NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Rulide D 50 mg dispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Rulide D tablets contain 50 mg of roxithromycin.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Rulide D tablets are practically white, scored, cylindrical tablets, 8mm in diameter.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Children
Rulide D 50mg 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Children

The recommended dose and duration of treatment should NOT be exceeded in children (see Section 4.4 Special Warnings and Precautions for Use).

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

Rulide D 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
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	Three tablets morning and evening

Rulide D 50mg tablets are administered to children as an aqueous suspension that is made by adding either a half, one, two or three 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: Rulide D 50mg tablets are designed to be mixed with water. 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.

4.3 CONTRAINDICATION

- Known hypersensitivity to macrolides, including erythromycin.
- Severely impaired hepatic function (see Section 4.4 Special Warnings and Precautions for Use).
- Concomitant therapy with vasoconstrictive ergot alkaloids (see Section 4.5 Interaction with other Medicines and other Forms of Interaction).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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), the dose should be reduced by half.

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.

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, 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 and drugs such as astemizole, cisapride or pimozide (see Section 4.5 Interaction with other Medicines and other Forms of Interaction).

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

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 Section 4.8 Undesirable Effects). If pseudomembranous colitis is suspected, roxithromycin must be stopped immediately.

Cases of severe bullous skin reactions such as Stevens Johnson Syndrome or Toxic Epidermal Necrosis have been reported with roxithromycin (see Section 4.8 Undesirable 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.

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.

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 ($3500/mm^3$) at the conclusion of therapy with roxithromycin. Of these, 4% had a neutrophil count of less than $1500/mm^3$ and 1.2% had a count of less than $1000/mm^3$. 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 the Elderly

No dosage adjustment is required in elderly patients.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Roxithromycin has a much lower affinity for cytochrome P450 than erythromycin and consequently has fewer interactions.

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. Absence of treatment with these alkaloids must always be checked before prescribing roxithromycin.

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.

Roxithromycin, like other macrolides, should be used with caution in patients receiving class IA and III antiarrhythmic agents (See Section 4.4 Special Warnings and Precautions for Use).

Vitamin K Antagonists

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 Ciclosporin
A slight increase in plasma concentrations of theophylline or ciclosporin A has been observed. This does not generally necessitate altering the usual dosage.

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).

4.6 PREGNANCY AND LACTATION

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.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Attention should be drawn to the possibility of dizziness, visual impairment and blurred vision.

4.8 UNDESIRABLE 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, acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome and Toxic Epidermal Necrosis (TEN) (See Section 4.4 Special Warnings and Precautions for Use).

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, agranulocytosis, neutropenia, thrombocytopenia, bronchospasm, hallucination, confusion, headache, dizziness, paraesthesia, tinnitus, malaise, moniliasis, pancreatitis, QT prolongation, disorders of taste and/or smell, visual impairment, blurred vision, temporary deafness, hypoacusis and vertigo.

Prolonged use of antibiotics including roxithromycin may result in superinfection; overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. In the event of superinfection, appropriate measures should be taken.

Reporting of suspected adverse reaction

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

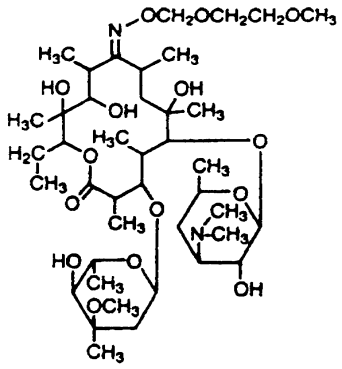
4.9 OVERDOSE

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

For advice on the management of overdose please contact the New Zealand National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

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.

Roxithromycin 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.

CAS number

Chemical Abstracts Number: [80214-83-1]

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: semi-synthetic macrolide antibiotic

Roxithromycin binds to the 50S subunit of the 70S ribosome thereby disrupting bacterial protein synthesis.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
Roxithromycin is absorbed after oral administration with an absolute bioavailability of approximately 50%. Peak plasma concentrations following administration of Rulide D 50 mg tablets for suspension is achieved approximately 3 hours post dose.

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

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: Cmin and AUC values are comparable for adults and children.

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. 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 CO_2 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.

5.3 PRECLINICAL SAFETY DATA

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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.

RULIDE D IS GLUTEN FREE, HOWEVER, THE STRAWBERRY FLAVOUR CONTAINS LACTOSE.

6.2 INCOMPATIBILITIES

Rulide D 50mg tablets are designed to be mixed with water.

6.3 SHELF LIFE

3 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a cool place below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Available in aluminium blister packs of 10 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements for disposal.

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

sanofi-aventis new zealand limited

Level 8, 56 Cawley Street

Ellerslie, Auckland

New Zealand

Freecall : 0800 283 684

Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

21 August 2014

10 DATE OF REVISION OF THE TEXT

11 November 2020

SUMMARY OF CHANGES

Section changed	Summary of new information
4.5	Interaction with disopyramide removed
2, 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 5.2	Editorial changes