference product.</p>
<b>Day 60</b>	23.11.06
<b>Outcome</b>	<p>At the CMD(h) meeting the RMS presented its view and the applicant's written explanation was discussed.</p> <p>The applicant had submitted the justification that in accordance with the guidance notes for the Investigation of Bioavailability and Bio-equivalence (CPMP/EWP/QWP/1401/98) any product is considered essentially similar to the reference product when it satisfies the criteria of the same qualitative and quantitative composition in terms of the active substance and having the same pharmaceutical form. Differences in the excipients for the tablets and capsules were not expected to cause any significant differences in efficacy or safety and dissolution data were provided to support similar bioavailability of the test and reference products. The company asserted that article 10.2(b) of the amended directive 2001/83/EC allows various oral immediate release dosage forms, such as tablets and capsules to be considered to be the 'same pharmaceutical form'.</p> <p>The view of the CMD(h) was that this has to be substantiated for each pharmaceutical form.</p> <p>The CMD(h) was of the opinion that it was the task of the Applicant to demonstrate bioequivalence against the relevant RMP, if there are different pharmaceutical forms available in different Member States and agreed that authorisation of the medicinal product could represent a serious public health concern in the CMS. In this case the RMP was available in alternative dosage forms.</p> <p>The applicant made the commitment to submit the results of a bioequivalence study between the test product and the capsule formulation of the RMP to accompany a further application.</p> <p>This was acceptable to CMS and resolution on the referral completed.</p>

<b>Name of the product in the RMS</b>	Infusiflux
<b>Active substance</b>	fluconazole
<b>Pharmaceutical form</b>	Solution for infusion
<b>Procedure number</b>	SE/H/605/01/MR
<b>CMS</b>	AT, DE, IT, NL, UK
<b>Legal basis</b>	Art 10.1, Directive 2001/83/EC - Generic
<b>Grounds for referral to</b>	Potential serious risk to public health concern was raised by one CMS

<b>CMD(h)</b>	regarding the posology for the treatment of systemic candida infections.
<b>Day 60</b>	23.11.06
<b>Outcome</b>	Agreement was reached based on the following posology: The dose in candidaemia and other invasive Candida infections is 400-800 mg on the first day and 200-400 mg daily thereafter. The dose depends on the type and severity of the infection. In most cases a loading dose of 800 mg on the first day followed by 400 mg daily thereafter may be preferable. The duration of treatment, often up to several weeks, is determined by the clinical response.

## **NEW APPLICATIONS**

### **Mutual Recognition Procedure**

The CMD(h) noted that **47** new Mutual Recognition Procedures were finalised during the month of November 2006. **12** Mutual Recognition Procedures for new applications were referred to CMD(h) in this period. **1** Mutual Recognition Procedures for a new application was referred to CHMP in this period.

The status as of 30<sup>th</sup> November of procedures under Mutual Recognition is as follows:

Year	Procedures from New applications finalised	Procedures from New applications in process	Procedures referred to CMD(h)	Agreement reached in the CMD(h)	Arbitrations referred to CHMP
2006	464	253	86 N.A.	48	20

**41** Mutual Recognition Procedures (regarding **66** products) started in November 2006. The categories of these procedures are as follows:

6 known active substances (already authorised in at least one member state).

**1** new active substance for a repeat use application.

**34** abridged applications, including **19** multiple and **1** repeat use applications.

The new procedures started in November related to **5** full dossiers, **28** generics, **6** hybrid applications and **2** bibliographic applications.

**All** of these procedures consisted of chemical substance applications.

**40** of these procedures related prescription-only medicinal products and **1** procedure related to a non-prescription medicinal product in the reference Member State<sup>1</sup>.

Number of countries involved in the new applications in Mutual Recognition procedure started in November 2006.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (1)	18
DE (1)	8
DE (2)	3
DE (1)	15
DE (1)	1
DE (1)	15
DE (1)	1
DE (1)	15
FI (2)	9

<sup>1</sup> In this category products are classified as prescription-only or Non-prescription (OTC) products when the RMS has approved them accordingly, although the legal status is not part of the Mutual Recognition Procedure.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
FI (2)	2
FI (1)	1
FI (1)	1
FI (1)	1
FI (2)	23
FR (3)	8
FR (1)	17
NL (3)	3
NL (2)	1
NL (2)	10
NL (3)	6
NL (3)	9
NL (3)	10
NL (3)	5
NL (2)	1
NL (2)	2
NL (1)	18
NL (2)	3
NL (2)	2
NL (1)	1
NL (1)	2
NL (1)	1
NL (2)	4
SE (1)	12
SE (1)	8
SE (1)	2
SE (1)	2
UK (1)	1
UK (1)	9
UK (2)	18

### Decentralised Procedure

The CMD(h) noted that there was **no** new Decentralised Procedure finalised during the month of November 2006. **1** Decentralised Procedure was referred to the CMD(h) in this period.

The status as of 30<sup>th</sup> November of procedures under Decentralised Procedure is as follows:

Year	Procedures from New applications finalised	Procedures from New applications in process	Procedures referred to CMD(h)	Agreement reached in the CMD(h)	Arbitrations referred to CHMP
2006	19	398	1	--	--

**58** Decentralised Procedures (regarding **158** products) started in November 2006. The categories of these procedures are as follows:

**52** abridged applications, including **25** multiple applications.

**2** known active substance applications.

**4** Line Extension applications, including **3** multiple applications.

The new Decentralised procedures started related to **45** generic, **7** hybrid, **4** full dossier, **1** informed consent and **1** bibliographic applications.

**All** of these procedures consisted of chemical substance applications.

All of these procedures related to prescription-only medicinal products in the reference Member State<sup>2</sup>.

Number of countries involved in the new applications in Decentralised procedures started in November 2006.

<b>Reference Member State (number of products involved in the procedure)</b>	<b>Number of CMSs involved in the procedure</b>
DE (2)	6
DE (1)	10
DE (1)	14
DE (1)	11
DE (1)	1
DE (4)	6
DE (1)	3
DE (3)	15
DE (3)	6
DE (3)	2
DE (1)	12
DE (1)	6
DE (2)	16
DE (1)	1
DE (1)	21
DE (1)	3
DE (1)	2
DE (1)	12
DE (1)	10
DE (1)	3
DE (1)	20
DE (1)	1
DE (1)	1
DK (2)	7
DK (2)	1
DK (1)	19
DK (4)	6
DK (3)	7
DK (1)	7
FI (1)	7
FI (7)	7
FI (7)	8
FR (1)	19
NL (3)	9
NL (1)	8
NL (3)	1
NL (6)	23
NL (6)	5
NL (6)	5
NL (6)	2
NL (6)	2
NL (1)	1
NL (1)	1
SE (1)	23
SE (1)	2
SE (1)	1
SE (1)	1
SE (6)	18
SE (6)	7
SE (6)	6
SE (6)	2
SE (6)	1
SE (6)	1
SE (4)	1
UK (1)	1
UK (3)	1
UK (3)	4
UK (1)	23

<sup>2</sup> In this category products are classified as prescription-only or Non-prescription (OTC) products as applied for in the RMS, although the legal status is not part of the Decentralised Procedure.

## VARIATIONS AND RENEWALS

### Mutual Recognition and Decentralised Procedures

The CMD(h) noted that **428** type IA variations, **163** type IB variations and **178** type II variations were finalised during the month of November 2006. **32** renewals were finalised in this period.

The status as of 30<sup>th</sup> November of variations and renewals under Mutual Recognition is as follows:

Year	Procedures from Type IA variations finalised	Procedures from Type IB variations finalised	Procedures from Type II variations finalised	Renewals finalised	Arbitrations referred to CHMP
2006	4118	2033	1709	325	--

**All documents mentioned in this press release can be found at the CMD(h) website at the European Medicines Authorities Windows under the heading *Press Releases*.**

*Information on the above mentioned issues can be obtained from the chair of the CMD(h):*

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*Or you could visit the **CMD(h) web site** at the EUROPEAN NATIONAL MEDICINES AUTHORITIES WINDOW:*

<http://heads.medagencies.org/>