19 May 2022
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Human Medicines Division

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

Draft minutes for the meeting on 20-21 April 2022

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

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 Nicole Visser as new alternate for the Netherlands.

1.3. Adoption of draft agenda

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

- Implementation of updated excipients guideline
- Sunset clause
- NSAIDs – use during pregnancy
- Implementation of outcome of user testing
- Generic MAA procedure including studies conducted by Synchron
- HaRP assessment report templates

1.4. Adoption of the minutes

The minutes of the March 2022 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
Rapporteurs were appointed for the Art. 46 submissions.

2.1.2. Non-Prescription Medicinal Products Task Force / TF Chair (DE)

The CMDh agreed an update of the BPG for authorisation of non-prescription medicines in DCP and MRP. The update was prepared and agreed by the non-prescription medicinal products Task Force and provides updated guidance to applicants based on the experience gained. The updated document will be published on the CMDh website (**Action: EMA**).

2.2. Meeting with Interested Parties / EMA, Chair

The EMA presented a draft agenda for the meeting with Interested Parties including the topics proposed by Interested Parties. The CMDh agree on the topics to be included on the agenda. Interested Parties will be informed accordingly (**Action: EMA**).

2.3. French Presidency meeting / FR

The CMDh thanked the French Presidency for organising a remote CMDh presidency meeting held on 7 April 2022. The minutes of the meeting will be drafted for the next meeting (**Action: FR**).

2.4. EU Pharmaceutical Strategy / Chair

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

2.5. Multi-Annual Workplan / Chair

The CMDh Multi-Annual Workplan was open for 2-month public consultation. The CMDh noted comments from EFPIA, BPI, AESGP, MfE and Prescrire.

The CMDh agreed that the MAWP topic leaders will review the comments received and reflect whether there is a need to update the MAWP or if there are additional action points (**Action: MSs**). The CMDh also agreed that the topic leaders will organise the necessary TC with the Drafting Groups and prepare responses for the comments received (**Action: MSs)**. The MAWP will be discussed in the next meeting.

2.6. Pilot – Relaunch of face-to-face Scientific Committee Meetings / EMA

The CMDh was informed about the expected set-up for returning to Committee face-to-face meetings.

2.7. Brexit / Chair

The CMDh noted that the Directive (EU) 2022/642 of the European Parliament and of the Council of 12 April 2022, amending Directives 2001/20/EC and 2001/83/EC as regards derogations from certain obligations concerning certain medicinal products for human use made available in the United Kingdom in respect of Northern Ireland and in Cyprus, Ireland and Malta has been publish in the Official Journal of the European Union on 20 April 2022. The CMDh Brexit guidance will be updated accordingly, as needed (**Action: SE**).

3. General items

3.1. CMDh guidance documents

3.1.1. CMDh recommendation on the classification of an unforeseen variation / EMA, IE

The CMDh agreed on updates to the request form and recommendation template for recommendations on the classification of an unforeseen variation under Article 5 of Commission Regulation (EC) NO 1234/2008. The documents have been updated to take into account that under the Veterinary Medicinal Products Regulation (Regulation (EU) 2019/6) the CMDv is no longer actively involved in Article 5 recommendations on unforeseen variations. Additionally, recommendations for unforeseen variations for veterinary medicinal products can no longer be requested under Art. 5 of the Variation Regulation (Commission Regulation (EC) NO 1234/2008).

The updated templates will be published on the CMDh website (**Action: EMA**). The EMA will be made aware of the updates as the same Art. 5 request form is also used for CAPs.

3.1.2. CMDh guidance on triggering Art. 29 referrals / NL, FR, SE

The CMDh discussed and agreed updates of the Best Practise Guide for Decentralised and Mutual Recognition Procedures, the Decentralised procedure member states' standard operating procedure and the document "Disagreement in Procedures – Referral to CMDh". In all three documents the part describing the notification of Art. 29(1) referrals has been updated to clarify the process of how an "automated" referral is triggered by the RMS, in case of a late change of position of the RMS from non-approvable to approvable after day 205 of the DCP. The CMDh agreed that a 2-step process should be followed, i.e. the RMS informs the CMS and CMDh secretariat in the same email of the updated AR/RMS position and that an automated referral will be triggered. No further email at day 210 needs to be sent by the RMS. CMSs will be given 7 more calendar days, after day 210, to confirm agreement with the RMS position or to mention their PSRPH and grounds for referral. If agreement from all CMSs is received, the referral procedure will be withdrawn by the RMS and the procedure can be closed positively. In case of receipt of CMS objections/grounds for referral, the RMS will circulate the referral notification.

The updated documents were adopted and will be published on the CMDh website (**Action: EMA**).

3.1.3. Template for request for MRP/RUP / DK

Following feedback from Interested Parties that, in addition to the template for request for MRP/RUP, many MSs ask also for the submission of a pre-filled application form (AF), DK presented a first proposal to update the template to include more information to avoid applicants having to pre-fill the AF at the same time. Before and during the meeting, comments were raised by MSs on the content of the template, e.g., to add further information related to the MDR or in relation to OTC or to align the content with the AR template. It was also noted that some MSs ask applicants to use adapted versions of the template, as currently also stated on the CMDh website, which should still be possible in the future. The CMDh also discussed that information on 0-day procedures should not be added to the template, as these are usually communicated directly via email. Also, information on the RefMP used in the CMS would not need to be included in the template as the template is directed to the RMS.

DK will prepare an updated version of the template following the discussion (**Action: DK**). MSs were asked to comment on the updated version, as needed, for further discussion in the CMDh meeting in May (**Action: MSs**).

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.

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

None

3.2.3. Submission of parallel national variations instead of worksharing

3.2.3.1.

Following a letter sent to the MAH with a request to (re-)submit their variation via variation worksharing to align the product information to the SWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug, feedback has been received from the MAH by the CMDh and by NCAs, arguing that the variations should continue at national level to avoid misalignment of the proposed changes.

The CMDh did not agree with the MAH's argumentation and agreed to send another letter to the MAH to repeat the initial request that the variation should be submitted in all MSs via variation worksharing (including in those where the variation is ongoing or has already been finalised). It will further be requested that the variation has to be submitted as a type II variation as additional data/calculation is necessary in this case (see February 2022 CMDh press release) (**Action: EMA**). It was noted that so far, the MAH has submitted different kinds of variations in different MSs.

3.2.3.2.

The CMDh was made aware of parallel nationally submitted type IB variations to implement the SWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug.

The CMDh agreed to send a letter to the MAH to request the submission of a type II variation via worksharing for their nationally authorised medicinal products to reach a harmonised outcome (**Action: EMA**).

3.3. GMP

None

3.4. GCP

None

3.5. TiO2 (E171) used as excipient / EMA, DE

The QWP Questions and Answers to provide technical and procedural guidance to replace/remove titanium dioxide (TiO2) in medicines were presented to the CMDh. The Q&As have been circulated to the CMDh for comments before the meeting. The comments received from CMDh and other parties have been compiled. The CMDh further suggested to be clear in the Q&As about the function of TiO2 in a medicinal product (whether it applies to the function as colouring agent only or also if TiO2 has a different function). The CMDh further proposed to clarify in the Q&As that a major reformulation of a product cannot take place during an ongoing MAA. Such a change should be submitted via variation after the MA has been granted. The draft Q&As will be presented at the QWP meeting with Interested Parties in May before adoption in CHMP and CMDh/CMDv in May. The CMDh chair and vice-chair will be invited to the QWP meeting with Interested Parties.

As a follow-up from the March meeting, the CMDh discussed a proposal to include reference to Commission Regulation (EU) 2022/63 in the AR of new applications for products that contain TiO2, to make the applicants aware of possible future implications. The statement was meant as a reminder to MAHs without an obligation to take immediate actions. During the discussion, the CMDh considered that such a statement could be confusing to the applicant in the AR and generally the AR would not be the right place for such a reminder. It was also considered that sufficient guidance for applicants and MAHs is already publicly available. The CMDh therefore agreed not to proceed with the statement in the ARs.

However, the CMDh generally reminds applicants/MAHs to take note that Commission Regulation (EU) 2022/63 of 14 January 2022 amending Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council as regards the food additive titanium dioxide (the Regulation) entered into force following its publication in the Official Journal of the European Union on 18 January 2022.

Whilst the Regulation foresees that titanium dioxide remains provisionally on the list of authorised additives to allow its use in medicinal products as a colourant, it also highlights that is of critical importance that pharmaceutical industry makes all possible efforts to accelerate the research and development of alternatives and replace titanium dioxide in both new and already authorised products, by submitting the necessary changes to the terms of the relevant marketing authorisations.

3.6. SmPC harmonisation / Chair

The CMDh discussed a proposal for a candidate for the CMDh list of products for SmPC harmonisation.

NL informed the CMDh that a previous proposal has not been brought forward anymore as not many generics are ongoing/expected. It was suggested to discuss this criterion for SmPC harmonisation for future cases.

3.7. "Freezing" of DCP due to COVID-19 pandemic / FI

FI informed the CMDh that an ongoing DCP has been frozen in accordance with the CMDh Practical guidance for facilitating the handling of processes during the COVID-19 crisis, as the applicant had problems providing critical data in order to solve outstanding major objections in the procedure due to COVID-19.

It was stressed that the freezing and rolling-back of new DCP MAAs is only possible if the delay is sufficiently justified to be COVID-related.

3.8. Digital Application Dataset Integration (DADI) Network Project / EMA

The EMA gave an update on the DADI project to the CMDh, in particular with regard to the consultation of the NtA expert group.

CMDh members were asked to make their national NtA members aware of the ongoing discussion (**Action: MSs**). MSs were encouraged to get in contact with the EMA with regard to any questions related to DADI.

The EMA confirmed that the CMDh will always be involved for any proposed changes to the content of the AF. Minor technical changes will be taken forward without CMDh consultation.

3.9. Request for extension of clock-stop / SK

The CMDh was informed of a request from an applicant to extend the clock-stop of an ongoing procedure by one year to allow a reformulation of the product.

Several MSs supported the RMS position that such a clock-stop extension is not acceptable.

Reference was made to a previous CMDh agreement that in such a case the application should be withdrawn and resubmitted as a new MAA as the proposed reformulation of the product would require substantial new assessment, which would be difficult to process in the second phase of the DCP.

The CMDh agreed that the acceptance of reformulations of products during clock-stop, which require the assessment of a large amount of data, are generally not acceptable. Some reformulations might be less complicated (e.g. i.v. formulations) and easier to assess. In such cases, it would be the decision of the RMS if an exemption can be made. Cases that require a prolonged clock-stop could be brought to the CMDh for agreement.

3.10. Repeat-use procedure / DE

In preparation of the Interested Parties meeting, the CMDh discussed proposals for the improvement of the repeat-use procedure (RUP) that do not need changes to legislation.

3.11. Risk of supply shortages of medicinal products / Chair, EMA

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

4. Generic/hybrid marketing authorisations

4.1. Interpretation of Guideline on the pharmacokinetic and clinical evaluation of modified release / EMA, DE

The CMDh was informed about the PKWP feedback to a CMDh question on the interpretation of the guideline on the pharmacokinetic and clinical evaluation of modified release with regard to formulation-related food interactions in the framework of a BE studies submitted in an ongoing procedure for Venlafaxine retard TEVA (DE/H/6399/001-002-003/E/001). The procedure could be finalised positively before the CMDh meeting based on the PKWP feedback.

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

None

5.1.2. List of questions

5.1.2.1.

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

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

None

5.2.3. Information on ongoing referral procedures

5.2.3.1. Amfepramone (Art. 31)

Tabled for information.

5.2.3.2. Terlipressin (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

The NISG agenda and notes were shared with the CMDh for information.

The CMDh agreed to remind applicants via the CMDh press release to follow the existing format of the Step 2 nitrosamines detected/nitrosamines not detected response templates as published on the EMA/CMDh websites and avoid adding extraneous information. Where new nitrosamines are detected for which acceptable intakes are not already listed in the Article 5(3) call for review or associated EMA/CMDh Q&As (EMA/409815/2020), the response template should clearly indicate that these nitrosamines are new.

At the same time, the CMDh would also like to remind applicants of the upcoming deadline for submission of step 2 and step 3 responses for the 'call for review', which is due for chemically synthesised medicinal products by 26 September 2022, responses to which will inform further regulatory action, as needed.

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.

5.4.1.4.

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

5.4.1.5.

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

5.4.1.6.

It is not possible for MAHs to use a limit agreed outside the EU until the limit has been confirmed by SWP. If compliance cannot be ensured an application should be refused. In line with Q14 of the CMDh Q&A on Applications for MA (CMDh/268/2012) there is no possibility to address this via post-approval commitments and/or a proposal to withhold a proposed medicinal product from marketing until further data are available.

Applicants should monitor new information on nitrosamine risk factors throughout the procedure and submit an updated risk evaluation / risk assessment if applicable.

It was noted that a second clock-stop is not possible in a DCP. All known risk factors for nitrosamine formation have to be taken into consideration for establishment of a positive benefit risk and hence the granting of a MA.

5.4.1.7.

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

5.4.1.8.

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

6. Pharmacovigilance

6.1. Report from the April 2022 PRAC meeting

The EMA reported from the PRAC meeting held from 4 to 7 April 2022.

6.2. Periodic Safety Update Reports (PSUR)

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

6.2.1.1. Dexamfetamine - PSUSA/00000986/202109

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 dexamfetamine.

[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.

6.2.1.2. Estradiol (except cream/balm/emulsion for application in female genital area) - PSUSA/00010440/202108

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 estradiol (except cream/balm/emulsion for application in female genital area).

6.2.1.3. Etonogestrel - PSUSA/00001331/202109

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 etonogestrel.

6.2.1.4. Modafinil - PSUSA/00010242/202108

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 modafinil.

In the framework of the PSUSA on modafinil, PRAC noted that all MAHs should implement in the RMP under Part III.1 and Annex 4, targeted follow-up questionnaire(s) to aid data capture from cases on drug abuse, misuse, dependence and diversion.

The follow-up questionnaire(s) should be able to capture at least the following data:

- Indication for which modafinil was prescribed
- Treatment duration
- Route of administration
- Concomitant medications
- The dose prescribed
- Medical history including drug abuse/psychiatric disorders
- How long the patient has been abusing/dependent on modafinil
- The dose the patient abused
- Route of modafinil abuse
- Concomitant substances abused

PRAC further noted that inconsistent information related to the interaction with contraceptives is included in sections 4.4, 4.5 and 4.6 of the SmPC of modafinil containing medicinal products. In several Member States, sections 4.4 and 4.5 of the SmPC include the interaction with steroidal contraceptives, while in section 4.6 it is noted that "modafinil may reduce the effectiveness of oral contraception". However, all types of hormonal contraceptives should be concerned, including those with a non-oral route of administration. This is clearly stated in section 2 of the PL, where all forms of hormonal contraception (pill, implants, intrauterine devices (IUDs) and patches) are mentioned. The Package Leaflet does not need to be updated.

Therefore, PRAC recommends that the following is included in the product information of all concerned products (new text **underlined and in bold**, deleted text ~~strike through~~):

Summary of Product Characteristics

• Section 4.6 - Fertility, pregnancy and lactation

Pregnancy

[...]

As modafinil may reduce the effectiveness of **hormonal** contraception alternative additional methods of contraception are required (see sections 4.4 and 4.5).

Affected MAHs are therefore requested to submit relevant variations to their national competent authorities.

6.2.1.5. Nifuroxazide - PSUSA/00002160/202108

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 nifuroxazide.

6.2.1.6. Oxcarbazepine - PSUSA/00002235/202108

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 oxcarbazepine.

6.2.2. Information on PRAC recommendations for PSUSAs for maintenance

6.2.2.1. Gadopentetic acid - PSUSA/00001504/202108

MAH(s) which have an RMP in place should address there the issue that post-marketing reports regarding potential persistent symptoms have limitations, especially concerning quality of information on medical history, further diagnostic investigations and the unverified evidence of gadolinium retention. In addition, a targeted follow-up questionnaire for cases of potential persistent symptoms should be implemented and included in the RMP.

A respective RMP update is to be submitted within 3 months.

6.2.2.2. Gadobenic acid - PSUSA/00001500/202108

MAH(s) which have an RMP in place should address there the issue that post-marketing reports regarding potential persistent symptoms have limitations, especially concerning quality of information on medical history, further diagnostic investigations and the unverified evidence of gadolinium retention. In addition, a targeted follow-up questionnaire for cases of potential persistent symptoms should be implemented and included in the RMP.

A respective RMP update is to be submitted within 3 months.

6.2.2.3. Gadoxetic acid disodium - PSUSA/00001509/202108

MAH(s) which have an RMP in place should address there the issue that post-marketing reports regarding potential persistent symptoms have limitations, especially concerning quality of information on medical history, further diagnostic investigations and the unverified evidence of gadolinium retention. In addition, a targeted follow-up questionnaire for cases of potential persistent symptoms should be implemented and included in the RMP.

A respective RMP update is to be submitted within 3 months.

6.2.2.4. Gadobutrol - PSUSA/00001502/202108

MAH(s) which have an RMP in place should address there the issue that post-marketing reports regarding potential persistent symptoms have limitations, especially concerning quality of information on medical history, further diagnostic investigations and the unverified evidence of gadolinium retention. In addition, a targeted follow-up questionnaire for cases of potential persistent symptoms should be implemented and included in the RMP.

A respective RMP update is to be submitted within 3 months.

6.2.2.5. Gadoteridol - PSUSA/00001507/202108

MAH(s) which have an RMP in place should address there the issue that post-marketing reports regarding potential persistent symptoms have limitations, especially concerning quality of information on medical history, further diagnostic investigations and the unverified evidence of gadolinium retention. In addition, a targeted follow-up questionnaire for cases of potential persistent symptoms should be implemented and included in the RMP.

A respective RMP update is to be submitted within 3 months.

6.2.2.6. Gadoteric acid (IV and intravascular formulations) - PSUSA/00001506/202108

MAH(s) which have an RMP in place should address there the issue that post-marketing reports regarding potential persistent symptoms have limitations, especially concerning quality of information on medical history, further diagnostic investigations and the unverified evidence of gadolinium retention. In addition, a targeted follow-up questionnaire for cases of potential persistent symptoms should be implemented and included in the RMP.

A respective RMP update is to be submitted within 3 months.

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

None

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 May 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

6.3.1.1. Dexketoprofen, tramadol - EMEA/H/N/PSR/S/0035

The CMDh, having considered the PRAC recommendation and the PRAC assessment report, agreed by consensus that the risk-benefit balance of the medicinal products containing the active substances dexketoprofen and tramadol concerned by the non-interventional imposed PASS final report remains unchanged, but recommends that the terms of the marketing authorisation should be varied as follows:

- The marketing authorisation holder(s) shall remove the condition imposed during the procedure ES/H/0317-0318/001/DC by submission of a type IA_{IN} variation C.I.11.a
- Consequently, since this imposed PASS was the only criteria for additional monitoring, MAH(s) should submit an additional type IA_{IN} variation, category C.I.12, to request the deletion of the black symbol and the related statement in the product information. This type IA variation can be grouped with the variation to delete the condition.
- The risk management plan (RMP) should be updated at the next regulatory opportunity, in order to remove the completed study from all relevant sections of the document.

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. Availability of information from RMPs / Chair

The CMDh was made aware of a letter from Medicines for Europe regarding access to RMPs of RefMPs. The letter will first be discussed in the PhV WSP WP.

[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.

6.6.2. Dolormin für Kinder Ibuprofensaft 20 mg/mL (DE/H/0392/II/032/G) / DE

The CMDh was informed on the PRAC advice on a variation for Dolormin für Kinder Ibuprofensaft 20 mg/mL (DE/H/0392/II/032/G) in relation to use during pregnancy. The variation has been submitted to implement a wording requested to MAHs by FDA but is not in line with an EU recommendation of the PhVWP from 2004.

While further PRAC discussions on the issue are expected, the CMDh agreed to keep related ongoing variations for this product and for other substances with the same content in clock-stop.

6.6.3. Follow-up of signal for paracetamol and in utero exposure / BE

The CMDh was made aware of a recent PRAC discussion on a recently published study on paracetamol and exposure in utero (Bauer et al. 2021). The evaluation of the study was circulated in a NUI as a follow-up information on a previously confirmed signal from 2019. The LMS concluded that the new data do not provide conclusive evidence on possible causal links and multiple uncertainties remain. Most of the key messages recommended in the study are already addressed in the PI. Additional warnings on the labels or packaging are not supported at this stage.

The CMDh discussed if there should be a coordinated communication reinforcing the conclusion of the PRAC signal as adopted in the PI update in 2019 on paracetamol and in utero exposure.

The majority of the CMDh considered that a coordinated communication at EU level is not needed. Several MSs mentioned that the conclusions are well-known and implemented at national level. The CMDh therefore agreed that, if needed, a communication could take place at national level.

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

7.1. Ibuprofen Strides 200 & 400 mg soft capsules (NL/H/5144/001-002/DC) / NL

NL informed the CMDh about the break-out session held for Ibuprofen Strides 200 & 400 mg soft capsules (NL/H/5144/001-002/DC). Major objections have been raised on the Art. 10(1) application with regard to the acceptability of the biowaiver for the 200mg strength. An acceptable BE study for the 400mg strength has been submitted. The applicant decided to withdraw the 200mg strength in all MSs. The procedure for the 400mg strength was finalised positively.

7.2. Softasept CHG coloured/uncoloured, cutaneous solution; 20 mg/ml+0,7 mg/ml (DE/H/6804/001-002/DC) / DE

DE informed the CMDh about the break-out session held for Softasept CHG (DE/H/6804/001-002/DC). Major objections have been raised with regard to the submitted data for an Art. 10a application due to the mode of administration. The RMS considered that the chosen legal basis is not appropriate for the application. Own clinical studies (other than bridging studies)

have been submitted with the application. The procedure was finalised negatively at day 210. The applicant was advised that an Art. 8(3) application would have been more suitable.

8. Miscellaneous

8.1. Report from the April CMDv meeting

The CMDv secretariat reported from the April CMDv meeting.

8.2. April 2022 CMDh Press Release

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

8.3. A.O.B.

8.3.1. Implementation of updated excipients guideline / EMA, IE

With reference to the discussion in October 2021, the CMDh was informed that the revised statement in the annex of the excipients guideline with regard to boric acid (and borates) is currently been translated and the EMA aims to publish the statement by the end of April.

8.3.2. Sunset clause / Chair, DE

The CMDh discussed a letter from a MAH requesting that procedures, which have not been marketed due to an ongoing application for a switch of the legal status, should generally be exempted from the provisions of the sunset clause.

While the CMDh acknowledged the arguments, it was agreed that no common response can be given by the CMDh as it is the responsibility of each NCA to grant exemptions to the sunset clause. The MAH should therefore address their request directly to the involved MSs. A corresponding response will be sent (**Action: EMA**).

8.3.3. NSAIDs – use during pregnancy / FR

The CMDh discussed how to proceed with an ongoing worksharing variation for a NSAID to update section 4.6 Pregnancy, breastfeeding and fertility (and in accordance section 4.3 Contraindications). The procedure has been restarted. (see also topic 6.6.2)

The CMDh agreed that an additional clock-stop/freezing of the procedure is not possible, as this is reserved for issues related to COVID-19 only. The CMDh agreed that that applicant could be asked to withdraw the application to await the outcome of the ongoing discussion at PRAC level. Alternatively, a CMS could consider raising a PSRPH to start a referral for the variation.

[*Post-meeting note: The applicant agreed to withdraw the application and to resubmit once a PRAC outcome is available*.]

8.3.4. Implementation of outcome of user testing / EMA

The CMDh discussed a query from a MAH if MAHs can change the agreed PL wording (e.g. following PRAC signal recommendations, PSUSA outcome, referral procedures) to implement

results of user testing in accordance with Article 59(3) and if generics can therefore deviate from the wording of the RefMP.

The CMDh agreed that text agreed by NCAs or at EU level should not be changed following user testing. The design and layout should be assessed to ensure that the way in which the information is set out in the document is accessible to the reader, easy to read and easy to navigate. Guidance on user testing of the package leaflet and recommendations for bridging are available on the CMDh website. A corresponding response will be sent (**Action: EMA**).

8.3.5. Generic MAA procedure including studies conducted by Synchron / HU

The CMDh discussed how to proceed with a generic MAA that includes a study conducted by Synchron for which an Art. 31 referral is currently ongoing. The procedure should have been kept in clock-stop but was restarted due to an oversight of the study.

The CMDh agreed that no second clock-stop is possible. Freezing of procedures is reserved to issues related to COVID-19 only. The CMDh discussed if a PSRPH should be raised in the procedure based on the concerns related to the CRO. A possible Art. 29(1) referral could then be aligned with the outcome of the Art. 31 referral. It was however agreed that it would be a better option if the procedure would be finalised positively (in case there are no other concerns related to the product), while the outcome of the Art. 31 referral is pending. As the respective products of these procedures are included the Art. 31 referral, in case there is a negative outcome of the referral (e.g. suspension of concerned products), the MAs could be suspended in line with the outcome of the referral. The same conditions to lift the suspension would then apply. The objecting CMSs will take the CMDh discussion into account in the procedure.

8.3.6.

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

8.3.7.

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

8.3.8. HaRP assessment report templates / Chair

The CMDh was informed that the HaRP assessment report template will be published on the CMDh website (**Action: EMA**). The template was already agreed in June 2018. They will now be published for transparency reasons and to increase accessibility.

9. Other topics and dates for next meeting

9.1. Draft meeting schedule and draft time schedule for referrals

The meeting schedule for May 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

List of participants

List of participants including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 20-21 April 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 participation in final deliberations and voting on:	6.2.1.2. Estradiol (except cream/balm/emulsion for application in female genital area) - PSUSA/00010440/202108
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	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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	
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	
Nicole Visser	Alternate	Netherlands	No interests declared	
Suzanne Gordon	Member	Norway		
Nina Malvik	Alternate	Norway	No interests declared	
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	
Miroslava Petrikova	Member	Slovakia	No interests declared	
Petra Docolomanska	Alternate	Slovakia	No interests declared	
Marjeta Jordan	Member	Slovenia	No interests declared	
Veronica Garcia Morales	Member	Spain	No interests declared	
Elisa Sulleiro	Alternate	Spain	No participation in final deliberations and voting on:	5.4.1.5. N-nitroso-aryl piperazine detected in quetiapine-containing medicinal product (Seroquel)
Christin Olofsson	Member	Sweden	No interests declared	
Adam Andersson	Alternate	Sweden	No interests declared	
Dino Soumpasis	Chair of CTS WG	Germany	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Martin Huber	Chair of Non-Prescription MPs TF	Germany	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.