

Report from the CMD(h) meeting held on 19th, 20th & 21st February 2007

New CMD(h) Website

Interested Parties are informed that as of 1st March 2007 the CMD(h) will have a new website - www.hma.eu

The CMD(h) will continue the on-going work on the new website, with a view to ensuring a better structure and an easy access by Interested Parties to information from the CMD(h).

CMD(h) Work plan for 2007

The CMD(h) has agreed a work plan for 2007. The work plan will be published on the website, for transparency reasons.

The CMD(h) agreed to concentrate its activities in 2007 on the improvement of existing MR and DC procedures, including the on-going activities of the Working groups on the Decentralised procedure and on Validation issues/National requirements, on the reduction of the number of referrals to the CMD(h) and active participation of all CMD(h) Members and on strengthening cooperation with the PhVWP.

Change of PSUR submission schedule in the framework of the PSUR Work sharing Project

The CMD(h) has agreed that where the published harmonised birthdates (HBDs) are to be adopted for the submission of PSURs for MRP/DCP in the framework of the PSUR work sharing project, Member States will not require a Type II variation for amendment of the PSUR cycle. This includes the agreement that generics, subject to specified exclusions, may move directly to the 3 years reporting cycle.

In these cases, a notification only is required, in line with Volume 9A, Part I., 6 of the rules governing medicinal products in the European Union.

EU Work sharing procedure in the assessment of paediatric data

The CMD(h) has agreed to publish, for transparency reasons, the list of active substances included in the EU Work sharing procedure in the assessment of paediatric data.

The list will be available together with the Public assessment reports for the procedures finalised on the CMD(h) website.

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 01.02.2007.

Name of the product in the RMS	Losartankalium "ratiopharm"		
Active substance	losartan potassium		
Pharmaceutical form	Film coated tablets 12,5 mg, 50 mg and 100 mg		
Procedure number	DK/H/917/01/MR	DK/H/917/03/MR	DK/H/917/04/MR
CMS	AT, DE, FI, IT, NO, SE	AT, BE, CZ, DE, FI, HU, IT, LU, NO, PL, SE	AT, BE, DE, FI, LU, NO, SE
Legal basis	Art 10.1, Directive 2001/83/EC - Generic Art 10.3, Directive 2001/83/EC – Hybrid (some strengths in some Member States)		
Grounds for referral to CMD(h)	A serious public health concern was raised by one Member States who considered that there was a lack of scientific evidence for the indication “ <i>treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment</i> ”.		

Day 60	01.02.2007
Outcome	At the CMD(h) meeting the RMS presented its view and the applicant's written response was discussed. Following the discussion all involved Member State could agree on the approval of the indication without any amendments. Furthermore losartan is included in the list of SPCs that will be harmonised by the CMD(h).

Name of the product in the RMS	Felartan
Active substance	losartan potassium
Pharmaceutical form	Film coated tablets 12,5 mg, 25 mg, 50 mg and 100 mg
Procedure number	DK/H/922/01-04/MR
CMS	AT, CZ, DE, EE, HU, IT, LT, LV, NL, NO, PL, PT, SE, SI, SK, UK
Legal basis	Art 10.1, Directive 2001/83/EC - Generic Art 10.3, Directive 2001/83/EC – Hybrid (some strengths in some Member States)
Grounds for referral to CMD(h)	A serious public health concern was raised by one Member States who considered that there was a lack of scientific evidence for the indication " <i>treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment</i> ". One Member State raised a serious public health concern because all strengths were gathered in one SPC, even though not all strengths could be used for all indications. One Member State raised a serious public health concern because the indications were not in line with the indications for the national brand leader (this referral was later withdrawn).
Day 60	01.02.2007
Outcome	At the CMD(h) meeting the RMS presented its view and the applicant's written response were discussed. Following the discussion all involved Member State could agree on the approval of the indication without any amendments. Furthermore losartan is included in the list of SPCs that will be harmonised by the CMD(h). It was agreed that the SPC could be joint or divided on a national basis according to national requirements. For practical reasons the SPC would be joint for all strengths during the procedure.

Name of the product in the RMS	Tarnasol
Active substance	losartan
Pharmaceutical form	Film coated tablets 12,5 mg, 50 mg and 100 mg
Procedure number	DK/H/914/01-03/DC
CMS	AT, BE, CZ, EE, FI, IE, LT, LU, LV, NO, PT, SE, SI, SK
Legal basis	Art 10.1, Directive 2001/83/EC - Generic Art 10.3, Directive 2001/83/EC – Hybrid (some strengths in some Member States)
Grounds for referral to CMD(h)	A serious public health concern was raised by one Member States who could not approve the indication "Renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria >0.5 g/day as part of an antihypertensive treatment" One Member State raised a serious public health concern because all strengths were not gathered in one SPC.
Day 60	01.02.2007
Outcome	At the CMD(h) meeting the RMS presented its view and the applicant's written response were discussed. The following indication was agreed: <i>Renal Protection in Type 2 Diabetic patients with Proteinuria: 'Tarnasol' is indicated to delay the progression of renal disease as measured by a reduction in the composite endpoints of doubling of serum creatinine, end stage renal disease (need for dialysis or renal transplantation) or death; and to reduce proteinuria (see section 5.1).</i> Furthermore losartan is included in the list of SPCs that will be

	<p>harmonised by the CMD(h). It was agreed that the SPC could be joint or divided on a national basis according to national requirements. For practical reasons the SPC would be joint for all strengths during the procedure.</p>
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Name of the product in the RMS	Vantas
Active substance	histrelin
Pharmaceutical form	Implant
Procedure number	DK/H/1010/01/MR
CMS	DE, ES, IE, IT, 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 the lack of randomised comparative clinical data in terms of efficacy and safety, the lack of genotoxic evaluation of histrelin acetate, the fact that the primary efficacy variable in the clinical studies, serum testosterone, does not address the clinical benefit of the treatment to patients and due to the limited size of the safety database.
Day 60	01.02.2007
Outcome	<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. Only the pre-clinical concern was solved. The major clinical issues were not resolved.</p> <p>Referred to CHMP for arbitration</p>

Name of the product in the RMS	NATECAL D3
Active substance	calcium carbonate + cholecalciferol
Pharmaceutical form	Chewable tablet
Procedure number	IT/H/112/01/E/01
CMS	DE, EL (wave 1) BE, FR, HU, NL, PL, UK (wave 2)
Legal basis	Art.10 a Dir 2001/83/EC - Bibliographic
Grounds for referral to CMD(h)	A serious public health concern was raised by one Member States who considered that the literature data included in the dossier would be insufficient to support the risk/benefit profile of the medicinal product and that the finished product manufacturer's method for ensuring homogeneity of colecalciferol in the powder concentrate was unacceptable.
Day 60	01.02.2007
Outcome	The Applicant submitted the results of a new literature search, which confirmed the efficacy profile of the product, and a detailed re-analysis of the studies already included in the dossier, which confirmed how the proposed SPC for Natecal adequately addressed any potential safety issue related to this medicinal product. Besides, the Applicant submitted data showing an adequate measure of homogeneity of Dry Vitamin D3. The responses of the Applicant were judged positively by the objecting Member State and therefore a positive conclusion was reached in advance of the meeting.

Name of the product in the RMS	Lansoprazol 15 & 30 Focus
Active substance	lansoprazole
Pharmaceutical form	Hard Gastro-resistant capsule
Procedure number	NL/H/802/01-02/MR
CMS	AT, BE, DE, FI, HU, IS, PL, PT, SE
Legal basis	Art 10.1, Directive 2001/83/EC - Generic
Grounds for referral to CMD(h)	A serious public health concern was raised by one Member State who stated that there is a possibility that exposure to lansoprazole of the test product could be increased under fed conditions as compared to fasting conditions.

Day 60	01.02.2007
Outcome	The applicant conducted an additional comparative bioavailability study, comparing lansoprazole pharmacokinetics under fasting and fed conditions, and the results were available before CMD(h) meeting. Agreement Reached.

Name of the product in the RMS	Fosinoprilnatrium/Hydrochlorothiazide 20/12.5 TEVA
Active substance	fosinopril / HCTZ
Pharmaceutical form	Tablet
Procedure number	NL/H/780/01/MR
CMS	AT, CZ, DE, ES, FR, HU, IT, LT, PL, PT, SK
Legal basis	Art 10.1, Directive 2001/83/EC - Generic
Grounds for referral to CMD(h)	The add-on indication in patients who cannot be adequately controlled with HCTZ alone was not accepted, because an add-on study in non-responders to HCTZ had not been carried out. The recommendation to use the lowest dose of half a tablet once daily in certain conditions as the starting dose was not acceptable as efficacy had not been established of this lowest dose of 10 mg fosinopril/6.25 mg HCTZ.
Day 60	01.02.2007
Outcome	Clinical data were insufficient to assess the safety of the higher dose of 20 mg fosinopril and 12.5 mg HCTZ in patients who have not responded to HCTZ. It was agreed to accept the add-on indication in non-responders to fosinopril and the substitution indication in patients who have been stabilised on the individual active substances given in the same proportions as separate medications. Since the half dose was mainly intended for safety reasons in those patients with renal dysfunction who had responded inadequately to HCTZ alone, and these patients are no longer included in the indication, it was agreed to delete the starting dose of half a tablet. The section on patients with impaired renal function under section 4.2 was reworded. Agreement Reached

Name of the product in the RMS	Enalapril hydrochlorothiazide teva 20 mg/12,5 mg
Active substance	enalapril / HCTZ
Pharmaceutical form	Tablet
Procedure number	FR/H/309/01/MR
CMS	AT, DE, DK, EE, ES, FI, HU, IE, IT, LT, LV, NL, NO, PL, PT, SE, SI, SK
Legal basis	Art 10.1, Directive 2001/83/EC - Generic
Grounds for referral to CMD(h)	A potential serious risk to public health was raised by two Member States due to differences regarding therapeutic indications and the posology in elderly patients. The problem raised on therapeutic indications is related to the absence of the add-on indication in patients who cannot be adequately controlled with HCTZ alone. With regard to the posology, the recommendation to use the lowest dose of half a tablet once daily in certain conditions as the starting dose was not acceptable as efficacy had not been established of this lowest dose of 10 mg enalapril/6.25 mg HCTZ.
Day 60	01.02.2007
Outcome	Clinical data were insufficient to assess the safety of the higher dose of 20 mg enalapril and 12.5 mg HCTZ in patients who have not responded to HCTZ. It was agreed to accept the add-on indication in non-responders to enalapril and the substitution indication in patients who have been stabilised on the individual active substances given in the same proportions as separate medications. With regard to the use in the elderly, there are very few safety and efficacy data on the use of half tablet once daily. It was agreed to delete the starting dose of half a tablet in section 4.2 of the SPC. Agreement Reached

Name of the product in the RMS	Fosinopril HCT Actavis 20/12.5mg	Fosinopril comp 20/12.5mg
Active substance	fosinopril / HCTZ	
Pharmaceutical form	Tablet	
Procedure number	DE/H/729/01/MR	DE/H/730/01/MR
CMS	AT, CZ, EE, HU, IS, IT, LT, LV, NL, PL, PT, SI, SK	AT, NL
Legal basis	Art 10.1, Directive 2001/83/EC - Generic	
Grounds for referral to CMD(h)	<p>Three MS regarded the lacking of the add-on indication for those patients who do not respond to HCTZ as a potential serious risk to public health.</p> <p>Other issues addressed by a single MS as a potential serious risk to public health have been:</p> <ul style="list-style-type: none"> • Missing of information that if patients have previously been treated with a diuretic as monotherapy, then the diuretic treatment should be stopped several days before starting treatment with the combination. • Missing of information concerning the usual starting dosage for patients with impaired renal function, which has to be reduced to half a tablet (10 mg fosinopril sodium and 6.25 mg hydrochlorothiazide). • ACE inhibitors should be contraindicated during the whole pregnancy. 	
Day 60	01.02.2007	
Outcome	<p>Clinical data were insufficient to assess the safety of the dose of 20 mg fosinopril and 12.5 mg HCTZ in patients who have not responded to HCTZ. It was agreed to accept the add-on indication in non-responders to fosinopril and the substitution indication in patients who have been stabilised on the individual active substances given in the same proportions as separate medications.</p> <p>MS have agreed, that a gapless switch from the monotherapy to the combination therapy is possible.</p> <p>As there is no scientific evidence concerning the efficacy of 6.25 mg hydrochlorothiazide, it was agreed not to recommend a starting dose of half a tablet for patients with impaired renal function. However, there was agreement to reword the section on patients with impaired renal function under SPC-section 4.2.</p> <p>With regard to the question to contraindicate or not ACE inhibitors during the whole pregnancy, MS will await the results of the discussion at the PhVWP on this subject.</p> <p>It was noted that the NfG on clinical investigation of medicinal products in the treatment of hypertension – Fixed combinations, is not absolute clear with the recommendations concerning the necessary studies for fixed combinations.</p> <p>Agreement Reached.</p>	

NEW APPLICATIONS

Mutual Recognition Procedure

The CMD(h) noted that **49** new Mutual Recognition Procedures were finalised during the month of January 2007. **6** Mutual Recognition Procedures for new applications were referred to CMD(h) in this period. There were **no** Mutual Recognition Procedures for a new application referred to CHMP in this period.

The status as of 31st January 2007 of procedures under Mutual Recognition is as follows:

Year	New applications	New applications in	Referred to CMD(h)	Agreement reached in the	Withdrawn in the CMD(h)	Arbitrations referred to
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	finalised	process		CMD(h)		CHMP
2007	49	101	6 N.A.	--	--	--

25 Mutual Recognition Procedures (regarding **66** products) started in January 2007. The categories of these procedures are as follows:

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

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

19 abridged applications, including **7** multiple applications.

1 line extension applications, which is a repeat use.

The new procedures started in January related to **3** full dossiers, **15** generics, **4** hybrid applications and **3** bibliographic applications.

These procedures consisted of **23** chemical, **1** biological blood product and **1** biological vaccine substances.

24 of these procedures related 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 January 2007.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
CZ (3)	2
DE (1)	7
DK (3)	21
NL (1)	5
NL (1)	14
NL (3)	9
NL (3)	9
NL (3)	15
PT (4)	3
SE (1)	2
SE (1)	5
SE (1)	2
SE (4)	1
SE (6)	2
SE (4)	1
SE (6)	1
SE (6)	4
UK (1)	6
UK (2)	9
UK (1)	1
UK (1)	8
UK (4)	20
UK (4)	3
UK (1)	14
UK (1)	10

Decentralised Procedure

The CMD(h) noted that there were **2** new Decentralised Procedures finalised during the month of January 2007. There were **1** withdrawn and **1** rejected new Decentralised Procedures, which were after day 120 of the procedure. There were **no** Decentralised Procedures referred to the CMD(h) in this period.

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.

The status as of 31st January 2007 of procedures under Decentralised Procedure is as follows:

Year	New applications finalised with positive outcome	New applications withdrawn ²	New applications finalised with negative outcome ²	New applications in process	Referred to CMD(h)	Agreement reached in the CMD(h)	Arbitrations referred to CHMP
2007	2	1	1	480	--	--	--

87 Decentralised Procedures (regarding **200** products) started in January 2007. The categories of these procedures are as follows:

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

2 known active substance applications, including **1** multiple application.

1 Line Extension application.

The new Decentralised procedures started in January related to **61** generic, **23** hybrid, **1** full dossier and **2** fixed combination applications.

All of these procedures consisted of chemical substance applications.

84 of these procedures related to prescription-only medicinal products and **3** procedures related to non-prescription medicinal products in the reference Member State³.

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

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (3)	5
DE (1)	11
DE (1)	2
DE (2)	6
DE (2)	1
DE (2)	8
DE (1)	6
DE (2)	3
DE (2)	5
DE (2)	2
DE (2)	1
DE (2)	2
DE (2)	1
DE (2)	7
DE (2)	8
DE (2)	16
DE (2)	5
DE (2)	16
DE (1)	3
DE (2)	1
DE (2)	1
DE (1)	1
DE (2)	1
DE (5)	18
DE (6)	2

² After day 120 of the procedure.

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.

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

VARIATIONS AND RENEWALS

Mutual Recognition and Decentralised Procedures

The CMD(h) noted that **437** type IA variations, **164** type IB variations and **146** type II variations were finalised during the month of January 2007. **33** renewals were finalised in this period.

The status as of 31st January 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	437	164	146	33	--

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):

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

NL – 2500 Den Haag , The Netherlands

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

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