AUSTRALIAN PRODUCT INFORMATION – BIAXSIG® (ROXITHROMYCIN)

1 NAME OF THE MEDICINE

Roxithromycin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

300 mg and 150 mg tablets contain 300 mg and 150 mg of roxithromycin per tablet respectively.

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

3 PHARMACEUTICAL FORM

Biaxsig 300 mg Tablets: white biconvex, cylindrical, 11 mm in diameter, film-coated tablets. Contains glucose (in film coating).

Biaxsig 150 mg Tablets: white biconvex, cylindrical, 9 mm in diameter, film-coated tablets. Contains glucose (in film coating).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Adults

Biaxsig 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:

- Upper Respiratory Tract Infections: Acute pharyngitis, tonsillitis, sinusitis
- Lower Respiratory Tract Infections: Acute bronchitis and acute exacerbations of chronic bronchitis; community acquired pneumonia
- Skin and skin structure infections
- Non-gonococcal urethritis

Children

Biaxsig is 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 Biaxsig 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

Adults

Biaxsig 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 for adults, the elderly and patients with impaired renal function is 300 mg per day taken as either one 150 mg tablet twice daily, or as one 300 mg tablet or two 150 mg tablets once daily.

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

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 Section 4.4 Special Warnings and Precautions for Use).

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

Biaxsig is administered twice daily at a dose of 5 to 8 mg/kg per day. The recommended dosage for children with bodyweight over 40 kg is one 150 mg tablet twice daily.

Children with a bodyweight less than 40 kg should not be treated with Biaxsig 150 mg tablets.

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 CONTRAINDICATIONS

- 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 Interactions with Other Medicines and Other Forms of Interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Prolonged or repeated use of antibiotics including Biaxsig may result in superinfection by resistant organisms. In the event of superinfection, Biaxsig 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 and drugs such as astemizole, cisapride or pimozide (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

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 Biaxsig, may be symptomatic of pseudomembranous colitis (See Section 4.8 Adverse Effects (Undesirable Effects)). If pseudomembranous colitis is suspected, Biaxsig must be stopped immediately.

Cases of severe bullous skin reactions such as Stevens Johnson Syndrome or Toxic Epidermal Necrosis have been reported with Biaxsig (see Section 4.8 Adverse Effects (Undesirable Effects)). If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, Biaxsig 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 Biaxsig.

Use in hepatic impairment

The safety of Biaxsig has not been demonstrated in patients with impaired hepatic function. Caution should be exercised if Biaxsig is administered to patients with impaired hepatic function. If administered to patients with impaired hepatic function (e.g. hepatic cirrhosis with jaundice and/or ascites), the dose should be reduced by half.

Use in renal impairment

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

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

Use in the elderly

No dosage adjustment is required in elderly patients.

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 to15 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 α-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.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Biaxsig 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 Biaxsig 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 Biaxsig 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 Biaxsig cannot be excluded, administration of Biaxsig 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.

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, Biaxsig 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 FERTILITY, PREGNANCY AND LACTATION

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.

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.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Biaxsig is generally well tolerated. In clinical trials, treatment discontinuation due to adverse effects occurred in only 1.2% of adult patients and 1% 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, e.g. 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 suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems

4.9 OVERDOSE

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).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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, Biaxsig 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.

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

Haemophilus influenzae, *Staphylococcus aureus* except methicillin resistant staph. aureus (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 National Committee for Clinical Laboratory Standard (NCCLS) method of susceptibility testing with a 15 microgram roxithromycin disc, susceptible organisms other than *Haemophilus influenzae* produce zones of inhibition 21 mm or greater. A zone size of 10 to 20 mm should be considered intermediate and a zone size of 9 mm or less indicates resistance. A bacterial isolate may be considered susceptible if the minimum 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 Haemophilus influenzae, zones of inhibition 10 mm or greater indicate susceptibility when CO_2 incubation and the Haemophilus test medium (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.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Roxithromycin is absorbed after oral administration with an absolute bioavailability of approximately 50%. Peak plasma concentrations are achieved in children and young and elderly adult patients approximately one to two hours after administration.

As food intake delays absorption, Biaxsig 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 150 mg 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 61mg.h/L.

Following administration of a single oral dose of Biaxsig 150 mg to healthy young adults, the mean peak plasma concentration was 6.6 mg/L and the AUC was 69 mg.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 148 mg.h/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.h/L.

Following administration of a single oral dose of Biaxsig 300 mg to healthy young adults, the mean peak plasma concentration was 9.7 mg/L and the AUC was 98 mg.h/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.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 197 mg.h/L.

Distribution

Roxithromycin is 92 to 96% bound to plasma proteins (principally α-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 α-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.

Biaxsig 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.

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

Mutagenesis

Roxithromycin has shown no mutagenic potential in standard laboratory tests for gene mutation and chromosomal damage.

Genotoxicity

No data available.

Carcinogenicity

Long term studies in animals have not been performed to evaluate the carcinogenic potential of roxithromycin.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Excipients present in Biaxsig® tablets are colloidal anhydrous silica, glucose, hyprolose, hypromellose, magnesium stearate, maize starch, poloxamer, povidone, propylene glycol, purified talc and titanium dioxide.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Biaxsig 300mg Tablets: store in a cool dry place below 30°C.

Biaxsig 150mg Tablets: store in a cool dry place below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Biaxsig 300mg Tablets: available in blister packs of 5 tablets.

Biaxsig 150mg Tablets: available in blister packs of 10 tablets.

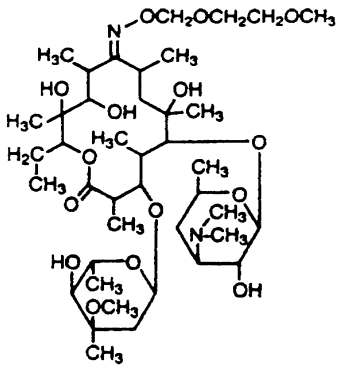
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Roxithromycin is an acid-stable 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.

Chemical structure



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

CAS number

80214-83-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4).

8 SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Rd
Macquarie Park NSW 2113
Australia
Tel: 1800 818 806

9 DATE OF FIRST APPROVAL

3 June 1994

10 DATE OF REVISION

23 September 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformat in line with the new form
4.5	Interaction with disopyramide removed
2; 4; 6; & 8	Editorial