29 July 2022
EMA/CMDh/642745/2022

Report from the CMDh meeting held on 19-20 July 2022

NSAID-containing medicinal products (for systemic use) and use during pregnancy

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.

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 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)[1] 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.

Of note, the above advice is only applicable to 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.

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

Nitrosamines: deadline for steps 2 and 3 of call for review exercise for medicines with chemically synthesised active substances

MAHs reminded to complete required testing and mitigation activities

In September 2019, EMA's Executive Director, in accordance with Article 5(3) of Regulation (EC) No 726/2004, requested a scientific opinion from the Committee for Medicinal Products for Human use (CHMP) regarding the detection, management and prevention of the presence of nitrosamines in medicinal products for human use.

In the same month, while the Article 5(3) procedure was underway, regulatory authorities launched a call for review of all human medicinal products in the EU containing chemically synthesised active pharmaceutical ingredients (APIs). This exercise was extended to cover human medicinal products containing biological APIs in July 2020 upon conclusion of the Article 5(3) procedure.

The call for review requires marketing authorisation holders (MAHs) to review their manufacturing processes in order to identify and, if necessary, mitigate the risk of nitrosamine impurities being present in their medicines and report back to authorities. The exercise consists of 3 steps described below.

- In step 1, MAHs are required to perform a risk evaluation to determine if APIs and/or finished products could be at risk of containing nitrosamines. (MAHs were required to report the outcome of the risk evaluation by 31 March 2021 for medicines with chemically synthesised APIs and by 1 July 2021 for medicines with biological APIs.)
- In step 2, if a risk is identified, MAHs are required to proceed with confirmatory testing in order to confirm whether nitrosamines are present or not. MAHs should report outcomes as soon as possible;
- In step 3, if the presence of nitrosamines is confirmed, MAHs are requested to implement effective risk mitigating measures through submission of variation applications. Both step 2 and 3 should be completed by the 26 September 2022 for medicines with chemically synthesised APIs and by the 1 July 2023 for medicines with biological APIs.

The deadline for completing the call for review exercise for human medicines containing chemically synthesised APIs is approaching. In consideration of the scientific developments since 2020, specifically in relation to active substance related nitrosamines, the deadline to submit **step 3 variations to the marketing authorisations** is now extended to **1 October 2023**. This extension is intended to allow companies to perform a thorough investigation and establish any required risk mitigating actions. Nevertheless, MAHs are encouraged to submit variation applications as soon as investigations are concluded and therefore in advance of the above deadline. The **step 2 confirmatory testing** deadline remains **26th September 2022**. Nonetheless, it is emphasised that MAHs should only submit complete step 2 outcomes.

MAHs are reminded of their responsibility to ensure the quality, safety and efficacy of their medicines and are requested to implement the required testing and risk mitigating activities as a matter of priority and in accordance with the recommendations from the Article 5(3) procedure. Further clarification on the call for review is available in the related Questions and Answers document "Information on nitrosamines for marketing authorisation holders".

The risk from nitrosamines in medicines remains low. However, MAHs are reminded of their responsibility to meet all obligations to limit the presence of nitrosamines in medicines. EMA and national authorities will continue to monitor the situation with respect to nitrosamines and take any actions necessary to uphold quality standards of medicines in the EU.

The CMDh has agreed an update of its practical guidance for MAHs of nationally authorised products (incl. MRP/DCP) in relation to the Art. 5(3) referral on nitrosamines to reflect this change. In addition, Q1.9 has been updated 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 updated documents will be published on the CMDh website under "Advice from CMDh > Nitrosamine impurities" and the EMA website, respectively.

EMA/CMDh explanatory notes on variation application form

The CMDh agreed an update of the EMA/CMDh explanatory notes on the variation application form (human medicinal products only). In the update it has been further specified which previous harmonisation of the product information needs to be declared by the applicant in the application form.

The updated document will be published on the CMDh website under "Procedural Guidance > Variation".

CMDh Best Practice Guide on Variation Worksharing

In May 2022, the CMDh agreed an update of its BPG on variation worksharing. To improve the worksharing procedures, it was agreed that for worksharing procedures which only include quality changes of type IB (or groupings with type IB as the highest type of change), the assessment report can be reduced to the minimum necessary information and that the timetable for type IB variations can be followed (30-30-30 days). In specific cases, the reference authority can extend this to the 60-day type II timetable, if needed.

The update of the BPG is published now as the necessary technical changes to CTS have been implemented and will be available with the next CTS client release.

The updated document will be published on the CMDh website under "Procedural Guidance > Variation".

RMS Validation Checklist for Human Medicinal Products in DCP and CMDh Procedural Advice on Validation of MRP/RUP/DCP

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 of the CMS validation checklist in DCP has been agreed.

The updated documents will be published on the CMDh website under "Procedural Guidance > Application for MA".

CMDh Recommendations on Informed Consent Applications in MRP and DCP

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 and 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 under "Procedural Guidance > Application for MA".

Best Practice Guide on Article 45 and 46 – Paediatric Regulation - EU Worksharing Procedure

The CMDh has agreed an update of its BPG on Article 45 and 46 – Paediatric Worksharing 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 under "Paediatric Regulation > Guidance documents".

CMDh Multi-Annual Workplan (MAWP) to 2025

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 are needed. A document summarising the main comments and the CMDh feedback to them has been prepared and will be published on the CMDh website alongside the updated MAWP. Also all received comments will be published for transparency.

The CMDh would like to thank all involved parties for their contributions.

CMDh positions following PSUSA procedures for nationally authorised products only

The CMDh, having considered the PSURs on the basis of the PRAC recommendations and the PRAC assessment reports, agreed by consensus on the variation of the marketing authorisations of medicinal products containing the following active substances:

- chlormadinone acetate / ethinylestradiol
- donepezil
- hydromorphone
- tapentadol

Further information regarding the above mentioned PSUSA procedures, including information on the implementation, will be published on the EMA website.

Medicinal products containing 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.

Outcome of PSUR Follow-up procedures

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, an update of the SmPC and the PL are deemed warranted.

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

The agreed CMDh recommendation, including the PI wording to be implemented, as appropriate, will be published on the CMDh website under "Pharmacovigilance > PSUR > PSUR Follow-up procedures".

MRP/DCP statistics in the first semester of 2022

Statistics regarding new applications in MRP and DCP in the first semester of 2022 according to the 5-levels of classification of the MRP/DCP Communication Tracking System database will be published on the CMDh website. The statistics will also include information on variation worksharing procedures,

referrals to the CMDh and rapporteurships in paediatric worksharing procedures according to Art. 45 and 46 of the Paediatric Regulation.

NEW APPLICATIONS

Mutual Recognition Procedure

Table 1. New applications in Mutual Recognition procedure started in June 2022

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	2	
Belgium		3
Bulgaria		1
Croatia		2
Cyprus	1	4
Czech Republic	1	4
Denmark	2	1
Estonia		
Finland	1	1
France		
Germany	3	2
Greece		2
Hungary	1	
Iceland		4
Ireland		2
Italy		1
Latvia		1
Liechtenstein		
Lithuania	1	2
Luxembourg		1
Malta		2
Netherlands	6	
Norway		1
Poland	1	2
Portugal		2
Romania		2
Slovak Republic		4
Slovenia		2
Spain	4	
Sweden		1
United Kingdom (Northern Ireland)		

Decentralised Procedure

Table 2. New applications in Decentralised procedure started in June 2022

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	6	15
Belgium		13
Bulgaria		16
Croatia		11
Cyprus		10
Czech Republic	6	15
Denmark	5	17
Estonia	2	13
Finland	4	15
France		21
Germany	17	17
Greece		11
Hungary	2	16
Iceland		6
Ireland	1	10
Italy		22
Latvia		14
Liechtenstein		
Lithuania	1	14
Luxembourg		8
Malta	2	3
Netherlands	10	16
Norway	1	20
Poland	2	21
Portugal	4	14
Romania		19
Slovak Republic	1	17
Slovenia	5	8
Spain	1	21
Sweden	2	22
United Kingdom (Northern Ireland)		1

Information on the above-mentioned issues can be obtained:

Chair of the CMDh
Mrs Kora Doorduyn-van der Stoep
Medicines Evaluation Board
P.O Box 8275
3503 Utrecht RG
The Netherlands

CMDh Secretariat
Or you could visit the CMDh website at:
E-mail: H-CMDhSecretariat@ema.europa.eu
http://www.hma.eu/cmdh.html