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 Drug reaction with eosinophilia and systemic symptoms (DRESS) from the literature and spontaneous reports including in some cases a close temporal relationship, the PRAC considers a causal relationship between fluconazole and DRESS is at least a reasonable possibility. The PRAC concluded that the product information of products containing fluconazole should be amended accordingly.

In view of available data on congenital malformations from the literature, the PRAC considers a causal relationship between fluconazole and congenital malformations is at least a reasonable possibility. The PRAC concluded that the product information of products containing fluconazole should be amended accordingly.

In view of available data on fluconazole resistance from the literature and spontaneous reports, the PRAC considers a causal relationship between fluconazole and a rise in resistance is at least a reasonable possibility. The PRAC concluded that the product information of products containing fluconazole should be amended accordingly.

The CMDh agrees with the scientific conclusions made by the PRAC.

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 reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing fluconazole 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 applicant/marketing authorisation holders take due consideration of this CMDh position.

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

Dermatological reactions

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported.

- Section 4.8

Summary of safety profile:

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with fluconazole treatment (see section 4.4).

Tabulated list of adverse reactions

The following adverse reaction should be added under the SOC Skin and subcutaneous tissue disorders with the frequency unknown:

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Package Leaflet

Section 2 - What you need to know before you use [product name]

Warnings and precautions

Talk to your doctor before <taking> <using> [product name]

- **If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after <taking><using> [product name]**

Serious skin reactions including drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with [product name] treatment. Stop <taking><using> [product name] and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

Section 4 – Possible side effects

Stop <taking><using> [product name] and seek medical attention immediately if you notice any of the following symptoms:

- **Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome).**

Summary of Product Characteristics

- Section 4.6

~~Data from several hundred pregnant women treated with standard doses (<200 mg/day) of fluconazole, administered as a single or repeated dose in the first trimester, show no undesirable effects in the foetus.~~

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.

Package Leaflet

Section 2 - What you need to know before you use [product name]

Pregnancy<,>< and> breast-feeding <and fertility>

~~You should not take Diflucan while you are pregnant or breast-feeding unless your doctor has told you to.~~**You should not take [product name] if you are pregnant, think you may be pregnant, are trying to become pregnant or breast-feeding, unless your doctor has told you so.**

Fluconazole taken during the first 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 bones and/or muscles.

Summary of Product Characteristics

- Section 4.4

Candidiasis:

Studies have shown an increasing prevalence of infections with *Candida* species other than *C. albicans*. These are often inherently resistant (e.g. *C. krusei* and *C. auris*) or show reduced susceptibility to fluconazole (*C. glabrata*). Such infections may require alternative antifungal therapy secondary to treatment failure. Therefore, prescribers are advised to take into account the prevalence of resistance in various *Candida* species to fluconazole.

- Section 5.1.

Susceptibility in vitro

C. glabrata shows ~~a wide range of susceptibility while C. krusei is resistant to fluconazole.~~ **reduced susceptibility to fluconazole while *C. krusei* and *C. auris* are resistant to fluconazole.**

Mechanisms of resistance

There have been reports of superinfection with *Candida* species other than *C. albicans*, which ~~are~~ often **have** inherently ~~not susceptible to fluconazole (e.g. Candida krusei)~~**reduced susceptibility (*C. glabrata*) or resistance to fluconazole (e.g. *C. krusei*, *C. auris*)**. Such ~~cases~~**infections** may require alternative antifungal therapy.

Package Leaflet

Section 2 - What you need to know before you use [product name]

Warnings and precautions

Talk to your doctor before <taking> <using> [product name]

- **<u>if the fungal infection does not improve, as alternative antifungal therapy may be needed.</u>**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	October 2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	27 December 2020
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	25 February 2021