Klacid (Clarithromycin)

Recommendations:

- **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~~p~~atients with coronary artery disease, severe cardiac insufficiency,~~hypomagnesaemia~~ ***conduction disturbances or clinically relevant*** bradycardia ~~(< 50 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 terfendine 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 (≥1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥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 ***ventricular fibrillation***
Psychiatric Disorders		Insomnia	Anxiety, Nervousness, ~~screaming~~	Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania

Leaflet wording (if available)

2. Before taking Klacid tablets or Klacid Forte
Do not take Klacid tablets or Klacid Forte tablets if:

.....

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”.

ANNEX I

RECOMMENDED CHANGES TO THE PRODUCT INFORMATION

For all formulations: Immediate release tablets, Granules for Oral Suspension, Powder for solution for injection, Extended release tablets, Modified release tablets

- In relation to colchicine it is noted that in section 4.5 the product information contains wording describing the colchicine-clarithromycin interaction followed by a statement advising that "Patients should be monitored for clinical symptoms of colchicine toxicity (sec secton 4.4)". As colchcine is now contraindicated with clarithromycin this statement is considered contradictory and should be amended.

- In relation to the cardiovascular risk in order to improve the accessibility of the product information to healthcare professionals and patients the MAH is requested to consider the following updates proposed by the assessor to sections 4.3 and 4.4 (additions in red, deletions in strikethrough). Additionally the MAH is requested to update section 4.8 with the PT ventricular fibrillation given the biological plausibility and the fact that there have been 48 cases of ventricular fibrillation reported in the MAH's database and 58 cases in Eudravigilance including a numbero cases where causality with clarithromycin cannot be excluded..

- Based on the analysis requested for the RSI the MAH is requested to consider further strengthening of risk minimisation in the SmPC to address drug and/or patient characteristics that may be relevant to mitigation of the QT risk and in particular consider the clarity of the current advice in the SmPC for management of drug-drug interactions.

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System Organ Class	Very common (≥1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥1/1,000 to < 1/100	Not Known (cannot be estimated from the available data)
Cardiac disorders			Cardiac arrest[1], atrial fibrillation[1], electrocardiogram QT prolonged[7], extrasystoles[1], palpitations	Torsade de pointes[7], ventricular tachycardia[7] ***ventricular fibrillation***

Patient Information Leaflet

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