

## Report from the CMD(h) meeting held on 19<sup>th</sup>, 20<sup>th</sup> and 21<sup>st</sup> March 2007

### Best Practice Guide EU Work Sharing Procedure in the Assessment of Paediatric Data

The CMD(h) has updated the Best Practice Guide for the EU Work Sharing procedure in the assessment of paediatric data, with information on the finalisation of the work sharing procedure and to address the implementation of the outcome of the EU work sharing procedure to generics.

The CMD(h) strongly recommends that the product information for generic medicinal products is updated with the information on the use in children, within 90 days of the update of the SPC for the reference medicinal product.

### Best Practice Guide for the preparation of the Public Assessment Report - EU Work Sharing Procedure in the Assessment of Paediatric Data

The CMD(h) has revised the Best Practice Guide for the preparation of the Public Assessment Reports within the framework of the EU work sharing procedure in the assessment of paediatric data, to clarify that the Paediatric Public Assessment Reports will be sent for publication on the CMD(h) website on a monthly basis, together with the press release and adopted documents.

The Paediatric Public Assessment Reports are available on the CMD(h) website, under the heading 'Paediatric data assessment'.

The Paediatric Public Assessment Report for Durogesic, fentanyl transdermal patch will be published on the CMD(h) website.

### Information on on-going studies prior to the start of a Mutual Recognition Procedure

Applicants are reminded to inform the RMS of on-going studies before the start of a MRP.

In case the studies might be required for the MRP, the appropriate variation procedure, to update the dossier with the results of the studies should be submitted to the RMS before the start of the MRP.

### 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 02.03.2007.

<b>Name of the product in the RMS</b>	Atacor	Atorpharm	Atorvin
<b>Active substance</b>	atorvastatin		
<b>Pharmaceutical form</b>	Film coated tablet		
<b>Procedure number</b>	IS/H/100/01-03/MR	IS/H/101/01-03/MR	IS/H/102/01-03/MR
<b>CMS</b>	CZ, EE, HU, LT, LV, MT, PL, SI, SK	CZ, EE, LT, LV, PL, SK	CZ, EE, HU, LT, LV, PL, SK
<b>Legal basis</b>	Art 10.1, Directive 2001/83/EC - Generic		
<b>Grounds for referral to CMD(h)</b>	Two impurities were detected in the product, which were potentially genotoxic. These impurities were not detected in the reference medicinal product sourced from one of the CMS and sufficient evidence on safety of these impurities was not provided. However in the dossier there are available results of determination of the above mentioned impurities by newly validated HPLC method at the time point 36 months after start of stability studies in tested product and in the reference product Lipitor coated tablets, sourced from Sweden. In this case the amount of impurities was similar for tested and reference product. The concerned impurities exist in all the products tested and show the tendency to increase with age. The final conclusion is that the impurity profile is very similar for Atacor® and the innovator product tested from the different European countries, Atacor® showing slightly higher value of the impurities concerned.		

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	Also the applicant did send results from a 4 week bridging study of Atorvastatin calcium with impurities and Atorvastatin calcium without impurities. By repeated oral administration to CD rats. In conclusion, no toxicological differences were noted between Atorvastatin with impurities and Atorvastatin without impurities.
<b>Day 60</b>	02.03.07
<b>Outcome</b>	The CMS that had asked for the referral declared that they agreed with the responses of the applicant and were prepared to grant a Marketing Authorisation for the product. The scientific discussion/oral explanation of the referral that was scheduled for the CMD meeting 20th February 2007 was consequently cancelled.  Agreement was reached.

<b>Name of the product in the RMS</b>	Eformax 6, 12
<b>Active substance</b>	formoterol
<b>Pharmaceutical form</b>	Inhalation powder
<b>Procedure number</b>	DK/H/970/01-02/MR
<b>CMS</b>	CY, CZ, DE, EE, LT, LV, MT, 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>	The procedure was referred to the CMD(h) on the basis that therapeutic equivalence to the RMP could not be shown due to an inappropriate design of the clinical studies, which were insensitive to detect differences between the test and the RMP.  The procedure was also referred to the CMD(h) on quality grounds, as the requirement to investigate a range of flow rates and compare the devices should be fulfilled and the delivered dose compared.
<b>Day 60</b>	02.03.07
<b>Outcome</b>	At the meeting the RMS presented its view and the applicant's written response was discussed. It was discussed which clinical studies should be required to prove efficacy and safety for inhalation products and no consensus was reached.  Referred to CHMP for arbitration.

<b>Name of the product in the RMS</b>	Simvastatin Krka
<b>Active substance</b>	simvastatin
<b>Pharmaceutical form</b>	Film coated tablet
<b>Procedure number</b>	DK/H/438/05/MR
<b>CMS</b>	FI, NO, SE
<b>Legal basis</b>	Art 10.1, Directive 2001/83/EC - Generic
<b>Grounds for referral to CMD(h)</b>	The procedure was referred to the CMD(h) on the grounds that bioequivalence with the reference medicinal product has not been shown, based on the following: - A multiple dose instead of a single-dose study was chosen to demonstrate BE; - The use of the metabolite $\beta$ -hydroxiacid simvastatin instead of the parent compound simvastatin; - C <sub>min</sub> and fluctuation of $\beta$ -hydroxiacid simvastatin
<b>Day 60</b>	02.03.07
<b>Outcome</b>	Referred to CHMP for arbitration

<b>Name of the product in the RMS</b>	Ciclosporin "Albertex"
<b>Active substance</b>	ciclosporin
<b>Pharmaceutical form</b>	Capsule, soft
<b>Procedure number</b>	DK/H/965/01-03/MR
<b>CMS</b>	DE, UK
<b>Legal basis</b>	Art 10.1, Directive 2001/83/EC - Generic

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<b>Grounds for referral to CMD(h)</b>	Lack of demonstration of bioequivalence between the test and reference product in fed conditions.  The efficacy of the product in the uveitis indication was not found to have been demonstrated.
<b>Day 60</b>	02.03.07
<b>Outcome</b>	The uveitis indication has been withdrawn by the applicant.  It was noted that at the time the medicinal product was approved in the RMS a fed BE study was not required, in accordance with the NfG. The Applicant committed to perform a fed study comparing the test and reference product after a high fat meal and to submit the results via type II variation, before commercialisation of the product.  Agreement reached.

<b>Name of the product in the RMS</b>	Ciclosporin "Recordati"
<b>Active substance</b>	ciclosporin
<b>Pharmaceutical form</b>	Capsule, soft
<b>Procedure number</b>	DK/H/966/01-03/MR
<b>CMS</b>	EL, ES, IT
<b>Legal basis</b>	Art 10.1, Directive 2001/83/EC - Generic
<b>Grounds for referral to CMD(h)</b>	Lack of demonstration of bioequivalence between the test and reference product in fed conditions; The validation of the bioanalytical method has not been performed according to the state of art; The existence of an outlier; The need to conduct a PK study in patients and to tighten the BE acceptance range for ciclosporin; The need for characterisation of the microemulsion formed at gastric level.
<b>Day 60</b>	02.03.07
<b>Outcome</b>	The MAH/applicant has withdrawn the MA/application in the RMS and all MS.

<b>Name of the product in the RMS</b>	Deximune 25, 50, 100mg
<b>Active substance</b>	ciclosporin
<b>Pharmaceutical form</b>	Capsule, soft
<b>Procedure number</b>	IE/H/164/01-03/MR
<b>CMS</b>	UK
<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 that the bioequivalence of the test product had not been confirmed.
<b>Day 60</b>	02.03.07
<b>Outcome</b>	At the CMD(h) meeting the RMS presented its view and the applicant's written response was discussed. The applicant made use of an oral hearing. The applicant has committed to the following:  - To perform a post-approval, pre-commercialisation biostudy comparing the test product to Neoral Soft Gelatin Capsules in volunteers administered a high-fat meal. The results of this study should demonstrate that the food effect for the test product is equal to or less than that for Neoral. The bioequivalence study will be performed within 6-8 months. Commercialisation will not commence until a satisfactory agreement is reached.  - To submit a Type II variation detailing the summary PK data in fed and fasted biostudy in section 5.2 of the SPC.  - To undertake a post-marketing study, most probably in renal transplant patients, in which acute graft rejection rates and renal function will be assessed over a defined and appropriate period. The Applicant will clearly define historical rejection rates, and anticipated changes in renal function in the study protocol

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	Agreement Reached.
<b>Name of the product in the RMS</b>	Ciclosporin Genfarma 25, 50, 100mg
<b>Active substance</b>	ciclosporin
<b>Pharmaceutical form</b>	Capsule, soft
<b>Procedure number</b>	IE/H/168/01-03/MR
<b>CMS</b>	UK
<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 that the bioequivalence of the test product had not been confirmed.
<b>Day 60</b>	02.03.07
<b>Outcome</b>	<p>At the CMD(h) meeting the RMS presented its view and the applicant's written response was discussed.</p> <p>The applicant has committed to the following:</p> <ul style="list-style-type: none"> <li>- To perform a post approval, pre- commercialisation bioequivalence study comparing the test product (Ciclosporin Genfarma 25mg, 50 mg and 100mg Capsules) to Neoral Soft Gelatin Capsules in volunteers administered a high-fat meal. The results of this study should demonstrate that the food effect for the test product is equal to or less than that for Neoral. The bioequivalence study will be performed within 6-8 months. Commercialisation will not commence until a satisfactory agreement is reached.</li> <li>- To submit a type II variation detailing the summary PK data in the fed and fasted bioequivalence study in section 5.2 of the SmPC.</li> <li>- To undertake a post marketing study, most probably in renal transplant patients, in which acute graft rejection rates and renal function will be assessed over a defined an appropriate period. The applicant will clearly define historical rejection rates and anticipated changes in renal function in the study protocol.</li> <li>- To submit a type II variation to update SmPC section 4.5 with the following statement: "Coadministration of ciclosporin and repaglinide may enhance the blood glucose lowering effect of repaglinide and increase the risk of hypoglycaemia".</li> </ul> <p>Agreement Reached.</p>

<b>Name of the product in the RMS</b>	Fentastad 25, 50, 75, 100µg/h	Fentador 25, 50, 75, 100µg/h	Matripain 25, 50, 75, 100µg/h	Matrigesic 25, 50, 75, 100µg/h	Fentrans 25, 50, 75, 100µg/h
<b>Active substance</b>	fentanyl				
<b>Pharmaceutical form</b>	Transdermal patch				
<b>Procedure number</b>	DK/H/997/01-04/MR	DK/H/998/01-04/MR	DK/H/999/01-04/MR	DK/H/1000/01-04/MR	DK/H/1001/01-04/MR
<b>CMS</b>	AT, BE, CZ, EE, ES, FI, FR, HU, IT, LT, LU, LV, NL, PL, PT, SE, SK, UK	DE	DE	AT, BE, CZ, EE, ES, FI, FR, HU, IT, LT, LU, LV, NL, NO, PL, PT, SE, SI, SK, UK	DE
<b>Legal basis</b>	Art 10.1, Directive 2001/83/EC - Generic				
<b>Grounds for referral to CMD(h)</b>	<p>The procedure was referred to the CMD(h) on the following grounds:</p> <ul style="list-style-type: none"> <li>- Scientific rationale to use DEET as solubiliser</li> <li>- Risk of neurotoxic effects associated with DEET</li> <li>- Lack of proof of sufficient patch adhesion of the largest patch size</li> <li>- Bioequivalence between test and reference product has not been demonstrated</li> <li>- SPC issues</li> </ul> <p>At the CMD(h) meeting the RMS presented its view and the applicant's written response was discussed. The applicant made use of an oral hearing.</p>				
<b>Day 60</b>	02.03.07				
<b>Outcome</b>	Referred to CHMP for arbitration				

<b>Name of the product in the RMS</b>	Nycofen	Matrimed
<b>Active substance</b>	fentanyl	
<b>Pharmaceutical form</b>	Transdermal patch	
<b>Procedure number</b>	SE/H/661/01-05/MR	SE/H/662/01-05/MR
<b>CMS</b>	FR	
<b>Legal basis</b>	Art 10.1, Directive 2001/83/EC - Generic	
<b>Grounds for referral to CMD(h)</b>	The CMS considered that a positive benefit/risk balance had not been demonstrated in the treatment of non cancer pain. The most important issues were in the indication, posology and contraindication sections. A child resistant package was also requested.	
<b>Day 60</b>	02.03.07	
<b>Outcome</b>	After the CMD(h) meeting RMS and the single CMS agreed on a SPC text with a change of the indication that now states that Nycofen/Matrimed is a substitution for an ongoing pain therapy with strong opioids, a conversion table of equianalgetic doses of different opioids is deleted and a contraindication for concomitant use of mixed agonist/antagonists is added. Other members of the CMD(h) - not concerned member states in this particular procedure - expressed different opinions on e.g. the indication. Later, the results from the ongoing referral to CHMP for another fentanyl patch may influence the future SPC text for Nycofen/Matrimed. The applicant agreed to change to a child resistant package.	

## **NEW APPLICATIONS**

### **Mutual Recognition Procedure**

The CMD(h) noted that **30** new Mutual Recognition Procedures were finalised during the month of February 2007. **4** Mutual Recognition Procedures for new applications were referred to CMD(h) in this period. **1** Mutual Recognition Procedure for a new application was referred to CHMP in this period.

The status as of 28<sup>th</sup> February 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 in the CMD(h)	Arbitrations referred to CHMP
2007	82	186	10 N.A.	8	--	1

**42** Mutual Recognition Procedures (regarding **79** products) started in February 2007. The categories of these procedures are as follows:

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

**30** abridged applications, including **16** multiple applications.

**5** line extension applications, including **4** repeat use applications.

The new procedures started in February related to **7** full dossiers, **30** generics, **1** hybrid applications and **4** bibliographic applications.

These procedures consisted of **39** chemical, **1** biological blood product, **1** biological other and **1** biological vaccine substances.

**41** 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>.

<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.

Number of countries involved in the new applications in Mutual Recognition procedure started in February 2007.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (2)	24
DE (1)	5
DE (2)	8
DK (2)	2
DK (2)	1
DK (1)	4
DK (1)	1
DK (1)	2
FI (3)	6
FI (3)	3
FI (3)	4
FI (3)	1
FI (3)	1
FI (3)	11
FI (1)	1
FI (3)	10
FI (1)	7
FI (3)	1
FI (1)	8
FI (1)	1
FI (1)	2
FI (1)	4
NL (1)	5
NL (1)	1
NL (1)	1
NL (1)	26
NL (1)	1
NL (1)	2
NL (1)	1
NL (2)	1
NL (2)	1
NL (1)	1
NL (1)	1
NL (1)	1
PT (4)	9
SE (1)	4
SE (7)	4
SE (1)	26
SE (7)	1
SE (1)	8
SE (1)	15
SE (1)	1

### **Decentralised Procedure**

The CMD(h) noted that there were **11** new Decentralised Procedures finalised during the month of February 2007. There was **1** Decentralised Procedure withdrawn at day 120 of the procedure. There were **2** Decentralised Procedures referred to the CMD(h) in this period.

The status as of 28<sup>th</sup> February 2007 of procedures under Decentralised Procedure is as follows:

Year	New applications finalised with positive outcome	New applications withdrawn <sup>2</sup>	New applications finalised with negative outcome <sup>2</sup>	New applications in process	Referred to CMD(h)	Agreement reached in the CMD(h)	Arbitrations referred to CHMP
2007	13	2	1	529	2	1	--

<sup>2</sup> After day 120 of the procedure.



Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DK (2)	1
EE (2)	6
FI (2)	11
FR (1)	2
IT (1)	1
NL (3)	8
NO (1)	3
SE (1)	8
SE (2)	12
SE (2)	6
UK (2)	19
UK (1)	12
UK (1)	11
UK (2)	3
UK (1)	23
UK (1)	1
UK (1)	1
UK (1)	1

**VARIATIONS AND RENEWALS**

**Mutual Recognition and Decentralised Procedures**

The CMD(h) noted that **367** type IA variations, **123** type IB variations and **122** type II variations were finalised during the month of February 2007. **36** renewals were finalised in this period.

The status as of 28<sup>th</sup> February 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	Arbitrations referred to CHMP
2007	804	287	268	69	--

**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>