NEW ZEALAND DATA SHEET – AZITHROMYCIN-AFT (AZITHROMYCIN) POWDER FOR INJECTION

1. AZITHROMYCIN-AFT 500 mg POWDER FOR INJECTION

Azithromycin 500 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial containing 500 mg of azithromycin (as dihydrate), providing 100 mg/mL solution following reconstitution. The formulation also contains anhydrous citric acid and sodium hydroxide.

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

3. PHARMACEUTICAL FORM

White lyophilised powder for solution for infusion.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

AZITHROMYCIN-AFT is indicated for the treatment of:

- Community acquired pneumonia (CAP) caused by susceptible organisms, including *Legionella pneumophila*, in patients who require initial intravenous therapy
- Pelvic inflammatory disease (PID) caused by susceptible organisms *(Chlamydia trachomatis, Neisseria gonorrhoea, Mycoplasma hominis*), in patients who require initial intravenous therapy.

4.2. Dose and method of administration

Azithromycin tablets, capsules and powder for oral suspension are unavailable in the AZITHROMYCIN-AFT brand. Information obtained using azithromycin tablets, capsules and powder for oral suspension formulations have been retained throughout the PI, where appropriate, for continuity and prescriber information.

Dose

The dose of AZITHROMYCIN-AFT for the treatment of adult patients with **community acquired pneumonia** is:

500 mg as a single daily IV dose for at least two days. IV therapy should be followed by oral therapy of 500 mg azithromycin administered as a single daily dose to complete a 7- to 10-day course of therapy. The timing of the conversion to oral azithromycin therapy should be done at the discretion of the physician and in accordance with clinical response.

The dose of AZITHROMYCIN-AFT for the treatment of adult patients with **pelvic inflammatory disease** is:

500 mg as a single daily intravenous dose for one or two days. IV therapy should be followed by oral therapy of 250 mg azithromycin administered as a single daily dose to complete a 7-day

course of therapy. The timing of the conversion to oral therapy should be done at the discretion of the physician and in accordance with clinical response.

After reconstitution and dilution, the recommended route of administration for IV azithromycin is by IV infusion only. Do not administer as an IV bolus or intramuscular injection.

Special populations

Elderly
No dose adjustment is necessary in elderly patients requiring azithromycin therapy.

Renal impairment
No dose adjustment is needed in patients with mild or moderate renal impairment. After oral administration of a single dose of azithromycin 1 g in subjects with severe renal impairment (GFR < 10 mL/min), mean $AUC_{0\text{-}120h}$ and mean C_{max} were increased by approximately 30% and 60%, respectively when compared to subjects with normal renal function. Caution should be exercised when azithromycin is administered to patients with severe renal impairment.

Hepatic impairment
The same dosage as in patients with normal hepatic function may be used in patients with mild to moderate hepatic impairment.

Paediatric population
The safety and efficacy of azithromycin powder for solution for infusion for the treatment of infections in children have not been established.

Azithromycin-AFT after reconstitution and dilution is for administration by IV infusion. Not to be given as a bolus or as an intramuscular injection.

The infusate concentration and rate of infusion for azithromycin powder for solution for infusion should be either 1 mg/mL over 3 hours or 2 mg/mL over 1 hour.

Method of administration

Preparation of the solution for IV administration is as follows:

Reconstitution

Prepare the initial solution of azithromycin powder for solution for infusion by adding 4.8 mL of sterilised Water for Injections to the 500 mg vial and shaking the vial until all of the medicine is dissolved. It is recommended that a standard 5 mL (non-automated) syringe be used to ensure that the exact amount of 4.8 mL of sterilised Water for Injections is dispensed. Each mL of reconstituted solution contains 100 mg azithromycin.

If particulate matter is evident in reconstituted fluids, the medicine solution should be discarded.
Dilute this solution further prior to administration as instructed below.

Dilution

To provide azithromycin over a concentration range of 1.0 mg/mL to 2.0 mg/mL, transfer 5 mL of the 100 mg/mL azithromycin solution into the appropriate amount of any of the diluents listed below.

Final infusion solution concentration (mg/mL)	Amount of diluent (mL)
1.0 mg/mL	500 mL
2.0 mg/mL	250 mL

It is recommended that a 500 mg dose of azithromycin powder for solution for infusion, diluted as above, be infused over a period of not less than 60 minutes.

AZITHROMYCIN-AFT is supplied in single use vials. The vial contents are reconstituted with 4.8 mL sterilised Water for Injections (azithromycin 100 mg/mL). For administration, the required volume of the reconstituted solution is added to a compatible infusion solution to produce a final azithromycin solution of 1.0 mg to 2.0 mg/mL.

Parenteral medicine products should be inspected visually for particulate matter prior to administration. If particulate matter is evident, the medicine solution should be discarded.

Chemical and physical in-use stability of the reconstituted product has been demonstrated for 24 hours at 30 °C. When diluted according to the instructions the diluted solution is chemically and physically stable for 24 hours at or below 30 °C or for 7 days if stored under refrigeration at 5 °C.

However, as this product contains no antimicrobial agent, to reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2 – 8 °C for not more than 24 hours.

This product is for single use in one patient on one occasion only. Discard any residue.

The reconstituted solution can be diluted with:

- Normal Saline (0.9% sodium chloride)
- ½ Normal Saline (0.45% sodium chloride)
- 5% Glucose in Water
- Lactated Ringer's Solution
- 5% Glucose in ½ Normal Saline (0.45% sodium chloride) with 20 mEq KCl
- 5% Glucose in Lactated Ringer's Solution
- 5% Glucose in ⅓ Normal Saline (0.3% sodium chloride)
- 5% Glucose in ½ Normal Saline (0.45% sodium chloride)

It is recommended that a 500 mg dose of azithromycin powder for solution for infusion, diluted as described above should be infused over a period of not less than 60 minutes.

4.3. Contraindications

AZITHROMYCIN-AFT is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any other macrolide or ketolide antibiotic, or to any of the excipients listed in **Section 6.1 List of excipients**.

4.4. Special warnings and precautions for use

Hypersensitivity

Rare, serious, allergic reactions, including angioedema and anaphylaxis (rarely fatal); dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal); and medicine reaction with eosinophilia and

systemic symptoms (DRESS) have been reported in patients on azithromycin therapy (see **Section 4.3 Contraindications**). Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is unknown at present.

If an allergic reaction occurs, the medicine should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Hepatotoxicity

No dose adjustment is recommended in patients with mild to moderate hepatic impairment.
Nonetheless, since liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease (see **Section 5.2 Pharmacokinetic properties**).

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur.

Ergot derivatives

In patients receiving ergot derivatives, ergotism has been precipitated by coadministration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergot and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered.

Superinfection

As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms, including fungi, is recommended.

Clostridium difficile-*associated diarrhoea*

Antibiotic-associated pseudomembranous colitis has been reported with the use of many antibiotics including azithromycin. 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 may respond to medicine discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *C difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Hypertoxin-producing strains of *C difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy.

Use in renal impairment

No dose adjustment is needed in patients with mild or moderate renal impairment (GFR 10 – 80 mL/min). In patients with severe (GFR < 10 mL/min) renal impairment a 33% increase in

systemic exposure to azithromycin was observed. Caution should be exercised when azithromycin is administered to patients with severe renal impairment.

Prolongation of the QT interval

There has been limited assessment of the potential for intravenous azithromycin to prolong the QT interval. In clinical studies no significant ECG abnormalities were reported in subjects who received intravenous azithromycin. Ventricular arrhythmias associated with prolonged QT interval, including ventricular tachycardia and *torsades de pointes* have been reported with macrolide products including azithromycin. Prescribers should consider the risk of QT prolongation (which can be fatal) when weighing the risks and benefits of azithromycin for at-risk groups including:

- patients predisposed to QT interval prolongation
- patients taking other medications 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 medicine-associated effects on the QT interval.

Myasthenia gravis

Exacerbations of the symptoms of myasthenia gravis have been reported in patients receiving azithromycin therapy.

Administration precautions

Do not administer AZITHROMYCIN-AFT as a bolus or as an intramuscular injection.

Reconstitute and dilute the powder for infusion as directed and administer as an IV infusion over not less than 60 minutes. All patients who received infusate concentrations above 2.0 mg/mL experienced local infusion site reactions and therefore, higher concentrations should be avoided.

Paediatric population

The safety and effectiveness of azithromycin powder for solution for infusion for the treatment of infections in children have not been established. Azithromycin powder for oral suspension is recommended for the treatment of paediatric patients.

Infantile hypertrophic pyloric stenosis (IHPS) has been reported following the use of azithromycin in neonates (treatment up to 42 days of life). Parents and caregivers should be informed to contact their physician if vomiting or irritability with feeding occurs.

Use in the elderly

No dose adjustment is necessary in elderly patients requiring azithromycin therapy.

4.5. Interactions with other medicines and other forms of interactions

Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to undergo the pharmacokinetic medicine interactions as seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome metabolite complex does not occur with azithromycin.

The following information on medicine interactions refers to oral azithromycin:

Medicines that should <u>not</u> be concomitantly administered with azithromycin

<u>Antacids:</u>

In a pharmacokinetic study investigating the effects of simultaneous administration of antacid with oral azithromycin, no effect on overall bioavailability was seen although peak serum concentrations were reduced by up to 30%. In patients receiving both oral azithromycin and aluminium and magnesium containing antacids, the medicines should not be taken simultaneously. Administration of oral antacids is not expected to affect the disposition of azithromycin given intravenously.

<u>Ergot:</u>

Due to the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered (see **Section 4.4 Special warnings and precautions for use, Ergot derivatives**).

Medicines that require <u>dosage adjustment</u> when administered concomitantly with azithromycin

<u>Cyclosporin:</u>

In a pharmacokinetic study with healthy volunteers who were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of cyclosporin, the resulting C_{max} and AUC_{0-5} were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these medicines. If coadministration of these medicines is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Medicines that have been studied with <u>no clinically significant interaction</u> shown

<u>Atorvastatin:</u>

Coadministration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on an HMG CoA-reductase inhibition assay). However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.

<u>Carbamazepine:</u>

In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

<u>Cetirizine:</u>

In healthy volunteers, coadministration of a 5-day regimen of azithromycin with 20 mg cetirizine at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

<u>Cimetidine:</u>

In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.

Coumarin-type oral anticoagulants:

In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single dose of 15 mg warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to coadministration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time, when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Didanosine:

Coadministration of daily doses of 1,200 mg azithromycin with 400 mg/day didanosine in six HIV positive subjects for 2 weeks had no effect on the steady state pharmacokinetics of didanosine compared to placebo.

Efavirenz:

Coadministration of a single dose of 600 mg azithromycin and 400 mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions. No dose adjustment is necessary when azithromycin is given with efavirenz.

Fluconazole:

Coadministration of a single dose of 1,200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and half-life of azithromycin were unchanged by the coadministration of fluconazole, however, a clinically insignificant decrease in C_{max} (18%) of azithromycin was observed. No dose adjustment is necessary when azithromycin is given with fluconazole.

Indinavir:

Coadministration of a single dose of 1,200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days. No adjustment of the dose of azithromycin is necessary when given with indinavir.

Methylprednisolone:

In a pharmacokinetic interaction study in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

Midazolam:

In healthy volunteers, coadministration of 500 mg/day azithromycin for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single dose of 15 mg midazolam.

Nelfinavir:

Coadministration of 1,200 mg azithromycin and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment was required.

Rifabutin:

Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either medicine. Neutropenia was observed in subjects receiving concomitant treatment with azithromycin

and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established.

Sildenafil:

In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC and C_{max}, of sildenafil or its major circulating metabolite.

Terfenadine, astemizole:

In a study in normal subjects, addition of azithromycin did not result in any significant changes in cardiac repolarisation (QTc interval) measured during the steady state dosing of terfenadine. However, there have been cases reported where the possibility of such an interaction could not be entirely excluded.

Theophylline:

There is no evidence of any pharmacokinetic interaction when azithromycin and theophylline are co-administered to healthy volunteers.

Triazolam:

In 14 healthy volunteers, coadministration of 500 mg azithromycin on Day 1 and 250 mg on Day 2 with 0.125 mg triazolam on Day 2 had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

Trimethoprim/sulfamethoxazole:

Coadministration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with 1,200 mg azithromycin on Day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim or sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies. No dose adjustment is necessary.

Zidovudine:

Single 1,000 mg doses and multiple 1,200 mg or 600 mg doses of azithromycin did not affect the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear.

Other interactions

Digoxin and colchicine:

Some of the macrolide antibiotics including azithromycin have been reported to impair the metabolism of P-glycoprotein substrates such as digoxin and colchicine (in the gut) in some patients and to result in increased serum levels. In patients receiving concomitant azithromycin, a related azalide antibiotic, and the possibility of raised digoxin levels should be borne in mind. During treatment with azithromycin and after discontinuation thereof, clinical monitoring and measurement of serum digoxin levels may be necessary.

4.6. Fertility, pregnancy and lactation

Fertility

No animal studies of fertility have been conducted by the IV route. In three oral fertility and general reproduction studies in rats, there was decreased fertility at doses of 20 and 30 mg/kg/day. The clinical significance of this is unknown.

Pregnancy – Category B1

Studies in mice and rats have demonstrated that azithromycin crosses the placenta. Following an oral dose of 200 mg/kg/day, azithromycin concentrations in mouse and rat foetal tissue homogenates were 5- to 10-fold higher than corresponding maternal plasma concentrations. No animal studies of embryofetal development have been conducted by the IV route. Azithromycin was not fetotoxic or teratogenic in mice and rats at oral doses that were moderately maternotoxic. Plasma levels for azithromycin were lower than the clinical C_{max} in both species at the high dose of 200 mg/kg/day. Azithromycin powder for solution for infusion should only be used in pregnant women where adequate alternatives are not available.

Lactation

Limited information available from published literature indicates that azithromycin is present in human milk at an estimated highest median daily dose of 0.1 – 0.7 mg/kg/day. Azithromycin should only be used in lactating women where adequate alternatives are not available.

4.7. Effects on ability to drive and use machines

There is no evidence to suggest that azithromycin powder for solution for infusion may have an effect on the patient's ability to drive or operate machinery.

4.8. Undesirable effects

Clinical trials

In clinical studies of azithromycin given by the IV route followed by the oral route in community acquired pneumonia, the most frequent treatment related events occurring at an incidence of ≥ 1% in azithromycin treated patients (n=871) were diarrhoea (4.7%), IV site pain (4.4%), nausea (4.2%), abdominal pain (2.8%), rash (1.5%), vomiting (1.4%), dyspepsia (0.9%) and LFTs abnormal (0.7%). Local inflammation at the infusion site has also been reported.

In clinical studies, the incidence of IV site disorders (infection/inflammation/oedema/pain/reactions) associated with the 1 mg/mL and 2 mg/mL infusion solution concentration was 4.2% and 5.6%, respectively.

A total of 2.4% patients discontinued azithromycin therapy either by the IV or oral route due to treatment related clinical or laboratory adverse events.

Treatment related laboratory abnormalities occurred in 0.6% of patients.

When azithromycin was given by intravenous and oral routes for the treatment of pelvic inflammatory disease in adult women, the most frequently reported side effects were diarrhoea, nausea, vaginitis, abdominal pain, anorexia, rash and pruritus. When azithromycin was co-administered with

metronidazole in these studies, a higher proportion of women experienced side effects of nausea, abdominal pain, vomiting, infusion site reaction, stomatitis, dizziness, or dyspnoea.

Adults

Multiple-dose regimen (oral):
The most frequently reported adverse events in patients receiving a multiple-dose regimen of azithromycin orally were diarrhoea/loose stools (5%), nausea (3%) and abdominal pain (3%). No other adverse events occurred in patients on the multiple-dose regimen with a frequency > 1%. Events that occurred with a frequency of 1% or less included:

Allergic:	rash, photosensitivity and angioedema
Cardiovascular:	palpitations and chest pain
Gastrointestinal:	dyspepsia, flatulence, vomiting, melaena and cholestatic jaundice
Genitourinary:	moniliasis (candidiasis), vaginitis and nephritis
Nervous system:	dizziness, headache, vertigo and somnolence
General:	fatigue

Hearing impairment has been reported in investigational studies, mainly where higher doses were used, for prolonged periods of time. In those cases where follow-up information was available the majority of these events were reversible.

Post-marketing experience
In post marketing experience, the following adverse events have been reported:

Infections and infestations:	moniliasis, vaginitis
Blood and lymphatic system disorders:	thrombocytopenia
Immune system disorders:	anaphylaxis (rarely fatal)
Metabolism and nutrition disorders:	anorexia
Psychiatric disorders:	aggressive reaction, nervousness, agitation, anxiety
Nervous system disorders:	dizziness, convulsions, headache, hyperactivity, hypoesthesia, paraesthesia, somnolence, syncope
Ear and labyrinth disorders:	hearing disturbances and/or impairment including hearing loss, deafness and/or tinnitus, vertigo
Cardiovascular disorders:	palpitations and arrhythmias including ventricular tachycardia have been reported; there have been rare reports of QT prolongation and *torsades de pointes*
Vascular disorders:	hypotension
Gastrointestinal disorders:	vomiting/diarrhoea (rarely resulting in dehydration), dyspepsia, pancreatitis, constipation, pseudomembranous colitis, rare reports of tongue discolouration
Hepatobiliary disorders:	abnormal liver function including hepatitis and cholestatic jaundice, hepatic necrosis and hepatic failure, which have resulted in death

Skin and subcutaneous tissue disorders: allergic reactions including pruritus, rash, photosensitivity, urticaria, oedema, angioedema, serious skin reactions including erythema multiforme, acute generalised exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), medicine reaction with eosinophilia and systemic symptoms (DRESS)

Musculoskeletal and connective tissue disorders: arthralgia

Renal and urinary tract disorders: acute renal failure, interstitial nephritis

General disorders and administration site conditions: asthenia, fatigue and malaise

Other: taste/smell perversion and/or loss.

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 https://nzphvc.otago.ac.nz/reporting.

4.9. Overdose

Adverse events experienced in higher than recommended doses are similar in type and may be more frequent than those seen at normal doses. In the event of overdosage, general symptomatic and supportive measures are indicated as required.

For information 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: Antibacterial for systemic use, macrolides

ATC classification: J01FA10

Mechanism of action

Azithromycin binds to the 23S rRNA of the 50S ribosomal subunit. It blocks protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit.

Cardiac electrophysiology

QTc interval prolongation was studied in a randomised, placebo-controlled parallel trial in 116 healthy subjects who received either chloroquine (1,000 mg) alone or in combination with azithromycin (500 mg, 1,000 mg, and 1,500 mg once daily). Coadministration of azithromycin increased the QTc interval in a dose- and concentration-dependent manner. In comparison to chloroquine alone, the maximum mean (95% upper confidence bound) increases in QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with the co-administration of 500 mg, 1,000 mg and 1,500 mg azithromycin, respectively.

Mechanism of resistance

The two most frequently encountered mechanisms of resistance to macrolides, including azithromycin, are target modification (most often by methylation of 23S rRNA) and active efflux. The occurrence of these resistance mechanisms varies from species to species and, within a species, the frequency of resistance varies by geographical location.

The most important ribosomal modification that determines reduced binding of macrolides is post-transcriptional (N_6)-dimethylation of adenine at nucleotide A2058 (*Eschericia coli* numbering system) of the 23S rRNA by methylases encoded by *erm* (*e*rythromycin *r*ibosome *m*ethylase) genes. Ribosomal modifications often determine cross resistance (MLS_B phenotype) to other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin), and the streptogramin B (which include, for example, the quinupristin component of quinupristin/ dalfopristin). Different *erm* genes are present in different bacterial species, in particular Streptococci and Staphylococci. Susceptibility to macrolides can also be affected by less frequently encountered mutational changes in nucleotides A2058 and A2059, and at some other positions of 23S rRNA, or in the large subunit ribosomal proteins L4 and L22.

Efflux pumps occur in a number of species, including Gram-negatives, such as *Haemophilus influenzae* (where they may determine intrinsically higher minimum inhibitory concentrations [MICs]) and Staphylococci. In Streptococci and Enterococci, an efflux pump that recognises 14- and 15-membered macrolides (which include, respectively, erythromycin and azithromycin) is encoded by *mef* (A) genes.

Microbiology

Methodology for determining the *in vitro* susceptibility of bacteria to azithromycin

Susceptibility testing should be conducted using standardised laboratory methods, such as those described by the Clinical and Laboratory Standards Institute (CLSI). These include dilution methods (MIC determination) and disk susceptibility methods. Both CLSI and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) provide interpretive criteria for these methods.

Based on a number of studies, it is recommended that the in vitro activity of azithromycin be tested in ambient air, to ensure physiological pH of the growth medium. Elevated CO_2 tensions, as often used for Streptococci and anaerobes, and occasionally for other species, result in a reduction in the pH of the medium. This has a greater adverse effect on the apparent potency of azithromycin than on that of other macrolides.

The CLSI susceptibility breakpoints, based on broth microdilution or agar dilution testing, with incubation in ambient air, are given in the table below.

CLSI dilution susceptibility interpretive criteria

	Broth microdilution MIC (mg/L)		
Organism	**Susceptible**	**Intermediate**	**Resistant**
Haemophilus species	≤ 4	---	---[b]
Moraxella catarrhalis	≤ 0.25	---	---
Neisseria meningitidis	≤ 2	---	---[b]
Staphylococcus aureus	≤ 2	4	≥ 8
Streptococci a	≤ 0.5	1	≥ 2

CLSI dilution susceptibility interpretive criteria

	Broth microdilution MIC (mg/L)		
Organism	**Susceptible**	**Intermediate**	**Resistant**

[a]Includes *Streptococcus pneumoniae*, β-haemolytic Streptococci and viridans Streptococci.

[b]The current absence of data on resistant strains precludes defining any category other than susceptible. If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.

Incubation in ambient air.

CLSI = Clinical and Laboratory Standards Institute; MIC = Minimal inhibitory concentration.

Source: CLSI M45, 2015. CLSI M100, 2018

Susceptibility can also be determined by the disk diffusion method, measuring inhibition zone diameters after incubation in ambient air. Susceptibility disks contain 15 µg of azithromycin. Interpretive criteria for inhibition zones, established by the CLSI on the basis of their correlation with MIC susceptibility categories, are listed in the table below.

CLSI disk zone interpretive criteria

	Disk inhibition zone diameter (mm)		
Organism	**Susceptible**	**Intermediate**	**Resistant**
Haemophilus species	≤ 12	---	---
Moraxella catarrhalis	≤ 26	---	---
Neisseria meningitidis	≤ 20	---	---
Staphylococcus aureus	≤ 18	14 – 17	≥ 13
Streptococci a	≤ 18	14 – 17	≥ 13

[a]Includes *Streptococcus pneumoniae*, β-haemolytic Streptococci and viridans Streptococci.

Incubation in ambient air.

CLSI = Clinical and Laboratory Standards Institute; mm = Millimeters.

Source: CLSI, 2012. CLSI, 2010

The validity of both the dilution and disk diffusion test methods should be verified using quality control (QC) strains, as indicated by the CLSI. Acceptable limits when testing azithromycin against these organisms are listed in the table below.

Quality control ranges for azithromycin susceptibility tests

Broth microdilution MIC

Organism	Quality control range (mg/L azithromycin)
Haemophilus influenzae ATCC 49247	1 – 4
Staphylococcus aureus ATCC 29213	0.5 – 2
Streptococcus pneumoniae ATCC 49619	0.06 – 0.25

Disk inhibition zone diameter (15 µg disk)

Organism	Quality control range (mm)
Haemophilus influenzae ATCC 49247	13 – 21
Staphylococcus aureus ATCC 25923	21 – 26
Streptococcus pneumoniae ATCC 49619	19 – 25

Incubation in ambient air.
MIC = Minimal inhibitory concentration; mm = Millimeters.
Source: CLSI M100, 2018.

EUCAST has also established susceptibility breakpoints for azithromycin based on MIC determination. The EUCAST susceptibility criteria are listed in the table below.

EUCAST susceptibility breakpoints for azithromycin

	MIC (mg/L)	
	Susceptible	**Resistant**
Staphylococcus species	≤ 1	> 2
Streptococcus pneumoniae	≤ 0.25	> 0.5
ß-haemolytic Streptococci[a]	≤ 0.25	> 0.5
Haemophilus influenzae	≤ 0.12	> 4
Moraxella catarrhalis	≤ 0.25	> 0.5
Neisseria gonorrhoeae	≤ 0.25	> 0.5

[a]Includes Groups A, B, C, G.
EUCAST = European Committee on Antimicrobial Susceptibility Testing; MIC = Minimal inhibitory concentration.
Source: EUCAST website.
EUCAST Clinical Breakpoint Table v. 8.0, valid from 2018-01-01
www.eucast.org/.../EUCAST.../Breakpoint_tables/v_8.0_Breakpoint_Tables.pdf

Antibacterial spectrum

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Azithromycin demonstrates cross resistance with erythromycin-resistant Gram-positive isolates. As discussed above, some ribosomal modifications determine cross-resistance with other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin), and the streptogramin B (which include, for example, the quinupristin component of quinupristin/dalfopristin). A decrease in macrolide susceptibility over time has been noted in

particular in *Streptococcus pneumoniae* and *Staphylococcus aureus*, and has also been observed in viridans streptococci and *Streptococcus agalactiae*.

Organisms that are commonly susceptible to azithromycin include:

Aerobic and facultative Gram-positive bacteria (erythromycin-susceptible isolates): *S. aureus, Streptococcus agalactiae*, S. pneumonia*, Streptococcus pyogenes*,* other β-haemolytic streptococci (Groups C, F, G), and viridans Streptococci. Macrolide-resistant isolates are encountered relatively frequently among aerobic and facultative Gram-positive bacteria, in particular among methicillin-resistant *S. aureus* (MRSA) and penicillin-resistant *S. pneumoniae* (PRSP).

Aerobic and facultative Gram-negative bacteria: *Bordetella pertussis, Campylobacter jejuni, Haemophilus ducreyi*, Haemophilus influenza*, Haemophilus parainfluenzae*, Legionella pneumophila, Moraxella catarrhalis*,* and *Neisseria gonorrhoeae*. Pseudomonas* spp. and most *Enterobacteriaceae* are inherently resistant to azithromycin, although azithromycin has been used to treat *Salmonella enterica* infections.

Anaerobes: *Clostridium perfringens, Peptostreptococcus* spp. and *Prevotella bivia*.

Other bacterial species: *Borrelia burgdorferi, Chlamydia trachomatis, Chlamydophila pneumonia*, Mycoplasma pneumonia*, Treponema pallidum,* and *Ureaplasma urealyticum.*

Opportunistic pathogens associated with HIV infection: *Mycobacterium avium* complex (MAC)*, and the eukaryotic microorganisms *Pneumocystis jirovecii* and *Toxoplasma gondii*.

*The efficacy of azithromycin against the indicated species has been demonstrated in clinical trials.

Clinical efficacy and safety

Treatment of community acquired pneumonia (CAP)

The efficacy of azithromycin in the treatment of CAP was assessed in an open, randomised comparative trial, conducted in the US between 1993 and 1995. Azithromycin (500 mg IV as a single dose for 2 – 5 days, followed by 500 mg/day orally to complete 7 – 10 days of therapy) was compared to cefuroxime (2.225 g/day in 3 divided doses administered IV for 2 – 5 days followed by 1 g/day in 2 divided doses to complete 7 – 10 days therapy), with erythromycin as required. Two hundred and ninety-one patients were evaluable for efficacy. Clinical success (cure + improvement) at 10 – 14 days post therapy was 77.4% in the azithromycin group vs 74.1 % in the comparator group.

In a separate open, non-comparative study, 94 patients received azithromycin by IV infusion (for 2 – 5 days) followed by azithromycin orally (to complete a total of 7 – 10 days therapy) for the treatment of CAP. The clinical success rates (cure + improvement) at 10 – 14 days post therapy was 88% (74/84) and at 4 – 6 weeks was 86% (73/85) among evaluable patients.

These two studies indicated an overall cure rate for patients serologically positive for *Legionella pneumophila* of 84% (16/19). Additionally, in an open, non-comparative study, patients diagnosed as positive for *Legionella pneumophila* (serogroup 1) using a specific urinary antigen test were treated with azithromycin IV followed by oral azithromycin. At 10 – 14 days, 16 out of 17 evaluable patients were clinically cured and at 4 – 6 weeks, 20 out of 20 evaluable patients were clinically cured.

Treatment of pelvic inflammatory disease

The results of an open study indicate that three treatment regimens (azithromycin versus azithromycin/metronidazole versus doxycycline, metronidazole, cefoxitin and probenecid) were comparable in terms of efficacy and safety in subjects with acute pelvic inflammatory disease. In another open, comparative study in patients with acute pelvic inflammatory disease, patients were treated with azithromycin IV/oral versus azithromycin IV plus metronidazole IV/oral versus oral doxycycline plus co-amoxiclav IV/oral. These treatment regimens were also comparable in terms of efficacy and safety. The data from these studies showed an overall clinical success rate (cured plus improved) of ≥ 97% in all treatment groups at the end of treatment, with ≤ 96% of pathogens eradicated. At follow-up, ≥ 90% of pathogens were eradicated.

Paediatric use

The safety and effectiveness of azithromycin powder for solution for infusion for the treatment of infections in children have not been established. Azithromycin powder for oral suspension is recommended for the treatment of paediatric patients.

Infantile hypertrophic pyloric stenosis (IHPS) has been reported following the use of azithromycin in neonates (treatment up to 42 days of life). Parents and caregivers should be informed to contact their physician if vomiting or irritability with feeding occurs.

5.2. Pharmacokinetic properties

Absorption

Following oral administration in humans, bioavailability is approximately 37%. Administration of azithromycin capsules following a substantial meal reduces bioavailability. The time taken to peak plasma levels is 2 – 3 hours. Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 - 4 days. In elderly volunteers (> 65 years), slightly higher AUC values were seen after a 5-day regimen than in young volunteers (< 40 years), but these are not considered clinically significant, and hence no dose adjustment is recommended.

In patients hospitalised with community acquired pneumonia receiving single daily one-hour intravenous (IV) infusions for 2 - 5 days of 500 mg azithromycin at a concentration of 2 mg/mL, the mean C_{max} ± SD achieved was 3.63 ± 1.60 µg/mL, while the 24-hour trough level was 0.20 ± 0.15 µg/mL, and the AUC_{24} was 9.60 ± 4.80 µg·h/mL. The mean C_{max}, 24-hour trough and AUC_{24} values were 1.14 ± 0.14 µg/mL, 0.18 ± 0.02 µg/mL, and 8.03 ±0.86 µg·h/mL, respectively, in normal volunteers receiving a 3-hour IV infusion of 500 mg azithromycin at a concentration of 1 mg/mL.

Comparison of the plasma pharmacokinetic parameters following the 1st and 5th daily doses of 500 mg IV azithromycin showed only an 8% increase in C_{max} but a 61% increase in AUC_{24} reflecting a threefold rise in C_{24} trough levels.

Pharmacokinetic studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the medicine is heavily tissue bound. Concentrations in target tissues, such as lung, tonsil and prostate exceed the MIC_{90} for likely pathogens after a single dose of 500 mg. High concentrations of azithromycin were found in gynaecological tissue 96 hours after a single 500 mg oral dose of azithromycin.

Distribution

Following oral administration in humans, azithromycin is widely distributed throughout the body.

Biotransformation

Very high concentrations of unchanged medicine have been found in human bile, together with 10 metabolites, formed by N- and O-demethylation, hydroxylation of the desosamine and aglycone rings, and cleavage of the cladinose conjugate. Comparison of HPLC and microbiological assays in tissues suggests that metabolites play no part in the microbiological activity of azithromycin.

Elimination

In a multiple-dose study in 12 normal volunteers utilising a 500 mg (1 mg/mL) one-hour IV dosage regimen for five days, the amount of administered azithromycin dose excreted in urine in 24 hours was about 11% after the 1st dose and 14% after the 5th dose. These values are greater than the reported 6% excreted unchanged in urine after oral administration of azithromycin. Biliary excretion is a major route of elimination for unchanged medicine, following oral administration.

Following a single oral dose of azithromycin 1 gram, the pharmacokinetics in subjects with mild to moderate renal impairment (GFR 10 – 80 mL/min) were not affected. Statistically significant differences in $AUC_{0\text{-}120}$ (8.8 µg.hr/mL vs. 11.7 µg.hr/mL), C_{max} (1.0 µg/mL vs. 1.6 µg/mL) and CLr (2.3 mL/min/kg vs. 0.2 mL/min/kg) were observed between subjects with severe renal impairment (GFR < 10 mL/min) and subjects with normal renal function.

In patients with mild (Class A) to moderate (Class B) hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to those with normal hepatic function. In these patients, urinary recovery of azithromycin appears to increase, perhaps to compensate for reduced hepatic clearance.

In animal studies, high azithromycin concentrations have been observed in phagocytes. In experimental models, higher concentrations of azithromycin are released during active phagocytosis than from non-stimulated phagocytes. In animal models this results in high concentrations of azithromycin being delivered to the site of infection.

5.3. Preclinical safety data

Animal toxicity

In high-dose animal studies, giving drug concentrations 40-fold higher than those expected in clinical practice, azithromycin has been noted to cause reversible phospholipidosis, generally without discernible toxicological consequences. There is no evidence that this is of relevance to the normal use of azithromycin in humans.

Genotoxicity

Azithromycin showed no genotoxic potential in a range of standard laboratory tests for gene mutations and chromosomal damage.

Carcinogenicity

No animal studies have been done to determine the carcinogenic potential of azithromycin

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Citric acid
Sodium hydroxide (pH adjusting agent)

6.2. Incompatibilities

AZITHROMYCIN-AFT reconstituted solution may be diluted using the instructions and compatible infusion solutions provided in **Section 4.2 Dose and method of administration**.

Other intravenous substances, additives or medications should not be added to AZITHROMYCIN-AFT, or infused simultaneously through the same IV line.

6.3. Shelf life

Powder for solution for injection: 24 months from the date of manufacture
Reconstituted solution: 24 hours after reconstituting as directed when stored below 30 °C

6.4. Special precautions for storage

Store below 30 °C.
For storage conditions after reconstitution of the medicine, see **Section 6.3 Shelf life**.

6.5. Nature and contents of container

AZITHROMYCIN-AFT is packaged in 10 mL glass vial (Type I) and closed with a chlorobutyl rubber stopper and aluminium crimp with a plastic flip-off overseal.

Pack size: 500 mg substance in each 10 mL vial; 5 vials packed per carton.

6.6. Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

AFT Pharmaceuticals Ltd
Level 1, 129 Hurstmere Road
Takapuna
Auckland 0622

Phone: 0800 423 823
Email: customer.service@aftpharm.com

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