13 December 2022
EMA/CMDh/947907/2022
Human Medicines Division

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

Minutes for the meeting on 8-10 November 2022

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

Health and safety information

In accordance with the Agency's health and safety policy, delegates are to be briefed on health, safety and emergency information and procedures prior to the start of the meeting.

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/729522/2016).

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1. Introduction

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

The Chair opened the meeting by welcoming all participants. Due to the current coronavirus (COVID-19) pandemic, and the associated EMA Business Continuity Plan (BCP), the meeting was held in-person with some members connected remotely (hybrid setting).

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 on the topics in the agenda of the meeting, the Committee Secretariat announced the restricted involvement of some Committee members, alternates and experts for concerned agenda topics.

Participants were asked to declare any changes, omissions, or errors to their declared interests concerning the matters for discussion. No new or additional competing interests were declared. Restrictions applicable to this meeting are captured in the list of participants included in the minutes. Due to restricted involvement, the Chair was replaced by the Vice-Chair for the discussion on topic(s) 2.1.1.

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. All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. CMDh membership

There have been no changes in the CMDh membership since the last meeting.

1.3. Adoption of draft agenda

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

- Multiple use of legal base Art. 10b
- Changes to PSMF summary following MA transfer
- Risk of supply shortages of medicinal products

1.4. Adoption of the minutes

The minutes of the October 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

The PARs on gabapentin, tretinoin, haemophilus influenzae type b vaccine conjugated to Tetanus Protein (Act-HIB) and vaccinum hepatitidis B (Euvax B) were adopted by the CMDh and will be published on the CMDh website (**Action: EMA**).

Public PdARs for paed. studies acc. Art. 46

The PARs on Haemocomplettan/iastap (human fibrinogen), Decapeptyl/Diphereline/Arvekap (triptorelin pamoate), act-HIB (Haemophilus influenzae type b vaccine conjugated to tetanus Protein), Dexilant (dexlansoprazole) and Zithromax (azithromycin dehydrate) were adopted by the CMDh and will be published on the CMDh website **(Action: EMA)**.

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

The WP Chair reported from the November 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 new process to optimise/rationalise the CMDh LoSC including the outline for CTS implementation and how to resume the processing of the LoSC. The concrete implementation is scheduled to begin in mid-November. The WP and the HaRP group summary of activities were presented.

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

The WG Chair gave an update to the progress of the pilot on procedures and on the EU reduced harmonised text.

The WG was progressing with the revision of the survey results and will determine any actions arising within scope of MLPWG/CMDh accordingly.

2.2. Czech Presidency meeting / CZ

The CMDh thanked the Czech Presidency for organising the presidency meeting. The minutes of the meeting will be prepared for the December 2022 CMDh meeting (**Action: CZ**).

The CMDh was debriefed on the main action points arising from the meeting.

2.3. Meeting with Interested Parties / Chair

The CMDh discussed the presentations in preparation of the meeting with Interested Parties and the feedback to be given during the meeting.

The topics discussed included, amongst others, multilingual labelling, resources, repeat-use procedure improvements, availability of updated PI following safety reviews, use of variation worksharing, CMDh workplan, the LoSC and nitrosamine impurities.

2.4. Improving Access to TB medicines in the WHO European Region / DE

The CMDh received a summary of the workshop on Improving Access to tuberculosis medicines in the WHO European Region held in June 2022. The main areas of focus were: access challenges, emergency response, the policy considerations and the some examples of national responses. A summary of the workshop will be drafted and circulated to the CMDh.

2.5.

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

2.6. Joint CMDh/CMDv meeting / Chair

The CMDh discussed and agreed on the topics to be included in the agenda of the Joint CMDh/CMDv meeting to be held in December 2022 in the margins of CMDv.

2.7. EC's Joint Action (JA) on increasing capacity building of the EU medicines regulatory network / Chair, MT, CY, IT, SE

As a follow-up from the CZ presidency meeting, the CMDh discussed the activities, resources and timing as part as the EC's joint action on increasing capacity building of the EU medicines regulatory network. The CMDh agreed on topic leads for some deliverables. The CMDh input and proposals will be sent to the rapporteur who will then forward this to the EC.

2.8. Multistakeholder group on digital RMM / CZ

The CMDh received a presentation from the first meeting held on the 6 October 2022 of the Multistakeholder group on digital RMM. The group's main goal is to draft a reflection paper for public consultation and possible basis for future GVP guidance.

The CMDh noted the importance of the consultation and involvement of all the relevant parties and to find a common language.

2.9. EU Pharmaceutical Strategy / EMA

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

3. General items

3.1. CMDh guidance documents

3.1.1. Addendum to the QRD templates specific for THMP / AT

The CMDh agreed an update of the Addendum to the QRD template for MRP/DCP specific for (Traditional) Herbal Medicinal Products ((T)HMPs). The update has been prepared and agreed by the Committee on Herbal Medicinal Products (HMPC). With the update, duplications of the regular QRD template have been removed and focus has been put on special aspects to be considered for (T)HMPs. Wherever justified, the wording of the herbal specific texts was not changed compared to the original version. Sections where better guidance was deemed necessary were expanded.

The updated document will be published on the CMDh website (**Action: EMA**).

3.1.2. CMDh position paper on the use of mobile scanning and other technologies to be included in labelling and PL / ES

ES presented an update of the CMDh position paper on the use of mobile scanning and other technologies to be included in labelling and PL. Discussion on the guidance document has already taken place in the CZ presidency meeting where some agreements could be reached (definitions of statutory and complementary information, location of the feature). There was also a discussion if annex 1 (list of elements that could be provided through mobile technology features for individual MS) should be kept or deleted. It was proposed to keep and update annex 1.

The CMDh discussed the role of the RMS in the assessment of complementary information. A new proposal for a wording of this part of the guidance document will be circulated for written comments/agreement (**Action: MSs**). If no agreement can be reached in writing, the document will be brought back for discussion in the December CMDh meeting.

3.1.3. Removal of information on provision of dispatch lists from CMDh BPGs / DE, PT, NL, SE

The discussion on the update of the BPGs was postponed to December.

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.

The CMDh was made aware that the MAH has submitted parallel national variations instead of using the variation worksharing procedure. The CMDh agreed to write to the MAH to request them to withdraw the ongoing variations and re-submit them together with already finalised ones, as applicable, as variation worksharing (**Action: EMA**).

3.2.3.2.

DE informed the CMDh of a request for variation worksharing that was subsequently withdrawn by the MAH as they considered that the changes do not qualify for worksharing. The reference authority was of the view that the variation worksharing procedure can be used. It was acknowledged that there are differences in the dossier of the concerned nationally authorised products, but variation worksharing could still be used as long as the applied changed are identical for all dossiers and would lead to a harmonised outcome. The CMDh agreed with the view of the reference authority. DE will provide feedback to the MAH (**Action: DE**).

3.2.3.3.

The CMDh was made aware that several parallel national variations have been submitted to add a warning related to flammability risk for paraffine of a topical gel. Reference was made to the CMDh discussions in 2017 and the feedback given to Interested Parties in May 2019. Several MSs informed the CMDh that the variation is either under assessment or has already been assessed. One MSs informed the CMDh that the variation was refused based on the previous discussions and based on the draft guideline on quality and equivalence of topical products. Public consultation on the draft guideline has closed in 2019, but the guideline has not yet been finalised. As MSs have taken different decisions with regard to the variation, the CMDh agreed to contact the MAH to ask them to withdraw ongoing variations and resubmit them, together with already finalised ones, using variation worksharing in order to reach a harmonised outcome (**Action: EMA**).

[*Post-meeting note: The finalisation of the guideline on quality and equivalence of topical products was put on hold due to the EMA BCP, but it is now included in the QWP 2023 workplan*.]

3.3. GMP

None

3.4. GCP

None

3.5. Information on overdose in Section 4.9 of the SmPC / FI

As a follow-up of the discussion in November 2021, FI informed the CMDh that the topic on overdose information in section 4.9 of the SmPC has been further discussed with the DARWIN group and with the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). DARWIN has looked into the possibility of conducting a study on the subject, but in view of

the limitations, this is currently not possible. Information has also been received from the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) that a new position statement from this group on activated charcoal is about to be published. FI proposed to work on a guidance document on which information on the treatment of overdose should be included in section 4.9 of the SmPC.

The importance of having the correct information on the treatment of overdose in section 4.9 was acknowledged. However, it was considered that guidance on a specific section of the SmPC would be outside of the remit of the CMDh and other groups should be in the lead. It was further noted that the SmPC Guideline gives already information on section 4.9, but companies seem to be reluctant to update the information. The need to keep the product information up-to-date (including section 4.9) was stressed again to trade associations in the IP meeting held in the margins of the November CMDh meeting.

3.6. Use of the recycling logo on the labelling of medicinal products / EC

The outcome of a survey on the use of the recycling logo on the labelling of human medicinal products in MSs was tabled for information. The survey was initiated on request of the EC with a view to the legislation on packaging and packaging waste. A similar survey was conducted by the CMDv for veterinary medicinal products.

It was noted that the limited space on the outer package should be considered in the deliberations. Also, one MS noted that the description of the packaging material is not part of module 3 and the correct recycling classification can therefore not be checked.

3.7. European Pharmacopeia monographs on Heparin sodium and Heparin calcium / EMA, Chair

Following the consultation of the CMDh and BWP by EDQM on the revision of the European Pharmacopeia monographs on Heparin sodium and Heparin calcium, the outcome of the BWP discussions were presented to the CMDh. The CMDh agreed with the BWP position to support the reduction of the residual protein limit from 0.5 to 0.1%. It was recommended to continue the dialogue with the manufacturers to ensure that there is no impact on market availability.

A joint CMDh/BWP response will be sent to EDQM (**Action: EMA**).

3.8. Reflection paper on criteria to be considered for the evaluation of new active substance (NAS) status of biological substances / EMA

The draft reflection paper on criteria to be considered for the evaluation of new active substance (NAS) status of biological substances as adopted by CHMP was presented to the CMDh for information. The document will be published for six months of public consultation.

3.9. Annex to the Guideline on Excipients in the labelling and package leaflet of medicinal products for human use / DE

The CMDh discussed a proposal to ask NcWP/the Excipients Drafting Group to include benzyl alcohol (administered orally) in a list of excipients to be re-considered.

The CMDh was informed that some oral flavoured antibiotic preparations contain concentrations of benzyl alcohol of less than 1 ppm. There is no threshold in the

recommendations of the excipients guideline and inclusion of the warnings as per the current guideline might lead to therapeutic failure.

The CMDh agreed to forward the request to CHMP (NcWP) (**Action: EMA**).

3.10. Simultaneous National Scientific Advice (SNSA) / DE

The CMDh was informed about the experiences and the outcomes of pilot phase 1 on Simultaneous National Scientific Advice (SNSA) and about the upcoming pilot phase 2 based on an optimised procedure, reducing the burden for both applicants and NCAs and contributing to a more efficient assessment of subsequent regulatory applications with the aim to increase regulatory support where it is key.

4. Generic/hybrid marketing authorisations

4.1. Product-specific bioequivalence guidance on lapatinib / AT

Based on disagreement in an ongoing MAA for a lapatinib-containing generic medicinal product, the CMDh discussed if a question should be sent to the Methodology WP (MWP)/PKWP. The PSBGL on lapatinib has been revised following public consultation. The CMDh agreed to forward the question to CHMP (MWP/PKWP) (**Action: EMA**).

4.2. Marketing Authorisation Applications for generics of Tecfidera (dimethyl fumarate) / Chair, EC

Following the information received in October 2022 about the publication of the opinion of the Advocate General in the joined cases C-438/21 P to C-440/21 P, the CMDh agreed that there is currently no need to change the handling of ongoing generic MAAs as the opinion of the Advocate General is not binding to the Court of Justice of the European Union. EC informed that a final judgement is expected in about 6 months.

MSs were asked to keep the CMDh and the EC informed of any ongoing court cases at national level (**Action: MSs**).

4.3. Legal basis – 10(1) vs 10(3)

4.3.1. Product for injection and/or infusion / DK

The CMDh discussed if an abridged application, submitted as solution for injection for the lowest strength and solution for infusion for the higher strengths, could be validated under Art. 10(1), when the RefMP is authorised as solution for injection/infusion for all strengths, or if the applicant should consider submitting the application under e.g. Art. 10(3) in this case. From the SmPC information of the RefMP, it can be ascertained that the lowest strength of the RefMP is intended for injection, while the other strengths are intended for infusion, as proposed in the abridged application.

The CMDh agreed that in this situation the RMS could check the SmPC of the RefMP at the validation stage and, based on this information, the MAA could be accepted under Art. 10(1).

4.3.2. Product for infusion without solvent / DK

The CMDh discussed if an abridged application, applied for as powder and solvent for solution for infusion (including solvent), could be validated under Art. 10(1), if the RefMP is authorised as powder for solution for injection/infusion (without solvent), or if the applicant should consider submitting the application under e.g. Art. 10(3).

There was no harmonised view among MSs on the most appropriate approach. Some MSs would accept the application under Art. 10(1) based on the fact that the pharmaceutical form at the time of administration is the same and with the same concentration. Others consider that an Art. 10(3) application would be appropriate in this case, as the fact to have a solvent included or not would lead to differences in the pharmaceutical form and to differences in the wording of the SmPC of the product applied for and the RefMP. It was suggested that the RMS should take a decision and justify it based on their considerations.

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

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

None

5.2.3. Information on ongoing referral procedures

5.2.3.1. Pholcodine (Art. 107i)

Tabled for information.

5.2.3.2. Topiramate (Art. 31)

Tabled for information.

5.2.4. PRAC recommendations for CMDh position

5.2.4.1. Amfepramone (Art. 31)

The CMDh, having considered the PRAC assessment report and recommendation, agreed by majority that the marketing authorisations for medicinal products containing amfepramone should be withdrawn (majority of 24 MSs (plus NO and IS), 3 divergent members (CZ, DK, SE)).

The PRAC recommendation follows a review which found that measures to restrict the use of these medicines for safety reasons have not been sufficiently effective. It found that the medicines were being used for longer than the recommended maximum period of 3 months, thereby potentially increasing the risk of serious side effects such as pulmonary arterial hypertension (high blood pressure in the lungs) and dependency. The medicines were also being used in patients with a history of heart disease or psychiatric disorders, increasing their risk of heart and psychiatric problems. In addition, there was evidence of use during pregnancy, which could pose risks to the unborn baby.

The review considered all available information relating to these concerns, including data from two studies on the use of amfepramone medicines in Germany and in Denmark. In addition, the PRAC received advice from a group of experts, comprising endocrinologists, cardiologists and a patient representative.

The PRAC considered introducing further measures to minimise the risk of side effects but could not identify any that would be sufficiently effective. The PRAC therefore concluded that the benefits of amfepramone medicines do not outweigh their risks and recommended that the medicines be removed from the market in the EU.

As the CMDh position was adopted by majority vote, it will now be sent to the European Commission, which will issue a final legally binding decision applicable in all EU Member States.

Further information regarding the above-mentioned referral has been published on the EMA website.

5.2.4.2. Terlipressin (Art. 31)

The CMDh, having considered the PRAC assessment report and recommendation, agreed by consensus that the marketing authorisations for medicinal products containing terlipressin, indicated in the treatment of type 1 hepatorenal syndrome (type 1 HRS), should be varied to introduce new measures to reduce the risk of respiratory failure and sepsis.

The new measures include adding to the product information a warning to avoid terlipressin-containing medicines in patients with advanced acute-on-chronic liver disease or advanced kidney failure. Patients with breathing problems should receive treatment to manage their condition before starting terlipressin-containing medicines. During and after treatment, patients should be monitored for signs and symptoms of respiratory failure and infection.

In addition, healthcare professionals can consider giving terlipressin-containing medicines as a continuous infusion (drip) into the vein as an alternative to giving it by bolus injection (full dose injected in one go) as this may reduce the risk of severe side effects.

The recommendations follow the PRAC's review of available data, including results from a clinical trial involving patients with type 1 HRS which suggested that patients who were

treated with terlipressin-containing medicines were more likely to experience and die from respiratory disorders within 90 days after the first dose than those who were given placebo.

Although respiratory failure is a known side effect of terlipressin, the frequency of respiratory failure seen in the study was higher (11%) than previously reported in the product information. In addition, the study reported sepsis in 7% of patients in the terlipressin arm compared with none in the placebo group.

There were limitations to the data, such as differences in how terlipressin was used in the clinical trials compared to clinical practice. After considering these limitations together with other available data and consulting an expert group composed of healthcare professionals with expertise in the field of hepatorenal syndrome, PRAC concluded that new measures are needed to ensure that the benefits of terlipressin-containing medicines continue to outweigh the risks.

As the CMDh position was adopted by consensus, it will be directly implemented by the Member States.

Further information regarding the above-mentioned referral has been published on the EMA website.

5.3. Outcome of referrals to CHMP

5.3.1. Synchron (Art. 31) / EMA

Tabled for information.

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

DE proposed that in case new nitrosamines have been detected after the EoP and some MSs have already issued the MA, but others have not, the MA should be issued in all MSs and confirmatory testing does not have to be provided before the MA can be granted. According to the EMA/CMDh Q&A No. 5 the MAH is obliged to maintain the quality of his product throughout its lifecycle and to consider newly identified risk factors and limits for nitrosamines. The CMDh agreed with the proposal. It was agreed that no specific reminder to the MAH of their obligation to monitor the quality of their product is needed.

The CMDh and the EMA agreed an update of the "Step 2 – Nitrosamine detected response template" considering the newly published Q.21 of the EMA/CMDh Q&A on nitrosamines and to emphasise the need for adherence to published AI limits for known nitrosamines.

The updated template will be published on the CMDh and EMA websites (**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. Novantrone (mitoxantrone) (Art. 30) / PT

The CMDh discussed the implementation of the Art. 30 referral on Novantrone (mitoxantrone), finalised in 2016, for generic medicinal products. As an outcome of the referral the PI was harmonised with regard to the oncology indication and the indication in multiple sclerosis. The CMDh agreed that it is not mandatory for generics of NAPs to implement both indications. Only if the indications have already previously been included in a generic product, they have to be aligned with the reference medicinal product/outcome of the referral.

6. Pharmacovigilance

6.1. Report from the November 2022 PRAC meeting

The EMA reported from the PRAC meeting held from 24-27 October 2022.

The CMDh was informed that further discussions on the handling of PSUFUs are being held at PRAC level. The PRAC proposals will then be discussed with CMDh (via the PhV WSP WP), once ready.

6.2. Periodic Safety Update Reports (PSUR)

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

6.2.1.1. Amoxicillin - PSUSA/00000187/202203

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 amoxicillin.

During the PSUSA on amoxicillin, the PRAC considered that the overall recommendations of the PSUSA should also be considered for combined medicinal products containing amoxicillin.

During the PSUSA on amoxicillin, the inclusion in the product information of interactions between amoxicillin and probenecid and between amoxicillin and methotrexate is recommended. The PRAC considered that these interactions should also be included in the product information of products containing the active substances methotrexate and probenecid (if not already included).

[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.

Suggested wording:

DDI between amoxicillin and methotrexate

SmPC, Section 4.5

Amoxicillin
Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

PL, Section 2

Penicillins may reduce the excretion of methotrexate causing a potential increase in side effects.

DDI between amoxicillin and probenecid

SmPC, Section 4.5

Amoxicillin
Concomitant use of amoxicillin is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin which may result in increased and prolonged blood levels of amoxicillin.

PL, Section 2

Concomitant use of probenecid and amoxicillin may reduce the excretion of amoxicillin and is not recommended.

6.2.1.2. Amoxicillin / clavulanate - PSUSA/00000188/202203

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 amoxicillin / clavulanate.

6.2.1.3. Erythromycin (systemic use) - PSUSA/00010808/202203

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 erythromycin (systemic use).

6.2.1.4. Fexofenadine - PSUSA/00001388/202203

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 fexofenadine.

6.2.1.5. Oxycodone - PSUSA/00002254/202204

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 oxycodone.

During the PSUSA on oxycodone, the PRAC considered that with the next regulatory possibility, all MAHs should update the list of safety concerns in the RMP (in case an RMP is in place), by removing the following important identified risks (if present): Respiratory

depression, Ileus, Intentional overdose, Use in patients with Hepatic Impairment, Use in patients with Renal Impairment, Hypersensitivity, Use in Patients with Head Injury (due to risk of increased intracranial pressure), Use in patients taking MAO Inhibitors, Interactions with CNS Depressants including alcohol, as well as the following important potential risks: Medication Error and Prolongation of QTc. The following important identified risks should be included / remain: Accidental overdose, Physical dependence and drug withdrawal syndrome (DWS), Drug abuse, and Psychological dependence, as well as the following missing information: Use in pregnant and lactating women.

Following the RMP update, the list of safety concerns in the PSUSA may be shortened accordingly.

The CMDh was informed that, based on the outcome of the PSUSA on oxycodone, PRAC will continue discussing an appropriate wording for the outer packaging of opioid containing medicinal products to increase awareness of the risk for opioid use disorder.

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

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 November 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

[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.

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 updated PI following safety reviews / CZ

As a follow-up to the discussion with trade associations on their project on "reference safety information", CZ presented an overview of how MSs make updated PI following safety reviews publicly available. It was acknowledged that there is room for improvement by MSs on updating PARs and uploading (updated) PI in CTS (and therefore in the MRI Product Index). Also the outcome of variation worksharing procedures should be made available. It was also stressed that the information is scattered across different locations (e.g. EMA, CMDh and EC website) and it was suggested to create "instructions for use" to guide MAHs and assessors.

The CMDh was informed that related issues were raised by companies at the 17th Industry Stakeholder Platform – Operation of EU Pharmacovigilance.

It was stressed that any action should keep in mind the limited capacities of NCAs. Therefore, digital solutions should be envisaged, where possible.

The CMDh agreed to form a small group to further discuss the issues raised. A call for volunteers will be sent (**Action: EMA**). MSs were asked to express their interest to participate before the December CMDh meeting (**Action: MSs**). Once CMDh proposals for next steps are available, other groups can be consulted, as needed.

6.6.2. Signal on hydrochlorothiazide – increased risk of skin cancer and inconsistency with SmPC section 5.3 / ES

The CMDh was made aware of an inconsistency in the product information of hydrochlorothiazide (HCTZ) containing medicinal products. Following a safety signal in September 2018 in relation to increased risk of skin cancer sections 4.4, 4.8 and 5.1 of the SmPC have been updated. However, a statement in section 5.3 of HCTZ containing medicinal products was not removed ('*…the extensive human experience with hydrochlorothiazide has failed to show an association between its use and an increase in neoplasms*'). This statement predates the 2018 PRAC recommendation and is inconsistent with the wording introduced in the signal procedure, which is still valid.

The EMA informed the CMDh that they will contact MAHs of CAPs to ask them to address the inconsistency in a suitable regulatory procedure.

The CMDh agreed to request MAHs of HCTZ containing medicinal products via the CMDh minutes to review section 5.3 of the SmPC and to remove any inconsistency with other sections of the SmPC as appropriate.

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

7.1. Sitagliptin Genericon /Sitagliptin +pharma/Cukifix (NL/H/5426-5428/001-003/DC) / NL

NL informed the CMDh about the break-out session held for Sitagliptin Genericon /Sitagliptin +pharma/Cukifix (NL/H/5426-5428/001-003/DC).

[*Post-meeting note: Based on the responses of the applicant, the major objections could be solved and the procedure was finalised positively*.]

8. Miscellaneous

8.1. Report from the September and October CMDv meetings

The CMDv secretariat reported from the September and October CMDv meetings.

8.2. November 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.

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

8.3.4. Multiple use of legal basis Art. 10b / Chair

Following the discussion in the September 2022 CMDh meeting, based on a court case in the Netherlands, the CMDh noted the EC reply to the CMDh question on multiple use of the legal basis Art. 10b of Directive 2001/83/EC for the same combination of active substances. The EC confirmed their previous position that any applicant that fulfils the requirements of Article 10b, and regarding data protection, can apply for a marketing authorisation in accordance

with this legal basis. The EC was of the view that the wording of Art. 10b ("*but not hitherto used in combination for therapeutic purposes*") does not imply that there cannot be multiple use of the legal basis Article 10b for applications with the same combination of active substances. Regulatory data protection requirements must be respected. It was stressed that the position from Commission services is without prejudice to any interpretation by the European Court of Justice, which is ultimately responsible for the interpretation of EU law.

MSs were asked to keep the CMDh informed of any related court cases at national level and/or any changes in handling of Art. 10b applications at national level.

Following a request for a respective update of the NtA, it was noted that previously, further clarifications on Art. 10b applications were not included in the NtA due to different national handling, based on national court rulings.

8.3.5. Changes to PSMF summary following MA transfer / Chair

In July 2021, the CMDh agreed to the request of a MAH for a derogation to submit a type IA variation C.I.8.a for the summary of the pharmacovigilance system in relation to a MAH transfer for a high number of MAs following a merger. In that exceptional case, it was agreed that the MAH may first finalise their MA transfers in all MSs for all concerned products (MRP/DCP and purely nationally authorised) before submitting a type IA variation using supergrouping for MRP/DCP products and grouped IA variations per MS for the purely national MAs.

The MA transfers were estimated to be finalised in November 2021. The MAH now informed the CMDh that there will be delays and the last MA transfers are expected end of 2023.

The CMDh agreed that the previous exceptional agreement can be extended due to the delays. The MAH will be informed accordingly (**Action: EMA**).

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. Risk of supply shortages of medicinal products / DE

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

8.3.8.

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 December 2022 and the annual schedule for 2023 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 8-10 November 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	To be replaced for the discussions, final deliberations and voting on:	2.2.1 Tretinoin PdAR
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	
Jitka Vokrouhlická	Member	Czechia	No interests declared	
Zuzana Fliegerová	Alternate	Czechia	No interests declared	
Katrine Damkjær Madsen	Member	Denmark	No interests declared	
Anne Kristine Hejlesen	Alternate	Denmark	No restrictions applicable to this meeting	
Annela Raidma	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	
Ragnhildur Heidarsdottir	Alternate	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	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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	No restrictions applicable to this meeting	
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	
Daniela Elena Popa	Alternate	Romania	No interests declared	
Miroslava Horváth Petriková	Member	Slovakia	No interests declared	
Petra Gubova	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 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	
Maria Luisa Casini	Chair of the PhV WS WP	Italy	No interests declared	
Siri Wang	Chair of CMDh WP on Paediatric Regulation	Norway	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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.