30 March 2022
EMA/CMDh/139884/2022

Report from the CMDh meeting held on 22-23 March 2022

Call for review for chemically synthesised and biological medicinal products regarding nitrosamine impurities

Authorities in the EU are aware that some active substances are at a higher risk of formation of active substance derived nitrosamine impurities.

Such active substances contain vulnerable amine functional groups that can undergo a reaction called nitrosation (often a secondary amine). Nitrosamines are thought to form when the nitrosatable amine group in the active substances and trace nitrite impurities in the inactive ingredients (excipients) react.

Active substances that contain secondary amines appear particularly vulnerable to this reaction, although some cases involving active substances with tertiary amines have also been observed.

More information on the root causes of nitrosamine impurities is available in Question-and-Answer document on the Article 5(3) CHMP opinion (Question 4).

All marketing authorisation holders for EU medicines should consider this risk factor in their risk evaluations as a matter of priority, if they have not already done so.

If a risk is confirmed, they should prioritise confirmatory testing. If testing confirms the presence of nitrosamines, companies should immediately report their findings to the relevant competent authority.

Guidance for marketing authorisation holders on confirmatory testing is available.

This is a precautionary step to ensure early detection of any potential risk, and to enable prompt regulatory action if necessary.

There is no immediate risk to patients who are taking these medicines. Patients who have any questions about their treatment should speak to their doctor.

Authorities will provide updates as necessary.

The CMDh in collaboration with the EMA agreed an update of the joint EMA/CMDh Questions and Answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products. Q&As 4, 8 and 15 have been amended to provide more guidance on the currently identified risk factors, confirmatory testing as part of step 2 of the call for review and when to include a test for nitrosamines

in the MA dossier. The updated Q&A document has been published on the EMA website. A link is provided from the CMDh website under "Advice from CMDh > Nitrosamine impurities".

Annual update of human influenza vaccines for season 2022/2023

Following the report of the CHMP BWP ad hoc Influenza Working Group, the CMDh agreed that the EU recommendation of the CHMP BWP ad hoc Influenza Working Group including the data requirements/ format for submission of the annual strain update is applicable also for MRP/DCP and purely nationally authorised seasonal influenza vaccines. The EU recommendation of the CHMP BWP ad hoc Influenza Working Group will be published on the EMA website.

NCAs and MAHs are requested to follow the labelling examples (strain descriptions) given in Annex III of the CMDh Best Practice Guide on variations, Chapter 9 on fast track procedure for the annual update of human influenza vaccines, that is equivalent to the labelling guidance for centrally-approved influenza vaccines according to the Guideline on influenza vaccines – submission and procedural requirements, and to also note additional specific details as outlined under "Note on labelling requirements" in the EU influenza recommendation.

Regulation (EC) No 1234/2008 on variations

The CMDh has discussed a recommendation for the classification of an unforeseen variation. The CMDh agreed that the proposed change ("The specification parameter "total thickness" for the blister foil (lidding aluminium foil) of the primary packaging material for a solid dosage form is widened due to a difference in grammage of the primer material.") should be submitted as a type IA variation under B.II.e.2.z (certain conditions apply). The outcome will be published on the CMDh website under "Procedural Guidance > Variation > Article 5 recommendations".

Active Substance Master File (ASMF) worksharing

In February, the CMDh agreed updates of the following documents prepared by the Working Group on ASMF procedures: ASMF WG mandate, Q&As on ASMF and the guidance on worksharing procedure for the assessment of ASMF. The updates mainly reflect changes related to the veterinary regulation. As the documents have now been adopted by all relevant groups, they will be published on the CMDh website under "CMD Working Parties/Working Groups > WG on ASMF procedures" and "Questions & Answers", respectively.

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 variations of the marketing authorisations of medicinal products containing the following active substances:

- amlodipine/rosuvastatin, perindopril/amlodipine/rosuvastatin
- leuprorelin (depot formulations)

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

Medicinal products containing amlodipine (as a single agent or in fixed dose combinations)

In the framework of the PSUSA on amlodipine/rosuvastatin, perindopril/amlodipine/rosuvastatin, the PRAC noted that the amlodipine component of the fixed dose combination of amlodipine/rosuvastatin and perindopril/amlodipine/rosuvastatin is also authorised as a single agent or in other fixed dose combination products.

The PRAC considered that the risk of non-cardiogenic pulmonary oedema in amlodipine overdose would also be relevant to be included in products containing amlodipine as a single agent or in fixed dose combinations (FDCs) of amlodipine. Although, the risk has been identified for the amlodipine mono-component, considering the pharmacokinetic and pharmacodynamic profile of the active substances present in FDCs and the exceptionally long half-life of amlodipine, and lack of evidence that would indicate an altered toxicity profile with FDCs as compared to the mono-components, the risk of delayed onset of non-cardiogenic pulmonary oedema is a reasonable possibility with the currently authorised combinations as well.

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

Gabapentin – Outcome of WS variation following PSUSA/00001499/201902

The CMDh endorsed the outcome of the WS variation following PSUSA/00001499/201902 for gabapentin.

Based on the assessment of the submitted data, an update of sections 4.4 and 4.8 of the SmPC and an update of section 4 of the PL are deemed warranted.

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

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

CMDh procedural advice on changing the Reference Member State

The CMDh agreed an update of its procedural advice on changing the RMS. The examples of cases, where a change of RMS might be needed, have been updated and the information on the new procedure numbers in the new RMS has been clarified. The updated document will be published on the CMDh website under "Procedural Guidance > General Information".

EU Work-sharing Articles 45 & 46 of the Paediatric Regulation – Public Assessment Reports

The CMDh has agreed public assessment reports for paediatric studies submitted in accordance with Article 45 of the Paediatric Regulation for:

- Eucalypti aetheroleum
- cinnarizine

- dalteparin
- fluticasone propionate
- ceftriaxone
- octreotide

which may include recommendations for the text to be included in SmPCs and package leaflets.

Marketing Authorisation Holders of medicinal products with same active substance and pharmaceutical form are requested to include this information in their SmPCs and package leaflets within 90 days of publication of the public assessment reports, in accordance with the Best Practice Guide on Article 45 and 46 - EU work-sharing procedure.

The public assessment reports will be published on the CMDh website under "Paediatric Regulation > Assessment reports".

NEW APPLICATIONS

Mutual Recognition Procedure

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

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	1	1
Belgium		1
Bulgaria		1
Croatia		1
Cyprus		2
Czech Republic		2
Denmark	3	4
Estonia		2
Finland	1	4
France		1
Germany	6	2
Greece		2
Hungary		2
Iceland		4
Ireland	4	1
Italy		5
Latvia		2
Liechtenstein		
Lithuania		2
Luxembourg		
Malta		7
Netherlands	8	
Norway		5
Poland	1	4

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Portugal	1	3
Romania		3
Slovak Republic	1	1
Slovenia	1	1
Spain	1	1
Sweden		3
United Kingdom (Northern Ireland)		

Decentralised Procedure

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

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	17	17
Belgium		12
Bulgaria		14
Croatia	4	14
Cyprus		9
Czech Republic	3	20
Denmark	7	16
Estonia		10
Finland	2	18
France		21
Germany	17	30
Greece		19
Hungary	4	18
Iceland	7	7
Ireland	2	11
Italy		33
Latvia	3	10
Liechtenstein		
Lithuania	1	12
Luxembourg		11
Malta	10	7
Netherlands	12	16
Norway		22
Poland	1	27
Portugal	9	17
Romania		13
Slovak Republic		19
Slovenia	6	7
Spain	1	28
Sweden	11	17
United Kingdom (Northern Ireland)		5

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