Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

31 May 2018
EMA/CMDh/727468/2017

Report from the CMDh meeting held on 28-30 May 2018

CMDh outcome on referrals pursuant to Article 107i of Directive 2001/83/EC

Hydroxyethyl starch (HES) containing medicinal products

The CMDh held detailed discussions on the PRAC recommendation to suspend the marketing authorisations for medicinal products containing hydroxyethyl starch (HES). The CMDh will discuss the issue further at its June plenary meeting.

Brexit preparedness

CMDh procedural advice on changing the RMS

The CMDh agreed an update of the CMDh procedural advice on changing the RMS. The information included in the document has been brought in line with the information published in April in the "Practical guidance for procedures related to Brexit for medicinal products for human use approved via MRP/DCP". This clarifies CMDh guidance that change of RMS during on-going procedures is not permitted, including new MA procedures. Further information on cases where all CMS have refused to become the new RMS has also been included.

The updated document will be published on the CMDh website under "Procedural guidance, General Information".

CMDh positions following PSUSA procedure for nationally authorised products only

The CMDh, having considered the PSURs on the basis of the PRAC recommendation and the PRAC assessment reports, agreed by consensus on the variations of the marketing authorisations of medicinal products containing the following active substances:

- adapalene / benzoyl peroxide
- calcium carbonate / famotidine / magnesium hydroxide
- etomidate

- famotidine
- fluvastatin

Further information regarding the above mentioned PSUSA procedures, including information on the implementation, will be published on the EMA website.

PSUR Follow-up procedure (PSUFU) for fluoxetine containing medicinal products

In the framework of the PSUSA for fluoxetine, the PRAC considered that the signals of neurodevelopmental disorders (including autism spectrum disorders (ASD)) after maternal use of SSRI/SNRI and cardiac valve disorders needs to be further assessed in a timely manner before the next PSUSA in a PSUR follow-up (PSUFU) procedure.

The MAH Lilly was therefore requested to submit by 25 May 2018 answers to the following questions as part of a PSUFU procedure, for which France will be the LMS:

A review of literature publications on risk of ASD after in utero exposure to SSRI in general and to fluoxetine in particular.

A review of literature publications on risk of neurodevelopmental disorders other than ASD after in utero exposure to SSRI in general and to fluoxetine in particular. According to the appropriateness of the analysis, different effects should be discussed separately.

A cumulative review of cardiac valve disorders and related PTs including a literature review. The MAH will present an analysis including all potential confounding factors, positive and negative dechallenge and rechallenge if mentioned and the time to onset after the treatment initiation. A discussion about the mechanism of a possible action of fluoxetine on cardiac valve disorders is also requested. Finally, the MAH should discuss if further update to the product information is needed.

The procedure number for this PSUFU procedure is FR/H/PSUFU/00001442/201709. More information on the PSUFU procedure can be found in the guidance published under "Pharmacovigilance, PSUR".

PSUR Follow-up procedure (PSUFU) for minocycline containing medicinal products

In the framework of the PSUSA for minocycline, the PRAC recommended that the MAHs included in the PSUSA should address the following as part of a PSUSA follow-up (PSUFU) for which Spain will be the LMS, within 2 months of the PRAC recommendation:

- All the MAHs included in the PSUSA should present a cumulative review of all the cases related to foetal exposure based on a multiaxial search using the SOCs "pregnancy, puerperium and perinatal conditions" and "Congenital, familial and genetic disorders" as well as the HLGTs "Cytogenetic investigations" and "Foetal and neonatal investigations" (both HLGTs are included in the SOC "Investigations") from spontaneous reports and any other source.
- All the MAHs included in the PSUSA should provide data on utilisation during pregnancy, overall data and divided per country. The total number of patients exposed during pregnancy should be presented, including a detailed analysis of the time of exposure during pregnancy (pregnancy week or trimester), the outcome of the pregnancy and on the consequences of exposure during pregnancy.
- Based on the cumulative review, the MAHs should propose measures in order to avoid use during pregnancy.

The procedure number for this PSUFU procedure is ES/H/PSUFU/00002065/201708. More information on the PSUFU procedure can be found in the guidance published under "Pharmacovigilance, PSUR".

Ferrous sulphate-containing tablets

Following the publication of a harmonised wording to be included in section 4.4 and 4.8 of the SmPC (and the corresponding text for the package leaflet) of ferrous sulphate-containing tablets in April, the CMDh specifies that the CMDh recommendation concerns all medicinal products within ATC B03A A07 "ferrous sulfate", except oral liquids.

The agreed text published on the CMDh website under "Advice from CMDh" will be updated with this clarification.

Best Practice Guide for Decentralised and Mutual Recognition Procedures

The CMDh agreed an update of the Best Practice Guide for Decentralised and Mutual Recognition Procedures. The BPG was brought in line with other guidance documents, e.g. SOP on DCP and the MRP timetable, and it was clarified that the procedure start for MRP/RUP should also be communicated via email (in addition to communication via CTS). Further editorial changes have been included.

The updated document will be published on the CMDh website under "Procedural Guidance, Application for MA".

Template for Preliminary Renewal Assessment Report

The CMDh agreed an update of the template for the Preliminary Renewal Assessment Report to include information on conditions to the marketing authorisation and to bring it in line with the Best Practice Guide on processing of renewals in MRP/DCP.

The updated template will be published on the CMDh website under "Templates, Assessment Reports, Renewals".

ASMF number request form

The CMDh agreed an update of the ASMF number request form to include information on the assessment history of the ASMF.

The updated form will be published on the CMDh website under "CMD Working Parties/Working Groups, Working Group on Active Substance Master File Procedures".

Meeting with Interested Parties

The CMDh convened a meeting with Interested Parties in the margins of the May CMDh plenary meeting. The topics discussed included parallel national MAAs, the use of variation worksharing, use of colours in medicines, Brexit, SPOR/IDMP, excipients in the labelling and package leaflet, improvement of communication after PSUSA procedures and a feedback from the non-prescription medicines task force. All presentations will be published on the CMDh website under "About CMDh, Contact with Representative Organisations".

EU Work-sharing Articles 45 & 46 of the Paediatric Regulation – Public Assessment Reports

The CMDh has agreed on a public assessment report for paediatric studies submitted in accordance with Article 45 of the Paediatric Regulation for:

- clostridium botulinum toxin

including recommendations for the text to be included in SmPCs and package leaflets.

Marketing Authorisation Holders of medicinal products with same active substance and pharmaceutical form are requested to include this information in their SmPCs and package leaflets within 90 days of publication of the public assessment report, in accordance with the Best Practice Guide – Article 45, EU work-sharing procedure.

The public assessment report will be published on the CMDh website under "Paediatric Regulation, Assessment reports".

NEW APPLICATIONS

Mutual Recognition Procedure

The CMDh noted that **20** Mutual Recognition Procedures were finalised during the month of April 2018 and **1** Mutual Recognition Procedure was referred to CMDh in this period. **No** Mutual Recognition Procedure was referred to CHMP in this period.

Table 1. The status as of 30 April 2018 of procedures under Mutual Recognition

Year	New applications finalised[1]	Referred to CMDh	Agreement reached in the CMDh For procedures referred in		Withdrawn during CMDh referral For procedures referred in		Applications referred to CHMP For procedures referred to CMDh in	
			2017	2018	2017	2018	2017	2018
2018	101	2	0	0	0	0	0	1

22 Mutual Recognition Procedures (regarding **32** products) started in April 2018. The categories of these procedures are as follows:

- **14** abridged applications (including **10** repeat use procedures);

- **8** known active substance applications (including **7** repeat use procedures);

The Mutual Recognition Procedures started in April 2018 related to the following applications: **2** full dossiers, **12** generic, **no** well-established use applications, **7** hybrid applications and **1** fixed combination application.

All of these procedures consisted of chemical substances.

[1] Due to late database updates cumulative yearly figure differs from the monthly figures. Cumulative yearly figure includes late database updates on finalised procedures not captured in the monthly figures published in press releases. The applications referred to CHMP are included in the 'new applications finalised.'

20 of these procedures related to prescription-only medicinal products and **2** procedures related to non-prescription medicinal products in the reference Member State[2].

Table 2. New applications in Mutual Recognition procedure started in April 2018

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	1	1
Belgium		1
Bulgaria		
Croatia		5
Cyprus		4
Czech Republic		
Denmark	4	1
Estonia		
Finland		
France		2
Germany	3	
Greece		1
Hungary		2
Iceland		5
Ireland		1
Italy		4
Latvia		
Liechtenstein		
Lithuania		
Luxembourg		
Malta		
Netherlands	7	
Norway		2
Poland		1
Portugal	1	6
Romania		3
Slovak Republic		
Slovenia		2
Spain	2	2
Sweden	3	1
United Kingdom	1	4

Decentralised Procedure

The CMDh noted that **86** Decentralised procedures with positive outcome and **1** procedure with negative outcome were finalised during April 2018. **4** Decentralised procedures were withdrawn after day 120 in this period. **No** Decentralised Procedure was referred to the CMDh in this period. **No** Decentralised Procedure was referred to the CHMP in this period.

[2] 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.

Table 3. The status as of 30 April 2018 of procedures under Decentralised Procedure

Year	New applications finalised[3]	New applications Withdrawn[3] (After day 120)	Referred to CMDh	Agreement reached in the CMDh For procedures referred in		Withdrawn during CMDh referral For procedures referred in		Applications referred to CHMP For procedures referred to CMDh in	
				2017	2018	2017	2018	2017	2018
2018	340	11	2	1	0	0	0	1	0

96 Decentralised Procedures (regarding **184** products) started April 2018. The categories of these procedures are as follows:

- **68** abridged applications (including **2** multiple applications);
- **26** known active substance applications (including **5** multiple applications);
- **2** extension applications;

The new Decentralised Procedures started in April 2018 related to the following applications: **1** full dossier, **70** generic, **13** well-established use and **11** hybrid applications.

All of these procedures consisted of chemical substances.

88 of these procedures related to prescription-only medicinal products and **8** procedures related to non-prescription medicinal products in the reference Member State[4].

Table 4. New applications in Decentralised procedure started in April 2018

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	3	5
Belgium	1	8
Bulgaria		5
Croatia		5
Cyprus		4
Czech Republic	2	12
Denmark	5	12
Estonia	1	4
Finland		12
France		17
Germany	16	29
Greece	1	9
Hungary	5	5
Iceland		4
Ireland	1	7

[3] Due to late database updates cumulative yearly figure differs from the monthly figures. Cumulative yearly figure includes late database updates on finalised procedures not captured in the monthly figures published in press releases. The applications referred to CHMP are included in the 'new applications finalised.
[4] 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.

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Italy	1	21
Latvia		5
Liechtenstein		
Lithuania		5
Luxembourg		10
Malta		12
Netherlands	16	15
Norway	3	9
Poland	1	13
Portugal	17	6
Romania		7
Slovak Republic		7
Slovenia		5
Spain	5	20
Sweden	5	18
United Kingdom	13	21

VARIATIONS AND RENEWALS

Mutual Recognition and Decentralised Procedures

The CMDh noted that **527** type IA variations, **485** type IB variations, **113** type II variations and **233** renewals were finalised during April 2018. **No** Type II variations, **no** variation worksharing, or renewal procedures were referred to the CMDh in this period. **No** type II variation procedures were referred to the CHMP in this period.

Table 5. The status as of 30 April 2018 of variations and renewals under Mutual Recognition[3]

Year	Type IA variations finalised	Type IB variations finalised	Type II variations finalised	Variation work-sharing[5] finalised	Renewals finalised
2018	1958	1918	374	112	672

2018	Referred to CMDh	Agreement reached in the CMDh For procedures referred in		Withdrawn during CMDh referral	Applications referred to CHMP For procedures referred to CMDh in	
		2017	2018		2017	2018
Type II	0	0	0	0	0	0
Worksharing	0	0	0	0	0	0
Renewal	0	0	0	0	0	0

[5] Finalised work sharing do not include work sharing involving centrally approved products coordinated by EMA

Information on the above mentioned issues can be obtained:

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Or you could visit the CMDh website at: *http://www.hma.eu/cmdh.html*