Roxithromycin

Core Safety Profile

Formulations:

- Film-coated tablets: 50 mg, 100 mg, 150 mg, 300 mg
- Powder for oral suspension: 50 mg
- Scored tablets for oral suspension: 50 mg

4.3 Contraindications

Roxithromycin is contraindicated in case of:

- hypersensitivity to macrolides
- concomitant therapy with vasoconstrictive ergot alkaloids (see 4.5)
- coadministration with medicinal products with narrow therapeutic windows and which are substrates of CYP3A4 (e.g. astemizole, cisapride, pimozide and terfenadine) (see 4.4 and 4.5).

4.4 Special warnings and precautions for use

Warning

Severe vasoconstriction ("ergotism") with possibly necrosis of the extremities has been reported when macrolides antibiotics have been associated with vasoconstrictive ergot alcaloids. Absence of treatment by these alcaloids must always be checked before prescribing roxithromycin (see section 4.4).

Precautions

- In severe hepatic insufficiency use of roxithromycin is not recommended."
- Roxithrromycin should ve be used with caution in patients with mild-moderate liver impairment.
- It is not necessary to adjust the dosage in the elderly.
- Renal excretion of roxithromycin and its metabolites accounts for approximately 10 % of an oral dose. The dosage should be kept unchanged in renal insufficiency.
- Medicinal products with a potential to prolong the QT interval Caution is warranted when roxithromycin is administered to patients taking other medicinal products with the potential to prolong the QT interval (see section 4.5). These include Class IA (e.g.quinidine, procainamide, disopyramide) and Class III (e.g. dofetilide, amiodarone) antiarrhythmic agents, citalopram, tricyclic antidepressants, methadone, some antipsychotics (e.g. phenothiazines), fluoroquinolones (e.g. moxifloxacin), some antifungals (e.g. fluconazole, pentamidine), and some antiviral drugs (e.g. telaprevir).As is known to happen with other macrolides, roxithromycin may have the potential to aggravate myasthenia gravis

- Monitoring of the liver and kidney function and the blood counts is recommended especially during long-term treatment. (i.e,. more than 2 weeks) (section 4.8)
- Clostridium difficile-associated disease: Diarrhea, particularly if severe, persistent and/or bloody, during or after treatment with roxithromycin, may be symptomatic of pseudomembranous colitis. If pseudo-membranous colitis is suspected, roxithromycin must be stopped immediately.
- Patients with rare hereditary disorders of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Association contra-indicated

Vasoconstrictive ergot alcaloids (see Contraindications).

Roxithromycin is a weak inhibitor of CYP3A4

• Astemizole, cisapride, pimozide

Other drugs, such as astemizole, cisapride or pimozide, which are metabolized by hepatic CYP3A isozyme have been associated with QT interval prolongation and/or cardiac arrhythmias (typically torsades de pointe) as a result of increase in their serum level subsequent to interaction with significant inhibitors of this isozyme, including some macrolide antibacterials. Although roxithromycin has no or limited ability to complex CYP3A and therefore to inhibit the metabolism of other drugs processed by this isozyme, a potential for clinical interaction of roxithromycin with the above mentioned drugs cannot be either ascertained or ruled out in confidence therefore, association of roxithromycin with such drugs is not recommended.

• Terfenadine

Certain macrolides are capable of pharmacokinetic interaction with terfenadine leading to increased serum concentration of the latter. This may result in severe ventricular arrhythmia, typically torsades de pointe. Although such a reaction has not been demonstrated with roxithromycin and studies in a linmited number of healty volunteers hav not shown any pharmacokinetic interaction or relevant ECG changes, the association of roxithromycin and terfenadine is not recommended.

Associations not recommended

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- Medicinal products with a potential to prolong the QT interval

Caution is warranted when roxithromycin is administered to patients taking other medicinal products with the potential to prolong the QT interval (see section 4.4). These include Class IA (e.g.quinidine, procainamide, disopyramide) and Class III (e.g. dofetilide, amiodarone) antiarrhythmic agents, citalopram, tricyclic antidepressants, methadone, some antipsychotics (e.g. phenothiazines), fluoroquinolones (e.g. moxifloxacin), some antifungals (e.g. fluconazole, pentamidine), and some antiviral drugs (e.g. telaprevir).

- Warfarin and other anticoagulantia

No interaction with warfarin has been found in studies in volunteers; however, increases in prothrombin time or International Normalized Ratio (INR) which may be explained by the infectious episode have been reported in patients treated with roxithromycin and vitamin K antagonists. It is prudent practice to monitor INR during combined treatment with roxithromycin and vitamin K antagonists.

- Disopyramide

An in-vitro study has shown that roxithromycin can displace protein-bound disopyramide ; such an effect in vivo may result in increased serum levels of free disopyramide. Consequently ECG and, if possible, disopyramide serum levels should be monitored.

Precautions for use

- Digoxin and other cardiac glycosides:

A study in healthy volunteers has shown that roxithromycin may increase the absorption of digoxin. This effect, common to other macrolides, may very rarely result in cardiac glycoside toxicity. This may be manifested by symptoms such as nausea, vomiting, diarrhea, headache or dizziness; cardiac glycoside toxicity may also elicit heart conduction and/or rhythm disorders. Consequently, in patients treated with roxithromycin and digoxin or another cardiac glycoside, ECG and, if possible, the serum level of the cardiac glycoside should be monitored; this is mandatory if symptoms which may suggest cardiac glycoside overdosage occur.

- Roxithromycin, like other macrolides, should be used with caution in patient receiving Class IA and III antiarrhythmic agents

Associations to be taken into account

• Co-administration of roxithromycin (300 mg daily) and midazolam (15 mg orally) increased the midazolam (a sensitive CYP3A4 substrate) AUC by 47%, which may lead to enhanced midazolam effets

• A slight increase has been detected in plasma concentrations of theophylline, but this does not generally require alteration of the usual dosage.

• Roxithromycin may increase the AUC and plasma concentrations of bromocriptine, which could lead to an increased risk for adverse effects of the compound.

• In a clinical study to assess the effects of roxithromycin on cyclosporin exposure, 8 heart transplant recipients treated with cyclosporine for at least 1 month received roxithromycin 150 mg bid for 11 days. Roxithromycin caused a 50% increase in plasma cyclosporin concentrations that progressively decreased on roxithromycin discontinuation.

• Roxithromycin can increase the plasma concentration of rifabutin.

Others

There is no clinically significant interaction with carbamazepine, ranitidine, aluminum or magnesium Hydroxide.

There are negative studies of clinical interactions to assess the effects of roxithromycin and oral contraceptives containing oestrogens and progestogens, although in very few subjects.

4.6 Fertility, pregnancy and lactation

Pregnancy

Studies in several animal species have not shown any teratogenic or fetotoxic effect At doses up to 200mg/kg/day, or 40 times the human therapeutic dose. The safety of roxithromycin for the fetus has not been established in human pregnancy.

Lactation

Small amounts of roxithromycin are excreted in human breast milk. Breast-feeding or treatment of the mother should therefore be discontinued as necessary.

4.7 Effects on ability to drive and use machines

Attention should be drawn to the possibility of dizziness.

4.8 Undesirable effects

System organ class	Very common (>1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Not known (cannot be estimated from available data)
Infections and Infestations				Superinfection (on prolonged use) Clostridium difficile colitis (pseudomembranous colitis)
Blood and lymphatic system disorders			Eosinophilia	Agranulocytosis Neutropenia Thrombocytopenia
Immune system disorders				Anaphylactic shock
Psychiatric disorders				Hallucination Confusional state (confusion)
Nervous system disorders		Dizziness Headache		Paraesthesia Dysgeusia (taste disturbance) Ageusia Parosmia (smell perversion) Anosmia
Respiratory, thoracic and mediastinal disorders				Bronchospasm
Gastrointestinal disorders		Nausea Vomiting Dyspepsia (epigastric pain) Diarrhoea		Diarrhoea haemorrhagic Pancreatitis
Hepatobiliary disorders				Hepatitis cholestatic (cholestatic or hepatocellular acute hepatitis)
Skin and subcutaneous tissue disorders		Rash	Erythema multiforme Urticaria	Angioedema Purpura Stevens-Johnson syndrome Toxic epidermal necrolysis
Investigation				Aspartate aminotransferase increased (ASAT) Alanine

				aminotransferase increased (ALAT) Blood alkaline phosphatise Increate
Cardiac disorders (1)				QT interval prolongation Ventricular tachycardia Torsade de pointes

1. As with other macrolides, cases of QT prolongation, ventricular tachycardia and torsades de pointes were rarely reported for roxithromycin.

4.9 Overdose

Management

Action to be taken in case of overdosage with symptomatic treatment. No specific antidote exists.