Bundesamt für Sicherheit
im Gesundheitswesen

BASG / AGES
Institut LCM
Traisengasse 5, A-1200 Wien

Datum: 10.08.2015
Kontakt: Veronika Iro
Abteilung: REGA
Tel. / Fax: +43 (0) 505 55 – 36247
E-Mail: pv-implemetation@ages.at
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Ihr Zeichen:

Betreff: 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) kommt es zu der Empfehlung, folgende Ergänzungen in die **Fach- und Gebrauchsinformation** aller Fluconazol – hältigen Arzneispezialitäten zur aufzunehmen.

Sollten diese bereits aufgenommen worden sein, betrachten Sie dieses Schreiben als gegenstandslos.

- Amendments to the Product Information

SmPC wordings

Section 4.3
The warning should be revised as follows:

4.3 Contraindications
.....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).

Section 4.5
A warning should be added as follows:
4.5 Interaction with other medicinal products and other forms of interaction
Concomitant use of the following other medicinal products is contraindicated:
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).*

Section 4.4
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***

Section 4.5
The warning should be revised as follows:

Anticoagulants: In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, 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.

Section 4.5
A warning should be added as follows:

Section 4.5 Interaction with other medicinal products and other forms of interaction, 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:

Hydrochlorothiazide: In a pharmacokinetic interaction study, coadministration 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.[1]

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

Section 4.6
The warning should be revised as follows:

4.6 Fertility, pregnancy and lactation

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.

Section 4.8
An asterics * 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 Diflucan
Do not take Diflucan
Include:
- if you are taking amiodarone (used for treating uneven heartbeats 'arrhythmias')

Warnings and precautions
Include:
- 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
Include:
amiodarone (used for treating uneven heartbeats 'arrhythmias')

4. Possible side effects
Include:
Diflucan may affect your adrenal glands and the levels of steroid hormones produced. The signs of adrenal problems include:
- tiredness
- muscle weakness
- loss of appetite
- weight loss
- abdominal pain

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