Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh)
Minutes for the meeting on 26-27 January 2021

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

26 January 2021, 09:00 – 18:00, Teleconference
27 January 2021, 09:00 – 18:00, Teleconference

**Non-prescription medicinal products Task Force**
25 January 2021, 10:30 – 12:00, Teleconference
Chair: Martin Huber

**Working Group on ASMF Procedures** – *Cancelled*
26 January 2021, 18:00 - 19:30, Teleconference
Chair: Nienke Rodenhuis

**Health and safety information**
In accordance with the Agency’s health and safety policy, delegates were 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 and therefore not disclosed. Ongoing procedures discussed by the CMDh are considered confidential.

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

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

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

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

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

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

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

1.2. CMDh membership

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

1.3. Adoption of agenda

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

- Rivaroxaban Intas 2.5 mg, 10 mg, 15 mg, and 20 mg film-coated tablets (NL/H/4916/001-004/DC);
- Nordimet - Extension of indication (EMEA/H/C/003983/II/0016);
- Brexit related variations for change of batch control site before completion of method transfer;
- Interaction of flucloxacillin with warfarin, probenecid and methotrexate;
- Request for splitting of MRP/DCP due to merger;

1.4. Adoption of the minutes

The minutes of the December 2020 meeting, including the comments received and discussed at the meeting, were adopted and will be published on the CMDh website (Action: EMA).
1.5. **Introduction of the new EMA Executive Director / EMA**

The CMDh welcomed Emer Cooke as new EMA Executive Director.

2. **Organisational issues/Reports from other meetings**

2.1. **CMDh Working Groups/Working Parties/Task Force**

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

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

**Public PdARs for paed. studies acc. Art. 46**
The Paed. PARs on OctaplasLG (plasma protein, human) and Fibryga (human fibrinogen) were adopted by the CMDh and will be published on the CMDh website (Action: EMA).

**Art. 45 worksharing**
The WP has further agreed a new short priority list for a next wave of Art. 45 worksharing. The list will also be circulated to the CMDh for MSs to volunteer as rapporteur (Action: MSs).

MSs were reminded to check the status of the ongoing Art. 45 procedures and send feedback by 20 February (Action: MSs).

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

2.1.2. **Multilingual packaging Working Group / IE**

The WG chair gave an update to the CMDh on the work undertaken and the status of the ongoing pilot on multilingual labelling and the survey under preparation regarding MS experiences with the pilot.

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

The WP chair gave a report from the January WP meeting including feedback from the HaRP group. The CMDh agreed that the CMDh pharmacovigilance mailbox can be used for the circulation of the HaRP ARs. The HaRP flowchart is being drafted and will be presented to PhV WSP WP and CMDh WG once finalised. The WP Chair informed the group about the upcoming Pharmacovigilance session organised during the Medicines for Europe Conference. The CMDh adopted the SmAR for Lunivia (eszopiclon) and it will be published on the CMDh website (Action: EMA).

2.1.4. **Working Group on ASMF Procedures / WG Chair (NL) - CANCELLED**

The ASMF WG meeting was cancelled.
2.1.5. Non-Prescription Medicinal Products Task Force / TF Chair (DE)

The TF Chair reported from the January meeting.

The TF discussed a query regarding procedures with mixed legal status and its impact in the product information. The TF received feedback on the high-level conference on the future of medicines, in particular on a dedicated session on switch to non-prescription status, whether more harmonisation is possible. The TF discussed the outcome of the survey results on switches from non-prescription status to prescription-only.

TF discussed an OTC procedure and the RMS role in the applications when the active substance is not classified as OTC for the first time in the RMS and the current information included in the BPG. The TF consulted the CMDh on the need to update the BPG to further specify when an AR on the change of classification has to be provided. The CMDh agreed that the TF will further discuss the BPG and agree on a concrete proposal to CMDh.

The TF Chair reported about an ongoing mapping exercise by EDQM to best use the network existing resources. The TF members were invited to reflect and propose topics for the 2021 priorities.

2.1.6. GCP Inspectors Working Group/CMDh Working Party / WP Chair (IE)

The WP Chair reported from the meetings of the WP held on 7 and 13 January 2021. The WP discussed, among others, CROs of interest, the 2021 CROs Inspection Programme and the WHO-EMA-EU MSs Collaboration.

A call for interest will be circulated to CMDh for additional CMDh members to join the GCP Inspectors WG/CMDh WP (Action: EMA)

2.2. Brexit

2.2.1. General update / Chair, EC

The CMDh received an update on ongoing Brexit discussions.

The EC informed that a revision of the notice to stakeholders on the withdrawal of the UK was published on 25 January 2021, replacing the original notice (C(2020) 9264), published on 23 December 2020, the notice includes the full detail of the exemptions which may be granted.

The EU-UK Trade and Cooperation Agreement is provisionally applicable since 1 January 2021, after having been agreed by EU and UK negotiators on 24 December 2020.

2.2.2. CMDh guidance on Brexit / SE, Chair

The CMDh discussed an update of its practical guidance for procedures related to Brexit for medicinal products for human use approved via MRP/DCP in line with the revised EC Notice on Application of the Union’s pharmaceutical acquis in markets historically dependent on medicines supply from or through Great Britain after the end of the transition period; with the applicable protocol on Ireland/Northern Ireland, and the provisionally applicable EU-UK Trade and Cooperation Agreement since the 1 January 2021.

The CMDh thoroughly discussed the Q&A documents in particular Q30, Q31 and Q37.
[Post-meeting note: The updated Q&A document was adopted via written agreement following the January meeting and will be published on the CMDh website].

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

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

2.3. Meeting with Interested Parties – November 2020 / Chair

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

2.4. Joint CMDh/CMDv meeting / Chair

The CMDh adopted the minutes of the joint CMDh/CMDv meeting were adopted. CMDv will adopt the minutes in the next meeting.

[Post-meeting note: The CMDv adopted the joint CMDh/CMDv minutes following its January meeting. The minutes were considered final and adopted.]

2.5. Multi-Annual Workplan / Chair

The Chair presented the proposed priority areas for the 2025 MAWP. Some volunteers have been identified to work together in three drafting groups, expression of interest to be rapporteur are still open for the remaining topics (Action: MSs). Further discussion is expected in the presidency meeting.

2.6. Mutual Recognition and Decentralised Procedure monitoring / EMA

The CMDh annual statistics of 2020 were presented.

[Post-meeting note: The CMDh adopted the annual statistics following its January meeting. The statistics will be published on the CMDh website (Action: EMA).]

2.7. CMDh Summary of activities 2020 / EMA

The CMDh secretariat presented the CMDh summary of activities of 2020. MSs were invited to comment on the document until the February meeting (Action: MSs). The document will be tabled for adoption in February.

2.8. Instrument of Pre-accession Assistance (IPA) / EMA

The CMDh received a presentation on the EMA sponsored advance IPA training for candidate countries and potential candidates. A second training session is being organised in Q1 2021.
and will focus on case studies, based on real life situations and anonymised. CMDh members were invited to volunteer for preparing the various case-studies by 2nd February. (Action: MSs).

2.9. **EMA policy on the handling of competing interests of scientific committees’ members and experts / EMA**

The CMDh received a presentation on the revised EMA policy on the handling of competing of scientific committees’ members and experts.

2.10. **Portuguese Presidency meeting / PT**

PT informed the CMDh that the Portuguese Presidency meeting will be held remotely on 12-13 April 2021. The first draft agenda was presented. MSs were requested to send feedback and volunteer as topic leads. Further discussion on the agenda is expected next month.

3. **General items**

3.1. **CMDh guidance documents**

3.1.1. **Applicant’s response document in MRP and DCP for MAAs / FR**

Following the agreement in the December CMDh meeting that the eAF should be used as reference document and be updated with new information on manufacturing sites, as applicable, during the procedure or with the closing sequence, FR prepared an update of the CMDh guidance document on the Applicant’s response document in MRP and DCP for MAAs. It was noted that only those manufacturing sites listed in the eAF will be considered for the MA to be issued and that the addition of new manufacturing sites during the procedure is normally not foreseen, unless they are added in response to the LoQ.

The CMDh agreed the updated document. It 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. **Variation introducing new ADRs / DE**

Following the discussion in December on a case of parallel national variations to update the safety information of a product authorised nationally in several MSs, an overview of the responses from MSs on the variations was presented. The variation has been submitted in
most MSs and also most MSs have the corresponding indication authorised. DE will request additional data from the MAH on the ADR to better understand if these are related to the indication. As the majority of MSs already has the ADRs listed in section 4.8 of the SmPC, a variation WS procedure will not be requested in this case. The variations will be concluded at national level. Also a harmonisation of the indication will not be requested as there have been different positions of MSs on the indication in the past.

The CMDh was further informed that another safety variation has been submitted nationally in MSs for the same product. It was noted that the company has used variation worksharing in the past for quality variations. The lack of harmonisation of the indications might hinder the use of variation worksharing for non-quality variations.

The CMDh agreed to write to the MAH to inform them that the parallel national variation submissions have been brought to the attention of the CMDh and recommend to them to withdraw the national variations and use variation worksharing instead for any general variations (Action: EMA).

3.2.4. Extension of shelf-life/re-test period in variation applications using extrapolation / EMA, EE

The CMDh was informed about the QWP response on the CMDh question on extension of shelf-life of the finished product or retest period of the active substance via extrapolation of stability data.

3.3. GMP

None

3.4. GCP

None

3.5. COVID-19

3.5.1. General update / Chair, EMA

The CMDh chair informed the group about the ongoing discussion in the EU executive steering group/EMRN meetings.

3.5.2. 

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

3.5.3. Extension of GMP certificates / Chair

The CMDh discussed a query from a MAH about the acceptability of type IA variation to submit changes to the manufacturing site of the primary or secondary packing of the finished product, in case the GMP inspection was more than 3 years ago, but the GMP certificate could still be accepted until the end of 2021 according to the COVID-19 guidance published on the EMA website. The applicant had been requested to upgrade a related variation submitted as
type IA to type IB as the condition of the variation was not fulfilled (a satisfactory inspection had to be carried out in the last three years).

The CMDh agreed that such a variation can be accepted as type IA. The condition can be interpreted in the light of the current guidance under the pandemic situation.

### 3.6. Chlorobutanol as excipient / IE, NL

The feedback from MSs on products on their market with chlorobutanol as excipient was tabled for information. The feedback will be compiled and analysed until the February CMDh meeting (Action: IE, NL), where proposals for the next steps will be discussed.

### 3.7. Q&A on QP declaration / NO, EMA

The QWP chair updated the CMDh on an interim feedback following discussion in the QWP on the question raised by CMDh on the applicability of Q5 of the Q&As on QP declaration to intermediate manufacturers. QWP raised some concerns on the Q&A and asked for clarification of some aspects of the question.

The CMDh stressed that the Q&A as such is not up for discussion but only a possible extension of the Q&A to intermediate manufacturers. The CMDh agreed that the rapporteurs of the question to QWP should address the concerns raised by QWP and involve the CMDh in a response, as needed (Action: IT, NL, NO, PL). It was also agreed that some CMDh members should participate in the next QWP discussion on the question to provide input on the regulatory consequences.

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

### 3.9. Legal basis for allergen product / DE

The CMDh discussed the most appropriate legal basis for a new MAA submission for an allergen product. The product refers to an old national MA. The manufacturer and the applied manufacturing process are intended to remain identical to the authorised product. The applicant intends to submit the MAA under Art. 10(1). The case was pre-discussed in the CMDh drafting group on allergens. Some MSs were of the view that Art. 10(1) is not appropriate, and the application for the biological product should be submitted under Art. 10(4) instead.

However, in agreement with the EMA and the EC, the CMDh agreed that according to the current legislation Art. 10(4) can only be used if the conditions for Art. 10(1) are not met. As the manufacturer/manufacturing process between the product and the RefMP is identical in this case, the application should be submitted under Art. 10(1). Further discussions on this aspect are expected in the NtA Group.

It was further noted that Art. 10a is strongly discouraged for biological medicinal products and would not be a suitable legal basis in the present case.

The applicant will be requested to update the Clinical Overview Module 2.5 for the submission to reflect the latest available literature data as well as to explicitly clarify that there are no
changes in any parts of the manufacturing (including type and source of the raw materials) and controls compared to the authorised product.

4. **Generic/hybrid marketing authorisations**

4.1. **Reference to medicinal products authorised in UK in ongoing MAAs and variations / IE**

The CMDh discussed how to deal with new DCPs and worksharing variations that are cross-referring to UK marketing authorisations for product information alignment.

For variations, reference was made to the outcome of a discussion in the VRWP in the past, where it was concluded that to harmonise the PI with a RefMP, when the UK RefMP is no longer acceptable, while it is not possible to change the RefMP of the initial MA application, another RefMP from the same GMA might be referred to for the purposes of product information. However, in case this RefMP is not harmonised a type II variation C.I.2.b would be needed to align the PI with this RefMP. In case no other product from the same GMA is available, adaptation to a different product, not being the RefMP, might be possible by a type II variation C.I.4. Reference was also made to the CMDh Q&As on variations Q3.23.

In the absence of another reference product from the same GMA, or where the MAH does not wish to adapt to a different product as above, MAH are reminded of their legal obligation to keep their PI up to date. Often safety updates of the PI are linked to recommendations by PRAC or CMDh and can be implemented via type IA/IB variations since they are publicly available, agreed positions at EU level. Moreover, bibliographic reviews should be performed.

For new MAA, a European RefMP should be used, but in exceptional cases UK RefMPs may still be used (see Q34 of the CMDh practical guidance on Brexit). For ongoing generic MRP/DCPs with UK ERP, where there also are other authorisations in EEA within the same GMA, the CMDh agreed that the applicant can keep the UK ERP but may be asked to align the product information to the EEA GMA if needed. An update of the clinical overview will not be requested routinely.

DE, IE and SE will check the published Q&As on variations and Brexit to see if there is a need to provide further guidance (Action: DE, IE, SE).

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. **Septocaine/Septocaine forte (SE/H/0325/01-02/II/30) / SE**

The RMS gave an overview of the Art. 13 referral procedure for Septocaine/Septocaine forte (SE/H/0325/01-02/II/30).

QWP was consulted during the procedure.
Agreement could be reached based on the outcome of the QWP discussion. The procedure was closed positively on 19 January 2021.

5.1.2. List of questions

5.1.2.1.

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

5.1.3. Upcoming Art. 29/13 referrals

5.1.3.1.

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

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

5.2.1. Referral timetables

Tabled for information.

5.2.2. Started referral procedures at PRAC

None

5.2.3. Information on ongoing referral procedures

5.2.3.1. Ifosfamide (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 discussed and agreed an update of its practical guidance for MAHs of NAPs (including MRP/DCP) in relation to the Art. 5(3) referral on nitrosamines to clarify for which products the call for review is applicable (if a nitrosamine evaluation has already taken place during the assessment of the MAA the call for review does not apply) and to inform MAHs
what is expected for a newly identified nitrosamine risk after the assessment in the MAA or after the call for review is finalised. The submission details in step 2 have also been further clarified. MAHs are reminded that confirmatory testing has to be carried out on the finished product. The updated document will be published on the CMDh website (Action: EMA).

The EMA presented an update of the templates for the submission of step 1 and step 2 to reflect the outcome of the Art. 5(3) procedure. For the step 2 template (nitrosamine detected), tick boxes have been introduced to declare the content of the detected nitrosamine. The templates will be published on the CMDh website (Action: EMA).

5.4.1.1. MeNP detected in rifampicin containing medicinal products / IT

The CMDh agreed that national competent authorities will be contacting all marketing authorisation holders of rifampicin-containing medicines to request them to implement testing of the medicines for the presence of nitrosamines in the finished product before they are released onto the market.

This is a precautionary step to ensure patient safety while ongoing investigations on these medicines are being finalised. The request is in line with the Article 5(3) review concluded in 2020, which introduced measures for companies to take to limit the presence of nitrosamines in medicines. Regulatory authorities will carefully monitor the responses to this request and take appropriate action where necessary.

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;*

6. Pharmacovigilance

6.1. Report from the January 2020 PRAC meeting

The EMA reported from the PRAC meeting held from 11 to 14 January 2021.

6.2. Periodic Safety Update Reports (PSUR)

6.2.1. PRAC recommendations on PSUSAs for CMDh position¹

6.2.1.1. Clotiazepam - PSUSA/00000827/202005

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 clotiazepam.

6.2.1.2. Iodixanol - PSUSA/00001766/202004

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 iodixanol.

¹ Subject to adoption via written procedure in advance of the meeting. For discussion/ adoption at the plenary if comments are received during written procedure.
6.2.1.3. Iomeprol - PSUSA/00001769/202004

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 iomeprol.

6.2.1.4. Irinotecan (except for liposomal formulations) - PSUSA/00001783/202005

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 irinotecan (except for liposomal formulations).

In the framework of the PSUSA on irinotecan (except for liposomal formulations), the PRAC recommended a PSUFU procedure to further analyse the need to update the SmPC regarding a reduced starting dose for irinotecan in patients with reduced UGT1A1 activity and in order to adopt risk minimisation measures in line with the current scientific knowledge including in particular European guidelines in oncology, case reports, and literature data. The MAHs are invited to follow a PSUSU procedure within 3 months after the finalisation of this PSUSA to provide more data and a thorough discussion on several points to be resolved. The requested data should be mainly focussed on the therapeutic indications already approved in the European Union.

For Sun Pharmaceutical Industries Europe B.V. (SPIL) only:

- Review of the 61 cases related to the risk “Drug toxicity in patients with reduced UGT1A1 activity” received during the reporting interval, including information on the reported UGT1A1 polymorphism, the action taken with irinotecan, the case outcome, the dose of irinotecan administered the seriousness and the severity of the reported ADRs.

For all MAHs:

- A synthesis of the available literature data including:
  a. A quantification of the increased incidence of adverse drug reactions, especially neutropenia and diarrhoea, in patients with reduced UGT1A1 activity, homozygous and heterozygous carriers of UGT1A1*28 or UGT1A1*6, versus patients with normal UGT1A1 activity;
  b. A discussion of the impact of the dose of irinotecan administered on this increased incidence of adverse drug reaction;
  c. A discussion of the impact of a reduced irinotecan starting dose in patients with UGT1A1 reduced activity on the incidence of adverse drug reaction and on the efficacy in terms of response or survival endpoints.

The synthesis of the available literature data should focus on irinotecan therapeutic indications already approved in the European Union.

- In view of the conclusions of the above points, the MAHs should make a well-argued decision about:
  a. The extension of the recommendation to reduce irinotecan starting dose in patients with heterozygous variants UGT1A1*28 or *6.
  b. The extension of the recommendation to reduce irinotecan starting dose in patients with reduced UGT1A1 activity whatever the irinotecan initially intended dose.
c. The level of dose reduction for irinotecan starting dose in patients with reduced UGT1A1 activity.

- In addition, the MAHs should:
  a. Discuss the clinical utility of UGT1A1 genotyping before treatment considering the initially intended irinotecan dose for a potential adjustment of the irinotecan starting dose, adjustment of the biological and clinical monitoring. RNPGx recommendations (1), as well as ESMO consensus guidelines for the management of patients with metastatic colorectal cancer (2) should be discussed.
  b. Propose an update of sections 4.2, 4.4 and 5.1 of irinotecan EU SmPC regarding patients with reduced UGT1A1 activity, in agreement with the European guideline on SmPC, dated September 2009, or justify the non-update of these sections of irinotecan SmPC. Regarding section 5.1, the whole subsection regarding "Patients with Reduced UGT1A1 Activity" should be revised taking into account the discussions and analysis of literature data. In particular, the threshold of 150mg/m² and the statement that data from a meta-analysis indicate that individuals with Crigler-Najjar syndrome or those who are homozygous for the UGT1A1*28 allele (Gilbert's syndrome) are at increased risk of haematological toxicity following administration of irinotecan at moderate or high doses (>150 mg/m²).
  c. Discuss the need for a DHPC, considering GVP module XV that states a DHPC should be disseminated in case of change in the recommended dose due to safety reasons and considering that the new recommendations could affect a significant proportion of patients among the patients treated with irinotecan. An estimation of the number of patients potentially involved should be provided.


France will be the Lead Member State (LMS) for this PSUFU. The procedure number for this PSUFU procedure will be FR/H/PSUFU/00001783/202005.

6.2.1.5. Mifepristone - PSUSA/00002060/202005

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 mifepristone.

In the framework of the PSUSA on mifepristone, the PRAC considered that the risk of acute generalised exanthematous pustulosis (AGEP) would also be relevant to be included in products containing mifepristone / misoprostol in fixed dose combinations in light of the two relatively well-documented cases of AGEP published in association with mifepristone, with causality in both cases assessed as at least a reasonable possibility.

Therefore, upon the finalisation of PSUSA/00002060/202005, MAHs with products containing mifepristone / misoprostol in fixed dose combinations should update their respective product information with regard to AGEP. The following changes are recommended (new text underlined and in bold):
Summary of Product Characteristics

Section 4.4
A warning should be added as follows:

**Severe cutaneous adverse reactions, including toxic epidermal necrolysis and acute generalised exanthematous pustulosis, have been reported in association with mifepristone (see section 4.8). In patients who experience severe cutaneous adverse reactions, treatment with mifepristone should be immediately discontinued. Re-treatment with mifepristone is not recommended.**

Section 4.8

The following adverse reaction should be added under the SOC Skin and subcutaneous tissue disorders with a frequency unknown:

**Acute generalised exanthematous pustulosis**

Package Leaflet

Section 2
The following warning should be added under Warning and precautions:

**Serious skin reactions including toxic epidermal necrolysis and acute generalized exanthematous pustulosis have been reported in association with [product name] treatment. Stop using [product name] and seek medical attention immediately if you notice any of the symptoms described in section 4. If you get a serious skin reaction you should not use mifepristone again in the future.**

Section 4 Possible side effects
The following should be added to the list of serious side effects requiring medical attention:

- **Reddish patches on the trunk, the patches are target-like macules or circular, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (toxic epidermal necrolysis, frequency: rare).**

- **A red, scaly widespread rash with bumps under the skin and blisters accompanied by fever. The symptoms usually appear at the initiation of treatment (acute generalised exanthematous pustulosis, frequency: not known).**

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

6.2.1.6. Tamoxifen - PSUSA/00002846/202004

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 tamoxifen.

During the reporting interval, the FDA published new guidance for Industry on evaluating reproductive toxicity for oncology pharmaceuticals entitled 'Oncology Pharmaceuticals:
Reproductive Toxicity Testing and Labelling Recommendations’. This guidance also provided recommendations for product labelling on duration of contraception following cessation of therapy to minimise the potential risk to a developing embryo or foetus. The recommended duration of contraception after cessation of a genotoxic pharmaceutical for female patients is 5 x half-life + 6 months.

Similarly, in the EU, the Safety Working Party (SWP) published a response document on questions from CMDh regarding genotoxicity and recommendations for contraception. SWP advised that for clinical trial applications, the recommended duration of contraception in female subjects participating in clinical trials should be until the end of relevant systemic exposure incl. potential genotoxic metabolites (i.e. five half-lives after the last dose) plus 6 months, which corresponds to ~9 months for tamoxifen, considering the half-life of the active metabolite, N-desmethyltamoxifen. The WP also advised that section 4.6 of the SmPC should reflect these recommendations for duration of contraception for women of childbearing potential. SWP advised that these recommendations should apply to any genotoxic active substance regardless of its therapeutic indication.

On the basis of the newly published regulatory recommendations and to ensure both the introduction of a consistent recommendation within the product information for both healthcare professionals and patients across the EU, and in order to minimise the potential risk to a developing embryo or foetus, all MAHs are recommended to update the product information for tamoxifen as outlined below:

**Summary of Product Characteristics**

- **Section 4.6**

  The warning should be amended as follows:

  "Pregnancy"

  .....  

  Women should be advised not to become pregnant whilst taking <medicine> and for nine months following the cessation of therapy and should use barrier or other non-hormonal contraceptive methods if sexually active. Premenopausal patients must be carefully examined before treatment to exclude pregnancy. Women should be appraised of the potential risks to the foetus, should they become pregnant whilst taking <medicine> or within two nine months of cessation of therapy.

**Package Leaflet**

- **Section 2**

  "Pregnancy and breast-feeding”

  You should not become pregnant while taking <medicine> and for nine months after you stop taking it. Please see your doctor for contraception advice.

**6.2.1.7. Tramadol - PSUSA/00003002/202005**

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 tramadol.
In the framework of the PSUSA on tramadol, the PRAC considered that the risks of adrenal insufficiency, sleep-related breathing disorders, including central sleep apnoea (CSA) and hiccups, for which recommendations have been proposed in the PSUSA, would also be relevant to be included in products containing tramadol/paracetamol and tramadol/dexketoprofen in fixed dose combinations in light of

- Adrenal insufficiency: data from non-clinical and clinical studies;
- Sleep-related breathing disorders, particularly central sleep apnoea (CSA): data from spontaneous reports and relevant literature;
- Hiccups: data from relevant spontaneous reports and literature including cases with positive dechallenge.

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

PRAC noted that inconsistent information related to risk minimisation measures to mitigate the risk of medication errors leading to unintentional overdose is included in section(s) 4.2, 4.4 of the Summary of Product Characteristics, in section 2 of the Package Leaflet and on the labelling of liquid formulations of tramadol containing medicinal products.

Therefore, PRAC recommends that the following measures should be duly considered by NCAs of EU countries where both presentations (dosing pump and dropper) of tramadol liquid formulations are marketed:

1. Additional warnings in SmPC/PIL (dosing pumps only) to avoid any ambiguity between the pump presses/drops and the amount of tramadol in mg (e.g. SmPC sections 4.2, 4.4 and PL section 2);
2. Improvement of the bottle labelling / outer packaging;
3. Inclusion of a prominent warning in the labelling with the dosage equivalence;
4. Pictograms, as well as other mentions or layout considerations which would improve the labelling should be discussed (e.g. inclusion of a pictogram of a dosing pump system/dropper applicator and further clarification, below the pictogram, that the presentation refers to the dosing pump/dropper applicator; removing the picture of the drop form from dosing pump label; colour codes to better distinguish both forms...);
5. Separation of marketing authorizations (MA) and PILs, in accordance with national regulations, are encouraged;
6. Dissemination of a DHPC, if deemed necessary.

6.2.1.8. Xylometazoline - PSUSA/00003134/202005

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 xylometazoline.

6.2.2. Information on PRAC recommendations for PSUSAs for maintenance

6.2.2.1. Amfepramone - PSUSA/00000138/202006

The CMDh was informed about the PRAC discussions on the PSUSA for amfepramone.
6.2.2.2. Mometasone - PSUSA/00002085/202005

MAHs which have an RMP in place should address the following issues in the next RMP update: Data supporting the removal of the elderly population as missing information in the EU RMP for mometasone furoate DPI have been presented and is agreed to. Furthermore, the important identified or potential risks of all mometasone formulations (orally inhaled, nasal and topical) should be reviewed and risks where there are no additional PhV activities or aRMMs in place considered for removal. To conclude, the safety concerns of the RMP should be updated to align with the GVP Module 5 rev 2. MAH(s) which have an RMP in place should address this issue in the next RMP update to be submitted within 6 months.

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

6.2.3.1. Fentanyl (transmucosal route of administration) - EMEA/H/C/PSUSA/00001369/202004

In the framework of the PSUSA on fentanyl (transmucosal route of administration) and in light of the concerns raised regarding off-label use, misuse and accidental exposure, the MAHs are requested to perform a thorough review of the current labelling (within 2 months) to ensure that it is appropriate to mitigate these risks. In particular, the labelling should include the following statements or their equivalent:


2. "Use only as prescribed. Accidental use can cause serious harm and be fatal." on the outer packaging.

   In addition, the labelling of nasal formulations of fentanyl containing products (PECFENT and INSTANYL) should include the following statements or their equivalent:

3. "Accidental use can be fatal." on small immediate packaging units.

In cases where need for improvements has been identified, the MAHs should propose a revision of the EU labelling via appropriate variation.

MAH of nationally authorised products should submit their review to the relevant national competent authorities as part of a PSUFU procedure for which France will be the LMS, and MAH of centrally authorised products should submit their review to the EMA within a LEG procedure in line with the current submission requirements.

The procedure number for this PSUFU procedure will FR/H/PSUFU/00001369/202004.

The PRAC noted inconsistent information related to the contra-indication (CI) between sodium oxybate and opioids included in section 4.3 and section 4.5 of the Summary of Product Characteristics and in sections 2 of the Package Leaflet of all (except Instanyl) fentanyl containing products for transmucosal route of administration.

Therefore, the Rapporteur recommends that the following mentions are included in all product information of concerned products (if not already adequately reflected):

SmPC

- Section 4.3

Patients being treated with medicinal products containing sodium oxybate.

- Section 4.5
Concomitant use of medicinal products containing sodium oxybate and fentanyl is contraindicated (see section 4.3). The treatment of sodium oxybate should be discontinued before start of treatment with <product>.

Affected MAHs are therefore requested to submit relevant variations to competent authorities within 2 months.

All MAHs (unless already implemented) are asked to submit an immediate variation to implement the list of key messages adopted by PRAC for Instanyl (Variation EMEA/H/C/000959/II/0052) in educational materials of their products with an update of the RMP.

6.2.3.2. Topotecan - EMEA/H/C/PSUSA/00002997/202005

MAH(s) which have an RMP in place should update the list of safety concerns in the next RMP update to be submitted within 6 months.

The list of safety concerns should be updated as follows:

In accordance with GVP Module V rev 2 affecting RMP, the important identified risks:

- Risk in patients with performance score > 1,
- Interactions with BCRP and P-gp inhibitors, cyclosporin A and platinum agents,

the important potential risk:

- Pregnancy (exposure in utero)
- and the following information:
- Use in subjects with severe renal impairment
- Use in subjects with hepatic impairment

should be removed from the list of safety concerns in the RMP.

In addition, as per the previous PRAC Procedure: EMEA/H/C/PSUSA/00002997/201505 dated 14 Jan 2016 for the PSUR covering the reporting interval from 29 May 2012 to 28 May 2015 the following important identified and potential risks were proposed to be removed from the summary of safety concerns from RMP:

- chemotherapy-induced diarrhoea
- bone marrow suppression
- neutropenic colitis
- gastrointestinal symptoms
- infection
- interstitial lung disease
- overdose.

These changes should be also implemented in the next RMP update to be submitted within 6 months.

The final version of the list of safety concerns proposed for the RMP update is as follows:
### Important Identified Risks
- Chemotherapy induced diarrhoea
- Bone marrow suppression
- Neutropenic colitis
- Gastrointestinal symptoms
- Infection
- Interstitial lung disease
- Risk in patients with performance score > 1
- Interactions with BCRP and P-gp inhibitors, cyclosporin A and platinum agents

### Important Potential Risks
- Pregnancy (risk of exposure in utero)
- Overdose

### Missing Information
- Use in subjects with severe renal impairment
- Use in subjects with hepatic impairment

#### 6.2.4. Outcomes of informal PSUR work sharing procedures / Chair

See 2.1.3

#### 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 in January 2022. The appointed lead member states will be published in the EURD list.

#### 6.2.6. PSUSA Follow-up procedures

6.2.6.1. Methotrexate (DE/H/PSUFU/00002014/201910) / DE

DE presented the ongoing PSUFU procedure on methotrexate including the PRAC advice. The CMDh agreed with the request for supplementary information.

The CMDh will reflect on the need to be involved at this step of the procedure in a future update of the PSUFU guidance (Action: NL).

#### 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.

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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. **Optimising of PSUSA procedural handling / EMA**

The CMDh discussed if there is a need to receive an email for information for each PSUSA procedure that ended with the outcome "maintenance" at PRAC or if it is sufficient to receive the information via the PSUSA PRAC/CMDh interaction table (excel).

Some MSs stated that they do not need a separate email. Others noted that the email is useful in case information in section 6 ('Other considerations') is mentioned.

The secretariat will discuss with the EMA if in such cases the email can still be sent (Action: EMA).

The CMDh also discussed the need to maintain the PSUR AR template published on the CMDh website. It was noted that the template is used in PSUR WS procedures for new products that are not yet on the EURD list and should be kept on the CMDh website. It should be reviewed for a need for update. Call for a new rapporteur of the template will be sent (Action: EMA).

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

7.1. **Ceftazidime PharmSol 500 mg/1g/2g Powder for Solution for Injection/Infusion (DE/H/6038/001-003/DC) / DE**

DE informed the CMDh about the break-out session held for Ceftazidime PharmSol 500 mg/1g/2g Powder for Solution for Injection/Infusion (DE/H/6038/001-003/DC). Agreement could be reached by day 210 based on additional information submitted by the applicant.

7.2. **Sereflo Ciphaler (fluticasone/salmeterol) (NL/H/4699/001-002/DC) / NL**

NL informed the CMDh about the break-out session held for Sereflo Ciphaler (fluticasone/salmeterol) (NL/H/4699/001-002/DC). Major objections have been raised on the efficacy of the lowest dose and regarding the data validity of the safety study. The applicant could address all outstanding issues by day 210 and the application was finalised positively.

7.3. **Midodrine HCl Brancaster 10 mg tabletten (NL/H/3123/003/DC) / NL**

NL informed the CMDh about the break-out session held for Midodrine HCl Brancaster 10 mg tabletten (NL/H/3123/003/DC). Major objections have been raised on the validity of the
biowaiver. Agreement could be reached by day 210 based on additional information submitted by the applicant.

7.4. **Botox 50, 100 & 200 Allergan Units Powder for solution for injection (IE/H/xxxx/WS/110) / IE**

IE informed the CMDh about the break-out session held for Botox 50, 100 & 200 Allergan Units Powder for solution for injection (IE/H/xxxx/WS/110). Major objections have been raised in relation to the proposed new indication. Agreement could be reached by accepting the proposal by the objecting CMS for the indication and mentioning the study results in section 5.1 of the SmPC.

7.5. **Linagliptin Intas 5 mg film-coated tablets (NL/H/4958/001/DC) / NL**

NL informed the CMDh about the break-out session held for Linagliptin Intas 5 mg film-coated tablets (NL/H/4958/001/DC). The applicant’s response was awaited at the time of the meeting.

8. **Miscellaneous**

8.1. **Report from the January CMDv meeting**

The CMDv secretariat reported from the January CMDv meeting.

8.2. **January 2021 CMDh Press Release**

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

8.3. **A.O.B.**

8.3.1. **Rivaroxaban Intas 2.5 mg, 10 mg, 15 mg, and 20 mg film-coated tablets (NL/H/4916/001-004/DC) / NL**

NL informed the CMDh about the break-out session held for Rivaroxaban Intas 2.5 mg, 10 mg, 15 mg, and 20 mg film-coated tablets (NL/H/4916/001-004/DC). The applicant’s response was awaited at the time of the meeting.

8.3.2. **Nordimet - Extension of indication (EMEA/H/C/003983/II/0016) / EMA**

The CMDh was informed that the CHMP issued a positive opinion for an extension of indication (EMEA/H/C/003983/II/0016) in the treatment of Crohn’s disease (CD) for Nordimet prefilled pens for subcutaneous use. Nordimet has been authorised as a hybrid medicinal product. The reference medicinal product does have an indication in CD. The submitted extension of indication application was based on literature data.

CHMP considered that the literature data submitted by the MAH only supported a narrower indication for Nordimet than some other medicinal products containing methotrexate authorised for the use in the CD indication, as a consequence of the legal basis of the application.
CMDh stated that this evaluation will not have an impact on nationally authorised products that are already approved in the broader indication.

8.3.3. Brexit related variations for change of batch control site before completion of method transfer / DK

The CMDh discussed variation applications in the context of Brexit where the applicant applies for EU batch control sites before the method transfer has been completed. As the method transfer is a condition for the type IA variation that is not fulfilled, applicants apply for type IB variations with a statement not to use the site before method transfer is complete. The CMDh discussed if the approach is acceptable or if the type IB variations should be refused or kept in clock-stop until the method transfer is completed.

Some MSs could agree that, in this exceptional case and only for changes of batch control sites from UK to the EU/EEA, the method transfer can be considered as a GMP issue and the variations can be approved with a commitment that the MAH will not perform batch control from that site before the method transfer is completed.

Some MSs stated that they might not be able to follow this approach and will refuse the variations, considering that sufficient notice has been given to MAHs to complete the transfer in time.

No consensus could be reached.

8.3.4. Interaction of flucloxacillin with warfarin, probenecid and methotrexate / PT

Following the discussion on the harmonisation of the PI of flucloxacillin containing medicinal products with regard to the interaction of flucloxacillin with warfarin, probenecid and methotrexate in December, the CMDh was informed that several MAHs for products authorised under Art. 8(3) have been identified in the Art. 57 database.

The CMDh agreed, in order to avoid parallel national variations, that the MAHs will be contacted and asked to submit the relevant variations as worksharing and ideally form a consortium for the update (Action: PT).

8.3.5. Request for splitting of MRP/DCP due to merger / FR

The CMDh was informed about requests of a MAH for splitting of procedures as a condition to a merger as agreed with the EC. As no information on the merger and request for splitting has yet been received by the CMDh from the EC, MSs were asked to await confirmation from the EC before agreeing to the splitting. A question to the EC has already been sent.

9. Other topics and dates for next meeting

9.1. Draft meeting schedule and draft time schedule for referrals

The meeting schedule for February 2021 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](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 26-27 January 2021 meeting

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
<th>Member State or affiliation</th>
<th>Outcome restriction following evaluation of e-DoI</th>
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<td>Priscilla Schoondermark</td>
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<td>Elisa Sulleiro</td>
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<td>Spain</td>
<td>No participation in final deliberations and voting on: 6.2.1.6 Tamoxifen - PSUSA/00002846/202004</td>
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<tr>
<td>Dino Soumpasis</td>
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<tr>
<td>Martin Huber</td>
<td>Chair of Non-Prescription MPs TF</td>
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<td>Maria Luisa Casini</td>
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</tr>
<tr>
<td>Jayne Crowe</td>
<td>Chair of GCP Inspectors Working Group/CMDh Working Party</td>
<td>Ireland</td>
<td>No interests declared</td>
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</table>

Representatives from the European Commission attended the meeting
Ad hoc experts* attended the meeting
Meeting run with support from relevant EMA staff
*Experts were evaluated against the product(s) they have been invited to talk about