13 September 2022
EMA/CMDh/771810/2022
Human Medicines Division

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

Minutes for the meeting on 19-20 July 2022

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

Health and safety information

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

Disclaimers

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

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

Note on access to documents

Some documents mentioned in this set of minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/729522/2016).

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1. Introduction

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

The Chair opened the meeting by welcoming all participants. Due to the current coronavirus (COVID-19) pandemic, and the associated EMA Business Continuity Plan (BCP), the meeting was held 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 on the topics in the agenda of the meeting, the Committee Secretariat announced the restricted involvement of some Committee members, alternates and experts for concerned agenda topics.

Participants were asked to declare any changes, omissions, or errors to their declared interests concerning the matters for discussion. No new or additional competing interests were declared. Restrictions applicable to this meeting are captured in the list of participants included in the minutes. Due to restricted involvement, the Chair was replaced by the Vice-Chair for the discussion on topic(s) 6.2.1.3. and 6.2.3.1.

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

The Chair announced the start of Czechia presidency of the Council of the European Union (EU).

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:

- Role of food supplement data in the context of a well-established use application (Art. 10a)
- Genotoxicity and contraception
- Paracetamol Bluefish, 500 mg, tablet (PT/H/2644/001/DC)
- CMDh Guidance on repeat-use procedure
- PSUSA Follow-up procedures

1.4. Adoption of the minutes

The minutes of the June 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)

The CMDh has agreed an update of its BPG on Article 45 and 46 – Paediatric WS procedures. With the update it was agreed that the appointed Art. 46 rapporteur will directly request the submission of the relevant data from the MAH (this was previously done by the EMA).

The relevant template emails have been included in the BPG as an annex. It has also been clarified that in case the need of new supporting data has been recommended during the worksharing procedure, the submission date of a type II variation will be discussed with the Rapporteur before the procedure is finalised. The updated document will be published on the CMDh website (**Action: EMA**)

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

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

Art. 46 worksharing
Rapporteurs were appointed for the Art. 46 submissions.

2.1.2. Joint GCP IWG/CMDh Working Party / IE

The WP chair reported from the July 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 to be held f2f on 12 October in Copenhagen and BE online training.

A proposal for a Q&A for industry explaining the requirements for monitoring of BE CTs was presented and adopted by CMDh. The Q&A needs further discussion in other groups and will be published on the EMA website.

2.2. Meeting with Interested Parties / Chair

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

2.3. Czech Presidency meeting / CZ

The draft agenda for the CZ presidency meeting to be held on 18-19 October was presented. There will be a joint session with PRAC.

2.4. Multi-Annual Workplan / Chair

Following the January 2022 CMDh meeting, the CMDh published its MAWP to 2025 for a 2-month public consultation. Following that period, the CMDh thoroughly assessed the comments received and considered that only minor updates to the MAWP were needed. A document summarising the main comments and the CMDh feedback was discussed and adopted and will be published on the CMDh website alongside the updated MAWP. In addition, all received comments will be published for transparency.

The CMDh agreed that currently no additional meeting will be necessary with IPs. The next meeting is planned on the margins of the November CMDh plenary.

2.5. Mutual Recognition and Decentralised Procedure monitoring

The EMA presented the statistics for MRP/DCP in the first semester of 2022. The statistics were adopted by the CMDh and will be published on the CMDh website (**Action: EMA**).

2.6. EMA records management system – update on Sharepoint migration / EMA

The CMDh received a presentation on the future migration of the EMA records management system to SharePoint. The CMDh members were encouraged to join any of the training sessions available in the EU NTC network.

The CMDh will further discuss how to adapt the current working practices, once the migration and training on SharePoint is completed.

2.7. CMDh Drafting Group on Allergens / DE, Chair

The CMDh Chair gave feedback from the meeting of the CMDh Drafting Group on Allergens held in June. The group discussed the status of their previously submitted proposal to the EC to amend Directive 2001/83/EC, Annex I, Part III. The proposal included the documentation that should be submitted in case of products for allergen immunotherapy, in vivo diagnosis and in case of NPP.

The DG will draft a questionnaire that will be sent to MSs regarding the status of the implementation of the recommendations provided in the CMDh document on common regulatory approaches for allergen products.

2.8. HMA/EMA tactical group on resourcing / Chair

The CMDh Chair gave a report from the meeting of the HMA/EMA tactical group on resourcing held on 16 June 2022.

The EMA presented the Network Capacity Project to CMDh. This is a joint EMA/CHMP/PRAC initiative to understand the root causes of the network capacity issues and put forward recommendations to HMA/EMA senior management that could be implementable without need for legislative changes.

2.9.

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

3. General items

3.1. CMDh guidance documents

3.1.1. EMA/CMDh explanatory notes on variation application form / NL

Following the update of the variation application form in 2021, the EMA/CMDh explanatory notes have been updated to give more information on the new sections regarding medical devices and sections of the product information that have previously been harmonised. Following a query from a MAH, it was noticed that the information currently included in the explanatory notes can be misleading/misunderstood.

The CMDh therefore agreed an update of the document to further specify which previously harmonised sections of the product information need to be declared by the applicant in the application form. The purpose of including this information is to ensure that previously agreed harmonisation of the product information is maintained.

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

3.1.2. Recommendations on informed consent applications in MRP/DCP / DK

The CMDh has agreed an update of its guidance document "Recommendations on Informed Consent Applications in MRP and DCP". The document has been updated to make it more reader friendly. Recent CMDh agreements have been included in the document. A new section on maintenance of the dossier following granting of the informed consent marketing authorisation has been added.

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

3.1.3. Information for similarity assessment to orphan medicinal products / DE

In order to reduce the burden on regulators without increasing the workload on applicants too much, the CMDh discussed a proposal for applicants to provide the information on approved orphan drugs and the applicant's position on similarity of their product with already authorised orphan products directly in the similarity AR template for submission in a DCP.

The CMDh agreed that the relevant template should be made available on the CMDh website for the applicants to be completed. The completed template should then be submitted in word and PDF format. The RMS could reduce the text proposed by the applicant in the word document to reduce the length and extensiveness of the summary of the response in the template.

Several guidance documents will need to be updated to reflect the new approach and to give sufficient instructions for applicants. The similarity AR report template also would need to include instructions which parts are for the applicant and which parts are for the RMS to be filled in. DE and NL, in consultation with the rapporteurs, will review the relevant guidance

documents and will propose updates, as needed, for further discussion in September (**Action: DE, NL**).

3.1.4. RMS Validation Checklist for Human Medicinal Products in DCP / DK

The CMDh agreed an update of its RMS validation checklist in DCP. Information on the documents to be provided for the risk evaluation on potential presence of nitrosamines has been included in the list as a non-validation issue (i.e. the RMS can start the procedure although the issues still have not been solved on Day 0). It has further been agreed that non-validation issues need to be rectified by the applicant by day 30 rather than day 50. A corresponding update of the CMDh Procedural Advice on Validation of MRP/RUP/DCP and the CMS validation checklist in DCP have been agreed.

The updated 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.

A request from a MAH, who struggled to find a reference authority for their worksharing variation, could be addressed among the concerned MSs before the meeting.

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

None

3.3. GMP

None

3.4. GCP

None

3.5. Legal basis for enantiomer claiming to be the same active substance as the racemate / SE

The CMDh discussed the most appropriate legal basis for an enantiomer of a well-established substance following a national request for scientific/regulatory advice. The enantiomer has not been authorised before in the EU but has been authorised outside the EU.

According to the reflection paper on the chemical structure and properties criteria to be considered for the evaluation of new active substance (NAS) status of chemical substances (EMA/CHMP/QWP/104223/2015), the enantiomer and the racemic mixture would be considered the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.

The CMDh agreed that an Article 10(3) application for the enantiomer making reference to racemate, containing a justification that the two substances are to be considered the same, could be validated. During the procedure, it would be assessed whether the two substances can be considered the same and, if not, the application would be rejected, unless the differences are not considered significant and well documented, see below.

If the applicant claims that the enantiomer has a better safety (and/or efficacy) profile, it could lead to the conclusion that the two substances differ significantly (if the criteria in the EMA guideline are fulfilled). Therefore it would not be possible to use the racemic mixture as reference medicinal product. In such scenario, an Art. 8(3) application should be considered instead, with possible (but not automatic) NAS status.

If the claims do not fulfil the EMA criteria "differ significantly", they may be accepted in the SmPC of a hybrid application, if sufficiently documented.

During the scientific advice, the NCA will also provide advice on the data requirements for such an application.

3.6. European Pharmacopeia monographs on Heparin sodium and Heparin calcium / Chair

The CMDh noted a letter from EDQM asking for the CMDh opinion on a proposed lowering of the limit for residual protein from 0.5% to 0.1% in monographs on unfractionated heparin (Heparin sodium (0333) and Heparin calcium (0332)) which are currently published for public consultation. The CMDh noted that the same question has also been addressed to BWP and will get in contact with the WP in order to send a joint response (**Action: EMA**).

The chair will further clarify with EDQM the scope of the CMDh feedback.

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

The EMA gave an update to the CMDh on the DARWIN EU project and the use of real-world evidence.

CMDh members were asked to volunteer for a group functioning as liaison between CMDh and DARWIN EU/TDA-DAT team (**Action: MSs**).

[*Post-meeting note: Glenn Lastennet (FR) volunteered to be part of the group*.]

MSs were also asked to continue sending study requests (**Action: MSs**).

3.8. Medicinal products containing calcidiol monohydrate (calcifediol)/ DE

Before the meeting, MSs were asked to provide information on the use of a conversion factor between calcifediol and vitamin D_3. All MSs that replied (20/30) informed that the products on their markets do not include a conversion factor (anymore). Only in BE a product with a conversion factor is authorised. The conversion factor that is used there is the one formerly specified by EFSA.

3.9.

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

3.10. Medical device regulation / Chair, DE, EMA

Following receipt of a question from a MAH, the CMDh agreed to correct the CMDh February 2022 minutes to clarify that transdermal patches **(using passive diffusion)** do not fall under the second subparagraphs of Article 1(8) or (9) of the MDR and therefore do not need to comply with Section 3.2., point 12, of Annex I of Directive 2001/83/EC, as amended by Article 117 MDR.

The clarification to the February 2022 minutes has been added to avoid confusion and contradiction with the MDCG guidance.

3.11.

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

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

The EMA informed the CMDh about the revised go-live scope of the DADI variations form.

In October 2022, the DADI human variations form supporting CAPs only will go live. The second release, supporting all types of EU variation procedures (CAPs and NAPs) will follow in March 2023.

It was clarified that for mixed CAP/NAP variation worksharing procedures the submission will continue to follow the old format until DADI supports all procedures. Guidance on such cases will be provided. The EMA is also looking into the issue that for MRP/DCP products variations may be submitted before a national MA is granted (though after the end of the EU phase). This should be solved before the go-live date for NAPs.

Further information will be provided before the go-live for NAPs.

4. Generic/hybrid marketing authorisations

4.1. Acceptability of hybrid application with reference to pro-drug / SE

Based on a recent request for a hybrid application for a modified release product with the pro-drug as reference medicinal product, which was given new active substance (NAS) status at the time of authorisation, the CMDh discussed if a claim for NAS could be re-assessed in the context of a hybrid application. It was noted that the data exclusivity period of the RefMP has elapsed and that new scientific information for the NAS assessment might be available.

There was a majority that considered that such an application could be submitted and validated under Art. 10(3), if a justification is included in the application why both substances should be considered the same. The justification would then be assessed during the

procedure. However, also several MSs raised concerns that they could not validate such an application as the previous decision to grant NAS status to the pro-drug should be respected.

4.2. Draft ibuprofen product-specific bioequivalence guidance / DE

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

5. Referrals

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

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

None

5.1.2. List of questions

None

5.1.3. Upcoming referral procedures

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. Amfepramone (Art. 31)

Tabled for information.

5.2.3.2. Terlipressin (Art. 31)

Tabled for information.

5.2.4. PRAC recommendations for CMDh position

None

5.3. Outcome of referrals to CHMP

None

5.4. Other topics related to referrals

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

The CMDh received a report from the NIOG meeting.

The CMDh agreed an update of Q1.9 of the CMDh practical guidance on nitrosamines to give information that in specific cases, it may be possible to correct a former step 1 outcome from "risk" to "no risk" by using the "Step 2 no nitrosamine detected response template". This template has been updated and now contains a tick box for such cases. The possibility to amend the step 1 outcome may only be used in cases where data was missing at the March 2020 deadline and is now available.

In case of necessary changes from a former "no risk" step 1 outcome to a "risk" due to new available data or an update of the EMA Q&As, no change of the step 1 outcome is needed. Instead, the process under step 2/3 has to be followed.

The Q&As 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 have been updated accordingly.

The CMDh practical guidance and the Q&As have also been updated to reflect the agreement about the extension of the step 3 deadline.

5.4.1.1.

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

5.4.1.2.

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

5.4.1.3.

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

5.4.1.4.

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

5.4.1.5.

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

5.4.1.6.

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

5.4.1.7.

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

5.4.1.8.

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

6. Pharmacovigilance

6.1. Report from the July 2022 PRAC meeting

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

6.2. Periodic Safety Update Reports (PSUR)

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

6.2.1.1. Chlormadinone acetate / ethinylestradiol - PSUSA/00000679/202111

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 chlormadinone acetate / ethinylestradiol.

In the framework of the PSUSA on chlormadinone acetate / ethinylestradiol, the PRAC noted that ethinylestradiol is also authorised as a single agent or in fixed dose combination products. The PRAC considered that the risk of elevated liver enzymes would also be relevant to be included in products containing ethinylestradiol as a single agent or in fixed dose combinations as the risk of elevated liver enzymes is associated with concomitant use of ethinylestradiol and sofosbuvir/velpatasvir/voxilaprevir. The same timelines as for the present PSUSA would apply in accordance with the CMDh guidance on implementing variations.

6.2.1.2. Donepezil - PSUSA/00001160/202111

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 donepezil.

[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. Hydromorphone - PSUSA/00001686/202111

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 hydromorphone.

6.2.1.4. Tapentadol - PSUSA/00002849/202111

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 tapentadol.

6.2.2. Information on PRAC recommendations for PSUSAs for maintenance

None

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

6.2.3.1. Sufentanil - PSUSA/00001160/202111

The PRAC noted that inconsistent information related to

- opioid induced hyperalgesia (SmPC, section 4.4 and PL, section 2)
- sleep-related breathing disorders (SmPC, section 4.4 and PL, section 2)
- opioid use disorder and tolerance (SmPC, section 4.4 and PL, section 2)
- gastrointestinal motility and spasm of sphincter of Oddi
- interaction with gabapentinoids (gabapentin and pregabalin) (SmPC, section 4.5 and PL, section 2)

is included in the product information of sufentanil containing medicinal products.

Therefore, the PRAC recommends that the SmPC sections 4.4 and 4.5 and PL section 2 accordingly should be harmonised in the product information of all medicinal NAP products in the EU. Standardised wording on the relevant issues can be found below. Affected MAHs are therefore requested to submit relevant variations to their national competent authorities within 6 months.

Update of section 4.4. of the SmPC to add a warning/precaution regarding opioid induced hyperalgesia and section 2 of the Package Leaflet accordingly.

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

Opioid induced hyperalgesia

As with other opioids, in case of insufficient pain control in response to an increased dose of sufentanil, the possibility of opioid-induced hyperalgesia should be considered. A dose reduction or discontinuation of sufentanil treatment or treatment review may be indicated

Package Leaflet

- Section 2

Warnings and precautions

Consult your doctor WHILE using [MEDICINAL PRODUCT NAME] if:

You experience pain or increased sensitivity to pain (hyperalgesia) which does not respond to a higher dosage of your medicine as prescribed by your doctor.

Update of section 4.4. of the SmPC to add a warning/precaution regarding sleep-related breathing disorder and section 2 of the Package Leaflet accordingly.

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Package Leaflet

- Section 2

Warnings and precautions

What do you need to know before you take [MEDICINAL PRODUCT NAME]:

Sleep-related breathing disorders

[MEDICINAL PRODUCT NAME] can cause sleep-related breathing disorders such as sleep apnoea (breathing pauses during sleep) and sleep related hypoxemia (low oxygen level in the blood). The symptoms can include breathing pauses during sleep, night awakening due to shortness of breath, difficulties to maintain sleep or excessive drowsiness during the day. If you or another person observe these symptoms, contact your doctor. A dose reduction may be considered by your doctor.

Harmonisation of section 4.4. of the SmPC and section 2 of the Package Leaflet regarding abuse potential and tolerance with proposed for other sulfentanil containing products to have the following wording:

Summary of Product Characteristics

- Section 4.4

The following amendments should be made to strengthen warning:

Tolerance and Opioid Use Disorder (abuse and dependence)

Tolerance, physical and–psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids.

Abuse or intentional misuse of [product name] may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Discontinuation of treatment and withdrawal syndrome
Repeated administration at short term intervals for prolonged periods may result in the development of withdrawal syndrome after cessation of therapy. Symptoms following withdrawal of [MEDICINAL PRODUCT NAME], including tachycardia, hypertension and agitation have been reported infrequently upon abrupt cessation, particularly after prolonged administration of more than 3 days. Where reported, re-introduction and tapering of the use has been beneficial.

Package leaflet

- Section 2

Talk to your doctor or nurse before using [MEDICINAL PRODUCT NAME].

Tell your doctor or nurse before treatment if you:

- ~~Have a history of medicine or alcohol abuse;~~

- Or anyone in your family have ever abused or been dependent on alcohol, prescription medicines or illegal drugs ("addiction").
- Are a smoker.
- Have ever had problems with your mood (depression, anxiety or a personality disorder) or have been treated by a psychiatrist for other mental illnesses.

This medicine contains sufentanil which is an opioid medicine. Repeated use of opioid painkillers may result in the drug being less effective (you become accustomed to it). It may also lead to dependence and abuse which may result in life-threatening overdose. If you have concern that you may become dependent on [MEDICINAL PRODUCT NAME], it is important that you consult your doctor.

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

Gastrointestinal effects

Sufentanil as a μ-opioid receptor agonist may slow the gastrointestinal motility. Therefore, [MEDICINAL PRODUCT NAME] should be used with caution in patients at risk of ileus.

Sufentanil as a μ-opioid receptor agonist may cause spasm of the sphincter of Oddi. Therefore, [MEDICINAL PRODUCT NAME] should be used with caution in patients with biliary tract disease, including acute pancreatitis

Package Leaflet

- Section 2

Warnings and precautions

Talk to your doctor or nurse before treatment if you:

- **have abnormally slow bowel movements;**
- **have a disease of the gall bladder or pancreas**

Update of section 4.5 of the SmPC to include the interaction with gabapentinoids (gabapentin and pregabalin) and section 2 of the Package Leaflet accordingly.

Summary of Product Characteristics

- Section 4.5

The interactions should be amended as follows:

Central nervous system (CNS) depressants

The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and death.

Package Leaflet

- Section 2

Other medicines and [MEDICINAL PRODUCT NAME]

Tell your doctor if you are taking, have recently taken or might take any other medicines. In particular, 28 tell your doctor if you are taking any of the following:

- **Medicines to treat epilepsy, nerve pain or anxiety (gabapentin and pregabalin), as they can increase the risk of opioid overdose, respiratory depression and may be life-threatening.**

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

6.2.6. PSUSA Follow-up procedures

None

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

6.3.1. PRAC recommendations on PASS results for CMDh position

None

6.4. Lists

6.4.1. Union Reference Date list

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

6.4.2. List of medicinal products under additional monitoring

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

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

None

6.6. Other topics related to pharmacovigilance

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

In July 2022, the PRAC gave advice to a Member State in relation to a type II variation for an ibuprofen-containing medicinal product for systemic use to update the product information in relation to use during pregnancy. The variation will be finalised in September including the below wording.

It was agreed that the product information should be updated by adding the following text:

Summary of Product Characteristics

- Section 4.6

[…]

From the 20th week of pregnancy onward, <x> use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have

[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.

been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, <x> should not be given unless clearly necessary. If <x> is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. **Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to <x> for several days from gestational week 20 onward. <x> should be discontinued if oligohydramnios or ductus arteriosus constriction are found.**

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (~~with~~ premature **constriction/**closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction **(see above)**;

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, <x> is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Package Leaflet

2. What you need to know before you <take/use> X

Pregnancy, breast-feeding and fertility

- Do not take <x> if you are in the last 3 months of pregnancy as it could harm your unborn child or cause problems at delivery. **It can cause kidney and heart problems in your unborn baby. It may affect your and your baby's tendency to bleed and cause labour to be later or longer than expected.** You should not take <x> during the first 6 months of pregnancy unless absolutely necessary **and advised by your doctor**. If you need treatment during this period or while you are trying to get pregnant, the lowest dose for the shortest time possible should be used. **If taken for more than a few days from 20 weeks of pregnancy onward, <X> can cause kidney problems in your unborn baby that may lead to low levels of amniotic fluid that surrounds the baby (oligohydramnios) or narrowing of a blood vessel (ductus arteriosus) in the heart of the baby. If you need treatment for longer than a few days, your doctor may recommend additional monitoring.**

It was further agreed that the changes to amend the product information, as shown above, would be applicable to other ibuprofen-containing medicinal products for systemic use

(including fixed dose combinations)[3] and to all other NSAID-containing medicinal products for systemic use. Of note, in case the product information already includes a stricter advice on use in pregnancy, the stricter advice remains valid and should remain.

Medicinal products containing acetylsalicylic acid are currently exempted from the request for implementation. Further advice for these products will be provided following conclusion of a worksharing variation of the originator.

The CMDh will send a request to the originator MAH requesting the submission of the worksharing variation (**Action: EMA**).

Of note, the above advice is only applicable to NSAID-containing medicinal products for systemic use. MAHs of topical NSAID-containing medicinal products are asked to review this topic in the upcoming PSURs for their products.

The CMDh requests concerned MAHs to implement the above PI update by submitting a type IB variation (C.I.3.z) within 3 months.

MAHs of diclofenac and dexketoprofen containing medicinal products, for which a PSUSA has been finalised in June 2022, are advised that the implementation of the above wording can be combined with the implementation of the PSUSA outcome in one variation (the deadline for the PSUSA implementation applies). The above wording supersedes the outcome of the PSUSA regarding use during pregnancy.

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

7.1. Mepidental 30 mg/ml solution for injection (NL/H/5377/001/DC) / NL

NL informed the CMDh about the break-out session held for Mepidental 30 mg/ml solution for injection (NL/H/5377/001/DC). A MO has been raised on the Art. 10a application due to missing genotoxicity data. The MO could be solved by comparison and extrapolation of genotoxicity data of other anaesthetics of the class. The procedure was closed positively.

7.2. Melatonin Omega Pharma 3 mg and 5 mg tablets (NL/H/5022/001-002/MR) / NL

NL informed the CMDh about the break-out session held for Melatonin Omega Pharma 3 mg and 5 mg tablets (NL/H/5022/001-002/MR). A PSRPH has been raised on the Art. 10a application due to insufficient data to grant a waiver for the bridging study. The concerns could be solved by providing additional data, including solubility studies at all pH values. The procedure was closed positively.

7.3.

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

[3] Except for the centrally authorised product Pedea (with a paediatric indication only)

7.4. Rivaroxaban Amarox 2.5, 10, 15 and 20 mg film-coated tablets (NL/H/5283/001-004/DC)/ NL

NL informed the CMDh about the break-out session held for Rivaroxaban Amarox 2.5, 10, 15 and 20 mg film-coated tablets (NL/H/5283/001-004/DC). Several MOs have been raised on the Art. 10(1) application.

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

8. Miscellaneous

8.1. Report from the July CMDv meeting

The CMDv secretariat reported from the July CMDv meeting.

8.2. July 2022 CMDh Press Release

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

8.3. A.O.B.

8.3.1. Role of food supplement data in the context of a well-established use application (Art. 10a) / IT, NL

Following the discussion in June, the CMDh discussed the question to be sent to the EC on the possible use of food supplement data in the context of well-established use applications, based on proposals by IT and NL. The CMDh agreed a final question including comments from MSs. The final question will be sent to the EC (**Action: EMA**).

8.3.2. Genotoxicity and contraception / Chair

The CMDh discussed questions received by Medicines for Europe on the SWP response to CMDh regarding genotoxic medicinal products and contraception duration. The questions were addressed to SWP and CMDh.

The CMDh noted that questions related to the scientific content should be answered by SWP (NcWP). CMDh discussed the regulatory questions by Medicines for Europe.

The CMDh confirmed that in case a RefMP is not authorised in the MS where the generic is authorised, the calculation can be taken over from a RefMP authorised in another MS (or another product) and no new calculation is required. Submission via a type IB variation is sufficient.

Medicines for Europe also asked which calculation to take over if there are several originator products with different calculations. The CMDh noted that this is a theoretical question. The generic should adapt to the product information of their RefMP. MSs are exchanging information on the calculation of the contraception period. In case there are major differences between products, this would need to be further looked into and aligned.

The CMDh will get into contact with NcWP in order to send a joint response (**Action: EMA**).

8.3.3. Paracetamol Bluefish, 500 mg, tablet (PT/H/2644/001/DC) / PT

PT informed the CMDh about the break-out session held for Paracetamol Bluefish, 500 mg, tablet (PT/H/2644/001/DC). A PSRPH has been raised on the Art. 10(1) application due to disharmonised product information of the RefMP. Agreement could be reached based on a proposal from the applicant. The procedure was closed positively.

8.3.4.

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

8.3.5. CMDh Guidance on repeat-use procedure / DE

The CMDh discussed a proposal to amend the RUP procedure to allow national translations to be submitted with procedure start and evaluated during the procedure. The proposal is based on a suggestion from Medicines for Europe as presented during the Interested Parties meeting.

Many MSs stated that the national way of working would have to be adapted if the proposal is implemented. More time would be needed to discuss the proposal internally. Some MSs also noted that it could lead to more work for MSs, e.g. if the translations are assessed and CMS is then withdrawn from the procedure. A national phase would anyway still be needed after the EU phase. It was noted that the new procedure should not be mandatory.

MSs were asked to consider the proposal and comment on it before the September CMDh meeting. An update of the relevant CMDh guidance document will be prepared for the September CMDh meeting (also including other changes) for further discussion (**Action: DE, PL**).

8.3.6. PSUSA Follow-up procedures / NO

The CMDh endorsed the outcome of the WS variations for the following active substances as a follow-up of previous PSUSAs:

- iopromide as a follow-up of PSUSA/00001773/202006
- iodixanol as a follow-up of PSUSA/00001766/202004 (NO/H/xxxx/WS/052 & NO/H/xxxx/WS/056)
- iomeprol as a follow-up of PSUSA/00001769/202004

Based on the assessment of the submitted data, updates of the SmPC and the PL or the RMP are deemed warranted.

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

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

It was noted that no PRAC advice for the procedures was necessary as all MSs were included in the WS variations.

8.3.7.

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

8.3.8.

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 September 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 19-20 July 2022 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Kora Doorduyn-van der Stoep	Chair	Netherlands	To be replaced for the discussions, final deliberations and voting on:	6.2.1.3. Hydromorphone - PSUSA/00001686 /202111 6.2.3.1. Sufentanil - PSUSA/00001160 /202111
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	
Tea Linhola	Member	Finland	No interests declared	
Pauliina Ikäheimo	Alternate	Finland	No interests declared	
Glenn Lastennet	Member	France	No interests declared	
Mathilde Geynet-Kovacs	Alternate	France	No interests declared	
Susanne Winterscheid	Member	Germany	No interests declared	
Wiebke Hoppensack	Alternate	Germany	No interests declared	
Eleftheria Nikolaidi	Member	Greece	No interests declared	
Stavroula Mamoucha	Alternate	Greece	No interests declared	
Magdolna Nemeth	Member	Hungary	No interests declared	
Orn Gudmundsson	Member	Iceland	No interests declared	
Nicole Kavanagh	Member	Ireland	No interests declared	
Laura Galatti	Member	Italy	No interests declared	
Marco Franceschin	Alternate	Italy	No interests declared	
Maija Cirkina	Member	Latvia	No interests declared	
Iveta Eglite	Alternate	Latvia	No interests declared	

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	
Helen Vella	Member	Malta	No interests declared	
Paula Cardona Xuereb	Alternate	Malta	No interests declared	
Priscilla Schoondermark	Member	Netherlands	No interests declared	
Nicole Visser	Alternate	Netherlands	No interests declared	
Nina Malvik	Alternate	Norway	No interests declared	
Andrzej Czeslawski	Member	Poland	No interests declared	
Pawel Pawlowski	Alternate	Poland	No interests declared	
Marta Marcelino	Member	Portugal	No interests declared	
Rui Pedro da Costa Vilar	Alternate	Portugal	No interests declared	
Cristian Dan Georgescu	Member	Romania	No interests declared	
Daniela Elena Popa	Alternate	Romania	No interests declared	
Miroslava Petrikova	Member	Slovakia	No interests declared	
Petra Docolomanska	Alternate	Slovakia	No interests declared	
Nevenka Prpar	Alternate	Slovenia	No interests declared	
Veronica Garcia Morales	Member	Spain	No interests declared	
Elisa Sulleiro	Alternate	Spain	No participation in final deliberations and voting on:	6.2.1.1. Chlormadinone acetate / ethinylestradiol - PSUSA/00000679/202111
Christin Olofsson	Member	Sweden	No interests declared	
Dino Soumpasis	Chair of CTS WG	Germany	No interests declared	
Martin Huber	Chair of Non-Prescription MPs TF	Germany	No interests declared	
Jayne Crowe	Chair of GCP Inspectors Working Group/CMDh Working Party	Ireland	No interests declared	

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

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