

## **Report from the CMD(h) meeting held on 15<sup>th</sup>, 16<sup>th</sup> and 17<sup>th</sup> October 2007**

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

The CMD(h) and the EMEA held a meeting on 15 October 2007 with representatives of Interested Parties, to discuss the procedural guidance developed to facilitate the submission of information pursuant to the Paediatric Regulation and a proposal for the revision of the questions and answers (Q&As) document, addressing the submission of Paediatric studies according to Articles 45 and 46 of the Paediatric Regulation and other Paediatric information.

The CMD(h) and the EMEA have agreed to revise the declaration concerning paediatric studies already submitted to the Competent Authority (Art. 45), to take into account the comments received at the meeting.

The line listing together with the declaration (Annex I) has to be submitted to the respective Competent Authority(ies) and copied to the EMEA by 26 January 2008.

The CMD(h) and the EMEA would welcome to receive also the wording of the SmPC (4.1 and/or 4.2) for medicinal products with paediatric use (Annex II), as a one-off exercise by 26 January 2008.

However, the CMD(h) and the EMEA agreed with the request from Interested Parties to extend the deadline for submission of information on the wording of the SmPC (4.1 and/or 4.2) for medicinal products with paediatric use by a period of 3 months, i.e. until 26 April 2008.

The revised declaration concerning paediatric studies already submitted to the Competent Authority (Art. 45) and the revised questions and answers document will be published on the website.

A list of addresses to be used for the submission of paediatric information for each Competent Authority will also be published on the website.

Marketing Authorisation Holders should refer to National Competent Authorities websites for further specific instructions.

The templates and the respective declarations should be sent to the Competent Authority(ies) where the medicinal products are authorised in electronic format only and copied to the EMEA ([paedstudies@emea.europa.eu](mailto:paedstudies@emea.europa.eu)).

### List of medicinal products for SPC harmonisation – Consultation with Interested Parties

The CMD(h) has agreed a new list of medicinal products for which a harmonised SPC should be drawn up, in accordance with Article 30(2) of Directive 2001/83/EC, as amended.

The list of medicinal products for SPC harmonisation will be published on the website for an eight week period for public consultation.

Any comments on the list of medicinal products for SPC harmonisation should be sent to the CMD(h) secretariat ([sonia.ribeiro@emea.europa.eu](mailto:sonia.ribeiro@emea.europa.eu)) by 2 January 2008, coordinated where possible by trade associations.

### CMD(h) meeting with representatives of Interested Parties

The CMD(h) has agreed to invite Interested Parties for a meeting on 12 November 2007. The main topics proposed for discussion with Interested Parties include MSs resources in the MRP and DCP, the revised DCP SOP, a report from the activities of the Working Group on Validation issues/ National requirements, experience with consultation with target patient groups and recommendations for bridging and an overview of MSs experience with national implementation following MRP/DCP.

### Decentralised Procedure – Member States Standard Operating Procedure

Further to the comments received on the draft revised Decentralised Procedure SOP, the CMD(h) has agreed a final version of the procedure that will be published on the website.

The CMD(h) would like to thank Interested Parties for the comments received on the SOP.

### Guidance on submission dates for Applicants of the Decentralised Procedure (DCP)

The CMD(h) has adopted an updated Guidance on submission dates for Applicants of the Decentralised Procedure, in order to facilitate planning of submission dates for new applications in the DCP in 2008.

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 clarify that if by the end of a CMD(h) referral procedure for a DCP there is consensus among the RMS and the CMS(s) that the application is not approvable, this will not be referred to the CHMP. An application can only be referred to the CHMP if the MSs involved in the procedure cannot reach consensus.

Questions and Answers – Guidance for Applicants on Biologicals

The CMD(h) has agreed a revised Q&A document, to clarify that biological medicinal products can be registered through the mutual recognition or decentralised procedures, provided that they do not fall within the Annex to Regulation (EC) No 726/2004 – Medicinal products to be authorised by the Community, in which case the centralised procedure has to be followed.

Consultation with Target Patient Groups – meeting the requirements of Article 59(3) without the need for a full test – Recommendations for bridging

The CMD(h) has agreed a document to support extending use of test results to related products, aimed at providing guidance on when bridging will be accepted by Competent Authorities and the type of evidence which will need to be provided, in the situations where a user test or evidence of compliance with Article 59(3) is required.

Application for the renewal of a marketing authorisation granted via the MRP or DCP prior to the granting of the marketing authorisation in all the MSs involved

The CMD(h) has agreed a Q&A to clarify that it should be possible to apply for the renewal of a marketing authorisation granted via the MRP or DCP, in the situation where not all of the Member States involved in the procedure have issued a national marketing authorisation, in view of the legal requirement to apply for the renewal of a marketing authorisation at least six months before the expiry of the marketing authorisation. However, if the national marketing authorisations have not been issued due to the lack of submission of high quality translation of the agreed SPC, PL and labelling after the end of the MRP or DCP, the renewal procedure will not be concluded until the respective national translations are provided.

The CMD(h) has also revised the Q&A addressing the languages to be used for applications for variations and renewals to marketing authorisations granted via the MRP or DCP to state that text proposals for the SPC, PL and labelling in English are accepted with the submission of type II variation and renewal applications, provided that translations of the agreed SPC, PL and labelling have been submitted after the end of the MRP or DCP for the initial marketing authorisation.

Informal CMD(h) meeting - Portugal

An informal meeting will be held in Lisbon on 25-26 October 2007. The meeting will include a joint session with the CHMP, mainly to discuss outcome of referrals to the CHMP. The CMD(h) will also discuss amongst other topics the implementation of the Paediatric Regulation, MSs experiences with national implementation following MRP/DCP and the various telematic projects.

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 27.09.2007.

<b>Name of the product in the RMS</b>	Losartan/Hydroklortiazid Pharmascope 50mg/12.5mg & 100mg/25mg
<b>Active substance</b>	losartan sodium hydrochlorothiazide
<b>Pharmaceutical form</b>	Film-coated tablet
<b>Procedure number</b>	FI/H/0602/001-002/MR
<b>CMS</b>	FI/H/0602/001/MR: AT, BE, CZ, DE, DK, ES, FR, HU, IT, LU, NL, NO, SE, UK FI/H/0602/002/MR: AT, DE, DK, ES, FR, IT, LU, NL, NO, SE

<b>Legal basis</b>	Art 10.1, Dir 2001/83/EC - Generic
<b>Grounds for referral to CMD(h)</b>	Referral was raised by a CMS on grounds of bioequivalence issues regarding the confidence interval of the parent compound losartan between the applied Medicinal Product and the Innovator.
<b>Day 60</b>	27.09.2007
<b>Outcome</b>	After having reviewed the supplementary documentation submitted by the company and after the presentation of the RMS, all outstanding issues were resolved.

<b>Name of the product in the RMS</b>	Clarium 200mg & 330mg
<b>Active substance</b>	clarithromycin
<b>Pharmaceutical form</b>	Prolonged release capsule, hard
<b>Procedure number</b>	FI/H/0624/001-002/MR
<b>CMS</b>	BE, DE, EL, LU, PL
<b>Legal basis</b>	Art 8.3(i) Dir 2001/83/EC - Full dossier
<b>Grounds for referral to CMD(h)</b>	Referral was raised by a CMS on grounds of duration of therapy, the lower limit of age for which Clarium could be indicated and the risk of emergence of resistance due to the PK profile of this product.
<b>Day 60</b>	27.09.2007
<b>Outcome</b>	All the issues were resolved and the SPC was modified accordingly. Consensus was reached and the final conclusion was that a marketing authorisation for Clarium 200 mg could be granted. Clarium 330 mg was withdrawn from the RMS and CMSs prior to the CMD(h) referral.

<b>Name of the product in the RMS</b>	Amisulpride Ratiopharm
<b>Active substance</b>	amisulpride
<b>Pharmaceutical form</b>	Tablet
<b>Procedure number</b>	FR/H/0321/001/MR
<b>CMS</b>	CZ, HU, SK
<b>Legal basis</b>	Art 10.1 Dir 2001/83/EC - Generic
<b>Grounds for referral to CMD(h)</b>	A potential serious risk to public health was raised by one Member State due to differences in Sections 4.3 (contraindications) and 4.4 (Special warnings and precaution for use) with the originator SPC regarding several interactions between amisulpride and drugs potentially cause " <i>Torsades de pointes</i> ".
<b>Day 60</b>	27.09.2007
<b>Outcome</b>	At the CMD(h) meeting, the RMS presented its view and the applicant's written response was discussed. Following the discussion, it was agreed to follow the PhVWP recommendations adopted in May 2006 on this issue and to mention these interactions in Section 4.4 of the SPC. Agreement reached.

<b>Name of the product in the RMS</b>	Omeprazole Sandoz infuus 40
<b>Active substance</b>	omeprazole
<b>Pharmaceutical form</b>	Powder for solution for infusion
<b>Procedure number</b>	NL/H/0719/001/DC
<b>CMS</b>	AT, BE, CZ, DK, EL, ES, FR, IT, PL, PT, SI, UK
<b>Legal basis</b>	Art 10.1 Dir 2001/83/EC - Generic
<b>Grounds for referral to CMD(h)</b>	There is a concern with regard to the contra-indication "Combination therapy with clarithromycin should not be used with hepatic impairment". The applicant was requested to justify this contra-indication.
<b>Day 60</b>	27.09.2007
<b>Outcome</b>	Consensus was reached prior to the CMD(h) meeting.  The SPC was adjusted to include in section 4.4 the following warning: "During combination treatment caution should also be exercised in patients with severe renal or hepatic dysfunction (for dose restriction

	see section 4.2).”, and the contra-indication was deleted from section 4.3.
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<b>Name of the product in the RMS</b>	Formocaps 12 microgram	Formoterol Stada 12 microgram
<b>Active substance</b>	formoterol	
<b>Pharmaceutical form</b>	Inhalation powder, hard capsule	
<b>Procedure number</b>	NL/H/1022/001/MR	NL/H/1023/001/MR
<b>CMS</b>	DE	DE, PL
<b>Legal basis</b>	Art 10.3 Dir 2001/83/EC – Hybrid	
<b>Grounds for referral to CMD(h)</b>	There is a concern with regard to the therapeutic equivalence of this product compared to the reference product. Study results suggest that this product might have a higher availability than the reference product.	
<b>Day 60</b>	27.09.2007	
<b>Outcome</b>	The applications were withdrawn in the RMS and both CMSs prior to start of the CMD(h) referral procedure. Therefore, the procedure was stopped and no discussion was held.	

<b>Name of the product in the RMS</b>	Rapinyl	
<b>Active substance</b>	fentanyl	
<b>Pharmaceutical form</b>	Sublingual tablet	
<b>Procedure number</b>	SE/H/0575/001-007/DC	
<b>CMS</b>	AT, BE, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, NO, PL, PT, SI, SK, UK	
<b>Legal basis</b>	Art 8.3(i) Dir 2001/83/EC - Full dossier	
<b>Grounds for referral to CMD(h)</b>	The procedure was referred to the CMD(h) by four CMSs on the basis that the data submitted by the applicant was insufficient to establish the efficacy and safety of the product and that a clinical study was needed to assess the dose ranging in terms of efficacy and safety.	
<b>Day 60</b>	27.09.2007	
<b>Outcome</b>	At the meeting the RMS presented its view that the bridging strategy presented in the application for marketing authorisation was sufficient. The applicant made use of an oral hearing. It was discussed whether clinical studies would be required to prove the efficacy and safety of the product and no consensus was reached.  Referred to CHMP for arbitration.	

<b>Name of the product in the RMS</b>	Fluconazole 2mg/ml	
<b>Active substance</b>	fluconazole	
<b>Pharmaceutical form</b>	Intravenous infusion	
<b>Procedure number</b>	UK/H/0871/001/MR	
<b>CMS</b>	AT, BE, EE, IE, LT, LU, LV, PL, SI	
<b>Legal basis</b>	Art 10.1 Dir 2001/83/EC - Generic	
<b>Grounds for referral to CMD(h)</b>	The procedure was referred to the CMD(h) due to potential serious risk to public health concerns relating to Sections 4.1 and 4.2 of the SPC	
<b>Day 60</b>	27.09.2007	
<b>Outcome</b>	The applicant addressed outstanding concerns satisfactorily and agreement was reached before the CMD(h) meeting. The final version of the SPC is in line with the outcome of the recent CMD(h) referral for fluconazole 2mg/ml (SE/H/605/01/MR).	

<b>Name of the product in the RMS</b>	Versatis 5%	Lidocaine 5%
<b>Active substance</b>	lidocaine	
<b>Pharmaceutical form</b>	Medicated plaster	
<b>Procedure number</b>	UK/H/1040/001/MR	UK/H/1041/001/MR

<b>CMS</b>	BE, DE, FR, LU, SE, SI	BE, DE, FR, LU, SE, SI
<b>Legal basis</b>	Art 8.3(i) Dir 2001/83/EC - Full dossier	
<b>Grounds for referral to CMD(h)</b>	These procedures were referred to CMD(h) on the grounds that the metabolic pathways of lidocaine result in the formation of several structures which raise potential serious risk to public health in relation to genotoxicity and potential carcinogenic properties (2,6-xylylidine and DMHA). There was concern that there were insufficient data to assess the magnitude of the risk, which was not considered acceptable for treatment to be given long-term.	
<b>Day 60</b>	27.09.2007	
<b>Outcome</b>	<p>At the CMD(h) meeting, the RMS, CMS and the applicant presented their view on the outstanding issues. Proposed changes to the SPC were presented by the applicant and these were agreed following further discussions with the RMS and CMSs after the referral discussion. The applicant committed to conduct additional genotoxicity studies for additional data on potential genotoxicity of lidocaine metabolites as a post approval commitment, and provided a satisfactory Risk Management Plan.</p> <p>Consensus was reached between concerned Member States that the benefit:risk was positive for these products in their intended use and that the products should be approved.</p>	

<b>Name of the product in the RMS</b>	CitraFleet Powder for oral solution
<b>Active substance</b>	sodium picosulfate citric acid
<b>Pharmaceutical form</b>	Powder for oral solution
<b>Procedure number</b>	UK/H/1047/001/MR
<b>CMS</b>	DE, DK, ES, FI, FR, IE, IT, NO, PL, PT, SE
<b>Legal basis</b>	Art 10a Dir 2001/83/EC – Bibliographic
<b>Grounds for referral to CMD(h)</b>	This referral procedure concerned the justification of the combination of actives and the need for comparative data of the combination product with the mono-therapy.
<b>Day 60</b>	27.09.2007
<b>Outcome</b>	The response from the applicant to the questions raised during this referral addressed satisfactorily the outstanding concerns. Agreement between the RMS and CMS was reached before the CMD(h) meeting and the procedure closed on 7th September.

## NEW APPLICATIONS

### Mutual Recognition Procedure

The CMD(h) noted that **15** Mutual Recognition Procedures were finalised during the month of September 2007. **1** Mutual Recognition Procedures was referred to CMD(h) in this period. **No** Mutual Recognition Procedure was referred to CHMP in this period.

The status as of 30<sup>th</sup> September 2007 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 2006	2007		For procedures referred to CMD(h) in 2006	2007
2007	344	183	34	25	21	2	9	4

**42** Mutual Recognition Procedures (regarding **89** products) started in September 2007. The categories of these procedures are as follows:

**9** known active substance (already authorised in at least one member state) applications, including **1** Multiple Application.

**26** abridged applications, including **6** multiple and **3** repeat use applications.

**7** line extension applications.

The new procedures started in September 2007 related to **11** full dossiers, **27** generics, **1** informed consent and **3** bibliographic applications.

**40** of these procedures consisted of chemical substances, **1** biological blood products and **1** biological other.

**41** 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 September 2007.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
CZ (1)	10
CZ (2)	2
CZ (2)	6
DE (1)	10
DE (1)	9
DE (4)	4
DE (4)	17
DE (1)	3
DE (1)	9
DE (3)	7
DE (4)	5
DK (1)	1
DK (1)	9
DK (3)	7
DK (1)	4
DK (1)	17
FI (2)	7
FR (2)	7
FR (1)	2
NL (4)	16
NL (3)	4
NL (1)	4
NL (2)	1
NL (2)	1
NL (3)	6
NL (3)	1
NL (3)	8
NL (3)	1
NL (3)	10
NL (2)	2
NL (4)	4
NL (4)	1
NL (4)	1
SE (1)	24
SE (1)	3
SE (1)	2
SE (3)	4
SE (2)	15
SE (1)	2

<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
SK (1)	5
UK (1)	7
UK (1)	6

### Decentralised Procedure

The CMD(h) noted that there were **39** Decentralised Procedures finalised during the month of September 2007. There was **1** Decentralised Procedure withdrawn at day 210. In addition, there was **1** Decentralised Procedure with negative outcome during this period. **1** Decentralised Procedure was referred to the CMD(h) in this period. **1** Decentralised Procedure was referred to the CHMP.

The status as of 30<sup>th</sup> September 2007 of procedures under Decentralised Procedure is as follows:

Year	New applications finalised		New applications withdrawn <sup>1</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				2006	2007		2006	2007
2007	230	4	16	926	21	1	10	3	--	2

**73** Decentralised Procedures (regarding **161** products) started in September 2007. The categories of these procedures are as follows:

**67** abridged applications, including **22** multiple applications.

**3** known active substance applications.

**3** Line extension applications.

The new Decentralised procedures started in September related to **67** generic and **6** full dossiers.

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

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

Number of countries involved in the new applications in Decentralised procedures started in September 2007.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (1)	8
DE (1)	5
DE (1)	21
DE (1)	9
DE (1)	5
DE (5)	16
DE (5)	16
DE (5)	8
DE (5)	7
DE (4)	2
DE (1)	1
DE (1)	2
DE (1)	1
DE (1)	1

<sup>1</sup> After day 120 of the procedure.

<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.

DE (1)	5
DE (1)	5
DE (1)	5
DE (1)	1
DK (4)	17
DK (4)	5
DK (4)	6
DK (4)	1
DK (4)	9
DK (4)	2
DK (4)	4
DK (4)	1
DK (4)	1
DK (4)	2
DK (3)	1
FI (3)	1
FI (3)	1
FI (3)	1
FI (3)	1
HU (1)	8
HU (1)	1
HU (1)	2
NL (2)	22
NL (6)	7
NL (3)	11
NL (4)	17
NL (1)	24
NL (1)	10
NL (1)	9
NL (1)	1
NL (1)	10
NL (1)	1
NL (1)	6
NL (1)	5
NL (1)	6
NL (1)	9
NL (1)	12
NL (1)	1
NL (1)	9
NL (1)	1
NL (1)	1
PL (2)	8
UK (1)	5
UK (1)	6
UK (2)	1
UK (6)	1
UK (1)	15
UK (3)	23
UK (4)	24
UK (1)	1
UK (1)	12
UK (1)	1
UK (1)	1
UK (2)	4
UK (1)	1
UK (5)	26
UK (1)	1
UK (1)	1
UK (2)	10

**VARIATIONS AND RENEWALS**

**Mutual Recognition and Decentralised Procedures**

The CMD(h) noted that **351** type IA variations, **173** type IB variations and **185** type II variations were finalised during the months of September 2007. **25** renewals were finalised in this period.

The status as of 30<sup>th</sup> September 2007 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
2007	4181	1690	1655	294	3

**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):*

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