Bundesamt für Sicherheit
im Gesundheitswesen

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

Datum: 19.11.2014
Kontakt: Veronika Iro
Abteilung: REGA
Tel. / Fax: +43 (0) 505 55 – 36247
E-Mail: pv-implemetation@ages.at
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Betreff: Itraconazol – 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: UK/H/PSUR/0033/001) kommt es zu der Empfehlung, folgende Ergänzungen in die **Fach- und Gebrauchsinformation** aller Itraconazol– hältige Arzneispezialitäten aufzunehmen.

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

Fachinformation

4.3 Contraindications
<Produkt> are contraindicated in patients with known hypersensitivity to itraconazole or to any of the excipients.

Co-administration of the following drugs is contraindicated with <Produkt> (see also section 4.5):

- CYP3A4 metabolized substrates that can prolong the QT-interval e.g., astemizole, bepridil, cisapride, dofetilide, levacetylmethadol (levomethadyl), mizolastine, pimozide, quinidine, sertindole and terfenadine are contraindicated with <Produkt>. Co-administration may result in increased plasma concentrations of these substrates, which can lead to QT prolongation and rare occurrences of torsade de pointes.
- CYP3A4 metabolized HMG-CoA reductase inhibitors such as atorvastatin, lovastatin and simvastatin
- Triazolam and oral midazolam
- Ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine)
- Eletriptan

- Nisoldipine

<Produkt> should not be administered to patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF except for the treatment of life-threatening or other serious infections. See section 4.4.

<Produkt> must not be used during pregnancy (except for life-threatening cases). See section 4.6.

Women of childbearing potential taking <PRODUKT> should use contraceptive precautions. Effective contraception should be continued until the menstrual period following the end of <PRODUKT> therapy.

4.4 Special warnings and precautions for use

Cross-hypersensitivity
There is no information regarding cross-hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used in prescribing <Produkt> to patients with hypersensitivity to other azoles.

Cardiac effects
In a healthy volunteer study with <PRODUKT> IV, a transient asymptomatic decrease of the left ventricular ejection fraction was observed; this resolved before the next infusion. The clinical relevance of these findings to the oral formulations is unknown.

Itraconazole has been shown to have a negative inotropic effect and <PRODUKT> has been associated with reports of congestive heart failure. Heart failure was more frequently reported among spontaneous reports of 400 mg total daily dose than among those of lower total daily doses, suggesting that the risk of heart failure might increase with the total daily dose of itraconazole.

<PRODUKT> should not be used in patients with congestive heart failure or with a history of congestive heart failure unless the benefit clearly outweighs the risk. This individual benefit/risk assessment should take into consideration factors such as the severity of the indication, the dosing regimen (e.g., total daily dose), and individual risk factors for congestive heart failure. These risk factors include cardiac disease, such as ischemic and valvular disease; significant pulmonary disease, such as chronic obstructive pulmonary disease; and renal failure and other edematous disorders. Such patients should be informed of the signs and symptoms of congestive heart failure, should be treated with caution, and should be monitored for signs and symptoms of congestive heart failure during treatment; if such signs or symptoms do occur during treatment, <PRODUKT> should be discontinued.

Calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole. In addition, itraconazole can inhibit the metabolism of calcium channel blockers. Therefore, caution should be used when co-administering itraconazole and calcium channel blockers (see section 4.5) due to an increased risk of CHF.

Hepatic effects
Very rare cases of serious hepatotoxicity, including some cases of fatal acute liver failure, have occurred with the use of <PRODUKT>. Most of these cases involved patients who, had pre-existing liver disease, were treated for systemic indications, had significant other medical conditions and/or were taking other hepatotoxic drugs. Some patients had no obvious risk factors for liver disease. Some of these cases were observed within the first month of treatment, including some within the first week. Liver function monitoring should be considered in patients receiving <PRODUKT> treatment. Patients should be instructed to promptly report to their physician signs and symptoms suggestive of hepatitis such as anorexia, nausea, vomiting, fatigue, abdominal pain or dark urine. In these patients treatment should be stopped immediately and liver function testing should be conducted. In patients with raised liver enzymes or active liver disease, or who have experienced liver toxicity with other drugs, treatment should not be

started unless the expected benefit exceeds the risk of hepatic injury. In such cases liver enzyme monitoring is necessary.

Reduced gastric acidity
Absorption of itraconazole from <Produkt> is impaired when gastric acidity is reduced. In patients also receiving acid neutralizing medicines (e.g. aluminium hydroxide) these should be administered at least 2 hours after the intake of <Produkt>. In patients with achlorhydria such as certain AIDS patients and patients on acid secretion suppressors (e.g., H2-antagonists, proton pump inhibitors) it is advisable to administer <Produkt> with a cola beverage.

Use in children
Clinical data on the use of <Produkt> in paediatric patients is limited. <Produkt> should not be used in paediatric patients unless the potential benefit outweighs the potential risks.

Use in elderly
Clinical data on the use of <Produkt> in elderly patients is limited. <Produkt> should not be used in these patients unless the potential benefit outweighs the potential risks.

Hepatic impairment
Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when the drug is administered in this patient population. (See section 5.2).

Renal impairment
Limited data are available on the use of oral itraconazole in patients with renal impairment. Caution should be exercised when this drug is administered in this patient population. The oral bioavailability of itraconazole may be lower in patients with renal insufficiency. Dose adaptation may be considered.

Hearing Loss
Transient or permanent hearing loss has been reported in patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated (see sections 4.3 and 4.5). The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

Immunocompromised patients
In some immunocompromised patients (e.g., neutropenic, AIDS or organ transplant patients), the oral bioavailability of <Produkt> may be decreased.

Patients with immediately life-threatening systemic fungal infections
Due to the pharmacokinetic properties (see Section 5.2), <Produkt> are not recommended for initiation of treatment in patients with immediately life-threatening systemic fungal infections.

Patients with AIDS
In patients with AIDS having received treatment for a systemic fungal infection such as sporotrichosis, blastomycosis, histoplasmosis or cryptococcosis (meningeal and non-meningeal) and who are considered at risk for relapse, the treating physician should evaluate the need for a maintenance treatment.

Neuropathy
If neuropathy occurs that may be attributable to <Produkt>, the treatment should be discontinued.

Disorders of Carbohydrate Metabolism
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Cross-resistance
In systemic candidosis, if fluconazole-resistant strains of *Candida* species are suspected, it cannot be assumed that these are sensitive to itraconazole, hence their sensitivity should be tested before the start of itraconazole therapy.

Interaction potential
<PRODUKT> has a potential for clinically important drug interactions. (See section 4.5).
Itraconazole should not be used within 2 weeks after discontinuation of treatment with CYP 3A4 inducing agents (rifampicin, rifabutin, phenobarbital, phenytoin, carbamazepine, *Hypericum perforatum* (St. John´s wort)). The use of itraconazole with these drugs may lead to subtherapeutic plasma levels of itraconazole and thus treatment failure.

4.5 Interaction with other medicinal products and other forms of interaction

1. Drugs affecting the absorption of itraconazole
Drugs that reduce the gastric acidity impair the absorption of itraconazole from <Produkt> (see section 4.4).

2. Drugs affecting the metabolism of itraconazole
Itraconazole is mainly metabolized through the cytochrome CYP3A4. Interaction studies have been performed with rifampicin, rifabutin and phenytoin, which are potent enzyme inducers of CYP3A4. Since the bioavailability of itraconazole and hydroxy-itraconazole was decreased in these studies to such an extent that efficacy may be largely reduced, the combination of itraconazole with these potent enzyme inducers is not recommended. No formal study data are available for other enzyme inducers, such as carbamazepine, *Hypericum perforatum* (St John's Wort), phenobarbital and isoniazid, but similar effects should be anticipated.

Potent inhibitors of this enzyme such as ritonavir, indinavir, clarithromycin and erythromycin may increase the bioavailability of itraconazole.

3. Effect of itraconazole on the metabolism of other drugs

3.1 Itraconazole can inhibit the metabolism of drugs metabolized by the cytochrome 3A family. This can result in an increase and/or a prolongation of their effects, including side effects. When using concomitant medication, the corresponding label should be consulted for information on the route of metabolism. After stopping treatment, itraconazole plasma concentrations decline gradually, depending on the dose and duration of treatment (see section 5.2). This should be taken into account when the inhibitory effect of itraconazole on co-medicated drugs is considered.

Examples are:

The following drugs are contraindicated with itraconazole:
- Astemizole, bepridil, cisapride, dofetilide, levacetylmethadol (levomethadyl), mizolastine, pimozide, quinidine, sertindole and terfenadine are contraindicated with <PRODUKT> since co-administration may result in increased plasma concentrations of these substrates, which can lead to QT prolongation and rare occurrences of torsade de pointes.
- CYP3A4 metabolized HMG-CoA reductase inhibitors such as atorvastatin, lovastatin and simvastatin.
- Triazolam and oral midazolam.
- Ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine)

- Eletriptan
- Nisoldipine
- Caution should be exercised when co-administering itraconazole with calcium channel blockers due to an increased risk of CHF. In addition to possible pharmacokinetic interactions involving the drug metabolizing enzyme CYP3A4, calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole.
- *The following drugs should be used with caution, and their plasma concentrations, effects or side effects should be monitored. Their dosage, if co-administered with itraconazole, should be reduced if necessary:*
- Oral anticoagulants;
- HIV Protease Inhibitors such as indinavir, ritonavir and saquinavir;
- Certain antineoplastic agents such as busulphan, docetaxel, trimetrexate and vinca alkaloids;
- CYP3A4 metabolized calcium channel blockers such as dihydropyridines and verapamil;
- Certain immunosuppressive agents: cyclosporine, rapamycin (also known as sirolimus) and tacrolimus;
- Certain glucocorticosteroids such as budesonide, dexamethasone, fluticasone and methylprednisolone;
- Digoxin (via inhibition of P-glycoprotein)
- Others: alfentanil, alprazolam, brotizolam, buspirone, carbamazepine, cilostazol, disopyramide, ebastine, eletriptan, fentanyl, halofantrine, midazolam IV, reboxetine, repaglinide, rifabutin.

3.2 No interaction of itraconazole with zidovudine (AZT) and fluvastatin has been observed. No inducing effects of itraconazole on the metabolism of ethinyloestradiol and norethisterone were observed.

4. Effect on protein binding

In vitro studies have shown that there are no interactions on the plasma protein binding between itraconazole and imipramine, propranolol, diazepam, cimetidine, indomethacin, tolbutamide and sulfamethazine.

4.6 Pregnancy and lactation

Pregnancy

<PRODUKT> must not be used during pregnancy except for life-threatening cases where the potential benefit to the mother outweighs the potential harm to the fetus (see section 4.3).
In animal studies itraconazole has shown reproduction toxicity (see section 5.3).

There is limited information on the use of <PRODUKT> during pregnancy. During post-marketing experience, cases of congenital abnormalities have been reported. These cases included skeletal, genitourinary tract, cardiovascular and ophthalmic malformations as well as chromosomal and multiple malformations. A causal relationship with <PRODUKT> has not been established.

Epidemiological data on exposure to <PRODUKT> during the first trimester of pregnancy – mostly in patients receiving short-term treatment for vulvovaginal candidosis – did not show an increased risk for malformations as compared to control subjects not exposed to any known teratogens.

Women of childbearing potential

Women of childbearing potential taking <Produkt> should use contraceptive precautions. Effective contraception should be continued until the menstrual period following the end of <PRODUKT> therapy.

Lactation

A very small amount of itraconazole is excreted in human milk. The expected benefits of <Produkt> therapy should therefore be weighed against the potential risk of breast-feeding. In case of doubt, the patient should not breast-feed.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. When driving vehicles and operating machinery the possibility of adverse reactions such as dizziness, visual disturbances and hearing loss (see Section 4.8), which may occur in some instances, must be taken into account.

4.8 Undesirable effects

Undesirable effects listed below have been reported in clinical trials with <Produkt> and/or from spontaneous reports from post-marketing experience for all <PRODUKT> formulations.
In clinical trials involving 2104 itraconazole-treated patients in the treatment of dermatomycoses or onychomycosis, the most frequently reported adverse experiences in clinical trials were of gastrointestinal, dermatological, and hepatic origin.
The table below presents adverse drug reactions by System Organ Class. Within each System Organ Class, the adverse drug reactions are presented by incidence, using the following convention:

Very common (1/10); Common (1/100 to < 1/10); Uncommon (1/1,000 to < 1/100); Rare (1/10,000 to < 1/1,000); Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

Adverse Drug Reactions	
Blood and lymphatic system disorders	
Rare	Leukopenia,
Not Known	Neutropenia, Thrombocytopenia
Immune system disorders	
Uncommon	Hypersensitivity*

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Adverse Drug Reactions	
Not Known	Anaphylactic Reaction, Anaphylactoid Reaction, Angioneurotic Oedema, Serum Sickness
Metabolism and nutrition disorders	
Not Known	Hypokalemia, Hypertriglyceridemia
Nervous system disorders	
Uncommon	Headache, Dizziness, Paraesthesia
Rare	Hypoaesthesia
Not Known	Peripheral Neuropathy*
Eye disorders	
Rare	Visual Disturbance
Not Known	Vision Blurred and Diplopia
Ear and labyrinth disorder	
Rare	Tinnitus
Not Known	Transient or permanent Hearing Loss*
Cardiac disorders	
Not Known	Congestive Heart Failure*
Respiratory, thoracic and mediastinal disorders	
Not Known	Pulmonary Oedema
Gastrointestinal disorders	
Common	Abdominal Pain, Nausea
Uncommon	Vomiting, Diarrhoea, Constipation, Dyspepsia, Dysgeusia; Flatulence
Rare	Pancreatitis
Hepatobiliary disorders	
Uncommon	Hyperbilirubinaemia, Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased
Rare	Hepatic Enzyme Increased
Not Known	Acute Hepatic Failure*, Hepatitis, Hepatotoxicity*
Skin and subcutaneous tissue disorders	
Common	Rash
Uncommon	Urticaria, Alopecia, Pruritus
Not Known	Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome, Erythema Multiforme, Exfoliative Dermatitis, Leukocytoclastic Vasculitis, Photosensitivity
Musculoskeletal and connective tissue disorders	
Not Known	Myalgia, Arthralgia
Renal and urinary disorders	
Rare	Pollakiuria,
Not Known	Urinary Incontinence
Reproductive system and breast disorders	
Uncommon	Menstrual disorder
Not Known	Erectile Dysfunction

Adverse Drug Reactions	
General disorders and administration site conditions	
Uncommon	Oedema
Rare	Pyrexia

* see section 4.4.

4.9 Overdose

No data are available.

In the event of an overdose, supportive measures should be employed. Within the first hour after ingestion, gastric lavage may be performed. Activated charcoal may be given if considered appropriate.

Itraconazole cannot be removed by hemodialysis.

No specific antidote is available.

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