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Betreff: Clarithromycin – 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: IE/H/PSUR/0020/003) kommt es zu der Empfehlung, folgende Ergänzungen in die **Fach- und Gebrauchsinformation** aller Clarithromycin – hältigen Arzneispezialitäten zur aufzunehmen.

Amendments to the Product Information

It has been agreed that the following amendments to the Product Information are required:

SmPC wording

4.3 Contraindications

Concomitant administration of clarithromycin and any of the following drugs is contraindicated: astemizole, cisapride, pimozide, terfenadine as this may result in QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsade de pointes (see section 4.5).

Clarithromycin should not be given to patients with history of QT prolongation (*congenital or documented acquired QT prolongation*) or ventricular cardiac arrhythmia, including torsades de pointe (see sections 4.4 and 4.5).

Clarithromycin should not be given to patients with hypokalaemia (risk of prolongation of QT-time)

4.4 Special warnings and special precautions for use

Prolongation of the QT Interval

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsade de pointes, have been seen in treatment with macrolides including clarithromycin (see section 4.8). Therefore as the following situations may lead to an

Increased risk for ventricular arrhythmias (including torsade de pointes), clarithromycin should be used with caution in the following patients;

~~Due to the risk for QT prolongation, clarithromycin should be used with caution in~~

- ~~P~~patients with coronary artery disease, severe cardiac insufficiency, ~~hypomagnesaemia~~ **conduction disturbances or clinically relevant bradycardia ($\leftarrow 50 \text{ bpm}$)**
- ***Patients with electrolyte disturbances such as hypomagnesaemia. Clarithromycin must not be given to patients with hypokalaemia (see section 4.3).***
- ~~Or Patients concomitantly taking when co-administered with other medicinal products associated with QT prolongation (see section 4.5).~~
- ***Concomitant administration of clarithromycin with astemizole, cisapride, pimozide and terfenadine is contraindicated (see section 4.3).***
- Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia (see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

[...]

CYP3A-based Interactions

[...]

The following drugs or drug classes are known or suspected to be metabolized by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, cyclosporine, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin), atypical antipsychotics (e.g. quetiapine), pimozide, quinidine, rifabutin, sildenafil, simvastatin, tacrolimus, terfenadine, triazolam and vinblastine, but this list is not comprehensive. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate

[...]

Colchicine

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. ~~Patients should be monitored for clinical symptoms of colchicine toxicity (see section 4.3 and 4.4).~~

4.8 Undesirable Effects

System Organ Class	Very common ($\geq 1/10$)	Common $\geq 1/100$ to $< 1/10$	Uncommon $\geq 1/1,000$ to $< 1/100$	Not Known* (cannot be estimated from the available data)
Cardiac disorders			Cardiac arrest, atrial fibrillation, electrocardiogram QT prolonged, extrasystoles, palpitations	Torsade de pointes, ventricular tachycardia <i>ventricular fibrillation</i>
Psychiatric Disorders		Insomnia	Anxiety, Nervousness, screaming	Psychotic disorder, confusional state,

				depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania
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Leaflet wording (if available)

2. Before taking Klacid tablets or Klacid Forte

Do not take Klacid tablets or Klacid Forte tablets if:

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You are taking medicines called terfenadine or astemizole (for hay fever or allergies) or cisapride or pimozide tablets as combining these drugs can sometimes cause serious disturbances in heart rhythm. Consult your doctor for advice on alternative medicines.

You are taking other medicines which are known to cause serious disturbances in heart rhythm

You have abnormally low levels of potassium ***or magnesium*** in your blood (hypokalaemia ***or hypomagnesaemia***)

You or someone in your family has a history of heart rhythm disorders (ventricular cardiac arrhythmia, including torsades de pointes) or abnormality of electrocardiogram (ECG, electrical recording of the heart) called "long QT syndrome".

* Sollte eine Häufigkeit bekannt sein oder errechnet werden können, so ist diese bitte anzugeben.

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