Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

28 July 2023
EMA/CMDh/328639/2023

Report from the CMDh meeting held on 18-20 July 2023

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

The CMDh in liaison with EMA and CHMP has agreed an update of the 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.

Q&A 10 has been amended to include the Carcinogenic Potency Categorisation Approach (CPCA) and the enhanced Ames test (EAT) for establishing Acceptable Intakes (AIs) for N-nitrosamines. The list of nitrosamines for which AIs have been established by the Non-clinical Working Party (NcWP) has been moved to a new Appendix 1, which includes new AIs for N-nitrosamines determined using the CPCA. Annex 2 and 3 have been added to further describe the CPCA and the EAT conditions.

A further update of Q&A 20 and 21 has been included to remove the universal temporary AI (t-AI), while a formal AI is established, as it is no longer considered necessary. Q&A 22 on the approach to control presence of N-nitrosamine exceeding the AI, while CAPAs are being implemented, has been amended to extend the scope to authorised products for chronic use and clarify the applicable limits and exemptions.

The new Q&As have been/will be published on the EMA website and a link is provided from the CMDh website under "Nitrosamine impurities".

The CMDh and EMA have further updated the template for the notification of step 2 confirmatory testing outcome: confirmation of nitrosamine detected, to reflect the new approaches.

As during the above-mentioned updates new and revised AIs have been published for some nitrosamines, MAHs of products concerned by those nitrosamines are requested to resubmit their step 2 response in the updated template to (re-) confirm under which scenario their products should be classified under the newly published AIs. This is particularly important in case a step 2 scenario A or D response was submitted.

Finally, the CMDh 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. As the process for handling nitrosamines is now well-established and AIs can be determined in a timely manner with the CPCA, the CMDh does not consider it necessary anymore to keep procedures in clock-stop due to missing data on nitrosamines. Any outstanding issues related to nitrosamines would have to be addressed before Day 210 of the DCP without the possibility for post-approval commitments.

All updated documents will be published on the CMDh website under "Nitrosamine impurities".

Phasing out of extraordinary COVID-19 regulatory flexibilities

The CMDh, in line with EMA, the European Commission (EC) and the Heads of Medicines Agencies (HMA), is phasing out the extraordinary regulatory flexibilities for medicines put in place during the COVID-19 pandemic to help address regulatory and supply challenges arising from the pandemic (see also EMA/EC/HMA announcement). This follows the end of the COVID-19 public health emergency declared by WHO in May 2023[1].

The extraordinary regulatory flexibilities covered different areas, including marketing authorisation and related regulatory procedures, manufacturing and importation of active pharmaceutical ingredients and finished products, quality variations, labelling and packaging requirements and compliance. Also, a series of measures to mitigate the impact of disruptions caused by the public health emergency on inspections of manufacturing facilities or other sites relevant for medicinal products in the EU was agreed during the pandemic. The extraordinary flexibilities ensured the continued availability of medicines while making sure that good manufacturing (GMP) and distribution practice (GDP) standards were being adhered to.

From now on, the regulatory flexibilities that were introduced specifically during the COVID-19 pandemic should no longer be granted. For already approved labelling flexibilities, e.g. the English-only labelling for COVID-19 vaccines, their application will be extended until the end of 2023, in order to ensure a smooth phase-out and avoid any supply difficulties or other disruptions due to a sudden change in applicable requirements. After 2023, the regular mechanisms foreseen in the legislation in relation to labelling exemptions should be followed.

Concerning on-site GMP and GDP inspections, these have been restarted after being postponed or carried out remotely during the pandemic, however, a considerable number of postponed inspections still need to be carried out. The validity of GMP and GDP certificates has currently been extended until the end of 2023, and the GMDP Inspectors Working Group will issue in the coming months an update on the approach for 2024. This Group has also reviewed experiences with remote working arrangements of Qualified Persons during the pandemic and will issue guidance on how those specific arrangements can be applied in the future.

As the CMDh specific practical guidance for facilitating the handling of processes during the COVID-19 crisis and the templates for the submission of applications for COVID-19 exceptional change management process (ECMP) are no longer needed, the CMDh has agreed to remove these documents from the CMDh website.

Core SmPC and Package Leaflet for Hormone Replacement Therapy (HRT) products

Further to the publication of the update of the Core SmPC and PL for HRT products in May 2023 to implement the product information wording regarding the known interaction between HRT products and lamotrigine, the CMDh agreed a correction of the Core PL for HRT products. Lamotrigine and medicines for Hepatitis C virus were inadvertently included under 'medicines that interfere with the effect of HRT' instead of under a separate category on the effect of HRT on other medicines.

[1] https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic

The updated document will be published on the CMDh website under "Product information > Core SmPC/PL".

Regulation (EC) No 1234/2008 on variations

The CMDh agreed an update of Chapters 4, 5, 7 and 9 of its Best Practice Guides (BPGs) for the Submission and Processing of Variations in the Mutual Recognition Procedure. A statement has been included in the chapters that the applicant should keep data synchronisation between modules 3-5 and module 1.2 during the procedures and submit an updated application form, each time the dossier information is modified in the context of response submissions. This is in line with the guidance given for new marketing authorisation applications.

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

CMDh position on PASS results according to Art. 107q of Directive 2001/83/EC concerning Trasylol (aprotinin) - EMEA/H/N/PSR/S/0030

The CMDh, having considered the results of a non-interventional imposed post-authorisation safety study (PASS) on the basis of the PRAC recommendation and the PRAC assessment report, agreed by consensus that the benefit-risk balance of the medicinal product Trasylol (aprotinin) is unchanged subject to the proposed changes to the product information:

- modification of SmPC sections 4.2, 4.4, 4.5, 4.8 and 5.1
- corresponding modification of the package leaflet
- submission of an updated risk management plan
- replacement of the conditions of a DHPC, a registry and a restricted distribution by physician educational material

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:

- apomorphine
- flurbiprofen
- lamotrigine

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

Outcome of PSUR Follow-up procedures

Lisdexamfetamine-containing medicinal products - SE/H/1839/01-06/II/40 & SE/H/1825/01-03/II/29

The CMDh endorsed the outcome of the WS variations (SE/H/1839/01-06/II/40 & SE/H/1825/01-03/II/29) for lisdexamfetamine containing medicinal products as a follow-up of a previous PSUSA.

Following the assessment of the safety signals concerning Intestinal ischaemia, Increased bleeding tendency and Vasoconstriction/vasospasm, following a request in the final AR for PSUSA/00010289/202202 concerning lisdexamfetamine changes to the SmPC section 4.8 and related parts of the PL have been agreed.

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, will be published on the CMDh website under "Pharmacovigilance > PSUR > Outcome of PSUR Follow-up procedures".

Outcomes of informal PSUR work-sharing procedures

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

- Acebis, Piramil Biso, Rabada, Ramipril + Bisoprolol fumarate Aristo, Ramipril+Bisoprolol fumarate Sandoz, Ramizek Plus (ramipril/bisoprolol)

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

EU Worksharing 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:

- Ginkgo folium

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

- Imovax Polio (Poliomyelitis vaccine (inactivated))
- Fragmin (dalteparin sodium)

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

MRP/DCP statistics in the first semester of 2023

Statistics regarding new applications in MRP and DCP in the first semester of 2023 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 2023

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

Decentralised Procedure

Table 2. New applications in Decentralised procedure started in June 2023

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	5	14

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Belgium		10
Bulgaria		8
Croatia	1	12
Cyprus		4
Czech Republic	5	14
Denmark	3	13
Estonia	2	9
Finland	1	9
France		19
Germany	20	25
Greece		8
Hungary	14	6
Iceland		9
Ireland	2	8
Italy		27
Latvia		10
Liechtenstein		
Lithuania	1	10
Luxembourg		10
Malta	1	7
Netherlands	11	16
Norway		13
Poland	2	17
Portugal	4	12
Romania		12
Slovak Republic	4	11
Slovenia	2	7
Spain	1	22
Sweden	2	19
United Kingdom (Northern Ireland)		1

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
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E-mail: H-CMDhSecretariat@ema.europa.eu
http://www.hma.eu/cmdh.html