



Datum: 26.04.2016
Kontakt: Ing. Veronika Iro B.Sc.
Abteilung: REGA
Tel. / Fax: +43 (0) 505 55 – 36247
E-Mail: pv-implementation@ages.at
Unser Zeichen: PHV-9042146-A-160426
Ihr Zeichen:

CMDh update:

Fluconazol– hältige Arzneispezialitäten – Änderungen der Fach- und Gebrauchsinformationen aufgrund des HBD – PSUR Worksharing Projektes

Sehr geehrte Damen und Herren,

basierend auf der Evaluierung des PSURs im EU-HBD-worksharing Projekt (Verfahrensnummer: DK/H/PSUR/0008/003) und aufgrund eines Updated Summary Assessment Reports kommt es zu der Empfehlung, folgende Ergänzungen in die **Fach- und Gebrauchsinformation** aller Fluconazol – hältigen Arzneispezialitäten zur aufzunehmen.

Die angeführten Textabschnitte stellen eine Mindestanforderung dar, zusätzliche nationale Hinweise in diesen Abschnitten sind zu belassen.



Recommendations:

- Amendments to the Product Information

During the assessment of the information in the PSUR the following issues were considered: drug interaction with amiodarone, indanedione anticoagulants, and hydrochlorothiazide, adrenal insufficiency, use in pregnancy, and fixed drug eruption.

It has been agreed that the following amendments to the Product Information are required (new text in *italics*, deleted text ~~strike through~~).

SmPC wordings

4.3 Contraindications

The contraindication should be revised as follows:

....Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 such as cisapride, astemizole, pimozide, quinidine, ~~amiodarone~~, and erythromycin are contraindicated in patients receiving fluconazole (see Sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

A warning should be added as follows:

Adrenal insufficiency

Ketoconazole is known to cause adrenal insufficiency, and this could also, although rarely seen, be applicable to fluconazole.

Adrenal insufficiency relating to concomitant treatment with Prednisone is described in section 4.5 The effect of fluconazole on other medicinal products.

4.5 Interaction with other medicinal products and other forms of interaction

The warning in the section `Concomitant use of the following other medicinal products is contraindicated` should be deleted:

~~Amiodarone: Concomitant administration of fluconazole with amiodarone may result in inhibition of amiodarone metabolism. Use of amiodarone has been associated with QT prolongation. Coadministration of fluconazole and amiodarone is contraindicated (see section 4.3).~~

A warning in the section `Concomitant use of the following other medicinal products cannot be recommended` should be added as follows:

Amiodarone: concomitant administration of fluconazole with amiodarone may increase QT prolongation. Therefore, caution should be taken when both drugs are combined, notably with high dose fluconazole (800 mg).

The warning in the section `The effect of fluconazole on other medicinal products` regarding anticoagulants should be revised as follows:

Anticoagulants: In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria, and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. During concomitant treatment with fluconazole and warfarin the prothrombin time was prolonged up to 2-fold, probably due to an inhibition of the warfarin metabolism through CYP2C9. In patients receiving coumarin-type or indanedione anticoagulants concurrently with fluconazole the prothrombin time should be carefully monitored. Dose adjustment of ~~warfarin~~ *the anticoagulant* may be necessary.

A warning under the subheadings `Concomitant use of the following other medicinal products lead to precautions and dose adjustments` and `The effect of other medicinal products on fluconazole` should be added as follows:

Hydrochlorothiazide: *In a pharmacokinetic interaction study, co-administration of multiple-dose hydrochlorothiazide to healthy volunteers receiving fluconazole increased plasma concentration of fluconazole by 40%. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving concomitant diuretics[†].*

[†] ~~Mesure R. Protocol 245. An open placebo-controlled crossover study to determine any effect of concomitant diuretic treatment on fluconazole pharmacokinetics in healthy volunteers.~~

4.6 Fertility, pregnancy and lactation

The warning should be revised as follows:

Pregnancy

~~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.~~

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.

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

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 increased risk of undesirable effects in the foetus.

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.

4.8 Undesirable effects

An asterisk * should be added after Drug Eruption. Beneath the table it should be stated ** including Fixed Drug Eruption.*

Package Leaflet

2. What you need to know before you take [X]

Do not take [X]

~~if you are taking amiodarone (used for treating uneven heartbeats 'arrhythmias')~~

Warnings and precautions

if you develop signs of 'adrenal insufficiency' where the adrenal glands do not produce adequate amounts of certain steroid hormones such as cortisol (chronic, or long lasting fatigue, muscle weakness, loss of appetite, weight loss, abdominal pain)

Other medicines and Diflucan

-amiodarone (used for treating uneven heartbeats 'arrhythmias')

-hydrochlorothiazide (a diuretic)