NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Arrow – Roxithromycin 150, 150 mg, coated tablets
Arrow – Roxithromycin 300, 300 mg, coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150 mg or 300 mg of roxithromycin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White, round, coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

Roxithromycin is indicated for the treatment of the following types of mild to moderately severe infections caused by or likely to be caused by susceptible micro-organisms:

- upper respiratory tract infection - acute pharyngitis, tonsillitis and sinusitis
- dental infections
- lower respiratory tract infection - acute bronchitis; acute exacerbations of chronic bronchitis and 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-organisms: acute pharyngitis, acute tonsillitis and 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.

4.2 Dose and method of administration

This product may not be interchangeable with other products containing this ingredient in the New Zealand's market. The bioequivalence with Rulide® marketed in Australia has been demonstrated.

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 film coated tablets must be swallowed whole with a drink.

Adults

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

Usual dosage: Roxithromycin 300 mg tablets: one tablet daily. Roxithromycin 150 mg tablets: one tablet twice daily or two tablets once daily.

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

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 twenty days for complete cure.

Special populations

Elderly
Roxithromycin 300 mg tablets: one tablet daily. Roxithromycin 150 mg tablets: one tablet twice daily or two tablets once daily.

Impaired renal function
Roxithromycin 300 mg tablets: one tablet daily. Roxithromycin 150 mg tablets: one tablet twice daily or two tablets once daily.

Impaired hepatic function
One roxithromycin 150 mg tablet once daily for patients with documented cirrhotic liver disease.

Paediatric population

Roxithromycin is administered twice daily at a dose of 5 to 8 mg/kg/day (see Special warnings and precautions for use).

For children 40 kg and over
One roxithromycin 150 mg tablet morning and evening.

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.

4.3 Contraindications
Arrow - Roxithromycin is contraindicated in the following conditions:

- known hypersensitivity to macrolides, including erythromycin
- severely impaired hepatic function (see Special warnings and precautions for use)
- concomitant therapy with vasoconstrictive ergot alkaloids (see Interaction with other medicines and other forms of interaction).

4.4 Special warnings and precautions for use
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.

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 *Cl. 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.

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

Cases of severe bullous skin reactions such as Stevens Johnson Syndrome or Toxic Epidermal Necrosis have been reported with roxithromycin (see Undesirable effects). If symptoms or signs of SJS or TEN (eg. 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 macrolide antibiotics have been associated with vasoconstrictive ergot alkaloids. Absence of treatment by these alkaloids must always be checked before prescribing roxithromycin.

Increased INR levels have been reported in patients when Arrow - Roxithromycin and coumarin anticoagulants are used concomitantly. Patients using Arrow - Roxithromycin and coumarin anticoagulants should be closely monitored (see Interaction with other medicines and other forms of interaction).

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides. Consideration of these findings should be balanced with treatment benefits when prescribing roxithromycin.

Prolongation of the QT Interval
Ventricular arrhythmias associated with prolonged QT interval, including ventricular tachycardia and torsades de pointes have been reported with macrolide antibiotics including roxithromycin. Prescribers should consider the risk of QT prolongation (which can be fatal) when weighing the risks and benefits of roxithromycin for at-risk groups including:

- Patients predisposed to QT interval prolongation such as those with a history of torsades de pointes or congenital long QT syndrome.
- Patients taking other medication known to prolong the QT interval such as antiarrhythmics of classes IA and III; antipsychotic agents; antidepressants; and fluoroquinolones.
- Patients with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia.
- Patients with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency.
- Elderly patients, as they may be more susceptible to drug-associated effects on the QT interval.

Impaired hepatic function
Caution should be exercised if roxithromycin is administered to patients with impaired hepatic function, as its serum half life is increased in patients with hepatic failure. If administered to patients with severe hepatic insufficiency (e.g. hepatic cirrhosis with jaundice and/or ascites), the dose should be reduced by half to 150 mg once daily.

Impaired renal function
In the elderly and those with renal failure, dosage reduction is not required for the normally short course of treatment.

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^3) at the conclusion of therapy with roxithromycin. Of these, 4% had a neutrophil count of less than 1,500/mm^3 and 1.2% had a count of less than 1,000/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. Interactions may be observed, however, with drugs that bind to alpha-1-acid glycoprotein, e.g. disopyramide.

Roxithromycin does not appear to interact with oral contraceptives, 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.

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
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 hence 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. Thus, 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 Special warnings and precautions for use).

Warfarin
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 warfarin.

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 suggesting cardiac glycoside overdosage have occurred.

Midazolam
Roxithromycin, like other macrolides, may increase the area under the midazolam concentration-time curve and the midazolam half-life. Thus, 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 and cyclosporin 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 Fertility, pregnancy and lactation

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.

Carcinogenicity, mutagenicity, 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.

4.7 Effects on ability to drive and use machines
Attention should be drawn to the possibility of dizzy sensations.

4.8 Undesirable 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, diarrhoea (very rarely 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 have received other drugs for which pancreatitis is a known adverse effect.

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 and Toxic Epidermal Necrosis (TEN) (see Special warnings and precautions for use).

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 are rarely reported.

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

4.9 Overdose
In case of overdosage, gastric lavage may remove residual drug in the stomach. Clinical monitoring should be considered along with symptomatic and supportive treatment as required. There is no specific antidote.

LD_{50} dosage was high in mice and rats at 0.75 g/kg and 1 - 1.7 g/kg, respectively. In dogs, a dose of 2 g/kg did not result in toxicity.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Macrolides, ATC code: J01FA06

Microbiology
Roxithromycin is a semi-synthetic macrolide antibiotic.

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 postantibiotic 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 micro-organisms: *Streptococcus pneumoniae, Strep. pyogenes, Mycoplasma pneumoniae, Moraxella catarrhalis, Ureaplasma urealyticum* and Chlamydia sp.

Roxithromycin has been demonstrated to have clinical activity against the following micro-organisms which are partially sensitive *in vitro* to roxithromycin: *Haemophilus influenzae* and *Staphylococcus aureus*, except methicillin resistant *Staph. aureus* (MRSA).

The following strains of micro-organisms are resistant: multi-resistant *Staph. aureus*, Enterobacteriaceae, Pseudomonas sp. and Acinetobacter sp.

Susceptibility tests
Using the National Committee for Clinical Laboratory Standards (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.

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

5.2 Pharmacokinetic properties

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 delays 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 twelve 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 to healthy young adults, the mean peak plasma concentration was 10.7 mg/L and the AUC was 146.0 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 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.

After a single oral dose of 150 mg roxithromycin, good concentrations are reached in respiratory tract tissues and secretions, male and female genital tracts, tonsils and paranasal sinuses, synovial fluid and the skin. Roxithromycin is not detected in saliva.

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 (C_{min}) 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.

5.3 Preclinical safety data

None.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Low substituted hydroxypropyl cellulose (hyprolose), colloidal anhydrous silica, povidone, purified talc, maize starch, magnesium stearate, hypromellose, anhydrous glucose, titanium dioxide and propylene glycol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store in a cool, dry place where it stays below 25°C, and protect from light and moisture.

6.5 Nature and contents of container
PVC/PVdC/Aluminium foil blister strips. Pack size of 10 tablets (150 mg) and 5 tablets (300 mg).

6.6 Special precautions for disposal
No special requirements for disposal.

7. MEDICINE SCHEDULE
Prescription Medicine

8. SPONSOR
Teva Pharma (New Zealand) Limited
PO Box 128 244
Remuera
Auckland 1541
Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL
28 September 2006

10. DATE OF REVISION OF THE TEXT
03 November 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Risk factors for QT prolongation updated. A class warning for macrolides and cardiovascular death added.