

## **Report from the CMD(h) meeting held on 21<sup>st</sup>, 22<sup>nd</sup> and 23<sup>rd</sup> April 2008**

### CMD(h) Best Practice Guide on the use of eCTD in the mutual recognition and decentralised procedures

Further to experience gained both by Industry and National Competent Authorities, the CMD(h) has developed guidance to facilitate the use of eCTD as submission format in the MRP and DCP.

The BPG will be published on the CMD(h) website. It is highly recommended and the aim of this BPG to encourage the submission of eCTD applications in the MRP and DCP and, therefore, to enable all parties to gain more experience.

Any comments should be sent to the CMD(h) Secretariat ([sonia.ribeiro@emea.europa.eu](mailto:sonia.ribeiro@emea.europa.eu)) until the end of 2008, coordinated where possible by trade associations.

The CMD(h) has also agreed revised versions of the template and recommendation on the cover letter for new applications submitted through MRP/DCP, to specify for eCTD applications if the “Comprehensive Model” or “Parallel National Model” is used.

### CMD(h)/EMEA Sub-Group on Paediatric Regulation

The CMD(h) and the EMEA have agreed on additional Q&As to address validation of applications and submission of paediatric investigation plans (PIPs) in accordance with Articles 7 and 8 of the Paediatric Regulation in the framework of the mutual recognition procedure. The new Q&As will be published on the website.

The CMD(h) has also agreed a Best Practice Guide on the EU work sharing procedure for paediatric studies submitted according to Article 45 of the Paediatric Regulation, addressing the organisation of the work-sharing, the timelines for assessment of the paediatric studies, etc.

The BPG will be published on the CMD(h) website for a one-month public consultation period. Any comments on the BPG should be sent to the CMD(h) secretariat ([sonia.ribeiro@emea.europa.eu](mailto:sonia.ribeiro@emea.europa.eu)) by 9<sup>th</sup> June 2008.

### EU Work sharing Project – Assessment of paediatric data

The Marketing Authorisation Holder for the medicinal product Fositen (fosinopril), involved in the EU work sharing project – assessment of paediatric data, is requested to submit, within 60 days of the finalisation of the procedure, i.e. by 17<sup>th</sup> June 2008, Type II variations to implement the agreed text for inclusion in the SPC.

The EU work-sharing procedure for the medicinal product Lamictal (lamotrigine) in the treatment of partial seizures with or without secondary generalisation in the add-on setting between 1 month and 24 months of age has been finalised.

The CMD(h) has agreed to update the list of active substances in the EU work sharing procedure in the assessment of paediatric data with the agreed text for inclusion in the SPC, for transparency reasons.

### 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 product in the RMS, active substance, pharmaceutical forms, procedure number, CMS, legal basis, grounds for referral to CMD(h), Day 60 and outcome of the procedure, for the referral to the CMD(h) finalised on 28.03.2008.

**Report from the CMD(h) meeting held in April 2008**

<b>Name of the product in the RMS</b>	Nebivolol Nucleus 5mg	Nebilat 5 mg	Taminal 5 mg	Nebivolol Actavis 5 mg
<b>Active substance</b>	nebivolol			
<b>Pharmaceutical form</b>	Tablet			
<b>Procedure number</b>	DE/H/0976/001/DC	DE/H/0977/001/DC	DE/H/0978/001/DC	DE/H/0979/001/DC
<b>CMS</b>	IT	IT	IT, PT	AT, IT, LT, MT, NL
<b>Legal basis</b>	Art 10.1 Dir 2001/83/EC - Generic			
<b>Grounds for referral to CMD(h)</b>	The application was referred to the CMD(h) on bioequivalence grounds, as the 90% confidence interval of the ratio of Cmax (78.51% - 91.83%) was outside the predefined acceptance limits of 0.80 – 1.25 and it was considered not acceptable to widen the acceptance range for the Cmax after completion of the study.			
<b>Day 60</b>	28 <sup>th</sup> March 2008			
<b>Outcome</b>	The applicant has performed a new bioequivalence study with predefined widening of the acceptance range. No discussion of the acceptance of the widening has happened, as the results of the bioequivalence study was within the normal acceptance limits of 0.80 – 1.25.  Agreement reached			

<b>Name of the product in the RMS</b>	Fluvastanever
<b>Active substance</b>	fluvastatin
<b>Pharmaceutical form</b>	Prolonged release tablet
<b>Procedure number</b>	DK/H/1096/001/DC
<b>CMS</b>	AT, BE, CZ, DE, ES, FI, FR, NL, PL, PT, SE, SK, UK
<b>Legal basis</b>	Art 10.1 Dir 2001/83/EC - Generic
<b>Grounds for referral to CMD(h)</b>	The procedure was referred on grounds that BE had not been adequately shown. A post hoc widening of the acceptance range was not considered acceptable and the explanation for the food effect was not considered supportable.
<b>Day 60</b>	28 <sup>th</sup> March 2008
<b>Outcome</b>	An agreement could not be reached and the application was withdrawn in all MS before day 60.

<b>Name of the product in the RMS</b>	Fluvastanono	Fluvastanicht
<b>Active substance</b>	fluvastatin	
<b>Pharmaceutical form</b>	Prolonged release tablet	
<b>Procedure number</b>	DK/H/1097/001/DC	DK/H/1098/001/DC
<b>CMS</b>	AT, DE, ES, FI, FR, HU, IE, LU, PL	AT, DE, ES, HU, PT
<b>Legal basis</b>	Art 10.1 Dir 2001/83/EC - Generic	
<b>Grounds for referral to CMD(h)</b>	The procedures were referred on grounds that BE had not been adequately shown. A post hoc widening of the acceptance range was not considered acceptable and the explanation for the food effect was not considered supportable.	
<b>Day 60</b>	28 <sup>th</sup> March 2008	
<b>Outcome</b>	An agreement was reached during the referral procedure regarding the concerned issues, and the procedures were closed on day 60 with positive outcome.	

<b>Name of the product in the RMS</b>	Estradiol/Norethisteronacetaat 30/95 & 40/130	Estradiol/Estradiol Norethisteronacetaat Kit 37,5 + 30/95 & 50 + 40/130
<b>Active substance</b>	estradiol/norethisterone	
<b>Pharmaceutical form</b>	Transdermal patch	
<b>Procedure number</b>	NL/H/1155/001-002/MR	NL/H/1156/001-002/MR
<b>CMS</b>	DE	
<b>Legal basis</b>	Art 8.3(i) Dir 2001/83/EC – Full dossier	
<b>Grounds for referral to CMD(h)</b>	There were concerns with regard to the following issues: 1. Endometrial safety was insufficiently demonstrated 2. Bleeding pattern is less favourable than reported for the reference products selected	
<b>Day 60</b>	28 <sup>th</sup> March 2008	

<b>Outcome</b>	<p>In response to the first question, the applicant demonstrated that the overall percentage of patients without any follow-up biopsy is comparable to number of biopsies reported in published studies. The upper limits of the 95% confidence intervals are below 2% for all 4 patches.</p> <p>In response to the second question, the applicant clarified that the bleeding pattern is less favourable than reported for the reference products selected in the clinical trials, but it is in the range of that noted with the continuous and sequentially combination patches approved through MRP. Clear information on the bleeding pattern is included in the SPC and PL.</p> <p>Agreement reached</p>
----------------	---

<b>Name of the product in the RMS</b>	Venlafaxine Sandoz
<b>Active substance</b>	venlafaxine hydrochloride
<b>Pharmaceutical form</b>	Prolonged release hard capsule
<b>Procedure number</b>	PT/H/0137/001-002/MR
<b>CMS</b>	<p><u>PT/H/0137/01/MR</u>: AT, BE, DE, DK, FI, FR, NL, NO, PL, SE, SI</p> <p><u>PT/H/0137/02/MR</u>: AT, BE, BG, CZ, DE, DK, EL, ES, FI, FR, HU, IT, LT, NL, NO, PL, SE, SI, UK</p>
<b>Legal basis</b>	Art 10.1 Dir 2001/83/EC - Generic
<b>Grounds for referral to CMD(h)</b>	The procedure was referred on grounds that BE had not been adequately shown. In the steady-state study a statistically significant difference in C <sub>ssmin</sub> was observed. The confidence interval for this parameter is not included in the normal acceptance range [80;125] % neither in the extended [75; 133]%. The consequences of such difference on the efficacy/safety profile of the product under review could not be predicted.
<b>Day 60</b>	28 <sup>th</sup> March 2008
<b>Outcome</b>	<p>There was an oral explanation by the Applicant and presentations made by the RMS and CMS. RMS as well as referring CMS presented their position on the acceptability of a predefined widened 90% CI limit for C<sub>ssmin</sub>.</p> <p>Agreement was reached with the commitment to refer the general issue of considering C<sub>min</sub> and %PTF as a primary evaluation criterion in steady-state BE studies to the PK sub-group, for a common approach.</p>

<b>Name of the product in the RMS</b>	Cilazapril 0.5, 1, 2.5 & 5mg Film-Coated Tablets
<b>Active substance</b>	cilazapril
<b>Pharmaceutical form</b>	Film-coated tablet
<b>Procedure number</b>	UK/H/1005/001-004/DC
<b>CMS</b>	<p><u>UK/H/1005/01/DC</u>: AT, CZ, DE, EE, EL, FR, LT, LV, PT, SE</p> <p><u>UK/H/1005/02/DC</u>: CZ, DE, EE, EL, ES, FR, LT, LV, PL, PT, SE</p> <p><u>UK/H/1005/03/DC</u>: AT, CZ, DE, EE, EL, ES, FR, LT, LV, PL, PT, SE, SK</p> <p><u>UK/H/1005/04/DC</u>: AT, CZ, DE, EE, EL, ES, LT, LV, PL, PT SE</p>
<b>Legal basis</b>	Art 10.1 Dir 2001/83/EC - Generic
<b>Grounds for referral to CMD(h)</b>	One CMS raised concern over the inclusion of the indication in heart failure and the data available to support this indication. Additional concerns were raised on the dosing proposed in renal failure.
<b>Day 60</b>	28 <sup>th</sup> March 2008
<b>Outcome</b>	<p>At the CMD(h) meeting there was discussion on the published data available to support the indication of heart failure. It was considered that the overall results support use of cilazapril in symptomatic treatment of heart failure and agreement was reached on inclusion of this indication. Agreement was also reached on the dosing schedule. Nevertheless, CMD(h) considered that the issue of dosing of cilazapril, and other long half life ACE inhibitors in renally impaired patients, including those undergoing haemodialysis, should be referred to the Safety Working Party and Efficacy Working Party for further discussion and advice.</p>

## NEW APPLICATIONS

### Mutual Recognition Procedure

The CMD(h) noted that **31** Mutual Recognition Procedures were finalised during the month of March 2008. **No** Mutual Recognition Procedures were referred to CMD(h) in this period. **1** Mutual Recognition Procedure was referred to CHMP in this period.

The status as of 31<sup>st</sup> March 2008 of procedures under Mutual Recognition is as follows:

Year	New applications finalised	New applications in process	Referred to CMD(h)	Agreement reached in the CMD(h)		Withdrawn during CMD(h) referral	Applications referred to CHMP	
				For procedures referred in			For procedures referred to CMD(h) in	
				2007	2008		2007	2008
2008	76	192	10	7	1	--	2	--

**40** Mutual Recognition Procedures (regarding **85** products) started in March 2008. The categories of these procedures are as follows:

**5** known active substance (already authorised in at least one member state) applications, including **4** repeat use applications.

**31** abridged applications, including **10** multiple and **8** repeat use applications.

**3** line extension applications, which are all repeat use applications.

**1** new active substance application, which is a repeat use application.

The new procedures started in March 2008 related to **6** full dossier, **31** generic, **1** fixed combination and **2** bibliographic applications.

**39** of these procedures consisted of chemical substance products and **1** procedure consisted of a biological blood product.

**39** of these procedures related to 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 March 2008.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (1)	8
DE (1)	2
DE (1)	2
DE (1)	5
DK (1)	2
DK (4)	3
DK (4)	1
DK (4)	4
DK (4)	5
DK (4)	11
DK (4)	9
FI (4)	6
FI (2)	1
FR (1)	4

<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
HU(1)	6
IT (1)	9
NL (1)	2
NL (1)	1
NL (1)	3
NL (1)	4
NL (1)	6
NL (1)	5
NL (1)	1
NL (1)	4
NL (1)	1
NL (2)	4
NL (2)	5
NL (5)	24
NL (4)	16
NL (1)	2
NL (4)	12
PT (1)	1
PT (3)	12
PT (4)	13
SE (3)	5
SE (3)	6
SE (3)	2
UK (1)	8
UK (1)	17
UK (2)	1

### Decentralised Procedure

The CMD(h) noted that there were **57** Decentralised Procedures finalised during the month of March 2008 with a positive outcome. There was **1** Decentralised procedure withdrawn after Day 120. **2** Decentralised Procedures were referred to the CMD(h) in this period. **2** Decentralised Procedures were referred to the CHMP in this period.

The status as of 31<sup>st</sup> March 2008 of procedures under Decentralised Procedure is as follows:

Year	New applications finalised		New applications withdrawn <sup>2</sup>	New applications in process	Referred to CMD(h)	Agreement reached in the CMD(h) For procedures referred in		Withdrawn during CMD(h) referral	Referred to CHMP For procedures referred to CMD(h) in	
	Positive outcome	Negative outcome				2007	2008		2007	2008
2008	143	--	1	1180	11	2	7	1	2	--

**110** Decentralised Procedures (regarding **216** products) started in March 2008. The categories of these procedures are as follows:

**104** abridged applications, including **40** multiple applications.

**4** known active substance applications.

**2** line extension applications.

The new Decentralised procedures started in March related to **100** generic, **5** bibliographic, **4** hybrid and **1** full dossier.

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

<sup>2</sup> After day 120.

**108** of these procedures related to prescription-only medicinal products and **2** to non-prescription medicinal products in the reference Member State<sup>3</sup>.

Number of countries involved in the new applications in Decentralised procedures started in March 2008.

<b>Reference Member State (number of products involved in the procedure)</b>	<b>Number of CMSs involved in the procedure</b>
AT (4)	4
AT (4)	2
AT (4)	1
AT (1)	16
AT (1)	3
AT (1)	1
AT (4)	4
AT (4)	4
CZ (1)	6
DE (1)	2
DE (1)	4
DE (1)	2
DE (1)	5
DE (1)	26
DE (4)	2
DE (2)	13
DE (3)	10
DE (2)	1
DE (2)	1
DE (2)	10
DE (2)	2
DE (2)	1
DE (4)	9
DE (1)	11
DE (4)	16
DE (2)	4
DE (2)	1
DK (1)	9
DK (1)	14
DK (1)	3
DK (2)	13
DK (2)	3
DK (2)	4
DK (2)	12
DK (2)	8
DK (2)	19
DK (2)	2
DK (2)	1
DK (2)	1
EE (3)	16
EE (3)	8
EE (3)	1
EE (3)	4
EE (3)	1
EE (3)	1
EE (3)	1
EE (3)	1
FI (3)	4
FR (1)	4
HU (2)	7
HU (4)	18
HU (4)	1
HU (4)	1
HU (2)	7
IS (2)	2

<sup>3</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.

IS (1)	2
IT (3)	1
IT (3)	8
NL (2)	12
NL (1)	28
NL (2)	16
NL (1)	5
NL (1)	6
NL (1)	4
NL (4)	18
NL (1)	8
NL (2)	12
NL (2)	8
NL (2)	4
NL (2)	1
NL (2)	5
NL (2)	1
NL (2)	1
NL (2)	5
NL (1)	11
NL (1)	8
NL (1)	4
NL (1)	1
NL (1)	5
NL (1)	1
NL (1)	1
NL (1)	5
NL (3)	4
NL (1)	10
SE (1)	9
SE (1)	9
UK (4)	20
UK (1)	5
UK (4)	18
UK (1)	5
UK (2)	4
UK (2)	2
UK (2)	8
UK (2)	1
UK (1)	13
UK (1)	17
UK (1)	23
UK (4)	1
UK (1)	23
UK (1)	15
UK (1)	1
UK (1)	4
UK (2)	3
UK (1)	1
UK (1)	2
UK (1)	1
UK (1)	1
UK (1)	15
UK (1)	1
UK (1)	1

## **VARIATIONS AND RENEWALS**

### **Mutual Recognition and Decentralised Procedures**

The CMD(h) noted that **428** type IA variations, **208** type IB variations and **196** type II variations were finalised during the month of March 2008. **26** renewals were finalised in this period. There was **no** procedure referred to the CHMP in this period.

The status as of 31<sup>st</sup> March 2008 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	Applications referred to CHMP
2008	1487	610	495	96	--

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

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

*Mrs. Truus Janse-de Hoog*

*Phone: + 31 70 356 74 08*

*College ter Beoordeling van Geneesmiddelen*

*Fax: + 31 70 356 75 15*

*Kalvermarkt 53*

*E-mail: [gm.janse@cbg-meb.nl](mailto:gm.janse@cbg-meb.nl)*

*NL – 2500 Den Haag , The Netherlands*

*Or you could visit the CMD(h) web site at:*

<http://www.hma.eu/cmdh.html>