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

31 July 2019
EMA/CMDh/380105/2019

Report from the CMDh meeting held on 23-25 July 2019

Brexit preparedness

Following a request by the United Kingdom, the European Council (Article 50) agreed on 11 April 2019 to extend further the period provided for in Article 50(3) TEU until 31 October 2019. Unless the United Kingdom ratifies the Withdrawal Agreement by 31 October 2019 or requests a third extension, to which the European Council (Article 50) agrees by unanimity, the period under Article 50(3) TEU will end then. The United Kingdom will then be a third country as of 1 November 2019.

On 21 February 2019 Commission services set out in a note on the "Withdrawal of the United Kingdom and EU rules for batch testing of medicinal products", the conditions for marketing authorisation holders to continue relying on quality control testing performed in the United Kingdom for a limited period of time after the UK becomes a third country. A key condition for this exemption is that "all necessary steps have been taken to prepare the transfer of the quality control testing site to the EU27". Furthermore, "marketing authorisation holders must confirm and set out their precise timetable for transfer of the quality control testing site (which should allow the process to be completed quickly and in principle by the end of 2019 at the latest)".

It is essential that marketing authorisation holders use the remaining time to complete their preparations so that by 1 January 2020 all batch testing facilities are fully transferred to the EU27/EEA and the necessary regulatory submissions are completed.

For further details please see the relevant communication:
https://ec.europa.eu/health/sites/health/files/files/documents/brexit_batchtesting_medicinalproducts_en.pdf

Naming of liposomal formulations to improve patient safety

The CMDh agreed in liaison with CHMP on a joint position for the naming of products containing liposomal drug delivery systems on the basis of concerns expressed by the CHMP Name Review Group (NRG).

This is further to a number of reports of serious medication errors resulting from confusion between liposomal and non-liposomal formulations of the same active substance. This risk is recognised as occurring across multiple liposomal and pegylated liposomal products throughout the European Union.

So far, there was no agreed approach to the product naming of liposomal formulations to enable healthcare professionals and patients to clearly distinguish them from non-liposomal products. This is particularly concerning when electronic prescribing and dispensing lists are used, as in the absence of a more descriptive term for the liposomal products, they can be mixed up with non-liposomal products. It is further acknowledged that invented name prescribing alone does not seem to adequately address the issue. The risk of confusion is considered to be further enhanced when product names composed of 'INN+company name/trademark' are used.

After consultation of PRAC, the CMDh and CHMP agreed on the following actions:

- Update to section 1 of the SmPC in regards to the addition of the qualifier '**liposomal**' or '**pegylated liposomal**' to the invented name, to be placed after the invented name and before the strength as per the standard practice for qualifiers.
- Update to section 1 of the SmPC in regards to the addition of the qualifier '**liposomal**' or '**pegylated liposomal**' to the INN+MAH/trademark name. In order to facilitate differentiation between formulations the qualifier should be placed between the INN and the company name or trademark.
- Consistent use of existing EDQM standard term 'dispersion'. The currently existing term 'dispersion', which includes liposomes in its definition, needs to be used consistently throughout the product information.

In light of the serious nature of the risk, marketing authorisation holders of liposomal and pegylated liposomal products are requested to address this as a matter of urgency. Concerned MAHs are requested to submit a type IB variation (A.2.b) to add the appropriate qualifier to their product name as soon as possible and at the latest by the end of September 2019.

The above common CMDh-CHMP position will ensure that all liposomal and pegylated liposomal medicinal products across the European Union are named in a consistent manner, strengthening the safe use of these products for all EU citizens.

CMDh positions following PSUSA procedures for nationally authorised products only

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

- azathioprine
- iron (parenteral preparations, except for iron dextran)
- iron dextran
- ketamine
- metoclopramide
- tapentadol

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

PSUR Follow-up procedures (PSUFU) for valaciclovir containing medicinal products

In the framework of the PSUSA on valaciclovir, the PRAC considered that the following issues need to be further assessed in the framework of a PSUFU:

- **Cumulative review of all cases indicating severe cutaneous reaction SCARs + more exhaustive research of DRESS**

  Data requested from the MAH GSK:

  1. Please provide a cumulative review of all cases indicating severe cutaneous reaction (SMQ Severe cutaneous adverse reactions (narrow) but with PT blister, skin exfoliation and skin erosion from the SMQ SCARs broad). Emphasis should be given to PT dermatitis bullous for which a case with positive rechallange was reported
  2. Please provide more exhaustive research of DRESS with the PT included in the SMQ Broad "Drug reaction with eosinophilia and systemic symptoms", using the criteria of the Regiscar score (e.g. crossing PT suggestive of drug reaction or drug hypersensitivity with PT suggestive of eosinophilia and/or those suggestive of lymphadenopathy). This additional research should be done for both valaciclovir and aciclovir-containing products.
  3. Please provide a case narrative for the DRESS case associated with aciclovir and reported positive patch test to aciclovir; as valaciclovir is a pro-drug of aciclovir, this case is relevant for the overall analysis.
  4. Please provide a proposal for update of product information, if warranted by the results of the analysis.

- **Possible interaction between valaciclovir and NSAIDs leading to acute kidney injury (AKI)**

  Data requested from the MAH GSK:

  1. Please provide the previously requested analysis of AKI cases (identified via SMQ Acute Renal Failure (narrow) in patients who used valaciclovir concomitantly with NSAID. Case by case analysis for the most probable explanation of AKI in a patient should be performed. Focus should be given on cases where no further explanation for AKI in a patient besides concomitant use of valaciclovir and NSAID is found. Exact number of these cases should be provided.
  2. Please provide the disproportionality analysis of AKI cases for individual NSAIDs.
  3. Please provide the literature search looking for information concerning a possible interaction between valaciclovir and NSAIDs.
  4. Please discuss the possible mechanism for this interaction, especially the individual NSAID´s ability to inhibit renal tubular secretion of aciclovir.
  5. If warranted, please provide a proposal for update of product information.

Both should be provided by the MAH GSK via a PSUSA follow-up procedure to be submitted to the Lead Member State (CZ) within 60 days following this CMDh communication of the follow up request. The procedure number for this PSUFU procedure will be CZ/H/PSUFU/00003086/201812.

Requested data from GSK will be assessed comprehensively with data already submitted from all other concerned MAHs, therefore the PSUFU AR will be sent to all the concerned MAHs for comments.

Medicinal products containing timolol for ophthalmic use

During the assessment of the PSUSA on bimatoprost / timolol, the PRAC noted that timolol is also authorised as a single agent or in fixed dose combination products with e.g. latanoprost + timolol and brimonidin + timolol fixed dose combinations. The PRAC considered that the ADR 'Hallucination' in patients with open-angle glaucoma or ocular hypertension indication would also be relevant to be included in the single agent and fixed dose combinations of timolol as this ADR is related to the systemic action of timolol. It is suggested to include the ADR 'Hallucination' in the PI in the following manner:

(Relevant for both products with and without preservative)

Summary of Product Characteristics

- Section 4.8

The following adverse reaction should be added under the SOC Psychiatric disorders with a frequency Not known:

Hallucination*

***adverse reactions observed with timolol ~~monotherapy~~**

(The note is only relevant for timolol combination products, not for timolol single substance)

Package Leaflet

4. Possible side effects

Side effects where the frequency is not known

Hallucination

Valid for all timolol containing medicinal products for ophthalmic use (including combination products)

Pilot on splitting of MRP/DCPs

Following the announcement of the CMDh decision to stop the pilot on splitting of MRP/DCPs in the CMDh press release of June, the CMDh has agreed an update of the related guidance document to include information on the end of the pilot and the reasons thereof. The updated guidance document will be published on the CMDh website under "Advice from CMDh". The "CMDh working document on merging and splitting of MRP/DCPs" will be removed from the CMDh website.

"Diethanolamine" and "coconut oil diethanolamine condensate" excipients

As announced in the CMDh minutes of April 2019, NCAs have contacted MAHs of concerned products containing "diethanolamine" and "coconut oil diethanolamine condensate" as excipients with a request to undertake a risk assessment and to reformulate their products to replace the excipient or to provide a justification why this cannot be done. Feedback from the MAHs was expected by 1 September 2019. After considering the rationales provided in several requests from MAHs received by Member States, the CMDh has agreed to extend the deadline for submission of the feedback until 1 December 2019. This request is only applicable to MAHs that have already received the relevant communication from one of the EU/EEA NCAs.

Recommendations on common regulatory approaches for allergen products – Public consultation extension

In April 2019, the CMDh published the guidance document "Recommendations on common regulatory approaches for allergen products" for a 3-month public consultation. In July, the CMDh agreed an extension of the deadline for submission of comments by one month. Comments should now be provided by 30 August 2019, via the respective associations, where appropriate, and using the comments template.

Active Substance Master File (ASMF) worksharing

The Working Group on ASMF procedures prepared an update of the assessment report templates for both the restricted and the applicant's part of an ASMF to include guidance that in the assessment report no reference should be made to the related drug product / variation application and/or medicinal product for which this ASMF is associated with (e.g. no information on QP-declaration, procedure numbers) in order to be able to re-use the assessment report for other products.

The Working Group further prepared an update of the assessment report template for type IB variations for an ASMF to include a tracking table highlighting the conclusion of the variation referring to a new ASMF version.

All templates were adopted by the CMDh and will be published on the CMDh website under "Templates, Assessment Reports, ASMF".

Update of CMDh Guidance on the Informal Work-Sharing procedure for follow-up for PSUSA for NAPs (PSUFU)

The CMDh agreed an update of the CMDh Guidance on the Informal Work-Sharing procedure for follow-up for PSUSA for NAPs (PSUFU). In the revision, more guidance on the creation of the public summary assessment reports has been included and historical information on the background of the document has been deleted. The corresponding PSUFU assessment report template has been updated accordingly.

The updated guidance document will be published on the CMDh website under "Pharmacovigilance, PSUR". The updated assessment report template will be published under "Templates, PSUR".

Outcomes of informal PSUR work-sharing procedures

The CMDh has adopted the conclusions of the PSUR assessment for:

- Anthrax Antigen Filtrate (Biothrax)

which may require changes to the product information or introduction of other risk minimisation measures.

The public summary will be published on the CMDh website under "Pharmacovigilance, PSURs, Outcome of informal PSUR worksharing procedures".

MAHs of the products concerned should implement the outcome of the assessment by the appropriate variation or other procedure (as advised) within 90 days of publication.

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

The CMDh has agreed on public assessment reports for paediatric studies submitted in accordance with Article 46 of the Paediatric Regulation for:

- Fibryga (hman fibrinogen)
- Crestor (rosuvastatin)
- Silkis ointment (calcitriol)

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

Statistical information on MRP/DCP finalised/started, referrals to CMDh, variations and paediatric worksharing in the first semester of 2019

Statistics regarding finalised and started new applications in MRP and DCP in the first semester of 2019 according to the 5-levels of classification of the MRP/DCP Communication Tracking System database will be published on the CMDh website.

The statistics will also include information on variation worksharing procedures, on applications referred to the CMDh/concluded by the CMDh and on rapporteurships in paediatric worksharing procedures according to Art. 45 and 46 of the Paediatric Regulation.

The information will be published on the CMDh website under 'Statistics'.

NEW APPLICATIONS

Mutual Recognition Procedure

The CMDh noted that **22** Mutual Recognition Procedures were finalised during June 2019 and **no** Mutual Recognition Procedures were referred to CMDh in this period. **No** Mutual Recognition Procedures were referred to CHMP in this period.

Table 1. The status as of 30 June 2019 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	
			2018	2019	2018	2019	2018	2019
2019	193	3	1	2	0	0	0	0

25 Mutual Recognition Procedures (regarding **47** products) started in June 2019. The categories of these procedures are as follows:

- **15** abridged applications (including **13** repeat use procedures);

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

The Mutual Recognition Procedures started in June 2019 related to the following applications: **2** full dossier, **17** generic, **4** well-established use and **2** hybrid applications.

The procedures consisted of **24** chemical and **1** biological (vaccine) substances;

21 of these procedures related to prescription-only medicinal products and **4** procedures related to non-prescription medicinal products in the reference Member State[2].

Table 2. New applications in Mutual Recognition procedure started in June 2019

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	1	4
Belgium		1
Bulgaria		1
Croatia		2
Cyprus		1
Czech Republic		1
Denmark	3	2
Estonia		2
Finland		4
France		2
Germany	5	4
Greece		
Hungary	1	
Iceland		3
Ireland		1
Italy	1	2
Latvia		1
Liechtenstein		

[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.'
[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.

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Lithuania		1
Luxembourg		
Malta	1	4
Netherlands	9	2
Norway		3
Poland		4
Portugal		2
Romania		3
Slovak Republic		
Slovenia		
Spain		4
Sweden		5
United Kingdom	4	1

Decentralised Procedure

The CMDh noted that **45** Decentralised procedures with positive outcome and **0** procedures with negative outcome were finalised during June 2019. **6** Decentralised procedures were withdrawn after day 120 in this period. **1** Decentralised Procedure was referred to the CMDh in this period. **1** Decentralised Procedure was referred to the CHMP in this period.

Table 3. The status as of 30 June 2019 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	
				2018	2019	2018	2019	2018	2019
2019	535	47	4	0	0	0	1	0	1

99 Decentralised Procedures (regarding **192** products) started in June 2019. The categories of these procedures are as follows:

- **73** abridged applications (including **5** multiple applications);
- **26** known active substance applications (including **5** multiple application);

The new Decentralised Procedures started in June 2019 related to the following applications: **5** full dossier, **74** generic, **3** well-established use, **11** hybrid, **5** fixed combination and **1** herbal traditional use application.

97 of these procedures consisted of chemical substances, **1** biological (vaccine) and **1** herbal.

[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.

97 of these procedures related to prescription-only medicinal products and **2** procedures related to non-prescription medicinal products in the reference Member State[4].

Table 4. New applications in Decentralised procedure started in June 2019

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	5	20
Belgium		15
Bulgaria		9
Croatia		12
Cyprus		7
Czech Republic	2	23
Denmark	7	16
Estonia	2	11
Finland		12
France		25
Germany	27	31
Greece		10
Hungary	1	14
Iceland		7
Ireland		11
Italy		32
Latvia		12
Liechtenstein		1
Lithuania		12
Luxembourg		15
Malta	9	5
Netherlands	19	10
Norway	1	15
Poland	1	24
Portugal	17	17
Romania		12
Slovak Republic		19
Slovenia		12
Spain		32
Sweden	8	20
United Kingdom		9

VARIATIONS AND RENEWALS

Mutual Recognition and Decentralised Procedures

The CMDh noted that **865** type IA variations, **562** type IB variations, **82** type II variations and **64** renewals were finalised during June 2019. **No** Type II variations, variation worksharing or renewal

[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.

procedures were referred to the CMDh in this period. **No** variation worksharing procedures were referred to the CHMP in this period.

Table 5. The status as of 30 June 2019 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
2019	4387	3149	509	199	418

2019	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)	
		2018	2019		2018	2019
Type II	0	0	0	0	0	0
Worksharing	0	0	0	0	0	0
Renewal	0	0	0	0	0	0

Information on the above mentioned issues can be obtained:

Chair of the CMDh
Ms Laura Oliveira Santamaria
Agencia Española del Medicamento y Productos Sanitarios *Phone: + 34 91 8225142*
Parque Empresarial Las Mercedes Edificio 8 *E-mail: loliveira@aemps.es*
C/Campezo 1
ES-28022 MADRID

CMDh Secretariat *E-mail: H-CMDhSecretariat@ema.europa.eu*

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

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