18 March~~25 February~~ 2022
EMA/CMDh/125087/2022
Human Medicines Division

Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh)

Draft minutes for the meeting on 25-27 January 2022

Chair: Kora Doorduyn-van der Stoep – Vice-Chair: Susanne Winterscheid

25 January 2022, 09:00 – 17:00, Teleconference
26 January 2022, 09:00 – 17:00, Teleconference
27 January 2022, 09:00 – 12:00, Teleconference

Non-Prescription Medicinal Products Task Force
24 January 2022, 10:30 - 12:00, Teleconference
Chair: Martin Huber

CMDh/CMDv ASMF Working Group
26 January 2022, 17:00 - 18:30, Teleconference
Chair: Nienke Rodenhuis

Disclaimers

Some of the information contained in this set of minutes is considered commercially confidential or sensitive and therefore not disclosed. Ongoing procedures discussed by the CMDh are considered confidential.

Of note, this set of minutes is a working document primarily designed for CMDh members and the work the Committee undertakes.

Note on access to documents

Some documents mentioned in this set of minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

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1. Introduction

1.1. Welcome and declarations of interest of members, alternates and experts

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of some meeting participants in upcoming discussions as included in the pre-meeting list of participants and restrictions.

Participants in this meeting were asked to declare any changes, omissions or errors to their declared interests and/or additional restrictions concerning the matters for discussion. No new or additional interests or restrictions were declared.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members.

The Chairperson opened the meeting by welcoming all participants. Due to the current coronavirus (COVID-19) outbreak, and the associated EMA Business Continuity Plan (BCP), the meeting was held remotely.

1.2. CMDh membership

The CMDh welcomed Eleftheria Nikolaidi as new member for Greece, Stavroula Mamoucha as new alternate for Greece and Kristina Povilaitienė as new member for Lithuania.

1.3. Adoption of draft agenda

The agenda of the meeting was adopted with the following topics under A.O.B:

- Risk related to critical excipients in solid pharmaceutical form of methadone and levomethadone medicinal products in misusers

1.4. Adoption of the minutes

The minutes of the December 2021 meeting, including the comments received and discussed at the meeting, were adopted and will be published on the CMDh website (**Action: EMA**).

2. Organisational issues/Reports from other meetings

2.1. CMDh Working Groups/Working Parties/Task Force

2.1.1. CMDh/EMA Working Party on Paediatric Regulation / WP Chair (NO)

Public PdARs for paed. studies acc. Art. 45
None

Public PdARs for paed. studies acc. Art. 46
None

Art. 46 worksharing

The appointed Rapporteurs for the Art. 46 submissions were asked to provide feedback whether a worksharing will be necessary, if not already done so **(Action: MSs).**

2.1.2. Multilingual packaging Working Group / WG chair (IE)

The WG Chair gave an update to the CMDh on the work undertaken and the WG priorities for 2022.

2.1.3. GCP Inspectors Working Group/CMDh Working Party / WP chair (IE)

The WP Chair reported from the meetings of the WP held in December 2021 and January 2022. The WP discussed, among others, CROs of interest, the 2022 CROs Inspection Programme, the 2021 BE Forum & Online Training and the ongoing revision of ICH M10.

2.1.4. Working Party on Pharmacovigilance Procedures Worksharing / WP Chair (IT)

The WP Chair reported from the January WP meeting including feedback from the HaRP group.

The WP discussed among others the update of the EURD list and continued the discussions on the various proposals on how to optimise/rationalise the CMDh LoSC excel list.

The WP reviewed its mandate to reflect the changing tasks of the WP over time. The CMDh adopted the update of the mandate that will be published on the CMDh website (**Action: EMA**).

2.1.5. CTS Working Group / WG Chair (DE)

The CMDh has re-elected Mr Dino Soumpasis (DE) as Chair of the CTS Working Group.

The CTS Chair updated the group about the development, updates and technical issues in CTS.

2.1.6. Non-Prescription Medicinal Products Task Force Chair (DE)

The TF Chair reported from the January meeting.

The TF discussed an update of the BPG for authorisation of Non-Prescription Medicines in DCP and MRP including the comments received from MSs. The TF reached agreement in most of the outstanding issues. The rapporteur will prepare an updated version for discussion after the meeting (**Action: SE**). MSs comments will be awaited within 1 month after circulation of the updated version (**Action: MSs**). The rapporteur will prepare a consolidated version for discussion in the next TF meeting in April (**Action: SE**).

2.1.7. Working Group on ASMF procedures / Chair (NL)

The WG discussed among others the updates of the user guide, the Q&As and the mandate. The documents will be circulated to CMDh and tabled for adoption in February (**Action: Chair ASMF**). The CMDv Secretariat will start giving support to the ASMF WG after the January meeting instead of CMDh Secretariat.

2.2. Brexit / Chair, SE

Following the publication of the EC Notice 2021/C 524/02, the CMDh discussed and agreed updates of the CMDh Practical guidance (PG) for procedures related to Brexit and IE/NI Protocol. The updates take into account the information provided in the Commission Notice, among others, that for MR/DC procedures which include the MSs IE, CY, MT or UK(NI), continued use of sites located in the UK for batch control and batch release, MAH, local representative and, for UK(NI) only, QPPV or PSMF, may be permitted under the conditions stated in the Notice.

The updated documents will be published on the CMDh website (**Action: EMA**). A further update of the PG is foreseen once the legislative proposals are adopted and enter into force.

The CMDh discussed how to handle UK(GB) sites in procedures without UK(NI), IE, CY and MT as CMS, that should have been deleted by end of 2021, via a submission of a type IA variation. The CMDh agreed that MAHs that still have UK(GB) sites mentioned in the dossier in addition to EU sites, e.g. alternative batch release or batch control sites (except for procedures where IE, CY, MT and/or UK(NI) are CMS and have granted an exemption for their markets), should remove these alternative sites from the MA, using the respective variation procedure type IA, category A.7. The CMDh noted that this should be done immediately for all procedures not including IE, CY, MT and/or UK(NI) as CMS, as the timeframe for submission of these variations had already expired on 31 December 2021. Further regulatory activity might be possible on a national level in case these variation submissions are further delayed.

2.3. Meeting with Interested Parties / Chair

The minutes of the CMDh meeting with Interested Parties including comments received from Interested Parties, as discussed and agreed at the meeting, were adopted and will be published on the CMDh website (**Action: EMA**).

2.4. Presidency meetings

2.4.1. French Presidency meeting / FR

The French Presidency meeting will be held remotely on 7 April 2022. MSs were requested to send feedback, propose topics and volunteer as topic leads (**Action: MSs**). The first draft agenda will be presented next month (**Action: FR**).

The CMDh was informed that the presidency meeting to be hosted by Czech Republic will be held on 18-19 October 2022.

2.5. EU Pharmaceutical Strategy / Chair, DK, DE

The CMDh discussed the ongoing activities and collaboration with the EC in the context of the implementation of the new EU Pharmaceutical Strategy.

2.6. Joint CMDh/CMDv meeting / Chair

The CMDh adopted the minutes of the joint CMDh/CMDv meeting. The CMDv will be send for adoption to CMDv.

2.7. Mutual Recognition and Decentralised Procedure monitoring / EMA

The CMDh adopted the annual statistics for MRP/DCP of 2021. The CMDh agreed to include statistics on the Reference authority for WS procedures. The statistics will be published on the CMDh website (**Action: EMA**).

2.8. HMA meeting / Chair

The Chair reported from the virtual HMA meeting held on 23-24 November.

The CMDh agreed to start the consultation face for the CMDh multi-annual workplan (MAWP). The previous CMDh MAWP finished in 2020. During 2021, the CMDh has been analysing the actions of the previous MAWP and worked on a new MAWP to 2025, which outlines the priorities of the CMDh for the coming years. The document has been developed in parallel and is complementary to the HMA MAWP. Any changes made during the finalisation of the HMA MAWP document will also be considered in the CMDh MAWP, as appropriate. The following five main priority areas have been included in the CMDh MAWP:

- Availability of essential medicines and coordination during crisis

- Optimisation of procedures

- Innovative projects

- Preparation for legislative changes

- Optimisation of communication/relationship/meetings with interested parties and stakeholders

The draft document will be published for 2 months of public consultation (**Action: EMA**). Comments should be sent to the CMDh Secretariat (H-CMDhSecretariat@ema.europa.eu) by 4 April 2022, coordinated by trade associations where possible.

2.9. HMA/EMA Task Force on Availability of Authorised Medicines for Human and Veterinary use (TF-AAM) / Chair, EMA

The CMDh received a presentation from EMA, on the proposal for a new structure of the HMA/EMA Task Force on Availability of Authorised Medicines for Human and Veterinary use (TF-AAM). The new structure aims to save resources and streamline the work. A call for nomination will be circulated for the 2 Thematic Working groups (TWGs) to the Heads of Agencies with deadline by 1 February. The CMDh noted the importance to have CMDh representatives in the TF (TWGs) and encouraged CMDh members to liaise with their Heads of Agency.

3. General items

3.1. CMDh guidance documents

3.1.1. Proposal for applicants to provide responses in AR template during DCP / FI

Following the discussion in December on a proposal for applicants to provide their responses during DCPs directly in the AR template, a further defined proposal was presented. A new template has been created for applicants to provide their responses during the procedure. The responses are proposed to be given by the applicant in one common joint word template, structured similarly as current AR templates.

The CMDh agreed that also aspects related to module 1 should be included in the template.

The CMDh discussed further details related to the new approach, e.g. how to present responses to PI comments and PI updates, how to handle responses to comments raised/updates of the AF and how to reflect ASMF related responses.

It was agreed that further guidance on the use of the new template will be included in an update of the CMDh guidance document on the Applicant's response document in MRP/DCP for MAA (**Action: FR**). Also, minor amendments to the existing AR templates will be needed (**Action: FI**).

The CMDh will discuss the updated documents in February. It will then also be decided as of when the new response template should be used.

3.1.2. Requirements on Submissions for New Marketing Authorisation Applications, Variations and Renewals within MRP, DCP and National Procedures / PL, SE

MSs were asked to provide their final feedback if any changes are needed to the lists of requirements on submissions by the end of the CMDh week (**Action: MSs**). MSs were asked to provide feedback also in cases where no changes are needed, however, in case no feedback is received, it is assumed that the included information is correct.

The updated lists will be published following the meeting (**Action: EMA**).

3.1.3. DCP End of Procedure template / RO

The CMDh discussed a proposal for an update of the DCP End of Procedure template. The template has been aligned with the respective template for MRP/RUP as agreed in November, where appropriate. Comments from MSs were discussed at the meeting and the template was updated accordingly. The CMDh agreed to keep two separate templates for MRP/RUP and DCP due to the differences in the procedures.

The update of the template was adopted and will be published on the CMDh website (**Action: EMA**).

3.2. Variations

3.2.1. Requests for worksharing procedures on Variations

The MSs chosen by the CMDh, based on the recommendations of MAHs, agreed to be reference authorities for the procedures.

The CMDh agreed that the monthly overview table of received letters of intent is no longer needed. Received letters of intent will be tabled directly in MMD.

3.2.2. Requests for recommendations on unforeseen Variation under Art. 5 of Variation Regulation

None

3.2.3. Variation introducing new ADRs / IE

Following the discussion in December 2021 about nationally submitted variations by a MAH despite the CMDh request to use variation worksharing in those MSs with the same indications, more MSs have confirmed that the national variations are still ongoing. Some MSs reported that the national variations have been withdrawn but no variation worksharing application has yet been submitted.

The CMDh agreed to contact the MAH again and to request them to submit the next safety updates of their products as variation worksharing as soon as possible in the agreed groups of Member States that have the same indications authorised, in order to harmonise the product information in those MSs. The MAH will also be requested to include the variations that already have been finalised nationally in order to have a harmonised outcome across MS (**Action: EMA**).

3.2.4. Submission of parallel national variations instead of worksharing / IE

Following the discussion in November on the submission of parallel national variations by a MAH to harmonise the safety information in the PI and the subsequent request from the CMDh to the MAH to resubmit the variations using variation worksharing, feedback has been received from the MAH that they did not consider their variations suitable for worksharing as different data packages would need to be submitted per MS.

The CMDh agreed that variation worksharing would be suitable for the variation. Reference was made to the CMDh Q&As on variations, question 4.21 that gives guidance on the submission of variations to harmonise different national product information. The MAH will be requested again to re-submit the variation using the worksharing procedure with reference to Q4.21. The worksharing should also include variations that are already in an advanced stage or have been finalised nationally in order to have a harmonised outcome across MSs (**Action: EMA**).

3.3. GMP

3.3.1.

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

3.4. GCP

None

3.5. Medical device regulation / Chair, EMA

The EMA informed the CMDh about the new classification system for companion diagnostics (CDx) and the obligation to undergo a conformity assessment by a notified body introduced by the In-Vitro Diagnostic Devices Regulation (Regulation (EU) 2017/746). The Regulation will apply from 26 May 2022 for new devices. A draft procedural guidance document is currently published on the EMA website for public consultation until 20 February 2022.

The CMDh noted that most of these procedures will be submitted in the centralised procedure, but some applications could also be submitted via DCP.

The CMDh agreed that once the first procedure is submitted in DCP, the RMS should bring it to the CMDh for further discussion on the most suitable procedure to be followed.

The CMDh was further informed about the proposed answers to the questions on the MDR raised by "Medicines for Europe" during the Interested Parties meeting in November 2021, which were pre-discussed in the small group. The CMDh was informed that for some of the questions further consultation with the EC is needed. The CMDh agreed that the answers can be shared with "Medicines for Europe" and the other Interested Parties that attended the meeting in November (**Action: EMA**).

The CMDh was also made aware of a first draft answer to a question from a MAH sent to a MSs on the application of medical device administrative information when co-packed with a medicinal product. The question was pre-discussed in the small group. Further discussion is foreseen in the QRD group and the Art. 117 task force. MSs were invited to send comments on the proposed answer in parallel to the QRD consultation (**Action: MSs**).

A further question from a MAH on transdermal patches will be discussed in the next meeting of the small group.

3.6. Detection of mutagenic impurity in losartan API / NL

Postponed.

3.7. National benefit-risk review / IT

MSs exchanged their views on the assessment done by IT based on which the indication of oral formulations and suppositories containing hyoscine-N-butylbromide and hyoscine-N-butylbromide/paracetamol in the relief of spasm of the genito-urinary tract were removed in IT. Some MSs agreed with the assessment. Others considered that no new data has been presented that would justify changing the benefit-risk balance of an established product.

IT and the MSs in agreement with the IT position were asked to discuss with the EMA the possibility to start an Art. 30/31 referral based on divergent decisions taken by Member States (**Action: IT/MSs**).

3.8. OMS mapping / DE

The CMDh was made aware of two major challenges identified by MSs with OMS, i.e. several LOC-IDs for multiple door numbers and continuation of IDs after merger/acquisition.

During the meeting several MSs confirmed that they have faced similar issues.

DE will send a questionnaire for MSs to confirm if the same issues have been encountered at national level and to collect other issues to be further discussed at EU level and with EMA in the SPOR key user group (**Action: DE, MSs**). MSs were encouraged to nominate further NCA representatives for the SPOR key user group (**Action: MSs**).

3.9. Formulations for the treatment of tuberculosis in the EU / EMA

The EMA informed the CMDh about an initiative that they have been working on in collaboration with the WHO, which aims to address the gaps and consequent TB therapeutic needs in the EU by facilitating access to anti-TB medicines, with particular emphasis on children. The CMDh involvement was sought to identify these gaps at the level of individual Member States, clarify local specific practices and to confirm the accuracy of the data in the Article 57 database.

MSs noted that they can provide links to therapeutic institutes to provide information on gaps in child-friendly formulations and which anti-TB medicines should be made available.

It was further proposed that the EU SPOC network and the Task Force on availability could be involved in the exercise.

A link to a survey to collect the requested information will be provided via email after the meeting (**Action: EMA**).

3.10. Court cases / NL

The CMDh was informed of the outcome of the court case on Xalof 0,05mg/ml following a third-party appeal against the granting of the MA. The Dutch court considered that the applicant (a regulatory consultancy) and the future MAH (to whom the MA would be transferred) should be considered as the same company and that information on the refusal of a marketing authorisation for the same medicinal product in France should have been provided in the application. The court also highlighted that withholding of information may lead to 'unclear and conflicting situations' and 'forum shopping', which opposes rectification of the information requirement in appeal thus the application should have been refused. Hence, for a future application of the same dossier, the French refusal should be mentioned in the initial application form and this refusal should be addressed in the assessment report.

The decision is only applicable to the Dutch MA and not to the positive outcome of the DCP. Only the national MA in NL should be revoked. As NL acted as RMS in the DCP, the MAH would need to select a new RMS among the CMSs. At the time of the discussion in the CMDh an appeal against the court decision was still possible. For the present case and with the information provided during the procedure the CMDh considered that a regulatory consultancy, functioning as an applicant for a MAA, should not be considered as the same

company as the future MAH. Reference was also made to the EC document on handling of duplicate MAAs.

A briefing paper from the third-party was noted by the CMDh.

3.11. Genotoxicity and contraception / DE

The CMDh discussed variations submitted in relation to the CMDh press release of July 2021 requesting MAHs to update their product information in line with the SWP response to the CMDh questions regarding genotoxic medicinal products and contraception duration period. The CMDh agreed with the assessment done by DE with regard to medicinal products containing moxifloxacin, cidofovir and flucytosine.

It was noted that some MAHs misinterpret the published SWP recommendation and submit variations to calculate the duration also for substances like moxifloxacin which have a genotoxic potential but not at levels of therapeutic exposure. The CMDh therefore agreed to send a question to SWP to ask for a small correction of the published SWP recommendation to avoid unnecessary variations (**Action: EMA**). The CMDh press release will be corrected accordingly once feedback from SWP is received.

The CMDh also discussed again how the PI update should be submitted. Previously, it was communicated that such variations including new data should be submitted via type II variations. The CMDh now agreed that for cases, where a calculation of the duration of contraception is submitted, an assessment is needed, and such cases should therefore also be submitted as type II variations. If the calculation is taken over from another product and no new calculation is required, a type IB variation is sufficient. This approach will be included in the future update of the CMDh press release.

4. Generic/hybrid marketing authorisations

4.1. PKWP product-specific bioequivalence guidelines (PSBGLs) / EMA

A list of potential candidates for PSBGLs proposed by MSs following a call sent in January was tabled. It was agreed that the list can be further discussed at PKWP level. The proposals might be taken forward in batches over the year. It was noted that for some of the candidates, PKWP advice has already been given in the past.

PKWP will provide feedback on the outcome of their discussion.

4.2. Generic marketing authorisations for deferasirox dispersible tablets / DE

The CMDh was informed that the originator of deferasirox was originally authorised as dispersible tablets (DT). Later, the originator brought film-coated tablets (FCT) on the market with slightly improved pharmacokinetic properties and a more convenient mode of administration. As the FCT formulation has a higher bioavailability, the dose of the FCTs should be 30% lower than the dose of the DTs. In order to prevent the risk of medication errors by switching formulations, the educational material for physicians and patients was amended to address the different posology regimes and the DT of the originator were eventually withdrawn from the EU market.

In order to mitigate/eliminate the risk of medication errors and to reduce the burden of educational material for HCPs/patients, DE also asked generic MAHs to withdraw DT formulations from the market.

Other MSs stated that they do not intent to take action to ask the generic MAHs to withdraw the DT formulations as these are the only available forms in some of the MSs. Educational material is in place to inform about the differences in formulations. Actions could only be taken if there are signals that the educational material is not sufficient.

DE will provide feedback from the CMDh discussion at national level and might consider a discussion at PRAC.

4.3. Request for amendment of information in PI of abridged application due to patent / DK

The CMDh discussed changes to the SmPC proposed by the MAH during the national phase of a procedure for a generic medicinal product containing paliperidone, due to a patent held by the originator MAH regarding "Dosing regimen associated with long acting injectable paliperidone esters".

The CMDh agreed that in line with the CMDh Q&A on usage patents, in case of a patented indication, the indication may be deleted for a generic product (in the national PI), but not modified (neither acceptable in the common English PI nor in the national PI).

The CMDh further agreed that also the proposed changes to sections 4.2 and 5.1 are not acceptable. The RMS will provide feedback to the MAH.

5. Referrals

5.1. Referrals to CMDh (pursuant to Art. 29(1) of Directive 2001/83/EC or Art. 13 of Regulation (EC) No 1234/2008)

5.1.1. Art. 29/13 referrals for discussion at CMDh

5.1.1.1. Deferasirox (NL/H/5119+5120/001/DC) / NL

The RMS gave an overview of the Art. 29 referral on deferasirox (NL/H/5119+5120/001/DC). A referral for the Art. 10(3) application for film-coated tablets containing deferasirox (different strengths compared to the RefMP) was triggered as the objecting CMS considered that the indication should be restricted as the corresponding posology for the proposed indication in paediatric patients aged 2-5 years cannot be reached with the proposed 900 mg tablet and minimum body weight limits should be added, corresponding to the recommended maximum daily dose for the indications concerned, to reduce the risk of medication errors.

The RMS was of the view that the indication should be kept in line with the RefMP and that the disclaimer in section 4.2. (that the 900 mg strength is not suitable for all dosages) was sufficient.

The objecting CMS informed the CMDh that they could accept as new proposal by the applicant to retain the originator's indications unchanged in section 4.1, but to include information in section 4.2 of the SmPC and section 1 of the PL that the product is unsuitable for patients below a certain weight. The educational material should be updated accordingly.

All CMS agreed to the proposed approach. The RMS will circulate a proposal for agreement following the meeting.

The CMDh agreed that the SmPC Advisory Group should be contacted to agree on a general approach on how to reflect non-suitability of a specific strength / pharmaceutical form of an abridged application for part of the intended patient population in the SmPC. A question to the SmPC Advisory Group will be prepared for discussion in the February CMDh meeting (**Action: NL, DE**).

5.1.2. List of questions

None

5.2. Referrals to PRAC (pursuant to Art. 31 or 107i of Directive 2001/83/EC)

5.2.1. Referral timetables

Tabled for information.

5.2.2. Started referral procedures at PRAC

5.2.2.1. Terlipressin (Art. 31)

The CMDh was informed about the start of the Art. 31 referral on terlipressin to assess the impact of the findings of the CONFIRM trial on the benefit-risk balance of medicinal products containing the active substance terlipressin when used for the treatment of hepatorenal syndrome (HRS).

5.2.3. Information on ongoing referral procedures

5.2.3.1. Amfepramone (Art. 31)

Tabled for information.

5.2.4. PRAC recommendations for CMDh position

None

5.3. Outcome of referrals to CHMP

None

5.4. Other topics related to referrals

5.4.1. Presence of nitrosamine impurities in human medicinal products containing chemically synthesised active pharmaceutical ingredients / Chair, EMA, NL, DE, IT

The CMDh in collaboration with the EMA agreed an update of the joint EMA/CMDh Questions and Answers for marketing authorisation holders/applicants on the CHMP Opinion for the

Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products. Q&A 10 has been amended to provide guidance on control options when more than one nitrosamine is identified in the same product and to address the calculation of acceptable limits. The updated Q&A document will be published on the EMA website. A link will be provided from the CMDh website (**Action: EMA**).

5.4.1.1.

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

5.4.1.2.

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

5.4.1.3.

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

5.4.2. Symbioflor (Art. 31) / DE

The CMDh was informed that the MAH Symbioflor has requested an extension of the deadline for the submission of the final study report of the efficacy and safety study requested as a condition of the Art. 31 referral finalised in 2017. According to the condition of the referral, the study report should be submitted by March 2022. The MAH now requested an extension of 2 years via submission of purely national variations in the concerned MSs. Before the start of the CMDh meeting, the variation was changed to a variation worksharing application in the MSs concerned.

The CMDh agreed that a variation submission is not the correct submission way in such a case, but the MAH should have contacted the CMDh directly to have a discussion on the delay at EU level. The CMDh agreed to the delay, as requested in this case. The MAH will be informed that the variation worksharing submission is no longer needed and may be withdrawn. The study results should be submitted to the concerned MSs using variation worksharing by the newly agreed deadline.

5.4.3. Pholcodine (Art. 31) / FR

The CMDh was made aware that during the assessment of the PSUSA on pholcodine (see 6.2.1.4) concerns were raised on the delay in finalising of the post-approval safety study (PASS) imposed as a condition following the Art. 31 referral finalised in 2012. The study has been conducted by a consortium of MAHs. Previous extensions of the submission of the final study report have been discussed and agreed with FR, where the study is conducted. These should have been brought to the attention of the CMDh by the MAH (see also 5.4.2). In the meantime, results of a case-control study (Sadleir et al 2021) have become available, which necessitate the timely finalisation of the PASS.

The CMDh agreed to request the consortium to submit the final study report by mid-2022 (**Action: EMA**).

6. Pharmacovigilance

6.1. Report from the January 2021 PRAC meeting

The EMA reported from the PRAC meeting held from 10 to 13 January 2022.

6.2. Periodic Safety Update Reports (PSUR)

6.2.1. PRAC recommendations on PSUSAs for CMDh position[1]

6.2.1.1. Paracetamol (IV formulation) - PSUSA/00002311/202105

The CMDh, having considered the PSUR on the basis of the PRAC recommendation and the PRAC assessment report, agreed by consensus on the variation of the marketing authorisations of medicinal products containing paracetamol (IV formulation).

In the framework of the PSUSA on paracetamol (IV formulation), the PRAC noted that paracetamol is also authorised as a single agent via other routes of administration and in fixed dose combinations. The PRAC considered that the risk of high anion gap metabolic acidosis (HAGMA) when paracetamol is administered concomitantly with flucloxacillin would also be relevant to be included in all paracetamol containing medicinal products (monosubstance via other routes of administration and fixed dose combinations of paracetamol). This product information update is needed for MAHs which do not have similar wordings already reflected in the SmPC and PL.

6.2.1.2. Lactulose - PSUSA/00001821/202105

The CMDh, having considered the PSUR on the basis of the PRAC recommendation and the PRAC assessment report, agreed by consensus on the variation of the marketing authorisations of medicinal products containing lactulose.

6.2.1.3. Levonorgestrel (all indications except emergency contraception) - PSUSA/00010828/202105

The CMDh, having considered the PSUR on the basis of the PRAC recommendation and the PRAC assessment report, agreed by consensus on the variation of the marketing authorisations of medicinal products containing levonorgestrel (all indications except emergency contraception).

The CMDh noted comments from a MAH on the proposed PI update, received after the PRAC discussion. The CMDh agreed that no changes to the PRAC recommendation/CMDh position are needed as the comments have already been sufficiently addressed during the PRAC discussion.

6.2.1.4. Pholcodine - PSUSA/00002396/202105

The CMDh, having considered the PSUR on the basis of the PRAC recommendation and the PRAC assessment report, agreed by consensus on the variation of the marketing authorisations of medicinal products containing pholcodine.

[1] Subject to adoption via written procedure in advance of the meeting. For discussion/adoption at the plenary if comments are received during written procedure.

In the framework of the PSUSA on pholcodine, the PRAC noted that pholcodine is also authorised in fixed dose combination products. The PRAC considered that the warnings regarding the risk of drug abuse and cross-reactivity with NMBAs (Neuromuscular Blocking Agents) would also be relevant to be included in medicinal products containing pholcodine in fixed dose combinations.

The same timelines as for the present PSUSA would apply in accordance with the CMDh guidance on implementing variations.

Actions related to the finalisation of the PASS imposed as a condition following an Art. 31 referral have been discussed under 5.4.3.

6.2.1.5. Loperamide, loperamide / simeticone - PSUSA/00010665/202105

The CMDh, having considered the PSUR on the basis of the PRAC recommendation and the PRAC assessment report, agreed by consensus on the variation of the marketing authorisations of medicinal products containing loperamide, loperamide / simeticone.

6.2.1.6. Remifentanil - PSUSA/00002617/202105

The CMDh, having considered the PSUR on the basis of the PRAC recommendation and the PRAC assessment report, agreed by consensus on the variation of the marketing authorisations of medicinal products containing remifentanil.

6.2.1.7. Benazepril / hydrochlorothiazide - PSUSA/00000314/202105

The CMDh, having considered the PSUR on the basis of the PRAC recommendation and the PRAC assessment report, agreed by consensus on the variation of the marketing authorisations of medicinal products containing benazepril / hydrochlorothiazide.

6.2.2. Information on PRAC recommendations for PSUSAs for maintenance

None

6.2.3. Information on PRAC recommendations for PSUSAs for CAPs/NAPs or CAPs

6.2.3.1. Sildenafil (Revatio) - EMEA/H/C/PSUSA/00002700/202105

In the framework of the PSUSA on Revatio (sildenafil; indication: pulmonary hypertension), the PRAC noted that sildenafil is also authorised in medicinal products indicated for erectile dysfunction. The PRAC considered that the risk of increase in hypotension in case of concomitant use of sildenafil and Entresto (sacubitril/valsartan) would also be relevant to be included in products containing sildenafil indicated for erectile dysfunction, as data from one PK/PD study are available (Hsiao et al.), in which 28 male patients with hypertension received sildenafil as add-on to sacubitril/valsartan at steady state.

The same timelines as for the present PSUSA would apply in accordance with the guidance on implementing variations.

6.2.4. Outcomes of informal PSUR work sharing procedures / Chair

None

6.2.5. PSUSA Lead Member State appointment

The CMDh appointed the lead Member States for single assessment of PSURs for NAPs to be started until January 2023. The appointed lead member states will be published in the EURD list.

6.2.6. PSUSA Follow-up procedures

None

6.3. Results of post-authorisation safety studies (PASS) imposed in the MA (in accordance with Art. 107q)[2]

6.3.1. PRAC recommendations on PASS results for CMDh position

None

6.4. Lists

6.4.1. Union Reference Date list

The CMDh noted the update of the Union Reference Date list.

6.4.2. List of medicinal products under additional monitoring

The CMDh noted the update of the list of medicinal products under additional monitoring.

6.5. Information from Member States on actions for nationally authorised products related to safety

None

6.6. Other topics related to pharmacovigilance

6.6.1. "Medicines for Europe"/AESGP Position Paper on reference safety information / Chair

Following the presentation of their Position Paper on reference safety information by "Medicines for Europe" in the CMDh meeting with Interested Parties in May 2020 and the CMDh feedback given in November 2020, the CMDh noted the further feedback from "Medicines for Europe" and AESGP.

A CMDh response will be pre-discussed in the next PhV WSP WP meeting, to be ready to be presented to Interested Parties in the next meeting in May (**Action: CZ**).

6.6.2. Pharmacovigilance activities for teriflunomide containing medicinal products / DE

The CMDh was informed about a PRAC advice for a generic teriflunomide-containing medicinal product in order to consider the need for pharmacovigilance activities. There are currently

[2] Subject to adoption via written procedure in advance of the meeting. For discussion/adoption at the plenary if comments are received during written procedure.

two ongoing category 3 post-authorisation safety studies (PASS), i.e. 2 pregnancy registries, for the reference product Aubagio to further characterise the important potential risk "teratogenicity". The PRAC advised that:

1. All applicants / MAHs of generic MAA for teriflunomide should not be required to conduct studies on pregnancy.
2. They should continuously collect and follow-up on cases of pregnancy with exposure to teriflunomide (either during pregnancy or in the relevant time interval before conception, given the product's very long half-life), including reports of (pregnancy) exposure without outcome data or with a normal outcome.
3. Targeted follow-up questionnaires, with the aim to collect data of interest about pregnancy exposure, should be implemented.
4. Structured analyses of cases reporting pregnancy exposure should be submitted regularly, at harmonised submission dates (3-year cycle) synchronised with Aubagio PSUR submission requirements. Provision of these analyses should be added to the RMP and the marketing authorisation of all teriflunomide generics.
5. The educational material for teriflunomide generics should be amended accordingly.

The CMDh agreed with the approach.

[*Post-meeting note: The CMDh will discuss the submission pathway in the February CMDh meeting*.]

6.6.3. NSAIDs – use during pregnancy / DE

The CMDh was informed that recently several national and European variation applications have been received to change the wording of the recommendation of the use of NSAIDs during pregnancy. The submissions are based on a FDA recommendation to avoid the use of NSAIDs in pregnancy at 20 weeks or later as they may cause rare but serious kidney problems in an unborn baby. This can lead to low levels of amniotic fluid surrounding the baby and possible complications.

As the proposed FDA wording is not in line with an agreed EU wording, based on a recommendation of the PhVWP from 2004, it was proposed to request PRAC advice for an ongoing variation with the aim to agree on a harmonised EU approach whether the previously agreed EU wording should be amended.

The CMDh agreed with the proposal to request PRAC advice. Ongoing variations should be held in clock-stop, if possible, until the PRAC advice is available.

7. Break-out sessions and CMDh scientific input to applications

7.1. Duxavrag/Huxvorta Hartkapseln Hexal (DE/H/6520-6522/001/DC) / DE

DE informed the CMDh about the break-out session held for Duxavrag/Huxvorta Hartkapseln Hexal (DE/H/6520-6522/001/DC). Major objections have been raised as the data provided by the applicant in support of the indication for the Art. 10a application was considered insufficient. The application was withdrawn on day 209.

7.2. Betahistine Amarox 8/16/24 mg tablets (NL/H/5212/001-003/DC) / NL

NL informed the CMDh about the break-out session held for Betahistine Amarox 8/16/24 mg tablets (NL/H/5212/001-003/DC). Potential serious risk to public health has been raised with regard to the demonstration of bioequivalence for the generic application, as the applicant used a metabolite to show bioequivalence instead of the parent compound. Agreement could be reached by switching to a biowaiver approach. Betahistine has been proposed as a candidate for a PKWP PSBGL.

7.3. Pineox 0,3 mg/ml eye drops, solution in single-dose container (NL/H/5325/001/DC) / NL

NL informed the CMDh about the break-out session held for Pineox 0,3 mg/ml eye drops, solution in single-dose container (NL/H/5325/001/DC). Major objections have been raised on the Art. 10(3) application for eye drops containing bimatoprost. Agreement could be reached following submission of additional data by the applicant as requested.

7.4. Esomeprazole ADOH 40 mg powder for solution for injection/infusion (NL/H/5323/001/DC) / NL

NL informed the CMDh about the break-out session held for Esomeprazole ADOH 40 mg powder for solution for injection/infusion (NL/H/5323/001/DC). Major objections have been raised on the Art. 10(1) application. The application was ongoing at the time of the CMDh meeting. The applicant has submitted additional data which will be taken into account in the finalisation of the procedure.

[*Post-meeting: The procedure was finalised positively on Day 210*.]

8. Miscellaneous

8.1. Report from the January CMDv meeting

The CMDv secretariat reported from the January 2022 CMDv meeting.

8.2. January 2022 CMDh Press Release

The CMDh press release will be circulated for written agreement (**Action: EMA**).

8.3. A.O.B.

8.3.1.

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

8.3.2.

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

8.3.3. Risk related to critical excipients in solid pharmaceutical form of methadone and levomethadone medicinal products in misusers / IT

The CMDh discussed the impact of misuse of opioid substitution treatment (OST) products related to intra-venous injection of oral products containing critical excipients which can cause serious side effects, when injected i.v..

The CMDh agreed that the discussion should be brought to the attention of the Opioid Task Force, workstream 3 on regulatory issues (**Action: FR**). Also, the LMSs of the upcoming PSUSAs on methadone and levomethadone should be made aware to pay special attention on any related signals during the assessment of the PSUSA (**Action: IE, AT**). It was noted that also other active substances may be concerned. IT may consider gathering more information from MSs via a NUI.

8.3.4.

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

9. Other topics and dates for next meeting

9.1. Draft meeting schedule and draft time schedule for referrals

The meeting schedule for February 2022 was tabled for information.

☞ More information about acronyms and abbreviations used in this document can be found on the CMDh website: http://www.hma.eu/457.html

10. List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 25-27 January 2022 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Kora Doorduyn-van der Stoep	Chair	Netherlands	No interests declared	
Jascha Johann Hörnisch	Member	Austria	No interests declared	
Sophie Colyn	Member	Belgium	No interests declared	
Lyudmil Antonov	Member	Bulgaria	No interests declared	
Teodor Nikolov	Alternate	Bulgaria	No interests declared	
Sabina Uzeirbegović	Member	Croatia	No interests declared	
Gorana Perina Lakoš	Alternate	Croatia	No interests declared	
Emilia Mavrokordatou	Member	Cyprus	No interests declared	
Natasa Kiza	Alternate	Cyprus	No interests declared	
Jitka Vokrouhlická	Member	Czechia	No interests declared	
Zuzana Fliegerová	Alternate	Czechia	No interests declared	
Katrin Damkjær Madsen	Member	Denmark	No interests declared	
Anne Kristine Hejlesen	Alternate	Denmark	No restrictions applicable to this meeting	
Margit Plakso	Member	Estonia	No interests declared	
Heili Tikk	Alternate	Estonia	No interests declared	
Tea Linhola	Member	Finland	No interests declared	
Pauliina Ikäheimo	Alternate	Finland	No interests declared	
Glenn Lastennet	Member	France	No interests declared	
Mathilde Geynet-Kovacs	Alternate	France	No interests declared	
Susanne Winterscheid	Member	Germany	No interests declared	
Wiebke Hoppensack	Alternate	Germany	No interests declared	
Eleftheria Nikolaidi	Member	Greece	No interests declared	
Stavroula Mamoucha	Alternate	Greece	No interests declared	
Magdolna Nemeth	Member	Hungary	No interests declared	
Orn Gudmundsson	Member	Iceland	No interests declared	
Nicole Kavanagh	Member	Ireland	No interests declared	
Laura Galatti	Member	Italy	No interests declared	
Marco Franceschin	Alternate	Italy	No interests declared	
Maija Cirkina	Member	Latvia	No interests declared	
Iveta Eglite	Alternate	Latvia	No interests declared	
Kristina Povilaitienė	Member	Lithuania	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Neringa Kalinauskaitė	Alternate	Lithuania	No interests declared	
Mylene Ferrier	Member	Luxembourg	No restrictions applicable to this meeting	
Helen Vella	Member	Malta	No interests declared	
Paula Cardona Xuereb	Alternate	Malta	No interests declared	
Priscilla Schoondermark	Member	Netherlands	No interests declared	
Suzanne Gordon	Member	Norway	No restrictions applicable to this meeting	
Andrzej Czeslawski	Member	Poland	No interests declared	
Pawel Pawlowski	Alternate	Poland	No interests declared	
Marta Marcelino	Member	Portugal	No interests declared	
Rui Pedro da Costa Vilar	Alternate	Portugal	No interests declared	
Cristian Dan Georgescu	Member	Romania	No interests declared	
Marina Popescu	Alternate	Romania	No interests declared	
Miroslava Petrikova	Member	Slovakia	No interests declared	
Petra Docolomanska	Alternate	Slovakia	No interests declared	
Nevenka Prpar	Alternate	Slovenia	No interests declared	
Veronica Garcia Morales	Member	Spain	No interests declared	
Elisa Sulleiro	Alternate	Spain	No restrictions applicable to this meeting	
Christin Olofsson	Member	Sweden	No interests declared	
Adam Andersson	Alternate	Sweden	No interests declared	
Dino Soumpasis	Chair of CTS WG	Germany	No interests declared	
Martin Huber	Chair of Non-Prescription MPs TF	Germany	No interests declared	
Maria Luisa Casini	Chair of the PhV WS WP	Italy	No interests declared	
Jayne Crowe	Chair of GCP Inspectors Working Group/CMDh Working Party	Ireland	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Nienke Rodenhuis	Chair of ASMF WG	Netherlands	No interests declared	
Siri Wang	Chair of CMDh WP on Paediatric Regulation	Norway	No interests declared	
Ad hoc experts* and a representative from the European Commission attended the meeting.				
Meeting run with support from relevant EMA staff				

* Experts were evaluated against the agenda topics or activities they participated in.