21 October 2022
EMA/CMDh/799421/2022

Report from the CMDh meeting held on 11-13 October 2022

Medicinal products containing metronidazole (except for external use on the skin)

In October 2022, the PRAC gave advice to a Member State in relation to a type II variation for a metronidazole-containing medicinal product authorised for H. pylori eradication to update the product information to include a contraindication for patients with Cockayne syndrome (CS) and to delete the current warning (in section 4.4 of the SmPC).

It was agreed that the contraindication should be included (and the current warning in section 4.4. deleted) in the PI of all metronidazole-containing medicinal products (either as mono-component or in combination) approved **only** for H. pylori eradication (new text **underlined and in bold**, deleted text ~~strike through~~):

Summary of product characteristics:

4.3 Contraindications

- ***Patients with Cockayne syndrome (see section 4.8)***

4.4 Special warnings and precautions for use

(…) ~~*Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should therefore be used after careful benefit-risk assessment and only if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued.*~~

~~*Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole.*~~

(…)

4.8 Undesirable effects

Adverse reactions reported to occur with metronidazole

- ***Cases of severe irreversible hepatotoxicity/acute liver failure, including cases with fatal outcomes with very rapid onset after initiation of systemic use of metronidazole, have been reported in patients with Cockayne Syndrome (see section 4.3).***

Package leaflet:

Section 2

Do not take [product name]

- **If you have Cockayne syndrome (see Warnings and precautions)**

Warning and precautions

Talk to your doctor or pharmacist before taking [product name]

~~*Cases of severe liver toxicity/acute liver failure, including cases with a fatal outcome in patients with Cockayne syndrome have been reported with products containing metronidazole.*~~ ***Cases of severe irreversible liver toxicity/acute liver failure, including cases with fatal outcomes with very rapid onset after initiation of systemic use of metronidazole, have been reported in patients with Cockayne Syndrome.***

~~*If you are affected by Cockayne syndrome, your doctor should also monitor your liver function frequently while you are being treated with metronidazole and afterwards.*~~

MAHs of other metronidazole containing medicines (either as mono-component or in combination, except for external use on the skin) authorised for indications other than H. pylori eradication only (i.e. either with other indications than H. pylori eradication or with other indications in addition to H. pylori eradication) the current warning for patients with CS should be strengthened. The following amendment to section 4.4 of the SmPC was agreed (new text **underlined and in bold**, deleted text ~~strike through~~):

Hepatotoxicity in patients with Cockayne Syndrome

Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should ~~*therefore be used after careful benefit-risk assessment*~~ ***not be used unless the benefit is considered to outweigh the risk*** *and* ~~*only*~~ *if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued. Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole* ***(see section 4.8)****.*

Section 2 of the Package Leaflet (PL) does not need to be updated as it does not include reference to the required benefit-risk assessment of the prescribing doctor.

Sections 4.8 of the SmPC and 4 of the PL should be updated to reflect the new data and cases reported (new text **underlined and in bold**, deleted text ~~strike through~~):

SmPC section 4.8:

To be added under the table:

Cases of severe irreversible hepatotoxicity/acute liver failure, including cases with fatal outcomes with very rapid onset after initiation of systemic use of metronidazole, have been reported in patients with Cockayne Syndrome (see section 4.4).

PL section 4:

To be added under the listed terms with frequency "Not known (frequency cannot be estimated from the available data)":

Acute liver failure in patients with Cockayne Syndrome (see section 2 "Warnings and precautions")

Concerned MAHs are requested to submit type IB variations under C.I.z within 2 months of the date of publication of the CMDh press release.

It is generally not foreseen to provide translations via the CMDh. However, it might be that some member states will voluntarily provide translations on their websites.

The submission of worksharing procedures is recommended, where applicable.

Any submission of a variation with deviating wording needs to be substantiated with additional data and submitted as type II variation under C.I.4.

Questions & Answers on the monitoring of bioequivalence clinical trials

The CMDh, in liaison with the GCP Inspectors Working Group, agreed Q&As to give guidance to applicants on the monitoring of bioequivalence clinical trials.

The Q&As have been published on the EMA website under the Q&As on GCP (https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp).

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. Q&A 10 has been updated to add the agreed limit for N-nitrosoduloxetine and a new Q&A (Q&A 21) has been added on the approach to control the presence of nitrosamines, while the acceptable intake (AI) is being established.

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

Regulation (EC) No 1234/2008 on variations

The CMDh has agreed an update of the Best Practice Guide for the handling of type II variations in MRP (Chapter 5 of the BPGs for the Submission and Processing of Variations in MRP). Guidance on the use of the template for MAH's responses during type II variations, as agreed in September 2022, has been included in the document. The document has also been updated with other changes to reflect the current way of working.

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

Update of CMDh Guidance on the Informal Worksharing procedure for follow-up for PSUSA for NAPs

The CMDh agreed an update of its guidance on the informal worksharing procedure for follow-up for PSUSA for NAPs (PSUFU). The CMDh agreed that in the very specific and exceptional situation where the MAH anticipates not being able to meet the required submission deadline and applies for an extension, the LMS/Reference Authority/RMS does no longer need to consult the Pharmacovigilance WSP WP, but can bring the request directly to the CMDh for discussion. The updated document will be published on the CMDh website under "Pharmacovigilance > PSUR".

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:

- carboplatin
- dorzolamide
- gabapentin
- ketoprofen (topical use only)
- levothyroxine
- mesalazine
- mesterolone

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

Medicinal products containing dorzolamide

In the framework of the PSUSA on dorzolamide, the PRAC noted that dorzolamide is also authorised in fixed dose combination products. The PRAC considered that the risks of tachycardia and hypertension and the need of nasolacrimal occlusion to limit absorption of dorzolamide into the general circulation in patients with glaucoma would also be relevant to be included in products containing dorzolamide in 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 levothyroxine

In the framework of the PSUSA on levothyroxine, the PRAC noted that levothyroxine is also authorised in fixed dose combination products. The PRAC considered that the DDI between levothyroxine and PPIs, the DDI between levothyroxine and St John's wort, and biotin interference with laboratory tests in patients with hypothyroidism would also be relevant to be included in fixed dose combinations products containing levothyroxine as the discussed mechanisms could involve levothyroxine and fixed

dose combination products containing levothyroxine. 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 (Ultravist) (NO/H/xxxx/WS/055) as a follow-up of PSUSA/00001773/202006
- iohexol (Omnipaque) (NO/H/xxxx/WS/054) as a follow-up of PSUSA/00001768/202006

Based on the assessment of the submitted data, an update of the SmPC/PL and/or the RMP 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".

Recommendations on submission dates for applicants of the DCP and MRP

The CMDh has adopted updated guidance documents with the timetables for MRP/DCP applications to be submitted in 2023. The updated guidance documents will be published on the CMDh website under "Procedural guidance > Application for MA > MRP/DCP".

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 46 of the Paediatric Regulation for:

- Pneumovax 23 (Pneumococcal vaccine polyvalent / 25 micrograms of 23 pneumococcal polysaccharide serotypes)

The public assessment report 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 September 2022

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	1	5
Belgium		1
Bulgaria		2

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

Decentralised Procedure

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

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	14	6
Belgium		7
Bulgaria		13
Croatia	2	8
Cyprus	1	4
Czech Republic	6	13
Denmark	4	10
Estonia		8
Finland	2	8

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
France		10
Germany	16	17
Greece		9
Hungary	2	12
Iceland	2	4
Ireland	1	5
Italy		21
Latvia	2	12
Liechtenstein		
Lithuania	1	12
Luxembourg		8
Malta		5
Netherlands	8	11
Norway	1	12
Poland	4	15
Portugal	4	10
Romania		12
Slovak Republic	1	15
Slovenia		6
Spain		22
Sweden	8	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