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At plasma concentrations achieved with the recommended therapeutic doses, roxithromycin has been demonstrated to have *in vitro* and clinical activity against the following microorganisms:

*Streptococcus pneumoniae*, *Strep. pyogenes*, *Mycoplasma pneumoniae*, *Moraxella catarrhalis*, *Ureaplasma urealyticum* and *Chlamydia* sp.

Roxithromycin has been demonstrated to have clinical activity against the following microorganisms which are partially sensitive *in vitro* to roxithromycin:

*Haemophilus influenzae* and *Staphylococcus aureus*, except methicillin resistant *Staph. aureus* (MRSA).

The following strains of microorganisms are resistant:

Multiresistant *Staph. aureus*, Enterobacteriaceae, *Pseudomonas* sp. and *Acinetobacter* sp.

#### Susceptibility Testing

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (eg. NCCLS).

Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that a pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Using the National Committee for Clinical Laboratory Standard (NCCLS) method of susceptibility testing with a 15mcg roxithromycin disc, susceptible organisms other than *Haemophilus influenzae* produce zones of inhibition 21mm or greater. A zone size of 10 to 20mm should be considered intermediate and a zone size of 9mm or less indicates resistance. A bacterial isolate may be considered susceptible if the MIC value for roxithromycin is less than or equal to 1 mg/L. Organisms are considered resistant if the MIC value is greater than 8 mg/L.

For *Haemophilus influenzae*, zones of inhibition 10 mm or greater indicate susceptibility when CO<sub>2</sub> incubation and the HTM agar is used with a 15mcg roxithromycin disc. An isolate may be considered susceptible if the MIC value for roxithromycin is less than or equal to 8mg/L.

#### Absorption

Roxithromycin is absorbed after oral administration with an absolute bioavailability of approximately 50%. Peak plasma concentrations following administration of 150 and 300

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mg film-coated tablets are achieved in young and elderly adult patients approximately one to two hours post-dose.

As food intake delays absorption, Roxithromycin Sandoz should be administered at least 15 minutes before food or, alternatively, on an empty stomach (i.e. more than three hours after a meal).

Absorption is not linear; with increasing doses in the range 150 to 300 mg, peak plasma levels and area under the curve (AUC) do not increase in proportion to the dose.

After repeated administration of 2.5mg/kg every 12 hours to children, the average peak plasma concentration at steady state was 9mg/L and the AUC was 61mg.h/L.

Following administration of a single oral dose of Roxithromycin 150 mg to healthy young adults, the mean peak plasma concentration was 6.6 mg/L and the AUC was 69mg.h/L. At steady state following doses of 150 mg twice daily, the mean peak plasma concentration was 9.3 mg/L and the AUC was 71mg.h/L.

In elderly patients, the mean peak plasma concentration following a single 150 mg dose was 9.1 mg/L and the AUC was 148mg.h/L. At steady state, a dosage regimen of 150 mg twice daily produced a mean peak plasma concentration of 11.3mg/L and an AUC of 83mg.h/L.

Following administration of a single oral dose of Roxithromycin 300 mg to healthy young adults, the mean peak plasma concentration was 9.7 mg/L and the AUC was 98mg.h/L. At steady state following doses of 300 mg once daily, the mean peak plasma concentration was 10.9mg/L and the AUC was 77mg.h/L.

In elderly patients, the mean peak plasma concentration following a single 300 mg dose was 10.8 mg/L and the AUC was 197mg.h/L.

After administration of a single oral dose of Roxithromycin Sandoz 150mg to healthy male and female adults, the mean peak plasma concentration was 6.58 mg/L and the AUC was 94.98 mg.hour/L

After administration of a single oral dose of Roxithromycin Sandoz 300mg to healthy male and female adults, the mean peak plasma concentration was 10.10 mg/L and the AUC was 143.48 mg.hour/L

### Distribution

Roxithromycin is 92 to 96% bound to plasma proteins (principally alpha-1-acid glycoprotein, but also albumin) at concentrations less than 4.2 mg/L. The binding is saturable; in subjects with normal plasma levels of alpha-1-acid glycoprotein, the extent of binding decreases when plasma concentrations of roxithromycin exceed 4.2 mg/L. At a plasma concentration of 8.4 mg/L approximately 87% of the drug is protein bound.

Roxithromycin is highly concentrated in polymorphonuclear leucocytes and macrophages, where levels 30 times those in serum have been reported.

### Elimination

The mean half-life of roxithromycin is approximately 12 hours in young adults and 20 hours in children. The apparently longer half-life in children does not cause excessive accumulation; minimum concentration (C<sub>min</sub>) and AUC values are comparable for adults and children.

The half-life is prolonged to 25 hours in patients with impaired hepatic function and 18 hours in patients with renal insufficiency.

The mean half-life in elderly patients is approximately 27 hours.

### Metabolism

Roxithromycin undergoes limited metabolism in the body, presumably in the liver. The major metabolite is descladinose roxithromycin. Two minor metabolites have also been identified. Plasma levels of roxithromycin are approximately twice those of all metabolites; a similar ratio is seen in the urine and faeces.

Approximately 7% of a dose is excreted in the urine and 13% is eliminated via the lungs. Faecal excretion, which represents the unabsorbed fraction and the small proportion excreted by the liver, accounts for approximately 53% of the dose. The fate of the remainder is unknown.

When roxithromycin plasma levels are above 4.2 mg/L, renal clearance increases because reduced plasma protein binding (see Distribution) causes increased levels of unbound roxithromycin which may be excreted by the kidneys.

## **INDICATIONS**

*Adults:* Roxithromycin Sandoz is indicated for the treatment of the following types of mild to moderately severe infections in adults caused by or likely to be caused by susceptible microorganisms.

- Upper respiratory tract infection: acute pharyngitis, tonsillitis and sinusitis.
- Lower respiratory tract infection: acute bronchitis and acute exacerbations of chronic bronchitis; community acquired pneumonia.
- Skin and skin structure infections.
- Nongonococcal urethritis.

*Children:* Roxithromycin Sandoz 150 mg tablets are indicated for the treatment of the following mild to moderately severe infections in children caused by or likely to be caused by susceptible microorganisms.

- Acute pharyngitis.
- Acute tonsillitis.
- Impetigo.

Appropriate culture and sensitivity tests should be performed when necessary to determine organism susceptibility and thus treatment suitability. Therapy with roxithromycin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

## **CONTRAINDICATIONS**

- Hypersensitivity to roxithromycin, macrolides, including erythromycin or to any of the excipients.
- Severely impaired hepatic function (see Precautions).
- Concomitant therapy with vasoconstrictive ergot alkaloids (see Interactions with other medicines).

- Coadministration with medicinal products with narrow therapeutic windows and which are substrates of CYP3A4 (e.g. astemizole, cisapride, pimozone and terfenadine) (see Precautions).

## PRECAUTIONS

### Impaired renal function

The safety of roxithromycin has not been demonstrated in patients with impaired renal function. Caution should be exercised if roxithromycin is administered to patients with impaired renal function.

Renal excretion of roxithromycin and its metabolites accounts for a small amount of an oral dose. The dosage should be kept unchanged in renal insufficiency.

### Impaired hepatic function

The safety of roxithromycin has not been demonstrated in patients with impaired hepatic function. Caution should be exercised if Roxithromycin Sandoz is administered to patients with impaired hepatic function, in severe cases, use of roxithromycin is not recommended. If administered to patients with severely impaired hepatic function (e.g. hepatic cirrhosis with jaundice and/or ascites), consideration should be given to reducing the daily dosage to half the usual dosage.

Roxithromycin, like erythromycin, has been shown *in vitro* to elicit a concentration dependent lengthening in cardiac action potential duration. Such an effect is manifested only at supra-therapeutic concentrations. Accordingly, the recommended doses should not be exceeded.

Prolonged or repeated use of antibiotics including roxithromycin may result in superinfection by resistant organisms. In the event of superinfection, roxithromycin should be discontinued and appropriate therapy instituted.

When indicated, incision, drainage or other appropriate surgical procedures should be performed in conjunction with antibiotic therapy.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics. A toxin produced by *Clostridium difficile* appears to be the primary cause. If pseudomembranous colitis is suspected, roxithromycin must be stopped immediately. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea particularly if severe, persistent and/or bloody, or colitis in association with antibiotic use (this may occur during treatment and up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases, appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement therapy should be provided when indicated.

Drugs that delay peristalsis, e.g. opiates and diphenoxylate with atropine (e.g. Lomotil), may prolong and/or worsen the condition and should not be used.

In certain conditions macrolides, including roxithromycin, have the potential to prolong

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the QT interval. Therefore roxithromycin should be used with caution in patients with congenital prolongation of the QT interval, with ongoing proarrhythmic conditions (ie uncorrected hypokalemia or hypomagnesaemia, clinically significant bradycardia), and in patients receiving 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). (see INTERACTIONS WITH OTHER MEDICINES).

As 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.

#### Use in the elderly

No dosage adjustment is required in elderly patients.

#### Carcinogenesis, mutagenesis, impairment of fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of roxithromycin. Roxithromycin has shown no mutagenic potential in standard laboratory tests for gene mutation and chromosomal damage.

There was no effect on the fertility of rats treated with roxithromycin at oral doses up to 180 mg/kg/day.

#### Use in pregnancy (Category B1)

Reproductive studies in rats, mice and rabbits at doses of 100, 400 and 135 mg/kg/day, respectively, did not demonstrate evidence of developmental abnormalities. In rats, at doses above 180 mg/kg/day, there was evidence of embryotoxicity and maternotoxicity. The safety of roxithromycin for the human fetus has not been established.

#### Use in lactation

Small amounts of roxithromycin are excreted in the breast milk. Breastfeeding or treatment of the mother should be discontinued as necessary.

#### Use in children

In young animal studies, high oral doses of roxithromycin were associated with bone growth plate abnormalities. However no abnormalities were observed in the animals at doses resulting in unbound plasma roxithromycin concentrations that were 10 to 15 times higher than the unbound concentration measured in children receiving the therapeutic dose. The maintenance of such safety margins is primarily dependent on high affinity binding of roxithromycin to plasma alpha-1-acid glycoprotein and will be compromised by any circumstances attenuating the extent of this binding. It is recommended that the approved paediatric dosage regimen (i.e. 5 to 8 mg/kg/day for a maximum of ten days) be adhered to strictly.

Neutropenia was observed in children treated with roxithromycin. 31.6% of 402 children in clinical trials had a neutrophil count below the lower limit of the normal range (3,500/mm<sup>3</sup>) at the conclusion of therapy with roxithromycin. Of these, 4% had a neutrophil count of less than 1,500/mm<sup>3</sup> and 1.2% had a count of less than 1,000/mm<sup>3</sup>. It

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is not known whether this is an effect of the drug, or whether it reflects a normal fluctuation of the neutrophil count or a response to infection in children.

Effects on Ability to Drive and use Machinery

Attention should be drawn to the possibility of dizziness.

## **INTERACTIONS WITH OTHER MEDICINES**

Roxithromycin has a much lower affinity for cytochrome P450 than erythromycin, and consequently has fewer interactions. Interactions may be observed, however, with drugs that bind to alpha-1-acid glycoprotein, e.g. disopyramide.

*Ergot alkaloids:* Reactions of ergotism with possible peripheral necrosis have been reported after concomitant therapy of macrolides with vasoconstrictive ergot alkaloids, particularly ergotamine and dihydroergotamine. Because a clinical interaction with roxithromycin cannot be excluded, administration of roxithromycin to patients taking ergot alkaloids is contraindicated. Absence of treatment with these alkaloids must always be checked before prescribing roxithromycin.

*Theophylline:* A study in normal subjects, concurrently administered roxithromycin and theophylline, has shown some increase in the plasma concentration of the latter. While a change in dosage is usually not required, patients with high levels of theophylline at commencement of treatment should have levels monitored.

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

*Terfenadine:* Some macrolide antibiotics (e.g. erythromycin) may increase serum levels of terfenadine. This can result in severe cardiovascular adverse events, including QT prolongation, torsades de pointes and other ventricular arrhythmias. Such a reaction has not been documented with roxithromycin, which has a much lower affinity for cytochrome P450 than erythromycin. However, in the absence of a systematic interaction study, concomitant administration of roxithromycin and terfenadine is not recommended.

*Astemizole, cisapride, pimozide:* Other drugs, such as astemizole, cisapride or pimozide, which are metabolised by the hepatic isozyme CYP3A4, have been associated with QT interval prolongation and/or cardiac arrhythmias (typically torsades de pointes) as a result of an 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 CYP3A4 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, concomitant administration of roxithromycin and such drugs is not recommended.

*Warfarin:* While no interaction was observed in volunteer studies, roxithromycin appears to interact with warfarin. Increases in prothrombin time (international normalised ratio

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(INR)) have been reported in patients treated concomitantly with roxithromycin and warfarin or the related vitamin K antagonist phenprocoumon, and severe bleeding episodes have occurred as a consequence. INR should be monitored during combined treatment with roxithromycin and Vitamin K antagonists.

*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, diarrhoea, 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 overdose occur. Roxithromycin, like other macrolides, should be used with caution in patients receiving Class IA and Class III antiarrhythmic agents (see PRECAUTIONS).

*HMG-CoA reductase inhibitors:*

When roxithromycin and an HMG-CoA reductase inhibitor (statin) are combined, there is a potential risk of muscle related adverse events, such as rhabdomyolysis due to a possible increase of the statin exposure.

Caution should be exercised when a statin is combined with roxithromycin and patients should be monitored for signs and symptoms of myopathy.

*Midazolam:* Roxithromycin, like other macrolides, may increase the area under the midazolam concentration-time curve and the midazolam half-life, therefore the effects of midazolam may be enhanced and prolonged in patients treated with roxithromycin. There is no conclusive evidence for an interaction between roxithromycin and triazolam.

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

*Rifabutin:* Roxithromycin can increase the plasma concentration of rifabutin.

*Theophylline and Cyclosporin:* A slight increase in plasma concentrations of theophylline or cyclosporin A has been observed. This does not generally necessitate altering the usual dosage.

Roxithromycin does not appear to interact with oral contraceptives containing oestrogens and progestogens, prednisolone, carbamazepine, ranitidine or antacids.

## **ADVERSE EFFECTS**

Roxithromycin is generally well tolerated. In clinical trials, treatment discontinuation due to adverse reactions occurred in only 1.2% of adult patients and 1.0% of children. The following side effects or serious adverse events possibly associated with roxithromycin have been reported.

*Gastrointestinal:* Nausea, vomiting, epigastric pain (dyspepsia), diarrhoea (sometimes containing blood), anorexia, flatulence. In clinical studies, the incidence of gastrointestinal events was higher with the 300 mg once daily dosage regimen than with

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150 mg twice daily. Symptoms of pancreatitis have been observed; most patients had received other drugs for which pancreatitis is a known adverse reaction.

*Hypersensitivity:* Urticaria, rash, pruritus, angioedema. Rarely, serious allergic reactions may occur, e.g. asthma, bronchospasm, anaphylactic like reactions, purpura, glottic oedema, generalised oedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome.

*Hepatic:* Moderate increases in serum transaminases (AST and ALT) and/or alkaline phosphatase levels have been observed and are somewhat more likely to occur in the elderly (> 65 years). Acute cholestatic hepatitis and acute hepatocellular injury (sometimes with jaundice) are rarely reported.

*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

*Cardiac disorders:* QT interval prolongation, ventricular tachycardia, Torsade de pointes

*Other:* Eosinophilia, bronchospasm, hallucination, headache, dizziness, paraesthesia, tinnitus, malaise, moniliasis (candidiasis), pancreatitis, disorders of taste and/or smell, temporary deafness, hypoacusis and vertigo.

## **DOSAGE AND ADMINISTRATION**

### *Adults*

Roxithromycin Sandoz should be taken at least 15 minutes before food or on an empty stomach (i.e. more than three hours after a meal).

The recommended dosage is 300 mg per day which may be taken according to one of the following dosage regimens.

### *Usual dosage:*

Roxithromycin Sandoz 300 mg tablets: one tablet daily.

Roxithromycin Sandoz 150 mg tablets: one tablet twice daily, or two tablets once daily.

### *Elderly:*

Roxithromycin Sandoz 300 mg tablets: one tablet daily.

Roxithromycin Sandoz 150 mg tablets: one tablet twice daily or two tablets once daily.

### *Impaired renal function:*

Roxithromycin Sandoz 300 mg tablets: one tablet daily.

Roxithromycin Sandoz 150 mg tablets: one tablet twice daily or two tablets once daily.

For atypical pneumonia, the recommended dosage is 150 mg twice daily.

Roxithromycin Sandoz 150mg and 300mg film-coated tablets must be swallowed whole with a drink. The usual duration of treatment is five to ten days depending on the indication and clinical response. Streptococcal throat infections require at least ten days of therapy. A small proportion of patients with nongonococcal genital infections may require 20 days for complete cure.

*Children:*

The recommended dose and duration of treatment should not be exceeded in children (see Precautions).

Roxithromycin Sandoz should be taken at least 15 minutes before food or on an empty stomach (i.e. more than three hours after a meal).

Roxithromycin Sandoz is administered twice daily at a dose of 5 to 8 mg/kg/day. Recommended dosage regimens are as follows.

*40 kg and over.*

One Roxithromycin Sandoz 150 mg tablet morning and evening. Roxithromycin Sandoz is not recommended for children of under 40kg.

The usual duration of treatment is five to ten days depending on the indication and clinical response. Streptococcal throat infections require ten days of therapy. The duration of treatment should not exceed ten days.

## **OVERDOSAGE**

Symptomatic treatment should be provided as required. There is no specific antidote. Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

## **PRESENTATION AND STORAGE**

Roxithromycin Sandoz 150mg film-coated tablets: white, round, convex film-coated tablets, scored on one face, embossment R 150. Available in blister packs of 10 tablets.

Roxithromycin Sandoz 300mg film-coated tablets: white, round, convex film-coated tablets, scored on one face, embossment R 300. Available in blister packs of 5 tablets.

Store below 25°C.

## **POISONS SCHEDULE OF THE MEDICINE**

Schedule 4 – Prescription Only Medicine

## **NAME AND ADDRESS OF THE SPONSOR**

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**DATE OF MOST RECENT AMENDMENT: 02/12/2015**