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 miconazole, hydrocortisone / miconazole nitrate, miconazole nitrate / zinc oxide, the scientific conclusions are as follows:

Topical formulations (dermatological and gynaecological):

In view of available data on bleeding events from the literature and spontaneous reports, reported in association with concomitant use of miconazole (dermatological and gynaecological formulations) and warfarin, including in some cases a close temporal relationship, a positive de-challenge and/or re-challenge and in view of a plausible pharmacokinetic interaction, the PRAC considers that a causal relationship between bleeding events and a drug-drug interaction between warfarin and miconazole, hydrocortisone / miconazole nitrate, miconazole nitrate / zinc oxide (topical formulations) is at least a reasonable possibility. The PRAC concluded that the product information of products containing miconazole, hydrocortisone / miconazole nitrate, miconazole nitrate / zinc oxide should be amended accordingly.

Oral formulations:

In view of available data on fixed drug eruption from the literature and spontaneous reports, including a close temporal relationship, a positive de-challenge and re-challenge and a positive challenge test, the PRAC considers a causal relationship between miconazole (oral formulations) and fixed drug eruption is at least a reasonable possibility. The PRAC concluded that the product information of products containing miconazole, hydrocortisone / miconazole nitrate, miconazole nitrate / zinc oxide (oral formulations) 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 miconazole, hydrocortisone / miconazole nitrate, miconazole nitrate / zinc oxide the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing miconazole, hydrocortisone / miconazole nitrate, miconazole nitrate / zinc oxide is unchanged subject to the proposed changes to the product information.

The CMDh recommends that the terms of the marketing authorisation(s) should be varied.

Annex II

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

Topical formulations (dermatological and gynaecological):

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**

For topical formulations (dermatological and gynaecological) that do not contain a drug-to-drug interaction with warfarin or other vitamin K antagonist in section 4.5, the following interaction should be added:

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

An interaction should be added as follows. If similar wording is already included in PL section "Other medicines" the new proposed text may be added to the existing information. Stricter information should remain.

- **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 are 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>.**

Oral formulations:

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 4.8**

The following adverse reaction should be added under the SOC Skin and subcutaneous tissue disorders with a frequency not known:

Fixed drug eruption

Package Leaflet

- ***Section 4***

Possible side effects

Frequency unknown

You should stop using <Product name> and see your doctor immediately if you get any of the following symptoms:

An allergic skin reaction, that may include round or oval patches of redness and swelling of the skin, blistering, and itching (Fixed drug eruption). Darkening of the skin in affected areas, which might persist after healing, may also occur. Fixed drug eruption usually reoccurs at the same site(s) if the medication is taken again.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	June 2025 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	3 August 2025
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	2 October 2025