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 fluconazole, the scientific conclusions are as follows:

In view of available data on adverse pregnancy outcomes from the literature, case reports and in view of a plausible mechanism of action, the PRAC considers that a causal relationship between fluconazole and adverse pregnancy outcomes is at least a reasonable possibility. The PRAC concluded that the product information of products containing fluconazole 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 fluconazole the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing fluconazole 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)

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 4.6

The information with regard to the risks of the product when used during pregnancy should be amended so that the section reads as follows:

Women of childbearing potential

Before initiating treatment, the patient should be informed of the potential risk to the fetus.

After single dose treatment, a washout period of 1 week (corresponding to 5-6 half-lives) is recommended before becoming pregnant (see section 5.2).

For longer courses of treatment, contraception may be considered, as appropriate, in women of childbearing potential throughout the treatment period and for 1 week after the final dose.

Pregnancy

~~An observational study has suggested~~ **Observational studies suggest** an increased risk of spontaneous abortion in women treated with fluconazole during the first **and/or second** trimester **compared to women not treated with fluconazole or treated with topical azoles during the same period.**

Data from several thousand pregnant women treated with a cumulative dose of ≤ 150 mg of fluconazole, administered in the first trimester, show no increase in the overall risk of malformations in the foetus. In one large observational cohort study, first trimester exposure to oral fluconazole was associated with a small increased risk of musculoskeletal malformations, corresponding to approximately 1 additional case per 1000 women treated with cumulative doses ≤450 mg compared with women treated with topical azoles and to approximately 4 additional cases per 1000 women treated with cumulative doses over 450 mg. The adjusted relative risk was 1.29 (95% CI 1.05 to 1.58) for 150 mg oral fluconazole and 1.98 (95% CI 1.23 to 3.17) for doses over 450 mg fluconazole.

~~There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were treated for at least three or more months with high doses (400-800 mg daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole use and these events is unclear.~~

Available epidemiological studies on cardiac malformations with use of fluconazole during pregnancy provide inconsistent results. However, a meta-analysis of 5 observational studies including several thousand pregnant women exposed to fluconazole during the first trimester finds a 1.8-2 fold increased risk of cardiac malformations when compared to no fluconazole use and/or topical azoles use.

Case reports describe a pattern of birth defects among infants whose mothers received high-dose (400 to 800 mg/day) fluconazole during pregnancy for 3 months or more, in the treatment of coccidioidomycosis. The birth defects seen in these infants include brachycephaly, ears dysplasia, giant anterior fontanelles, femoral bowing and radio-humeral synostosis. A causal relationship between fluconazole use and these birth defects is uncertain.

~~Studies in animals have shown reproductive toxicity (see section 5.3).~~

~~Before becoming pregnant a washout period of approximately 1 week (corresponding to 5-6 half-lives) is recommended after a single-dose or discontinuation of a course of treatment (see section 5.2).~~

Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary.

Fluconazole in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections.

Package Leaflet

- Section 2

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

If you are planning to become pregnant, it is recommended to wait a week after a single dose of fluconazole before becoming pregnant.

For longer courses of treatment with fluconazole, talk to your doctor on the need for appropriate contraception during treatment which should continue for one week after the last dose.

You should not take fluconazole if you are pregnant, think you may be pregnant, are trying to become pregnant, unless your doctor has told you so. If you become pregnant while taking this medicine or within 1 week of the most recent dose, contact your doctor.

Fluconazole taken during the first **or second** trimester of pregnancy may increase the risk of miscarriage. Fluconazole taken ~~at low doses~~ during the first trimester may ~~slightly~~ increase the risk of a baby being born with birth defects affecting **the heart,** bones and/or muscles.

There have been reports of babies born with birth defects affecting the skull, ears, and bones of the thigh and elbow in women treated for three months or more with high doses (400-800 mg daily) of fluconazole for coccidioidomycosis. The link between fluconazole and these cases is not clear.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	November 2023 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	24 December 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	22 February 2024