8 November 2022
EMA/CMDh/886704/2022
Human Medicines Division

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

Minutes for the meeting on 11-13 October 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).

Table of contents

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 remotely.

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 meeting, the Committee Secretariat announced that no restriction in the involvement of meeting participants for agenda topics was identified.

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.

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:

- Marketing Authorisation Applications for generics of Tecfidera (dimethyl fumarate)
- Request for CMDh advice for case of not marketed RefMP
- Request for submission of worksharing variation

1.4. Adoption of the minutes

The minutes of the September 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)

Report from the October 2022 meeting

The WP Chair reported from the October 2022 meeting of the WP.

The WP received an update on WS procedures for vaccines and blood products.

The WP discussed the ongoing project to clean up/speed up Art. 45 procedures in the published Art. 45 list. MSs with ongoing Art. 45 procedures were reminded to draft the PAR. The WP discussed the pre-screening of Art. 45 studies prior the assessment.

The WP discussed whether variation type IA should be reflected in the Art. 45/Art. 46 Paediatric assessment report templates. The WP agreed that type IA variations are relevant only in a limited number of cases, and therefore the update was considered not necessary. The WP discussed how to progress with the Art. 33 Paediatric register. EMA will provide a list of NAP entries with missing information on MA.

Public PdARs for paed. studies acc. Art. 45

None

Public PdARs for paed. studies acc. Art. 46

The PAR on Pneumovax 23 was adopted by the CMDh and will be published on the CMDh website (**Action: EMA**).

Art. 46 worksharing

There were no new studies submitted since the last appointment of rapporteurs.

2.1.2. Joint GCP IWG/CMDh Working Party / IE

The WP chair reported from the October meeting of the WP. The WP discussed, amongst other, CROs of interest, the CRO Inspection Programme, collaboration on BE inspections, statistical issues on bioequivalence inspections, the 2022 BE forum held on 12 October in Copenhagen and BE online training.

The CMDh agreed the Q&As to give guidance to applicants on the monitoring of bioequivalence clinical trials. The document is published on the EMA website.

MSs were requested to send a list of CROs from 2022 by end of November (**Action: MSs**)

A call for interest was made for additional CMDh members to join the GCP Inspectors WG/CMDh.

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

The meeting was cancelled.

2.2. Czech Presidency meeting / CZ

The agenda for the CZ presidency meeting to be held on 18-19 October was presented. There will be a joint session with PRAC. CZ informed the CMDh on the organisation of the meeting to be held in Prague on 18-19 October.

2.3. Meeting with Interested Parties / Chair

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

2.4. HMA meeting / Chair

The Chair reported from the HMA meeting held in Prague on 22-23 September.

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

The topic was postponed.

2.6.

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

2.7. Industry Standing Group (ISG) meeting on EMA's extended mandate / NL, Chair

The Chair reported from the Industry Standing Group (ISG) meeting on EMA's extended mandate held on the 26 September. The agenda and presentations from the meeting are available on the EMA website.

2.8. HMA Risk-Assessment tool for medicinal product testing

2.8.1. Usage of HMA RA tool / DE

The CMDh was reminded that since the launching of the HMA RA tool in March 2020, the RA-template has to be filled out for every DCP/MRP procedure that had a start date after 1 March 2020. An overview of the procedures finalised, and corresponding RA templates was presented together with the potential reasons of missed templates and the proposals for improvement. The CMDh agreed to implement as an improvement a pop-up message in CTS when finalising a procedure so the RA template is filled in.

MSs were encouraged to take measures to assure the creation of the template for every DCP/MRP and rediscuss within the NCAs what could be the potential issues preventing the completion of the template (**Action: MSs**).

MSs were requested to send feedback by 1st of November on whether they would agree for CTS to perform automatic actions for past procedures (**Action: MSs**).

2.8.2. OMCL Network / Stakeholder meeting re. HMA Risk Assessment Tool / CZ

The CMDh was informed about the discussions held on the OMCL network-stakeholders meeting regarding the HMA risk assessment tool. The lessons learnt were presented. The CMDh agreed that it would be beneficial if the HMA Post-Marketing Risk-Assessment Tool WG could further discuss the action items in the next WG meeting and once a mature proposal is available to bring it back to CMDh. The CMDh supported the organisation of a new training and recording at the EU NTC website.

2.9. Scientific Coordination Board / Chair

The Chair reported from the scientific coordination board meeting held on 30 September 2022.

2.10. Joint CMDh/CMDv meeting / Chair

MSs were requested to circulate topics for discussion in the CMDh/CMDv joint meeting. The agenda will be further discussed next month (**Action: EMA**)

3. General items

3.1. CMDh guidance documents

3.1.1. CMDh Guidance on the Informal Work-Sharing procedure for follow-up for PSUSA for NAPs / NL

The CMDh agreed an update of its guidance on the informal worksharing procedure for follow-up for PSUSA for NAPs (PSUFU). The CMDh agreed that in the very specific and exceptional situation where the MAH anticipates not being able to meet the required submission deadline and applies for an extension, the LMS/Reference Authority/RMS does no longer need to consult the Pharmacovigilance WSP WP but can bring the request directly to the CMDh for discussion. The updated document will be published on the CMDh website (**Action: EMA**).

Based on a current example, the CMDh also discussed if every PSUFU procedure (or related WS variation) has to go for PRAC advice. While the CMDh acknowledged that there might be cases where a PRAC advice is not necessary (e.g. in worksharing variations where all MSs are involved and the assessment does not need any further discussion), the CMDh confirmed that the current process should be maintained, i.e. PRAC advice should be requested for all PSUFUs, as the request originated from PRAC and all PRAC members should have a chance to review the assessment. PRAC could discuss and agree if a change in the process is preferred. This could then be further discussed in the CMDh.

3.1.2. CMDh Best Practice Guide for handling of Type II variations in MRP / NO, FI, DE

The CMDh has agreed an update of the Best Practice Guide for the handling of type II variations in MRP (Chapter 5 of the BPGs for the Submission and Processing of Variations in MRP). Guidance on the use of the template for MAH's responses during type II variations, as agreed in September 2022, has been included in the document. The document has also been updated with other changes to reflect the current way of working. The CMDh has agreed that the dispatch list does not need to be provided anymore as all applications are now submitted via CESP.

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

3.1.3. MRP/DCP submission dates in 2023 / DK

The CMDh has adopted updated guidance documents with the timetables for MRP/DCP applications to be submitted in 2023. The updated guidance documents 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.

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 of parallel national variations instead of using the variation worksharing procedure. The CMDh agreed that in order to save resources and to achieve and maintain harmonisation of the product information across MSs the MAH should be asked to withdraw the national variations and to re-submit using variation worksharing. Where comments have been made on the previously submitted national variations, these should be taken into account in the resubmission as worksharing. A letter from the CMDh will be sent to the MAH (**Action: EMA**).

3.2.3.2.

The CMDh was made aware of parallel national variations instead of using the variation worksharing procedure. The CMDh agreed that in order to save resources and to achieve and maintain harmonisation of the product information across MSs the MAH should be asked to withdraw the national variations and to re-submit using variation worksharing. Where comments have been made on the previously submitted national variations, these should be taken into account in the resubmission as worksharing. A letter from the CMDh will be sent to the MAH (**Action: EMA**).

3.3. GMP

None

3.4. GCP

None

3.5. TiO2 (E171) used as excipient / EMA

The EMA gave an update on the actions to replace TiO2 as excipient in medicinal products.

3.6. Water for injection included in MAs of medicinal products / IT

Following the discussion in September, the CMDh continued the discussion if it could be possible for a product consisting of an active ingredient and a solvent (also separately

approved) that the dossier does not contain the full quality information of the solvent, but a cross reference to its stand-alone MA.

While the CMDh acknowledged the practical aspects of such an approach, it was agreed that a MA should include all the particulars and requirements in accordance with Annex I of Directive 2001/83/EC. Therefore, inclusion of a cross-reference to the dossier of another MA, should, in principle, not be possible. This is also in line with the position of the EMA taken in the centralised procedure.

The discussion was triggered based on products where this approach was taken in agreement with the RMS and most of the quality information of the solvent was removed from the dossiers and instead a reference to the stand-alone solvent MA was included.

The CMDh agreed to contact the MAH to ask them to re-introduce the information following discussion and agreement at EU level (**Action: EMA**).

3.7. Data Analysis and Real World Interrogation Network (DARWIN EU) / EMA

The CMDh received an update on the DARWIN EU Coordination Centre.

CMDh members were encouraged to request RWE data analyses relevant to their work.

3.8. Good Practice Guide for the use of the EU metadata catalogue / EMA

The CMDh was informed of the start of the public consultation on the Good Practice Guide for the use of the Metadata Catalogue of Real-World Data Sources. The public consultation is open until 16 November 2022 and comments will be addressed during Q4 2022/Q1 2023. A final version of the Good Practice Guide for publication is expected in Q1 2023.

3.9. Data Quality Framework / EMA

The CMDh was informed of the start of the public consultation on the first release of the Data Quality Framework for the EU medicines regulation. The public consultation ends on 18 November 2022. A webinar on Data Quality Framework is planned for 18 October 2022.

3.10. Role of food supplement data in the context of a well-established use application (Art. 10a) / Chair

The CMDh noted the reply from the EC to the CMDh question on the role of food supplement data in the context of a well-established use (WEU) application (Art. 10a).

In its response the EC referred to the Notice to Applicants (NtA), Volume 2A, Chapter 1 and explained that the derogation of the well-established use legal provision must be interpreted strictly. It is possible to replace results of the pre-clinical and clinical trials by detailed references to published scientific literature, if it can be demonstrated that the active substance(s) of a medicinal product in the claimed therapeutic indication have been in well-established medicinal use within the Union for at least ten years, with recognised efficacy and an acceptable level of safety. In this regard, the provisions of Annex I of Directive 2001/83/EC shall apply.

In view of this, the EC considers that it would not be appropriate to use data related to a specific substance as food supplement to demonstrate the efficacy and safety of a WEU

application. The use of food supplement data can indeed not be considered as "medicinal use", considering the lack of therapeutic indication.

Regarding the question as to whether food supplement data can provide proof of 10 years of WEU in case they are reported in national or EU treatment guidelines, the NtA specifies that "*The well-established medicinal use legal basis is to be used only in cases where all aspects of the safety and efficacy are demonstrated by reference to published scientific literature*". It would derive that it should not be considered as an alternative to another legal basis such as Article 10 of Directive 2001/83/EC. It also clarifies that the adequacy of the bibliographic evidence has to be assessed on a case-by-case basis in the understanding that applications under Article 10a do not lower the requirements of safety and efficacy that must be met. It has therefore to be assessed on case-by-case basis whether the food supplement data reported in national or EU guidelines are also reported in published scientific literature confirming the safety and efficacy.

3.11. Renewal submission and MA validity / FI

The CMDh discussed national practices with regard to MA validity when a renewal has been submitted on time but due to procedural reasons has not been started/finalised in time. Most MSs informed the CMDh that in case the renewal has been submitted on time, the national legislation allows them to keep the MA valid even if the renewal has not been finalised in time. However, it was also noted that this is a national issue that is dependent on national legislation and outside of the scope of the CMDh.

Similarly, in the opposite case, where renewals are submitted less than 9 months before the renewal date, most MSs do not accept the submission anymore and the MA will cease to be valid at the time of the renewal. In the same way, this is a national issue and dependent on national legislation.

3.12. Prescription status issues and referrals to the CMDh / IE

The CMDh discussed questions related to the prescription status of products and under which circumstances they would trigger a referral to the CMDh under Art. 29(1).

It was agreed that if a CMS is withdrawn during an ongoing MAA (in the second phase, i.e. assessment step II in case of a DCP) due to disagreement with the prescription status, this should not automatically trigger a referral to the CMDh at the end of the procedure.

It was noted that the legal status is a national decision and as such cannot be the basis of a potential serious risk to public health (PSRPH) on which an Art. 29 referral is based. Some MSs stated that in case they cannot agree with a proposed OTC status, they would finalise the procedure with prescription-only status. Others considered that a referral based on safety concerns (e.g. linked to the aRMMs) should be possible as the benefit-risk profile of a product is being assessed in the framework of its legal status. It was generally noted that the RMS should not validate a PSRPH raised by a CMS. In case a CMS requests an Art. 29 referral based on a PSRPH, the procedure should be referred to the CMDh, where a discussion on the referral can take place (see also Q&As on CMDh referrals, Q3).

It was agreed that the question should be further discussed in the TF on non-prescription medicinal products, based on a practical example.

4. Generic/hybrid marketing authorisations

4.1. Different composition of generic medicinal product to be marketed than was used in the BE study / SK

The CMDh discussed if a generic MAA could be acceptable if there are (slight) differences in the composition of the product used in the BE study compared to the product to be marketed, e.g. because the product has been further developed since the BE study has been conducted.

The CMDh agreed that no general answer can be given and a case-by-case decision needs to be made. It needs to be justified why the composition has been changed and assessed what impact this could have on the bioavailability. Generally, the product used in the BE study should be representative of the product to be marketed. Minor changes in the composition can be acceptable in case they do not affect the bioavailability. The BE study also needs to fulfil the current requirements.

4.2. Legal basis of a fixed dose combination with different strength than the RefMP / NL

The CMDh discussed if a hybrid application for a fixed-dose combination medicinal product (with different strength than the RefMP) could be supported by bioequivalence studies vs. the mono-components (instead of the RefMP).

Reference was made to a letter received from the EC in 2017, where it was stated that a hybrid application can only refer to one global marketing authorisation (GMA). As the mono-components and the FDC form separate GMAs, such a reference would therefore not be possible under Art. 10(3).

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. Gelisia (NL/H/5357/001/DC) / NL

The RMS gave an overview of the Art. 29 referral on Gelisia (NL/H/5357/001/DC). The referral concerned an Art. 10(3) application for an eye gel containing timolol 1 mg/g.

A referral was triggered as the objecting CMS considered that equivalence between the applied product and the reference product cannot be concluded. Extended pharmaceutical equivalence and an in vitro drug release test (IVRT) should be performed.

Based on the data submitted by the applicant during the referral, the RMS was of the view that equivalence has been demonstrated.

There was a discussion about the statistical methodology, the sample size used in the comparison and about viscosity over the storage period.

There was an oral explanation with the applicant who presented their responses to the questions raised.

There was a trend vote in the CMDh with a majority in agreement with the position of the RMS to conclude the procedure positively.

The RMS will circulate a proposal for agreement after the CMDh meeting.

[*Post-meeting note: The procedure was referred to CHMP.*]

5.1.1.2. Ferric carboxymaltose Sandoz (NL/H/5359/001/DC) / NL

The RMS gave an overview of the Art. 29 referral on Ferric carboxymaltose Sandoz (NL/H/5359/001/DC). The referral concerned an Art. 10(1) application for a solution for injection or infusion.

A referral was triggered as the objecting CMS considered that comparability with the reference product was not sufficiently demonstrated as they are not within the determined limits of the reference product.

There was an oral explanation with the applicant who presented their responses to the questions raised.

There was a trend vote in the CMDh with a majority in agreement with the position of the RMS to conclude the procedure positively.

The RMS will circulate a proposal for agreement after the CMDh meeting.

[*Post-meeting note: Agreement could be reached after the meeting and the procedure was closed positively.*]

5.1.1.3. Tranylcypromin Aristo 10&20 mg Filmtabletten (AT/H/1123/001-002/MR) / AT

The RMS informed the CMDh about the conclusion of the Art. 29 referral on Tranylcypromin Aristo 10&20 mg Filmtabletten (AT/H/1123/001-002/MR). PSRPH has initially been raised by a CMS with regard to the Art. 10a application as bridging data to the literature (data supporting a biowaiver) were missing. Agreement could be reached before the CMDh meeting based on additional data submitted by the applicant. The procedure was closed positively.

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. Amfepramone (Art. 31)

Tabled for information.

5.2.3.2. Terlipressin (Art. 31)

Tabled for information.

5.2.3.3. Pholcodine (Art. 107i)

Tabled for information.

5.2.3.4. Topiramate (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 CMDh and the EMA agreed an update of the joint Questions and Answers for MAHs/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 updated to add the agreed limit for N-nitrosoduloxetine and a new Q&A (Q&A 21) has been added on the approach to control the presence of nitrosamines, while the acceptable intake (AI) is being established. The updated document has been published on the EMA website.

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.

5.4.2. Angiotensin-II-receptor antagonists (sartans) containing a tetrazole group (Art. 31) / EMA

The EMA informed the CMDh about requests from MAHs of sartan-containing medicinal products asking about a possible extension of condition B of the Art. 31 referral, in the light of the recent extension of the deadline for step 3 of the call for review of nitrosamines. The requests were triggered by more recent nitrosamine detection in combination products.

The EMA advised MAHs of CAPs (of sartans used in combination with another active substance) that have fulfilled step 2 (confirmatory testing in case of risk), but exceptionally not step 3 (subsequent variations) to submit a variation requesting an extension of the deadline for the Annex II Condition B to align with the recently extended timelines for step 3.

The CMDh agreed that for NAPs, in this exceptional case, an extension of the deadline for condition B for sartan-containing combination products, where nitrosamines (other than NDMA/NDEA) have been identified due to the combination with another active substance, can be accepted without the submission of a variation. This does not apply to sartan mono-component products.

6. Pharmacovigilance

6.1. Report from the October 2022 PRAC meeting

The EMA reported from the PRAC meeting held from 26-29 September 2022.

6.2. Periodic Safety Update Reports (PSUR)

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

6.2.1.1. Carboplatin - PSUSA/00000559/202201

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 carboplatin.

6.2.1.2. Dorzolamide - PSUSA/00003168/202202

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 dorzolamide.

In the framework of the PSUSA on dorzolamide, the PRAC noted that dorzolamide is also authorised in fixed dose combination products. The PRAC considered that the risks of tachycardia and hypertension and the need of nasolacrimal occlusion to limit absorption of

[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.

dorzolamide into the general circulation in patients with glaucoma would also be relevant to be included in products containing dorzolamide in fixed dose combinations. The same timelines as for the present PSUSA would apply in accordance with the CMDh guidance on implementing variations.

6.2.1.3. Gabapentin - PSUSA/00001499/202202

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 gabapentin.

6.2.1.4. Ketoprofen (topical use only) - PSUSA/00009205/202201

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 ketoprofen (topical use only).

6.2.1.5. Levothyroxine - PSUSA/00001860/202201

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 levothyroxine.

The CMDh agreed a minor change in the recommended wording of the PSUSA outcome for the PL with regard to the interaction with St. John's Wort. It was agreed not to mention examples of indications of St. John's Wort as these might vary in MSs.

A set of key elements for further communication on the risk of biotin interference with thyroid immunoassays, at the national level, if deemed necessary by the MS, as agreed by PRAC, was included in the CMDh position.

In the framework of the PSUSA on levothyroxine, PRAC noted inconsistent information related to contraindication of "*treatment in acute myocardial infarction, acute myocarditis, and acute pancarditis*" and the drug-drug interaction of "*levothyroxine with orlistat*", respectively included in section 4.3 and section 4.5 of the Summary of Product Characteristics and in Section 2 subsection "*Do not take [product]*" and subsection "*Other medicines and [product]"* of the package leaflet of levothyroxine containing medicinal products.

Therefore, PRAC recommends that the following is included in all product information of concerned products, if similar information has not already been included in the product information:

- A contraindication of "*treatment in acute myocardial infarction, acute myocarditis, and acute pancarditis*" should be added as follows:

Summary of product characteristics

Section 4.3:

Treatment with <Invented Name> must not be initiated in acute myocardial infarction, acute myocarditis, and acute pancarditis.

Package leaflet

Section 2:

Do not take <Invented Name>

If you have the following diseases or conditions:
o an acute myocardial infarction,
o acute inflammation of the heart muscle (myocarditis),
o acute inflammation of all the heart walls (pancarditis).

- A drug-drug interaction of levothyroxine with orlistat should be added as follows:

Summary of product characteristics

Section 4.5:

"*Hypothyroidism and / or reduced control of hypothyroidism may occur when levothyroxine and orlistat are taken at the same time. This could be due to a decreased absorption of levothyroxine"*.

Package leaflet

Section 2:

Other medicines and levothyroxine
- Orlistat–used to treat obesity

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

In the framework of the PSUSA on levothyroxine, the PRAC also noted that levothyroxine is also authorised in fixed dose combination products. The PRAC considered that the DDI between levothyroxine and PPIs, the DDI between levothyroxine and St John's wort, and biotin interference with laboratory tests in patients with hypothyroidism would also be relevant to be included in fixed dose combinations products containing levothyroxine as the discussed mechanisms could involve levothyroxine and fixed dose combination products containing levothyroxine. The same timelines as for the present PSUSA would apply in accordance with the CMDh guidance on implementing variations.

6.2.1.6. Mesalazine - PSUSA/00001990/202202

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 mesalazine.

6.2.1.7. Mesterolone - PSUSA/00010551/202201

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 mesterolone.

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 October 2023. The appointed lead member states will be published in the EURD list.

6.2.6. PSUSA Follow-up procedures

6.2.6.1. Iopromide (Ultravist) - NO/H/xxxx/WS/055 / NO

The CMDh endorsed the outcome of the WS variation for iopromide (Ultravist) (NO/H/xxxx/WS/055) as a follow-up of PSUSA/00001773/202006.

Based on the assessment of the submitted data, an update of the RMP is deemed warranted.

All MAHs of concerned medicinal products are requested to update their products in accordance with the recommendation.

The agreed CMDh recommendation will be published on the CMDh website (**Action: EMA**).

6.2.6.2. Iohexol (Omnipaque) - NO/H/xxxx/WS/054 / NO

The CMDh endorsed the outcome of the WS variation for iohexol (Omnipaque) (NO/H/xxxx/WS/054) as a follow-up of PSUSA/00001768/202006.

Based on the assessment of the submitted data, an update of the SmPC/PL is deemed warranted.

All MAHs of concerned medicinal products are requested to update their product information in accordance with the recommendation.

The agreed CMDh recommendation, including the PI wording to be implemented, will be published on the CMDh website (**Action: EMA**).

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.

[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.

6.4.2. 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. Bismuth subcitrate, metronidazole, tetracycline (Pylera) and product information warning for patients with Cockayne syndrome / DE

In October 2022, the PRAC gave advice to a Member State in relation to a type II variation for a metronidazole-containing medicinal product authorised for H. pylori eradication to update the product information to include a contraindication for patients with Cockayne syndrome (CS) and to delete the current warning (in section 4.4 of the SmPC).

It was agreed that the contraindication should be included (and the current warning in section 4.4. deleted) in the PI of all metronidazole-containing medicinal products (either as mono-component or in combination) approved **only** for H. pylori eradication (new text **underlined and in bold**, deleted text ~~strike through~~):

Summary of product characteristics:

4.3 Contraindications

- ***Patients with Cockayne syndrome (see section 4.8)***

4.4 Special warnings and precautions for use

(…) ~~*Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should therefore be used after careful benefit-risk assessment and only if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued.*~~

~~*Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole.*~~

(…)

4.8 Undesirable effects

Adverse reactions reported to occur with metronidazole

- ***Cases of severe irreversible hepatotoxicity/acute liver failure, including cases with fatal outcomes with very rapid onset after initiation of systemic use of metronidazole, have been reported in patients with Cockayne Syndrome (see section 4.3).***

Package leaflet:

Section 2

Do not take [product name]

- **If you have Cockayne syndrome (see Warnings and precautions)**

Warning and precautions

Talk to your doctor or pharmacist before taking [product name]

~~*Cases of severe liver toxicity/acute liver failure, including cases with a fatal outcome in patients with Cockayne syndrome have been reported with products containing metronidazole.*~~ ***Cases of severe irreversible liver toxicity/acute liver failure, including cases with fatal outcomes with very rapid onset after initiation of systemic use of metronidazole, have been reported in patients with Cockayne Syndrome.***

~~*If you are affected by Cockayne syndrome, your doctor should also monitor your liver function frequently while you are being treated with metronidazole and afterwards.*~~

MAHs of other metronidazole containing medicines (either as mono-component or in combination, except for external use on the skin) authorised for indications other than H. pylori eradication only (i.e. either with other indications than H. pylori eradication or with other indications in addition to H. pylori eradication) the current warning for patients with CS should be strengthened. The following amendment to section 4.4 of the SmPC was agreed (new text **underlined and in bold**, deleted text ~~strike through~~):

Hepatotoxicity in patients with Cockayne Syndrome

Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should ~~*therefore be used after careful benefit-risk assessment*~~ ***not be used unless the benefit is considered to outweigh the risk*** *and* ~~*only*~~ *if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued. Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole* ***(see section 4.8)****.*

Section 2 of the Package Leaflet (PL) does not need to be updated as it does not include reference to the required benefit-risk assessment of the prescribing doctor.

Sections 4.8 of the SmPC and 4 of the PL should be updated to reflect the new data and cases reported (new text **underlined and in bold**, deleted text ~~strike through~~):

SmPC section 4.8:

To be added under the table:

Cases of severe irreversible hepatotoxicity/acute liver failure, including cases with fatal outcomes with very rapid onset after initiation of systemic use of metronidazole, have been reported in patients with Cockayne Syndrome (see section 4.4).

PL section 4:

To be added under the listed terms with frequency "Not known (frequency cannot be estimated from the available data)":

Acute liver failure in patients with Cockayne Syndrome (see section 2 "Warnings and precautions")

Concerned MAHs are requested to submit type IB variations under C.I.z within 2 months of the date of publication of the CMDh press release.

It is generally not foreseen to provide translations via the CMDh. However, it might be that some member states will voluntarily provide translations on their websites.

The submission of worksharing procedures is recommended, where applicable.

Any submission of a variation with deviating wording needs to be substantiated with additional data and submitted as type II variation under C.I.4.

6.6.2. Topical NSAID-containing medicinal products and use during pregnancy / IE

Based on a nationally submitted variation for a topical medicinal product containing benzydamine to implement the FDA drug safety communication in relation to use during pregnancy, the CMDh discussed how such variations should be handled. In July 2022, following a PRAC advice to MSs, the CMDh published a recommendation for NSAID-containing medicinal products (for systemic use) and use during pregnancy. At the time, the CMDh communicated that MAHs of topical NSAID-containing medicinal products are asked to review this topic in the upcoming PSURs for their products.

The CMDh discussed and agreed that if MAHs of topical NSAID-containing medicinal products submit variations before the next PSUSA to update the wording in the SmPC in relation to use during pregnancy and include supporting data, these variations have to be assessed. A PRAC advice should be sought during the procedure to achieve a harmonised position. In case no supporting data is submitted and only reference to the FDA drug safety communication is made, the variations should be rejected due to missing data (in case the MAH will not submit these in a second round of the variation), as previously communicated. A review with the next PSUSA will take place in any case.

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

None

8. Miscellaneous

8.1. Report from the September and October CMDv meeting

The report from the September and October CMDv meeting was postponed to November.

8.2. October 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. Marketing Authorisation Applications for generics of Tecfidera (dimethyl fumarate)/ EC, EMA

The CMDh was made aware of the publication of the opinion of the advocate general in the joined cases C-438/21 P to C-440/21 P. The opinion is not binding. A final judgement is expected in about 6 months.

8.3.3. Request for CMDh advice for case of not marketed RefMP / Chair

The CMDh discussed a request for advice from a company that has several finalised and ongoing generic applications that have BE studies performed by the CRO Synchron. Due to the outcome of the Art. 31 referral new BE studies need to be conducted. However, the RefMP used in the dossier, or any other EU RefMP is not available on the market anymore. The company asked if a UK RefMP (authorised as informed consent application to the previous RefMP) could be used instead or if the BE study could be performed against another generic product authorised in the EU.

The CMDh agreed that both options are not possible. A UK RefMP in a BE study is only acceptable if no EU RefMP is available and the study has already been completed before the end of the transition period. BE studies against other generic products are not acceptable. In case the company is not able to find another EU RefMP of the same GMA to perform the BE study against, they will not have a possibility to lift the suspension of the Art. 31 referral for authorised medicinal products. Ongoing generic applications will have to be finalised negatively unless the company is able to provide evidence of bioavailability between test and reference product. A response will be sent (**Action: EMA**).

8.3.4. Request for submission of worksharing variation / Chair

MSs were asked to volunteer to become reference authority for the variations worksharing procedure. MSs were asked for feedback by the end of the week (**Action: MSs**).

8.3.5.

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

8.3.6.

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 November 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 11-13 October 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 restrictions applicable to this meeting	
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	
Katrin 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	
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	
Maija Cirkina	Member	Latvia	No interests declared	
Iveta Eglite	Alternate	Latvia	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Kristina Povilaitienė	Member	Lithuania	No interests declared	
Neringa Kalinauskaitė	Alternate	Lithuania	No interests declared	
Mylene Ferrier	Member	Luxembourg	No restrictions applicable to this meeting	
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	
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 Petrikova	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	
Jayne Crowe	Chair of GCP Inspectors Working Group/CMDh Working Party	Ireland	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
Aude L'Hirondel	EC Representative	European Commission	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.