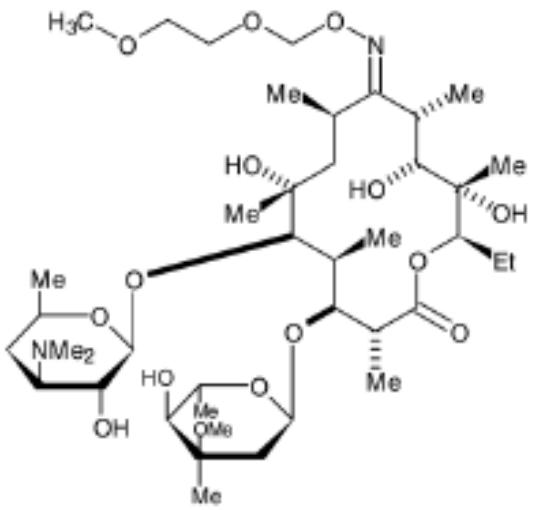
TERRY WHITE CHEMISTS Roxithromycin Tablets

NAME OF THE MEDICINE

Active Ingredient: Roxithromycin

Chemical names: (3*R*, 4*S*, 5*S*, 6*R*, 7*R*, 9*R*, 11*S*, 12*R*, 13*S*, 14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-O-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-10-[(*E*)-[(2-methoxyethoxy)-methoxy]imino]-3,5,7,9,11,13,-hexamethyl-6-[(3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl)oxy]-oxacyclotetradecan-2-one.

Structural formula:



Molecular formula: $C_{41}H_{76}N_2O_{15}$.

Molecular weight: 837.07

CAS Registry Number: 80214-83-1

DESCRIPTION

Roxithromycin is a semi-synthetic macrolide antibiotic. Each Roxithromycin film-coated tablet contains either 150 mg or 300 mg of roxithromycin as the active ingredient.

Roxithromycin tablets also contain the following inactive ingredients: maize starch, hydroxypropylcellulose, colloidal anhydrous silica, sodium starch glycollate, poloxamer, povidone, magnesium stearate, purified talc, propylene glycol, glucose, titanium dioxide and hypromellose.

PHARMACOLOGY

Microbiology

Roxithromycin is bacteriostatic at low concentrations and bactericidal at high concentrations. It binds to the 50S subunit of the 70S ribosome, thereby disrupting bacterial protein synthesis.

A prolonged post-antibiotic effect has been observed with roxithromycin. Whilst the clinical significance of this remains uncertain, it supports the rationale for once daily dosing. Although clinical data have demonstrated the efficacy and safety of once daily dosing in adults, these have not been demonstrated in children.

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

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* spp. and *Acinetobacter* spp.

Susceptibility tests

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint should be used following a regularly updated, recognised and standardised method (e.g. National Committee for Clinical Laboratory Standards [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 the 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 NCCLS method of susceptibility testing with a 15 microgram roxithromycin disc, susceptible organisms other than *Haemophilus influenzae* produce zones of inhibition of diameter 21 mm or greater. A zone diameter of 10 to 20 mm should be considered intermediate and a zone diameter of 9 mm or less indicates resistance. A bacterial isolate may be considered susceptible if the minimal inhibitory concentration (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 *H. influenzae*, zones of inhibition of diameter 10 mm or greater indicate susceptibility when CO_2 incubation and the HTM agar is used with a 15 microgram roxithromycin disc. An isolate may be considered susceptible if the MIC value for roxithromycin is less than or equal to 8 mg/L.

Pharmacokinetics

Absorption

Roxithromycin is absorbed after oral administration with an absolute bioavailability of approximately 50%. Peak plasma concentrations following administration of 150 and 300 mg film coated tablets are achieved in young and elderly adult patients approximately one to two hours post-dose. As food intake decreases absorption, roxithromycin 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 2.5 mg/kg every 12 hours to children, the average peak plasma concentration at steady state was 9 mg/L and the AUC was 61 mg.hour/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 69 mg.hour/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 71 mg.hour/L.

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

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

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

Metabolism

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 (Cmin) 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.

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.

Excretion

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 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.
- Non-gonococcal urethritis.

Children

Roxithromycin 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 micro-oganisms:

- Acute pharyngitis
- Acute tonsillitis
- Impetigo.

Appropriate culture and sensitivity tests should be performed when necessary to determine an organism's 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

- Known hypersensitivity to macrolides, including erythromycin.
- Severely impaired hepatic function (see **PRECAUTIONS**).
- Concomitant therapy with vasoconstrictive ergot alkaloids (see **INTERACTIONS WITH OTHER MEDICINES**).

PRECAUTIONS

Prolonged or repeated use of antibiotics including roxithromycin may result in super infection by resistant organisms. In the event of super infection, 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.

Pseudomembranous colitis

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur 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, may prolong and/or worsen the condition and should not be used.

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.

Clostridium difficile-Associated Disease

Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with roxithromycin, may be symptomatic of pseudomembranous colitis (see **ADVERSE EFFECTS**). If pseudomembranous

colitis is suspected, roxithromycin must be stopped immediately.

QT Prolongation

In certain conditions macrolides, including roxithromycin, have the potential to prolong the QT interval. Therefore, roxithromycin should be used with caution in patients with congenital prolongation of the QT interval, with ongoing proarrhythmic conditions (i.e. uncorrected hypokalemia or hypomagnesaemia, clinically significant bradycardia), and in patients receiving Class IA and III antiarrhythmic agents (see **INTERACTIONS WITH OTHER MEDICINES**, **Astemizole, Cisapride, Pimozide**).

Myasthenia Gravis

As with other macrolides, roxithromycin may have the potential to aggravate the myasthenia gravis.

Skin Conditions

Cases of severe bullous skin reactions such as Stevens Johnson Syndrome (SJS) or Toxic Epidermal Necrosis (TEN) have been reported with roxithromycin (see **ADVERSE EFFECTS**). If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, roxithromycin treatment should be discontinued.

Ergotism

Severe vasoconstriction ("ergotism") with possibly necrosis of the extremities has been reported when macrolides antibiotics have been associated with vasoconstrictive ergot alkaloids. Absence of treatment by these alkaloids must always be checked before prescribing roxithromycin. (See **INTERACTIONS WITH OTHER MEDICINES**, **Ergot Alkaloids**.)

Use in Impaired Renal Function

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

Use in Impaired Hepatic Function

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

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/mm3) at the conclusion of therapy with roxithromycin. Of these, 4% had a neutrophil count of less than 1,500/mm3 and 1.2% had a count of less than 1,000/mm3. It 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 Fertility

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 foetus has not been established.

Paediatric Use

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.

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 the Elderly

No dosage adjustment is required in elderly patients.

Carcinogenesis and Mutagenesis

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.

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, such as disopyramide.

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

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.

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.

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.

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

Roxithromycin, like other macrolides, should be used with caution in patients receiving class IA and III antiarrhythmic agents. 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.

Vitamin K Anatagonists

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

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 overdosage occur.

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.

CYP3A

Roxithromycin is a weak CYP3A inhibitor. The effect of roxithromycin on exposure to drugs predominantly cleared by CYP3A metabolism would be expected to be 2-fold or less. Caution should be exercised when roxithromycin is concomitantly prescribed with drugs metabolised by CYP3A (such as rifabutin and bromocriptine).

ADVERSE EFFECTS

Roxithromycin is generally well tolerated. In clinical trials, treatment discontinuation due to adverse effects 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, pseudomembranous colitis. In clinical studies, the incidence of gastrointestinal events was higher with the 300 mg once daily dosage regimen than with 150 mg twice daily. Symptoms of pancreatitis have been observed; most patients had received other drugs for which pancreatitis is a known adverse effect.

Hypersensitivity

Urticaria, rash, pruritus, angioedema. Rarely, serious allergic reactions may occur, such as asthma, bronchospasm, anaphylactic-like reactions, anaphylactic shock, purpura, glottic oedema, generalised oedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome and Toxic Epidermal Necrosis (see **PRECAUTIONS**).

Hepatic

Moderate increase 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 of age). Acute cholestatic hepatitis and acute hepatocellular injury (sometimes with jaundice), are rarely reported.

Hematological Effects

Transient eosinophilia and thrombocytosis have been reported in patients receiving roxithromycin 150 mg twice a day for 10 days.

Dermatologocal

Mild itching (1 to 5%), nail discoloration.

Other

Headache, bronchospasm, hallucination, confusion, headache, dizziness, paraesthesia, tinnitus, malaise, moniliasis (candidiasis), pancreatitis, QT prolongation, disorders of taste and/or smell, temporary deafness, hypoacusis and vertigo.

DOSAGE AND ADMINISTRATION

Adults

Roxithromycin 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:

	Roxithromycin 300 mg tablets	Roxithromycin 150 mg tablets
Usual dosage	One tablet daily	One tablet twice daily or Two tablets once daily
Elderly	One tablet daily	One tablet twice daily or Two tablets once daily
Impaired renal function	One tablet daily	One tablet twice daily or Two tablets once daily

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

Roxithromycin 150 and 300 mg 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 non-gonococcal 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 should be taken at least 15 minutes before food or on an empty stomach (i.e. more than three hours after a meal).

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

40 kg and over: One Roxithromycin 150 mg tablet morning and evening.

Roxithromycin tablets are not recommended for children weighing less than 40 kg.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Terry White chemists Roxithromycin are intended for oral administration. Each tablet contains 150 mg or 300 mg roxithromycin, as the active ingredient.

Terry White Chemists Roxithromycin 150 mg tablets
White to off-white, round, convex and film-coated tablets. Blister packs (PVC/Al) of 10.
AUST R 133752

Terry White Chemists Roxithromycin 300 mg tablets
White to off-white, round, convex and film-coated tablets. Blister packs (PVC/Al) of 5.
AUST R 133753

* Not all strengths, pack types and/or pack sizes may be available.

Storage
Store below 25^{o} C
Protect from heat and moisture.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):10 APRIL 2008

DATE OF MOST RECENT AMENDMENT: 27 November 2015