

Report from the CMD(h) meeting held on 23rd and 24th April 2007

Sub-group meeting on Harmonisation of SPCs

There was a meeting of the Sub-group on harmonisation of SPCs.

The Sub-group acknowledged that the medicinal products included in list for SPC harmonisation would be referred to the CHMP, in accordance with Article 30(1) of Directive 2001/83/EC, as amended, during the course of 2007. Prior to the start of the Article 30 referral procedures, the respective Marketing Authorisation Holders will be invited for pre-referral meetings at the EMEA.

The Sub-group started to work on a new list of medicinal products for which a harmonised SPC should be drawn up and will consider the proposals from Member States at the next meeting of the Sub-group, scheduled to take place in June 2007.

Possibility to use a medicinal product authorised in a Member State prior to its accession to the EU as reference medicinal product for the purpose of the data exclusivity period

The CMD(h) has agreed a Q&A to clarify that a medicinal product authorised in a Member State prior to its accession to the EU can only be used as a reference medicinal product for the purpose of the data exclusivity period as of the date of accession of the Member State to the EU, provided that the medicinal product is in compliance with the Community acquis.

EU Work sharing Project – Assessment of paediatric data

The Marketing Authorisation Holders for the following medicinal products, involved in the EU work sharing project - assessment of paediatric data, are requested to submit, within 60 days, national variations to implement the agreed text for inclusion in the SPC:

- Ciloxan (ciprofloxacin);
- Cibacen (benazepril).

Informal CMD(h) meeting - Germany

An informal meeting will be held in Bonn on 7-8 May 2007. The main topics for the meeting include MSs experience with work sharing initiatives, including a proposal for work sharing for patient consultation, evaluation of referrals to the CMD(h), MSs follow up to Article 30 and 31 referral procedures, the revision of the Variation Regulation and the impact of the Paediatric Regulation on National Competent Authorities business processes.

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 29.03.2007.

Name of the product in the RMS	Paroxetine Kiron 20mg/20 drops
Active substance	paroxetine
Pharmaceutical form	Oral drops, solution
Procedure number	NL/H/877/01/MR
CMS	AT, BE, DE, ES, IT, UK
Legal basis	Art 10.1 Dir 2001/83/EC - Generic
Grounds for referral to CMD(h)	There is a concern regarding the practicality of counting up to 60 drops to achieve the required dose. Counting of > 20 drops to obtain the required dose is not considered practical without undue increase in medication errors and possible overdose. There is therefore concern regarding the safety in use of the product.
Day 60	29.03.07

Outcome	<p>At the CMD(h) meeting the RMS presented its view and the applicant's written response were discussed. The applicant made use of an oral hearing. Following the discussion all involved Member States could agree on a proposal to adapt the SPC.</p> <p>In section 4.2 of the SPC it is included that for doses requiring more than 40 drops, other pharmaceutical forms (e.g. tablets, oral suspension) should be considered. However if necessary, the patient should seek advice from the health care provider about alternative ways of administration, such as the use of an oral syringe. Moreover it will temporarily (see below) be included in the SPC that in case the health care provider advises the use of an oral syringe, the dropper device is removable, allowing the insertion of an oral syringe. The corresponding volumes required for doses greater than 40 drops are included as well in section 4.2 of the SPC. Inclusion of the possibility to remove the dropper device will only be temporary until the new presentation will be authorised.</p> <p>The applicant has committed to submit a variation application to add another presentation, namely a bottle without dropper device, as soon as possible after finalisation of the procedure. A syringe will then be delivered separately.</p>
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Name of the product in the RMS	Finaburg 5 mg Finasteride ratiopharm 5 mg Finasteride-ct 5 mg Finawald 5 mg Finahold 5 mg Finasteride ratiopharm 5 mg Finagalen 5 mg
Active substance	finasteride
Pharmaceutical form	Film-coated tablet
Procedure number	NL/H/903/01/MR NL/H/905/01/MR NL/H/906/01/MR NL/H/908/01/MR NL/H/909/01/MR NL/H/911/01/MR NL/H/912/01/MR
CMS	903: DE 905: DE, DK, FI, FR, IT, LU, NO, PL, SE, UK 906, 908, 909, 911, 912: DE
Legal basis	Art 10.1 Dir 2001/83/EC - Generic
Grounds for referral to CMD(h)	There is a concern regarding the amount of selenium present in the active substance and the possibility of formation of diphenyl diselenide (DDS) during synthesis.
Day 60	29.03.07
Outcome	The applicant provided additional batch data on the amount of selenium in the active substance, and the validation of the method of analysis. Furthermore a specification was set. Agreement was reached before the CMD(h) meeting.

Name of the product in the RMS	Bicaluplex 50 mg
Active substance	bicalutamide
Pharmaceutical form	Tablet
Procedure number	CZ/H/0133/01/MR
CMS	AT, BE, DE, DK, EE, EL, FR, HU, IE, IT, LT, LU, LV, NL, NO, PL, PT, SE, SI, 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) on the following grounds: A positive benefit risk ratio for the proposed indication: <i>'Treatment of advanced prostatic carcinoma in combination with luteinising</i>

	<i>hormone-releasing hormone (LHRH) analogue or surgical castration</i> . has not been proven.
Day 60	29.03.07
Outcome	Before the CMD(h) meeting the RMS and CMS concluded that the benefit risk ratio for the indication of this generic product is identical to that of the originator. Therefore, no Potential serious risks to public health were identified. Agreement Reached.

Name of the product in the RMS	Bicaluplex 150 mg
Active substance	bicalutamide
Pharmaceutical form	Tablet
Procedure number	CZ/H/0133/02/MR
CMS	AT, DE, DK, EE, EL, FR, HU, IT, LT, LV, NL, NO, PL, PT, SE, SI, 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) on the following grounds: A positive benefit risk ratio for the proposed indications has not been proven.
Day 60	29.03.07
Outcome	Referred to CHMP for Arbitration.

Name of the product in the RMS	Diklofenak BMM Pharma
Active substance	diclofenac sodium
Pharmaceutical form	Gastro-resistant tablet
Procedure number	SE/H/600/01-02/MR
CMS	DK, FI, NO
Legal basis	Art 10.1 Dir 2001/83/EC - Generic
Grounds for referral to CMD(h)	Potential serious risk to public health was raised by two Member States mainly due to the lack of a post-prandial study. The national approval in the RMS was based on a bioequivalence study under fasting conditions only. However, during the MRP a post-prandial study became available to the applicant and was submitted. Although submitted during the ongoing procedure, the study was accepted and assessed by the RMS. The study could however not be accepted for formal reasons.
Day 60	29.03.07
Outcome	Since the post-prandial study could not be formally accepted during the MRP, it was re-submitted during the CMD referral. There was a discussion regarding the widening of the acceptance criteria to 70-143%. The RMS argued that such a widening was in accordance with the relevant guideline although the EWP Q&A document was unclear as to whether a widening outside 75-133% would be acceptable. The Member States involved in the procedure agreed that the widening of the acceptance criteria in this case did not have any clinical relevance. A contributing fact was that the product is recommended not to be administered with food. Agreement of approval was reached.

Name of the product in the RMS	Menitorix
Active substance	Hib/MenC conjugate vaccine
Pharmaceutical form	Powder and Solvent for Solution for Injection
Procedure number	UK/H/954/01/MR
CMS	BE, EL, ES, IE, PL
Legal basis	Art 8.3(i) Dir 2001/83/EC - Full Dossier

Grounds for referral to CMD(h)	Issues of potential serious risk to public health had been raised by three CMS. These three CMS considered that: <ul style="list-style-type: none"> • Immunological correlates of protection were not established for MenC conjugates. • Pre-licensure effectiveness data were required to cover infant and toddler use. • It was not acceptable that there were no data on use of Menitorix or on antibody persistence beyond the second year of life.
Day 60	29.03.07
Outcome	The RMS, CMS and Company presented their positions. The three CMS with issues of potential serious risk to public health retained their position. Referred to CHMP for arbitration.

Name of the product in the RMS	Xeomin
Active substance	clostridium botulinum type A neurotoxin complex
Pharmaceutical form	Powder for solution for injection
Procedure number	DE/H/0722/01/MR
CMS	AT, DK, ES, FI, FR, IT, LU, NO, PL, PT, SE, UK
Legal basis	Art 8.3(i) Dir 2001/83/EC - Full Dossier
Grounds for referral to CMD(h)	Potential serious risks to public health concerns were raised by three Concerned Member States related to the safety profile and posology of the medicinal product. On the safety side the data presented was found not to be sufficient to provide proof for the safe use of the product under repetitive use conditions. Specifically the potential for immunogenicity could not fully be evaluated. Furthermore the posology as recommended was deemed not having been firmly established with regard to the optimal dose in view of the clinical data submitted.
Day 60	29.03.07
Outcome	At the CMD(h) meeting the RMS presented its view on the product. The Applicant was given opportunity to present its case in an oral explanation. Following the meeting the SPC was updated to include notion of limited experience in treatment of naïve patients and long-term treatment, but finally the objections were maintained and no consensus could be achieved. Referred to CHMP for arbitration.

Name of the product in the RMS	LENOXe 100% (V/V)
Active substance	xenon (133Xe)
Pharmaceutical form	Inhalations gas, liquid
Procedure number	DE/H/0696/01/MR
CMS	AT, BE, DK, ES, FR, IT, LU, NL, PT, SE, UK
Legal basis	Art 8.3(i) Dir 2001/83/EC - Full Dossier
Grounds for referral to CMD(h)	A number of issues were stated to represent potentially serious public health concerns by four CMS. The issues in question may be summarised as follows: <ul style="list-style-type: none"> • the potential of the medicinal product to provide sufficient and reliable anaesthesia considering the active comparator used in the clinical trials; • appropriateness of the active comparator chosen in the trials; • lack of evaluation and guidance on concomitantly used anaesthetics and analgesics for a balanced anaesthesia; • adequacy of using the bispectral index monitor (BIS) to assess the depth of an anaesthesia; • incidence of post operative nausea and vomiting (PONV); • limited data for xenon based anaesthesia in high risk patients (e.g. elderly, renal and hepatic impairment, heart disease); • lacking technical information on the anaesthetic devices appropriate for xenon based anaesthesia.

Day 60	29.03.07
Outcome	Following further responses addressing the issues, the applicant presented its position during the CMD(h) meeting. The RMS endorsed its support of the applicant's presentation. Subsequent to the meeting the SPC was further updated to address outstanding concerns including e.g. doses used with concomitantly administered analgesics, limited experience with concomitant administration of volatile anaesthetics, addition of warnings or contraindications for high risk patients, mentioning of PONV occurrences. The applicant furthermore committed to address some safety related issues post-marketing within the formal context of a Risk Management Plan. At day 60 of the procedure agreement could be achieved that the medicinal product can be authorised.

Name of the product in the RMS	Venlanofi XR 37.5 & 75mg	Venlanofi XR 150 mg
Active substance	venlafaxine	
Pharmaceutical form	Prolonged release capsule, hard	
Procedure number	NL/H/933/01-02/MR	NL/H/933/03/MR
CMS	DE, ES, FR, IT, PT	DE, ES, IT, PT
Legal basis	Art 10.1 Dir 2001/83/EC - Generic	
Grounds for referral to CMD(h)	A concern was raised with regard to the maximum daily dose of up to 375 mg, the wording of the indication 'major depressive episodes', the limitation of the indications 'generalised anxiety disorder' and 'social anxiety disorder' to short term use, and the indication 'panic disorder with or without agoraphobia'.	
Day 60	29.03.07	
Outcome	The applicant and RMS provided supportive data for the maximum daily dose and the above mentioned indications. The applicant committed to harmonise the SPC of this product with the outcome of the art 30 referral for venlafaxine that will start in the near future. Agreement was reached before the CMD(h) meeting.	

NEW APPLICATIONS

Mutual Recognition Procedure

The CMD(h) noted that **56** new Mutual Recognition Procedures were finalised during the month of March 2007. **3** Mutual Recognition Procedures for new applications were referred to CMD(h) in this period. **10** Mutual Recognition Procedures for new applications were referred to CHMP in this period.

The status as of 31st March 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	138	166	12 N.A.	29	1	11

32 Mutual Recognition Procedures (regarding **55** products) started in March 2007. The categories of these procedures are as follows:

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

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

2 line extension applications, which were repeat use applications.

The new procedures started in March related to **4** full dossiers, **18** generics, **5** hybrid applications, **1** fixed combination and **4** bibliographic applications.

These procedures consisted of **29** chemical, **1** biological other and **2** biological vaccine substances.

31 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 March 2007.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
CZ (1)	6
CZ (4)	21
DE (2)	12
DE (2)	10
DE (3)	10
DE (2)	3
DE (1)	17
DE (1)	6
DK (2)	2
DK (4)	1
DK (1)	13
DK (2)	3
FI (2)	6
FI (2)	4
FR (2)	18
HU (3)	6
NL (1)	13
NL (1)	23
NL (1)	4
NL (1)	2
NL (1)	1
NL (1)	1
NL (1)	1
NL (1)	2
NL (1)	7
NO (3)	2
SE (1)	8
SE (1)	7
UK (2)	1
UK (1)	9
UK (3)	4
UK (1)	1

Decentralised Procedure

The CMD(h) noted that there were **14** new Decentralised Procedures finalised during the month of March 2007. There were **3** Decentralised Procedures referred to the CMD(h) in this period.

The status as of 31st March 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	27	2	1	607	5	1	--

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.

² After day 120 of the procedure.

83 Decentralised Procedures (regarding **152** products) started in March 2007. The categories of these procedures are as follows:

75 abridged applications, including **34** multiple applications.

2 known active substance applications.

6 Line Extension applications.

The new Decentralised procedures started in March related to **68** generic, **3** full dossier, **1** informed consent, **10** hybrid and **1** bibliographic applications.

All of these procedures consisted of chemical substance applications.

81 of these procedures related to prescription-only medicinal products and **2** 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 March 2007.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
AT (2)	3
AT (2)	2
AT (2)	4
CZ (2)	12
CZ (4)	4
DE (5)	14
DE (2)	14
DE (1)	2
DE (1)	5
DE (1)	20
DE (1)	4
DE (1)	11
DE (2)	10
DE (1)	10
DE (1)	4
DE (1)	1
DE (1)	6
DE (1)	5
DE (2)	19
DE (2)	16
DE (2)	1
DE (2)	1
DE (2)	1
DK (2)	9
DK (2)	9
DK (2)	21
DK (1)	2
DK (1)	1
DK (1)	4
DK (1)	5
DK (1)	5
DK (2)	1
DK (2)	1
DK (2)	1
DK (2)	1
DK (2)	1
DK (2)	1
DK (2)	1
DK (2)	1
DK (2)	1
DK (2)	3
DK (2)	3
DK (2)	1

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
DK (2)	1
DK (2)	3
DK (2)	4
DK (2)	1
DK (2)	18
DK (2)	1
DK (4)	6
DK (6)	5
DK (1)	3
DK (1)	1
FI (2)	12
FI (2)	4
FI (1)	2
FI (2)	3
FI (1)	1
NL (3)	13
NL (2)	1
NL (2)	4
NL (1)	23
NL (3)	3
NL (2)	4
NL (1)	1
NL (1)	3
NL (1)	6
NL (1)	1
NL (1)	1
NL (4)	1
UK (1)	14
UK (4)	12
UK (1)	1
UK (3)	15
UK (1)	15
UK (1)	15
UK (3)	1
UK (1)	3
UK (3)	4
UK (1)	1
UK (1)	1
UK (1)	1
UK (1)	1
UK (1)	1
UK (1)	1
UK (1)	3

VARIATIONS AND RENEWALS

Mutual Recognition and Decentralised Procedures

The CMD(h) noted that **592** type IA variations, **199** type IB variations and **221** type II variations were finalised during the month of March 2007. **55** renewals were finalised in this period.

The status as of 31st March 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	1396	486	489	124	--

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

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