~~29 June~~18 July 2022
EMA/CMDh/587072/2022, Corr. 1

Report from the CMDh meeting held on 21-22 June 2022

Request form for MRP/RUP for Medicinal Products for Human Use

The CMDh has revised its template for request for MRP/RUP for medicinal products for human use. The revision was started due to comments received from applicants that besides the request form, some Member States also ask for a pre-filled application form. It has now been decided to include more information in the request form and to base the form on the assessment report template. The pre-filled template can then be used by the RMS to prepare the updated Assessment Report, avoiding duplication of work.

As with the previous form, applicants are advised to check the websites of national competent authorities, as due to the different organisations and thereby also different working procedures for the approved medicinal products in member states, the request form may need to be adapted at national level and is not mandatory for the NCAs to be used. The request form is published on the CMDh website to be transparent, but MAHs should approach the reference member state to discuss the update of the AR in the MRP/RUP procedure as appropriate and use the request form available from the RMS, if applicable.

It is advised to use the new form for requests submitted as of 1 September 2022 but it can already be used on a voluntary basis before that date.

Risk of azido-impurity in losartan-containing medicinal products

In September 2021 the CMDh has published a letter addressed to MAHs of losartan-containing medicinal products to ask them to review if there is a risk of contamination of their product with an azido impurity (5-[4' -[(5-(Azidomethyl)-2-butyl-4-chloro-1 H-imidazol-1-yl)methyl]-[1,1'-biphenyl]2-yl]-1H-tetrazole (CAS 727718-93-6) ('losartan azide impurity')). This request was issued after it was confirmed that this impurity has tested positive in a bacterial mutagenicity (Ames) test and that therefore it should be ensured that the impurity is controlled at or below the Threshold of Toxicological Concern (TTC) as outlined in ICH M7 for known mutagens with unknown carcinogenic potential (class 2) via a suitable control strategy. In November 2021 the CMDh communicated that uncertainties regarding the validity of the Ames test have been raised. Since then, further information has been provided. It has now been confirmed by ~~this new information~~an in-vivo Comet assay that the losartan azide impurity is not an in vivo mutagen. This means that losartan azide is classified as a class 5

impurity in accordance with ICH M7(R1) and can be controlled as a nonmutagenic impurity in accordance with ICH Q3A/B.

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

The CMDh and the EMA agreed an update of the joint questions and answers 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. Information has been included in the document to provide clarifications on the expectation for MAHs to continue to re-visit risk evaluations when new information becomes available (Q&A 5), with specific reference to API-nitrosamine risk. Q&A 10 has been updated to include newly adopted AIs and to indicate APIs where related nitrosamines have been identified. Clarification on how to set limits for products containing salt, hydrate or solvate forms of the API has also been included. In Q&A 14, reference to the new risk evaluation template for use in marketing authorisation applications has been added.

The updated document will be published on the EMA website. A link is provided from the CMDh website under "Advice from CMDh > Nitrosamine impurities".

Technical and procedural guidance to replace/remove titanium dioxide (TiO_2) in medicines

Following publication of Commission Regulation (EU) 2022/63 of 14 January 2022 amending Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council as regards the food additive titanium dioxide, the EMA's Quality Working Party has prepared Questions and Answers to provide technical and procedural guidance to replace/remove titanium dioxide (TiO_2) in medicines. The CMDh has been consulted in the drafting of the document and fully supports the recommendations given. MAHs are advised to take due notice of the document in the pharmaceutical development of their products. The Q&A document will be published on the EMA website under Quality of medicines – Questions and Answers.

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:

- dexketoprofen
- diclofenac (systemic formulations)
- methylphenidate
- rabeprazole
- soybean phospholipids (oral use)
- teicoplanin

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

Medicinal products containing dexketoprofen

In the framework of the PSUSA on dexketoprofen, the PRAC noted that dexketoprofen is also authorised in fixed dose combination products and considered that the risk of foetal renal dysfunction, oligohydramnios and neonatal renal impairment, when this is used by the mother after gestational week 20, would also be relevant to be included in fixed dose combination products containing dexketoprofen. In case the product information of the fixed dose combination includes a stricter advice on use in pregnancy due to the other substance, the stricter advice remains valid and should remain in the SmPC and PL of the specific fixed dose combinations.

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

Medicinal products containing diclofenac (systemic formulations)

In the framework of the PSUSA on diclofenac (systemic formulations), the PRAC noted that diclofenac is also authorised in fixed dose combination products (systemic formulations). The PRAC considered that the risk of foetal renal dysfunction, oligohydramnios and neonatal renal impairment, when diclofenac (systemic formulations) is used by the mother after gestational week 20, would also be relevant to be included in products containing diclofenac in fixed dose combinations (systemic formulations) as the risk is also applicable to fixed dose combinations. In case the product information of the fixed dose combination includes a stricter advice on use in pregnancy due to the other substance, the stricter advice remains valid and should remain in the SmPC and PL of the specific fixed dose combinations.

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

Medicinal products containing tenofovir alafenamide

In the framework of the PSUSA on tenofovir alafenamide and the PSUSA on elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide, the PRAC noted that tenofovir alafenamide is also authorised in (other) fixed dose combination (FDC) products. The PRAC considered that an update to the existing warning on nephrotoxicity is also relevant to be included in the FDCs of tenofovir alafenamide (TAF), independent of the indication of the medicinal product.

The proposed updates to the TAF-containing products should be submitted within 6 months of the publication of the EC decision of the above-mentioned PSUR procedures.

PSUR Follow-up procedure (PSUFU) for methotrexate

In the framework of the PSUSA on methotrexate, the PRAC considered that, in the light of recent literature and recommendations from the Safety Working Party (SWP)[1], MAHs are requested to submit within 3 months a comprehensive review and discussion of available evidence in relation to the mechanism of genotoxicity of methotrexate and to conclude whether there is sufficient evidence that this mechanism is known to have a threshold which is not expected to be attained in patients, as part of a PSU follow-up measure for NAPs for which Germany will be the LMS or within a LEG procedure for CAPs, as applicable.

[1] 2 March 2022 – EMA/CHMP/SWP/74077/2020 corr. 3*

In this regard MAHs should comment if findings from this review can inform current advice on the duration of contraceptive use following the end of treatment with methotrexate. This question should be discussed separately for men and women. In the absence of sufficient evidence for such mechanism the SWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug will apply.

In addition, MAHs of methotrexate-containing products with indications requiring low-dose methotrexate therapy are also requested to comment on the significance of the finding by Grosen et al. (2021)[2] and to include a review of any new data on methotrexate presence in semen.

The procedure number for this PSUFU procedure will be DE/H/PSUFU/00002014/202110.

Outcomes of informal PSUR work-sharing procedures

The CMDh has adopted the conclusions of the PSUR assessment for:

- Granocyte (lenograstim)

The summary assessment report will be published on the CMDh website under "Pharmacovigilance > PSURs > Outcome of informal PSUR worksharing procedures".

Change in the Presidency of the Council of the European Union

The June 2022 CMDh meeting was the last one under the French Presidency of the Council of the European Union. Czechia will take over the Presidency in July 2022. Jitka Vokrouhlická will be the appointed Presidency vice-chairperson of the CMDh during the Czech Presidency of the Council of the European Union.

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

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

- eplerenone

which includes 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 report will be published on the CMDh website under "Paediatric Regulation > Assessment reports".

The CMDh further agreed a minor update of the Paediatric assessment report templates (AR and public AR templates for Art. 45 and 46) to align the recommendations for the implementation of the outcome to be either type IB or type II.

[2] Grosen A, Bellaguarda E, Nersting J, Hvas C, Liljeqvist-Soltic I, Stein A, et al. Low-dose Methotrexate Therapy Does Not Affect Semen Parameters and Sperm DNA. Inflammatory Bowel Diseases. 2021: izab205. doi: 10.1093/ibd/izab205.

The updated templates will be published on the CMDh website under "Templates > Assessment Reports > Paediatric Data".

NEW APPLICATIONS

Mutual Recognition Procedure

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

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

Decentralised Procedure

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

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	8	9
Belgium		13
Bulgaria		8
Croatia	2	8
Cyprus		2
Czech Republic	5	14
Denmark	2	14
Estonia	1	10
Finland	2	14
France		19
Germany	19	25
Greece		6
Hungary	2	6
Iceland	15	2
Ireland	2	14
Italy		24
Latvia	1	12
Liechtenstein		
Lithuania	1	10
Luxembourg		10
Malta	3	5
Netherlands	11	12
Norway		20
Poland	5	15
Portugal	5	14
Romania		10
Slovak Republic	2	10
Slovenia	3	8
Spain		22
Sweden	8	12
United Kingdom (Northern Ireland)		5

Information on the above-mentioned issues can be obtained:

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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