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EMADOC-1700519818-2914693
Co-ordination group for Human Use (CMDh)
EURD number: PSUSA/00002042/202507

Position of the Co-ordination Group for Mutual Recognition and Decentralised Procedures for human use on Periodic Safety Update Reports for

Active substance(s): metronidazole / miconazole

Nationally authorised Medicinal product(s): See PRAC PSUR Assessment Report appendix

Basis for position

Pursuant to Article 107b of Directive 2001/83/EC, the Marketing Authorisation Holder(s) for nationally authorised medicinal products (for details see PRAC PSUR Assessment report) submitted to the European Medicines Agency periodic safety update reports (PSURs) for the medicinal products containing the above referred active substance(s).

The evaluation procedure started on 16 October 2025.

The steps taken for the assessment of the PSURs are detailed in the appended Pharmacovigilance Risk Assessment Committee (PRAC) assessment report.

The recommendation was adopted by the PRAC on 12 February 2026.

Position

1. The CMDh, having considered in accordance with Article 107g(1) of Directive 2001/83/EC the PSUR on the basis of the PRAC recommendation and the PRAC assessment report as appended, reaches its position by consensus on the variation to the terms of the Marketing Authorisation(s) for the medicinal products containing the above referred active substance(s), concerning the following change(s):

Update of sections 4.4 and 4.5 of the SmPC to add an interaction and warning/precaution regarding risk of serious drug-drug interaction between miconazole and warfarin or other vitamin K antagonists. The Package leaflet is updated accordingly.

The CMDh member(s) of Iceland, Liechtenstein and Norway agree with the above-mentioned recommendation of the CMDh. The scientific conclusions are set out in Annex I.

2. The amendments to be introduced to the product information of the medicinal products containing

the above referred active substance(s) are set out in Annex II.

3. The timetable for the implementation of this CMDh position is set out in Annex III.

To the extent that other medicinal products containing metronidazole / miconazole, not listed in the PRAC assessment report are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that the concerned Member States and Marketing Authorisation Holders take due consideration of this CMDh position.

This position is forwarded to Member States, to Iceland, Liechtenstein and Norway, to the MAHs together with its annexes and appendix(ces).

Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for metronidazole / miconazole the scientific conclusions are as follows:

In view of available data on risk of serious drug-drug interaction between miconazole and warfarin from the literature including in some cases a close temporal relationship, a positive re-challenge and in view of a plausible mechanism of action, the PRAC considers a serious drug-drug interaction between miconazole and warfarin is at least a reasonable possibility. The PRAC concluded that the product information of products containing metronidazole / miconazole should be amended accordingly.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for metronidazole / miconazole, the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing metronidazole / miconazole is unchanged subject to the proposed changes to the product information.

The CMDh recommends that the terms of the marketing authorisation(s) of the medicinal product(s) containing metronidazole / miconazole should be varied.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

Miconazole administered systemically is known to inhibit CYP3A4/2C9, which can lead to prolonged effects of warfarin or other vitamin K antagonists. While systemic absorption is limited with topical formulations, the concomitant use of <Product name> and warfarin or other vitamin K antagonists should be done with caution and the anticoagulant effect should be carefully monitored and titrated. Patients should be advised of the symptoms of bleeding events and to immediately stop treatment with miconazole and seek medical advice should they occur (see section 4.5).

- Section 4.5

An interaction should be added as follows:

~~No interaction is known with vaginally applied metronidazole and miconazole nitrate yet.~~

Miconazole administered systemically is known to inhibit CYP3A4/2C9. Due to the limited systemic availability after topical application, clinically relevant interactions are rare. However, in patients on warfarin or other vitamin K antagonists, caution should be exercised and anticoagulant effect should be monitored.

Package Leaflet

- Section 2

What you need to know before you use <Product name>

Warnings and precautions

If you are taking oral anticoagulant agents such as warfarin, stop using <Product name> immediately and seek advice from your doctor or pharmacist if you experience unexpected bleeding or bruising, nosebleeds, coughing up blood, blood in the urine, black tarry stools or coffee ground vomit during treatment with <Product name>. Close monitoring of International Normalized Ratio (INR) levels is required under the supervision of a healthcare professional during treatment with [Product name].

Other medicines and <Product name>

Talk to your doctor, pharmacist or dentist if you are taking, have recently taken or might take any other medicines

- **Oral anticoagulant agents (drugs used to thin the blood), such as warfarin, may be affected by <Product name>.**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	February 2026 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	11 April 2026
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 June 2026

APPENDIX I

PRAC PSUR Assessment Report