

Report from the CMD(h) meeting held on 17th and 18th March 2008

CMD(h)/EMA Sub-Group on Paediatric Regulation

Further to the line listings received for authorised medicinal products (including purely national, MRP and DCP), in accordance with Article 45 of the Paediatric Regulation, the EMA is currently preparing an overview of medicinal products with paediatric studies for assessment in the work-sharing procedure.

Due to the high number of line listings received, it is expected that the preparation of the work-sharing, including prioritisation of studies for assessment and assignment of Rapporteurs, will take some time.

Marketing Authorisation Holders are therefore requested to inform the CMD(h) secretariat (sonia.ribeiro@emea.europa.eu) by 11 April 2008, if they consider that any or some of the paediatric studies submitted for their medicinal products should be given priority for the start of the work-sharing procedure.

The CMD(h) has agreed a Best Practice Guide on the EU work sharing procedure for paediatric studies submitted in accordance with Article 45 of the Paediatric Regulation. The Best Practice Guide will be published on the CMD(h) website.

EU Work sharing Project – Assessment of paediatric data

The Marketing Authorisation Holder for the medicinal product Zantac injection 50 mg/2 ml, Zantac tablets and effervescent tablets 150, 300 mg and Zantac Syrup 150 mg/10 ml (ranitidine), 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 13th May 2008, a Type II variation to implement the agreed text for inclusion in the SPC.

EU Work sharing Project – Assessment of paediatric data

The Paediatric public assessment report for Trusopt 2% eye drops solution, dorzolamide will be made available on the CMD(h) website, under Paediatric data assessment, Assessment reports on paediatric data.

Best Practice Guide on the compilation of the dossier for new applications submitted in MRP and DCP

The Best Practice Guide on the compilation of the dossier for new applications submitted in MRP and DCP will be published on the CMD(h) website, under Procedural guidance, Application for MA.

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 03.03.2008.

Name of the product in the RMS	Dorzolamid Sandoz 20mg/ml
Active substance	dorzolamide
Pharmaceutical form	Eye drops
Procedure number	DE/H/0766/001/DC
CMS	CZ, DK, EE, FI, LT, LV, NL, PL, SE, SK, UK
Legal basis	Art 10.1 Dir 2001/83/EC - Generic
Grounds for referral to CMD(h)	The procedure was referred to the CMD(h) due to issues related to the equivalence between the reference medicinal product and the applied generic.
Day 60	03 rd March 2008
Outcome	The applicant submitted an acceptable response addressing the questions raised in the oral explanation. This was achieved with a comprehensive review of the dose ranging sustainability effects for the active substance. In addition the applicant has accepted to modify the release and shelf life viscosity specification. Agreement was reached.

Name of the product in the RMS	Norspan
Active substance	buprenorphine
Pharmaceutical form	Transdermal patch
Procedure number	DK/H/0718/001-003/E/01
CMS	AT, CZ, DE, HU, IE, IS, LU, NO, PT, SE, SK, UK (wave 1) BE, EE, FI, LT, LV, NL, PL (wave 2)
Legal basis	Art 10.3 Dir 2001/83/EC - Hybrid
Grounds for referral to CMD(h)	The procedure was referred to the CMD(h) due to issues related to the effect size, the maintenance of effect and due to a lack of proven efficacy in a major indication.
Day 60	03 rd March 2008
Outcome	The applicant submitted an acceptable response addressing the issues raised and further more the applicant made the commitment to update the SPC in accordance with the comments received (section 4.1 and other relevant sections) via a type II variation. Agreement was reached.

Name of the product in the RMS	ALK 225 Phleum pratense (Soluprick SQ)
Active substance	phleum pratense pollen allergen (extract)
Pharmaceutical form	Solution for pricktest
Procedure number	DK/H/1263/001/MR
CMS	BE, BG, CY, EE, EL, ES, FR, HU, IE, IT, LT, LU, LV, MT, PL, PT, RO, SI
Legal basis	Art 8.3(i) Dir 2001/83/EC – Full dossier
Grounds for referral to CMD(h)	The procedure was referred to the CMD(h) due to quality and clinical issues related to the definition of the product considered not in line with the regulatory requirements, inadequate justification of the proposed in-use shelf-life, justification of the proposed indication and discussion of the recommended quantification of the product to be administered in section 4.2 of the SPC.
Day 60	03 rd March 2008
Outcome	An agreement was reached during the referral procedure, the SPC has been updated in accordance with the comments received, and the procedure has been closed. The applicant has made commitments regarding further studies in order to define the product and to further justify the in-use shelf-life claimed.

Name of the product in the RMS	Enalaprilmeleaat/ Hydrochloorthiazide 20 mg / 12.5	Enalaprilmeleaat/ Hydrochloorthiazide 20 mg / 12.5	Enalaprilmeleaat/ Hydrochloorthiazide 20 mg / 12.5
Active substance	enalapril/ hydrochlorothiazide		
Pharmaceutical form	Tablet		
Procedure number	NL/H/1095/001/MR	NL/H/1096/001/MR	NL/H/1097/001/MR
CMS	AT, DE, DK, ES, FI, FR, IT, RO, SI	DE, EE, LT, LV, PL	IT, PT
Legal basis	Art 10.1 Dir 2001/83/EC - Generic		
Grounds for referral to CMD(h)	There were concerns with regard to the following issues: 1. Bioequivalence was demonstrated on the basis of the metabolite data, and not on the basis of the parent. 2. The pictogram and text in the SPC and Package Leaflet give the impression that there is a dose recommendation for ½ a tablet, but there is no such recommendation. This may confuse prescribing physicians and patients.		
Day 60	03 rd March 2008		
Outcome	At the CMD(h) meeting the RMS presented its view and the applicant's written response was discussed.		

	<p>There was a discussion on whether bioequivalence should be demonstrated only on the active metabolite enalaprilat data, or whether bioequivalence should also be demonstrated on the parent compound enalapril. The applicant made a post-approval commitment to perform an additional single dose fasten BE-study on the parent compound.</p> <p>The SPC and Package Leaflet were adapted regarding information about the score line.</p> <p>Agreement reached.</p>
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Name of the product in the RMS	Activelle 0.5 mg/0.1 mg
Active substance	estradiol/norethisterone
Pharmaceutical form	Film-coated tablet
Procedure number	SE/H/0150/002/MR
CMS	AT, BE, BG, CZ, DE, DK, EE, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, NL, NO, PT, RO, SI, SK, UK
Legal basis	Art 8.3(i) Dir 2001/83/EC – Full dossier
Grounds for referral to CMD(h)	The procedure was referred to the CMD(h) due to potential serious risk to public health concerns on grounds that endometrial safety was insufficiently demonstrated and due to the lack of 12 months vaginal bleeding data. Furthermore, changes to the SPC with regard to mammographic density and osteoporosis were requested by the objecting CMSs.
Day 60	03 rd March 2008
Outcome	<p>At the CMD(h) meeting, the RMS, CMS and the applicant presented their view on the outstanding issues. The applicant committed to perform a randomised, double blind study with an active comparator to address the issue of bleeding. It was also agreed to delete the SPC statements in section 5.1 regarding mammographic density and osteoporosis. No agreement was reached between Member States with regard to the need of an endometrial safety study for the proposed combination and the objecting CMSs were of the opinion that endometrial safety has to be demonstrated before approval of the medicinal product.</p> <p>Referred to CHMP for arbitration.</p>

Name of the product in the RMS	Sabumalin	Sanohex	Sabufarm
Active substance	salbutamol		
Pharmaceutical form	Inhalation suspension		
Procedure number	SE/H/0601/001/DC	SE/H/0602/001/DC	SE/H/0603/001/DC
CMS	BE, DE, DK, EE, EL, ES, FI, HU, IT, LT, LV, NL, NO, PL, PT, SI, UK	AT, DE, ES, IE	DE, EE
Legal basis	Art 10.3 Dir 2001/83/EC - Hybrid		
Grounds for referral to CMD(h)	The procedure was referred to the CMD(h) due to potential serious risk to public health concerns on grounds that the product is not approvable since the comparative <i>in vitro</i> data presented are insufficient for waiving the non-conclusive clinical studies. The proposed storage orientation of the device was also raised as a major concern.		
Day 60	03 rd March 2008		
Outcome	<p>At the CMD(h) meeting, the RMS, CMS and the applicant presented their view on the outstanding issues. However, some member states did still not support the view that the <i>in vitro</i> data available are sufficient for solving the equivalence issue. The storage orientation of the device is also a remaining issue for some CMS. It was nevertheless agreed that the recommendation for storage orientation, which also concern related approved products, should be referred to the QWP for advice on how to handle the issue.</p>		

	SE/H/0601-0602/001/DC Sabumalin/SanoHex: No agreement was reached between Member States and the procedures were referred to CHMP for arbitration.
	SE/H/0603/001/DC Sabufarm: Agreement reached.

NEW APPLICATIONS

Mutual Recognition Procedure

The CMD(h) noted that **23** Mutual Recognition Procedures were finalised during the month of February 2008. **9** 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 29th February 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 2007	2008		For procedures referred to CMD(h) in 2007	2008
2008	45	187	10	--	--	--	1	--

39 Mutual Recognition Procedures (regarding **78** products) started in February 2008. The categories of these procedures are as follows:

7 known active substance (already authorised in at least one member state) applications, including **2** repeat use applications.

29 abridged applications, including **1** multiple and **10** repeat use applications.

3 line extension applications.

The new procedures started in February 2008 related to **4** full dossier, **29** generic and **6** bibliographic applications.

All of these procedures consisted of chemical substance products.

38 of these procedures related to prescription-only medicinal products and **1** procedure related to a non-prescription medicinal product in the reference Member State¹.

Number of countries involved in the new applications in Mutual Recognition procedure started in February 2008.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
CZ (2)	1
CZ (1)	4
DE (3)	8
DE (4)	12
FI (1)	10
FI (1)	1
FI (1)	1
FR (1)	2
FR (2)	1
FR (1)	28

¹ 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
FR (1)	6
FR (1)	2
FR (1)	5
FR (2)	1
NL (1)	12
NL (1)	7
NL (2)	3
NL (3)	3
NL (3)	2
NL (3)	5
NL (2)	3
NL (2)	2
NL (4)	15
NL (3)	23
NL (3)	17
NL (3)	1
NL (3)	1
NL (2)	1
NL (3)	6
PT (2)	11
PT (2)	1
PT (2)	1
SE (1)	1
UK (1)	7
UK (1)	14
UK (1)	6
UK (1)	14
UK (2)	1
UK (2)	22

Decentralised Procedure

The CMD(h) noted that there were **49** Decentralised Procedures finalised during the month of February 2008 with a positive outcome. There were **no** Decentralised procedures withdrawn after Day 120. **No** Decentralised Procedures were referred to the CMD(h) in this period. **No** Decentralised Procedures were referred to the CHMP in this period.

The status as of 29th February 2008 of procedures under Decentralised Procedure is as follows:

Year	New applications finalised		New applications withdrawn ²	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	86	--	--	1143	9	--	--	--	--	--

113 Decentralised Procedures (regarding **228** products) started in February 2008. The categories of these procedures are as follows:

107 abridged applications, including **37** multiple applications.

5 known active substance applications.

1 new active substance application.

The new Decentralised procedures started in February related to **92** generic, **1** bibliographic, **2** fixed combination, **15** hybrid and **3** full dossiers.

² After day 120.

111 of these procedures consisted of chemical substance applications, 1 biological other application and 1 herbal application.

111 of these procedures related to prescription-only medicinal products and 2 to non-prescription medicinal products in the reference Member State³.

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

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
AT (1)	7
AT (1)	8
AT (3)	17
AT (3)	3
AT (3)	4
AT (3)	1
AT (3)	1
AT (3)	1
AT (3)	1
BE (3)	3
BE (1)	1
CZ (1)	2
CZ (3)	2
CZ (2)	2
DE (1)	1
DE (1)	1
DE (2)	8
DE (1)	2
DE (2)	5
DE (2)	3
DE (2)	4
DE (2)	10
DE (3)	14
DE (3)	13
DE (1)	10
DE (3)	3
DE (3)	1
DE (2)	4
DE (1)	3
DE (1)	1
DE (1)	1
DE (1)	1
DE (1)	1
DE (1)	1
DE (1)	10
DE (1)	6
DE (4)	6
DE (4)	15
DE (2)	4
DE (5)	26
DE (1)	8
DE (1)	8
DE (1)	1
DE (1)	1
DE (1)	3
DK (1)	5
DK (1)	5
DK (1)	14
DK (5)	5
DK (5)	7

³ 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.

DK (5)	4
DK (4)	3
DK (4)	6
FI (1)	2
FI (1)	14
FR (1)	14
FR (1)	23
FR (1)	23
HU (3)	14
MT (2)	19
MT (1)	20
NL (3)	24
NL (3)	3
NL (4)	4
NL (4)	2
NL (4)	3
NL (4)	16
NL (4)	1
NL (4)	6
NL (1)	13
NL (1)	2
NL (1)	1
NL (1)	1
NL (1)	1
NL (1)	3
NL (1)	6
NO (1)	20
NO (1)	1
NO (1)	18
NO (1)	1
NO (1)	1
NO (1)	5
SE (1)	2
SE (2)	4
SE (4)	6
SE (1)	1
SK (4)	8
UK (2)	10
UK (1)	14
UK (1)	14
UK (1)	10
UK (1)	26
UK (2)	26
UK (1)	12
UK (1)	7
UK (2)	17
UK (2)	2
UK (1)	20
UK (1)	12
UK (1)	1
UK (1)	7
UK (1)	10
UK (2)	1
UK (2)	1
UK (2)	1
UK (1)	7
UK (2)	7
UK (2)	11
UK (2)	2
UK (1)	3
UK (1)	3
UK (2)	2

VARIATIONS AND RENEWALS

Mutual Recognition and Decentralised Procedures

The CMD(h) noted that **565** type IA variations, **256** type IB variations and **162** type II variations were finalised during the month of February 2008. **46** renewals were finalised in this period. There was **no** procedure referred to the CHMP in this period.

The status as of 29th February 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	1059	402	299	70	--

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>