

PRODUCT INFORMATION

RULIDE® & RULIDE® D

NAME OF THE MEDICINE

Rulide Tablets

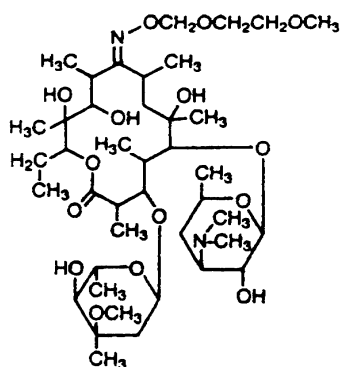
Rulide D Tablets

Non-proprietary Name

Roxithromycin

Chemical Structure

Roxithromycin has the following structural formula:



The empirical formula for roxithromycin is $C_{41}H_{76}N_2O_{15}$. Its molecular weight is 837.07.

CAS number

Chemical Abstracts Number: [80214-83-1]

DESCRIPTION

Roxithromycin is a semi-synthetic macrolide antibiotic. It is a white crystalline powder. Roxithromycin is very slightly soluble in water, freely soluble in acetone, in alcohol and in methylene chloride. It is slightly soluble in dilute hydrochloric acid.

Rulide tablets contain 150mg or 300mg of roxithromycin. Rulide D tablets contain 50mg of roxithromycin.

Rulide tablets also contain hydroxypropylcellulose, poloxamer, povidone, colloidal anhydrous silica, magnesium stearate (470), purified talc (553), maize starch, hypromellose, anhydrous glucose, titanium dioxide (171) and propylene glycol (1520).

Rulide D tablets also contain microcrystalline cellulose, crospovidone, magnesium stearate, fumaric acid, colloidal anhydrous silica, sodium saccharin, methacrylic acid copolymer, sodium hydroxide, purified talc, sodium lauryl sulfate, Macrogol 6000, triethyl citrate and liquorice and strawberry flavours.

PHARMACOLOGY

Pharmacokinetics

Absorption

Roxithromycin is absorbed after oral administration with an absolute bioavailability of approximately 50%. Peak plasma concentrations following administration of 150mg and 300mg film-coated tablets are achieved in young and elderly adult patients approximately 1 to 2 hours post-dose. However, Rulide D 50 mg tablets for suspension appear to be absorbed more slowly than the Rulide film-coated tablets, with peak plasma concentrations achieved approximately 3 hours post dose.

As food intake decreases absorption, Rulide should be administered at least 15 minutes before food or, alternatively, on an empty stomach (*i.e.* more than 3 hours after a meal).

Absorption is not linear; with increasing doses in the range 150mg to 300mg, peak plasma levels and 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 Rulide 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 Rulide 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.

Distribution

Roxithromycin is 92-96% bound to plasma proteins (principally alpha-1-acid glycoprotein, but also albumin) at concentrations less than 4.2mg/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 4.2mg/L. At a plasma concentration of 8.4mg/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: C_{min} and AUC values are comparable for adults and children.

The half-life is prolonged to 25 hours in adults with impaired hepatic function and 18 hours in adults 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 4.2mg/L, renal clearance increases because reduced plasma protein binding (see 'Distribution') causes increased levels of unbound roxithromycin, which may be excreted by the kidneys.

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 has demonstrated the efficacy and safety of once daily dosing in adults, this has 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*, *Chlamydia* spp.

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

Haemophilus influenzae, *Staphylococcus aureus* (except MRSA).

The following strains of microorganisms are resistant:

Multiresistant *Staphylococcus aureus*, Enterobacteriaceae, *Pseudomonas* spp., *Acinetobacter* spp.

Susceptibility Tests

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 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 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 CO₂ 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.

INDICATIONS

Adults

Rulide 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 micro-organisms:

- URTI: acute pharyngitis, tonsillitis, sinusitis
- LRTI: acute bronchitis and acute exacerbations of chronic bronchitis; community acquired pneumonia
- Skin and skin structure infections
- Non gonococcal urethritis.

Children

Rulide D 50mg tablets and Rulide 150mg 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-organisms:

- 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

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

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. 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 which delay peristalsis, eg. opiates and diphenoxylate with atropine (LOMOTIL®), 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.

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 (ie uncorrected hypokalemia or hypomagnesaemia, clinically significant bradycardia), and in patients receiving Class IA and III antiarrhythmic agents (see INTERACTIONS WITH OTHER MEDICINES).

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

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 10 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 (3500/mm³) at the conclusion of therapy with roxithromycin. Of these, 4% had a neutrophil count of less than 1500/mm³ and 1.2% had a count of less than 1000/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.

Use in Pregnancy (Category B1)

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

Use in Lactation

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

Use in the Elderly

No dosage adjustment is required in elderly patients.

Carcinogenesis, Mutagenesis and Effects on 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 180mg/kg/day.

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 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.

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.

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 (eg. 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 metabolized 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 normalized 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 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 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.

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.

ADVERSE REACTIONS

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 150 mg twice daily.

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.

Liver

Moderate increase in serum transaminases, AST-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.

Others

Eosinophilia, bronchospasm, hallucination, headache, dizziness, paraesthesia, tinnitus, malaise, moniliasis, pancreatitis, disorders of taste and/or smell.

DOSAGE AND ADMINISTRATION

Adults

Rulide should be taken at least 15 minutes before food or on an empty stomach (*i.e.* more than 3 hours after a meal).

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

	Rulide 300mg Tablets	Rulide 150mg 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 one 150 mg tablet twice daily.

Rulide 150mg and 300mg film-coated tablets must be swallowed whole with a drink.

The usual duration of treatment is 5 to 10 days depending on the indication and clinical response. Streptococcal throat infections require at least 10 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).

Rulide should be taken at least 15 minutes before food or on an empty stomach (*i.e.* more than 3 hours after a meal).

Rulide is administered twice daily at a dose of 5 to 8 mg/kg per day. Recommended dosage regimens are presented in the following table:

BODYWEIGHT	RULIDE D 50mg TABLETS	RULIDE 150mg TABLETS
6 - 11 kg	Half a tablet morning and evening	
12 - 23 kg	One tablet morning and evening	
24 - 40 kg	Two tablets morning and evening	
> 40 kg		One tablet morning and evening

Rulide D 50mg tablets are administered to children weighing less than 40kg as an aqueous suspension that is made by adding either a half, one or two tablets to a spoonful of water. After waiting for 30 to 40 seconds for the tablet(s) to disintegrate into fine granules, the suspension is given to the child. A drink of water should follow the dose.

Note: Only Rulide D 50mg tablets are designed to be mixed with water. The 150mg and 300mg film-coated tablets must be swallowed whole with a drink.

The usual duration of treatment is 5 to 10 days depending on the indication and clinical response. Streptococcal throat infections require 10 days of therapy. The duration of treatment should not exceed 10 days.

OVERDOSAGE

Symptomatic treatment should be provided as required. There is no specific antidote.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Rulide 300mg Tablets

White, biconvex, cylindrical, 11mm diameter, film-coated tablets, debossed on one side with 164J.
Available in blister packs of 5 tablets.
Store in a cool dry place below 30°C.
Contains glucose (in film-coating).

Rulide 150mg Tablets

White, biconvex, cylindrical, 9 mm diameter, film-coated tablets, debossed on one side with 164.
Available in blister packs of 10 tablets.
Store in a cool dry place below 25°C.
Contains glucose (in film-coating).

Rulide D 50mg Tablets for Suspension

Practically white, scored, cylindrical tablets, 8mm in diameter.
Available in aluminium blister packs of 10 tablets.
Store in a cool place below 30°C.
Contains saccharin sodium.

NAME AND ADDRESS OF THE SPONSOR

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Macquarie Park NSW 2113
Australia

POSITION SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE ARTG

18 June 1992

DATE OF MOST RECENT AMENDMENT

16 July 2012