16 November 2022
EMA/CMDh/864833/2022

Report from the CMDh meeting held on 8-10 November 2022

CMDh outcome on referrals pursuant to Article 31 of Directive 2001/83/EC

Amfepramone-containing medicinal products

The CMDh, having considered the PRAC assessment report and recommendation, agreed by majority that the marketing authorisations for medicinal products containing amfepramone should be withdrawn.

The PRAC recommendation follows a review which found that measures to restrict the use of these medicines for safety reasons have not been sufficiently effective. It found that the medicines were being used for longer than the recommended maximum period of 3 months, thereby potentially increasing the risk of serious side effects such as pulmonary arterial hypertension (high blood pressure in the lungs) and dependency. The medicines were also being used in patients with a history of heart disease or psychiatric disorders, increasing their risk of heart and psychiatric problems. In addition, there was evidence of use during pregnancy, which could pose risks to the unborn baby.

The review considered all available information relating to these concerns, including data from two studies on the use of amfepramone medicines in Germany and in Denmark. In addition, the PRAC received advice from a group of experts, comprising endocrinologists, cardiologists and a patient representative.

The PRAC considered introducing further measures to minimise the risk of side effects but could not identify any that would be sufficiently effective. The PRAC therefore concluded that the benefits of amfepramone medicines do not outweigh their risks and recommended that the medicines be removed from the market in the EU.

As the CMDh position was adopted by majority vote, it will now be sent to the European Commission, which will issue a final legally binding decision applicable in all EU Member States.

Further information regarding the above-mentioned referral has been published on the EMA website.

The CMDh, having considered the PRAC assessment report and recommendation, agreed by consensus that the marketing authorisations for medicinal products containing terlipressin, indicated in the treatment of type 1 hepatorenal syndrome (type 1 HRS), should be varied to introduce new measures to reduce the risk of respiratory failure and sepsis.

The new measures include adding to the product information a warning to avoid terlipressin-containing medicines in patients with advanced acute-on-chronic liver disease or advanced kidney failure. Patients with breathing problems should receive treatment to manage their condition before starting terlipressin-containing medicines. During and after treatment, patients should be monitored for signs and symptoms of respiratory failure and infection.

In addition, healthcare professionals can consider giving terlipressin-containing medicines as a continuous infusion (drip) into the vein as an alternative to giving it by bolus injection (full dose injected in one go) as this may reduce the risk of severe side effects.[1]

The recommendations follow the PRAC's review of available data, including results from a clinical trial[2] involving patients with type 1 HRS which suggested that patients who were treated with terlipressin-containing medicines were more likely to experience and die from respiratory disorders within 90 days after the first dose than those who were given placebo.

Although respiratory failure is a known side effect of terlipressin, the frequency of respiratory failure seen in the study was higher (11%) than previously reported in the product information. In addition, the study reported sepsis in 7% of patients in the terlipressin arm compared with none in the placebo group.

There were limitations to the data, such as differences in how terlipressin was used in the clinical trials compared to clinical practice. After considering these limitations together with other available data and consulting an expert group composed of healthcare professionals with expertise in the field of hepatorenal syndrome, PRAC concluded that new measures are needed to ensure that the benefits of terlipressin-containing medicines continue to outweigh the risks.

As the CMDh position was adopted by consensus, it will be directly implemented by the Member States.

Further information regarding the above-mentioned referral has been published on the EMA website.

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 substance:

- amoxicillin
- amoxicillin / clavulanate

[1] Cavallin M, Piano S, Romano A, et al. Terlipressin given by continuous intravenous infusion versus intravenous boluses in the treatment of hepatorenal syndrome: A randomized controlled study. *Hepatology*. 2016;63(3):983-92. doi:10.1002/hep.28396

[2] Wong F, Pappas SC, Curry MP, et al. Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. *N Engl J Med*. 2021;384(9):818-828. doi: 10.1056/NEJMoa2008290

- erythromycin (systemic use)
- fexofenadine
- oxycodone

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

Combined medicinal products containing amoxicillin

During the PSUSA on amoxicillin, the PRAC considered that the overall recommendations of the PSUSA should also be considered for combined medicinal products containing amoxicillin.

Medicinal products containing methotrexate or probenecid

During the PSUSA on amoxicillin, the inclusion in the product information of interactions between amoxicillin and probenecid and between amoxicillin and methotrexate is recommended. The PRAC considered that these interactions should also be included in the product information of products containing the active substances methotrexate and probenecid (if not already included).

Suggested wording:

DDI between amoxicillin and methotrexate

SmPC, Section 4.5

Amoxicillin
Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

PL, Section 2

Penicillins may reduce the excretion of methotrexate causing a potential increase in side effects.

DDI between amoxicillin and probenecid

SmPC, Section 4.5

Amoxicillin
Concomitant use of amoxicillin is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin which may result in increased and prolonged blood levels of amoxicillin.

PL, Section 2

Concomitant use of probenecid and amoxicillin may reduce the excretion of amoxicillin and is not recommended.

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

The CMDh and the EMA agreed an update of the "Step 2 – Nitrosamine detected response template" considering the newly published Q.21 of the EMA/CMDh Q&A on nitrosamines and to emphasise the need for adherence to published AI limits for known nitrosamines.

The updated template will be published on the CMDh website under "Advice from CMDh > Nitrosamine impurities".

Addendum to the QRD template for MRP/DCP specific for (Traditional) Herbal Medicinal Products ((T)HMPs)

The CMDh agreed an update of the Addendum to the QRD template for MRP/DCP specific for (Traditional) Herbal Medicinal Products ((T)HMPs). The update has been prepared and agreed by the Committee on Herbal Medicinal Products (HMPC). With the update, duplications of the regular QRD template have been removed and focus has been put on special aspects to be considered for (T)HMPs. Wherever justified, the wording of the herbal specific texts was not changed compared to the original version. Sections where better guidance was deemed necessary were expanded.

The updated document will be published on the CMDh website under "Templates > QRD".

HaRP Assessment Report Template

The CMDh agreed a new version of the HaRP assessment report template. The template has been updated and improved based on the experience gained since the beginning of the project and based on questions raised on how the assessment is performed.

The updated template will be published on the CMDh website under "Templates > RMP".

Meeting with representatives of Interested Parties

The CMDh convened a meeting with Interested Parties in the margins of the November CMDh plenary meeting. The topics discussed included, amongst others, multilingual labelling, resources, repeat-use procedures, availability of updated PI following safety reviews and nitrosamines. All presentations will be published on the CMDh website under "About CMDh > Contact with Representative Organisations".

CMDh Presidency meeting under the Czech Presidency of the Council of the EU

The CMDh convened for a Presidency meeting on 18 and 19 October 2022 in Prague, Czechia, held as part of a programme of events organised under the Czech Presidency of the Council of the EU.

In the meeting the CMDh discussed, amongst others, topics related to resources, renewals, validation, possible worksharing initiatives and 0-day procedures. Part of the meeting was held as a joint meeting with PRAC. In the joint part with PRAC, the CMDh and PRAC discussed, amongst others, topics related to pharmacovigilance and timely provision of safety information to health care professionals and patients.

EU Worksharing 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:

- Gabapentin
- Tretinoin

- Haemophilus influenzae type b vaccine conjugated to Tetanus Protein (Act-HIB)
- Vaccinum hepatitidis B (Euvax B)

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 CMDh has also agreed public assessment reports for paediatric studies submitted in accordance with Article 46 of the Paediatric Regulation for:

- Haemocomplettan/Riastap (human fibrinogen)
- Decapeptyl/Diphereline/Arvekap (triptorelin pamoate)
- Act-HIB (Haemophilus influenzae type b vaccine conjugated to Tetanus Protein)
- Dexilant (dexlansoprazole)
- Zithromax (azithromycin dehydrate)

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 October 2022

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	2	1
Belgium		1
Bulgaria		3
Croatia		2
Cyprus	1	
Czech Republic		1
Denmark		3
Estonia		3
Finland	1	1
France	1	1
Germany	4	3
Greece		
Hungary		1
Iceland		2
Ireland		1
Italy		1
Latvia		2

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Liechtenstein		
Lithuania		3
Luxembourg		
Malta	1	2
Netherlands	4	5
Norway	1	3
Poland		3
Portugal	1	
Romania		1
Slovak Republic		1
Slovenia		3
Spain		3
Sweden	2	2
United Kingdom (Northern Ireland)		1

Decentralised Procedure

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

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	8	10
Belgium		11
Bulgaria		8
Croatia		6
Cyprus		5
Czech Republic	8	14
Denmark	7	15
Estonia		8
Finland	2	9
France		24
Germany	23	21
Greece		10
Hungary	1	11
Iceland	5	3
Ireland	2	8
Italy		28
Latvia		12
Liechtenstein		
Lithuania	1	11
Luxembourg		8
Malta	2	4
Netherlands	13	11
Norway		12

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Poland	1	17
Portugal	8	11
Romania		9
Slovak Republic	1	17
Slovenia	2	3
Spain		30
Sweden	14	13
United Kingdom (Northern Ireland)		

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