PACKAGE INSERT – AZITHROMYCIN-AFT (AZITHROMYCIN DIHYDRATE)

1. NAME OF THE MEDICINE

AZITHROMYCIN-AFT powder for solution for infusion 500 mg/ vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial containing 500 mg of azithromycin (as dihydrate), providing 100 mg/mL solution following reconstitution.

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

3. PHARMACEUTICAL FORM

White lyophilized powder for solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Azithromycin is indicated for infections caused by susceptible organisms; in lower respiratory tract infections including bronchitis and pneumonia, in odontostomatological infections, in skin and soft tissue infections, in acute otitis media and in upper respiratory tract infections including sinusitis and pharyngitis/tonsillitis. (Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. Azithromycin is generally effective in the eradication of streptococci from the oropharynx; however, data establishing the efficacy of azithromycin and the subsequent prevention of rheumatic fever are not available at present.)

In sexually transmitted diseases in men and women, azithromycin is indicated for the treatment of uncomplicated genital infections due to *Chlamydia trachomatis*. It is also indicated for the treatment of chancroid due to *Haemophilus ducreyi* and uncomplicated genital infections due to non-multiresistant *Neisseria gonorrhoeae*; concurrent infection with *Treponema pallidum* should be excluded.

Azithromycin is indicated, either alone or in combination with rifabutin, for prophylaxis against *Mycobacterium avium*-intracellulare complex (MAC) infection, an opportunistic infection prevalent in patients with advanced human immunodeficiency virus (HIV).

Azithromycin IV is indicated for the community acquired pneumonia (CAP) caused by susceptible organisms including *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Legionella pneumophilia*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Staphylococcus aureu*s or *Streptococcus pneumoniae*, in patients who require initial IV therapy.

Azithromycin IV is indicated for the treatment of pelvic inflammatory diseases (PID) caused by susceptible organisms, including *Chlamydia trachomatis, Neisseria gonorrhoeae,* or *Mycoplasma hominis*, in patients who require initial IV 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

For the treatment of adult patients with CAP due to the indicated organisms, the recommended dose of IV azithromycin 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.

For the treatment of adult patients with PID due to the indicated organisms, the recommended dose of IV azithromycin is 500 mg as a single daily dose by the IV route for 1 or 2 days. IV therapy should be followed by oral azithromycin at a single daily dose of 250 mg 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. If anaerobic microorganisms are suspected of contributing to the infection, an antimicrobial anaerobic agent may be administered in combination with azithromycin.

Special populations

Use in elderly

No dose adjustment is necessary in elderly patients requiring azithromycin therapy. Elderly patients may be more susceptible to the development of *torsades de pointes* arrhythmia than younger patients (see **Section 4.4 Special warnings and precautions for use**).

Use in patients with renal impairment

No dose adjustment is needed in patients with mild or moderate renal impairment (GFR 10 – 80 mL/min). 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 (see **Section 4.4 Special warnings and precautions for use** and **Section 5.2 Pharmacokinetic properties, Pharmacokinetics in special patient groups – renal impairment**).

Use in patients with hepatic impairment

The same dosage as in patients with normal hepatic function may be used in patients with mild to moderate hepatic impairment (see **Section 4.4 Special warnings and precautions for use**).

Use in children

The safety and effectiveness of IV 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 only. 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. An IV dose of 500 mg azithromycin should be infused for a minimum duration of 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 sterile Water for Injections to the 500 mg vial and shaking the vial until all of the drug is dissolved. Since azithromycin IV is supplied under vacuum, It is recommended that a standard 5 mL (non-automated) syringe be used to ensure that the exact amount of 4.8 mL of sterile Water for Injections is dispensed. Each mL of reconstituted solution contains 100 mg azithromycin.

Dilute this solution further prior to administration as instructed below.

Dilution

To provide azithromycin over a concentration range of 1.0 – 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 sterile 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 – 2.0 mg/mL.

Parenteral drug products should be inspected visually for particulate matter prior to administration. If particulate matter is evident, the drug 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% Dextrose 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)

- Normosol®-M in 5% Dextrose
- Normosol®-R in 5% Dextrose

4.3 Contraindications

Azithromycin is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any other macrolide or ketolide antibiotic, or to any of the excipients (see **Section 6.1 List of Excipients**).

4.4 Special warnings and precautions for use

Hypersensitivity

As with erythromycin and other macrolides, 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 drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients on azithromycin therapy. 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 drug 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.

Ergot derivatives

In patients receiving ergot derivatives, ergotism has been precipitated by coadministration of some macrolide antibiotics (see **Section 4.5 Interactions with other medicines and other forms of interactions, Drugs that should not be concomitantly administered with azithromycin**). 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 coadministered.

Superinfection

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

Clostridium difficile-associated diarrhoea (CDAD)

CDAD has been reported with the use of many antibiotics including azithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of *C. difficile*.

Mild cases may respond to drug 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.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all

patients who present with diarrhoea following antibiotic use. Careful medical history is necessary, since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Prolongation of the QT interval

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides, 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 with congenital or documented QT prolongation
- patients currently receiving treatment with other active substances 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.

QTc interval prolongation was studied in a randomized, placebo-controlled parallel trial in 116 healthy subjects who received either chloroquine (1000 mg) alone or in combination with azithromycin (500 mg, 1000 mg, and 1,500 mg once daily). Co-administration 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, 1000 mg and 1,500 mg azithromycin, respectively.

Myasthenia gravis

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

Intravenous administration

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 (see **Section 4.2 Dose and method of administration**) . All patients who received infusate concentrations above 2.0 mg/mL experienced local infusion site reactions and therefore, higher concentrations should be avoided.

Use in hepatic impairment

No dose adjustment is recommended for 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.

Use in renal impairment

No dose adjustment is needed in patients with mild or moderate renal impairment (GFR 10 – 80 mL/min). 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 (see **Section 5.2 Pharmacokinetic properties**).

Use in the elderly

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

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.

Effects on laboratory tests

No data available.

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 drug 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 drug interactions refers to oral azithromycin:

Drugs that should not be concomitantly administered with azithromycin

Antacids: 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 drugs should not be taken simultaneously. Administration of oral antacids is not expected to affect the disposition of azithromycin given intravenously.

Ergot: 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).**

Drugs that require dosage adjustment when administered concomitantly with azithromycin

Cyclosporin: 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 $AUC_{0\text{-}5}$ were found to be significantly elevated. Consequently, caution should be exercised before considering

concurrent administration of these drugs. If coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Drugs that have been studied with no clinically significant interaction shown

Atorvastatin: 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.

Carbamazepine: 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.

Cetirizine: 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.

Cimetidine: 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 (Dideoxyinosine): Coadministration of daily doses of 1,200 mg azithromycin with didanosine in six HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as 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 drug. 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 (see **Section 4.8 Adverse effects (undesirable effects**).

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 coadministered 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, but it may be of benefit to patients.

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 digoxin, 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

Effects on 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.

Use in pregnancy

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 embyrofetal 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. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

Use in 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. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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 Adverse effects (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.

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:

Infections and infestations:
Moniliasis (candidiasis), vaginitis, and nephritis.

Blood and lymphatic system disorders:
Transient episodes of mild neutropenia have occasionally been observed in clinical trials, although a causal relationship to azithromycin has not been established.

Nervous system:
Dizziness, headache, vertigo and somnolence.

Ear and labyrinth disorders:
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.

Cardiac disorders:
Palpitations, chest pain.

Gastrointestinal disorders:
Dyspepsia, flatulence, nausea, vomiting, diarrhoea, loose stools, melaena, cholestatic jaundice, abdominal discomfort (pain/cramps).

Hepatobiliary disorders:
Abnormal liver function.

Skin and subcutaneous tissue disorders:
Allergic reactions including rash, photosensitivity and angioedema.

General disorders and administration site conditions:
Fatigue.

Post-marketing experience

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

Infections and infestations:
Moniliasis and vaginitis.

Blood and lymphatic system disorders:
Thrombocytopenia.

Immune system disorders:

Anaphylaxis (rarely fatal) (see **Section 4.4 Special warnings and precautions for use**).

Metabolism and nutrition disorders:
Anorexia.

Psychiatric disorders:
Aggressive reaction, nervousness, agitation, anxiety.

Nervous system disorders:
Dizziness, convulsions, headache, hyperactivity, hypoesthesia, paraesthesia, somnolence, syncope. There have been rare reports of taste/smell perversion and/or loss.

Ear and labyrinth disorders:
Deafness, - tinnitus, hearing impaired and vertigo.

Cardiac disorders:
Palpitations and arrhythmias including ventricular tachycardia have been reported. There have been rare reports of QT prolongation and *torsades de pointes* (see **Section 4.4 Special warnings and precautions for use**).

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 (see **Section 4.4 Special warnings and precautions for use**).

Skin and subcutaneous tissue disorders:
Allergic reactions including pruritus, rash, photosensitivity, urticaria, oedema, angioedema, serious skin reactions including erythrema multiforme, acute generalised exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug 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.

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 to the Product Owner listed at the end of this package insert (see **Section 8 Product Owner**).

4.9 Overdose

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

As with many cationic amphiphilic drugs, phospholipidosis has been observed in some tissues of mice, rats and dogs given multiple doses of azithromycin. It has been demonstrated in numerous organ systems in dogs administered doses which, based on pharmacokinetics, are as low as 2 – 3 times greater than the recommended human dose and in rats at doses comparable to the human dose. This effect is reversible after cessation of azithromycin treatment. The significance of these findings for humans with overdose of azithromycin is unknown.

For information on the management of overdose, contact the nearest Accident & Emergency department.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial for systemic use, macrolides
ATC classification: J01FA10

Mechanism of action

Azithromycin is the first of a subclass of macrolide antibiotics, known as azalides, and is chemically different from erythromycin. Chemically it is derived by insertion of a nitrogen atom into the lactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A. The molecular weight is 749.0.

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'.

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 (N6)-dimethylation of adenine at nucleotide A2058 (*Escherichia coli* numbering system) of the 23S rRNA by methylases encoded by erm (erythromycin ribosome methylase) genes. Ribosomal modifications often determine cross-resistance (MLSB 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 minimal inhibitory concentrations [MICs]) and staphylococci. In streptococci and enterococci, an efflux pump that recognizes 14- and 15-membered macrolides (which include, respectively, erythromycin and azithromycin) is encoded by *mef* (A) genes.

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

Susceptibility testing should be conducted using standardized 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

[a] Includes *Streptococcus pneumoniae*, β-hemolytic 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-hemolytic streptococci and viridans streptococci.
Incubation in ambient air.
CLSI = Clinical and Laboratory Standards Institute; mm = Millimeters.
Source: CLSI M45, 2015; CLSI M100, 2018.

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.
CLSI = Clinical and Laboratory Standards Institute; 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
B-hemolytic 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 Web site.
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 susceptibility of bacterial species to azithromycin is shown below.

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.

In-vitro susceptibility data do not always correlate with clinical results.

Commonly susceptible species

Aerobic gram-positive bacteria:

Streptococci (Groups C, F, G) and *Viridans group streptococci.*

Aerobic gram-negative bacteria:

Bordetella pertussis, Haemophilus ducreyi, Haemophilus influenzae$^{\$}$, Haemophilus parainfluenzae*, Legionella pneumophila, Moraxella catarrhalis** and *Neisseria gonorrhoeae.*

Other:

Chlamydia pneumoniae, Chlamydia trachomatis, Mycoplasma pneumoniae** and *Ureaplasma urealyticum.*

Species for which acquired resistance may be a problem

Aerobic gram-positive bacteria:

*Streptococcus pneumoniae**
*Streptococcus pyogenes**
Staphylococcus aureus

Inherently resistant organisms:

Enterobacteriaceae
Pseudomonas spp.

Note: Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive strains and most strains of methicillin resistant staphylococci.

*Species for which efficacy has been demonstrated in clinical trials.
$^{\$}$Species with natural intermediate susceptibility.

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.

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} ± S.D. 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.

Distribution

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

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.

Pharmacokinetic studies in humans have shown markedly higher azithromycin levels in tissues than in plasma (up to 50 times the maximum observed concentration in plasma), indicating that the drug is heavily tissue bound. Concentrations in target tissues, such as lung, tonsil and prostate, exceed the MIC90 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.

Metabolism

Very high concentrations of unchanged drug 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.

Excretion

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. Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 – 4 days. Approximately 12% of an intravenously administered dose is excreted in the urine over 3 days as the parent drug, the majority in the first 24 hours. Biliary excretion of azithromycin is a major route of elimination for unchanged drug, following oral administration.

Pharmacokinetics in special patient groups

Use in the elderly

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.

Use in renal impairment

The pharmacokinetics of azithromycin in subjects with mild to moderate renal impairment (GFR 10 – 80 mL/min) were not affected following a single 1-gram dose of immediate release azithromycin. Statistically significant differences in $AUC_{0\text{-}120}$ (8.8 µg·h/mL vs. 11.7 µg·h/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 the group with severe renal impairment (GFR < 10 mL/min) and the group with normal renal function.

Use in hepatic impairment

In patients with mild cases (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 clearance of azithromycin appears to increase, perhaps to compensate for reduced hepatic clearance.

5.3 Preclinical safety data

Phospholipidosis (intracellular phospholipid accumulation) has been observed in several tissues (e.g. eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and/or pancreas) of mice, rats, and dogs given multiple doses of azithromycin. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs. The effect has been shown to be reversible after cessation of azithromycin treatment. The significance of the finding for animals and humans is unknown.

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 monohydrate
Sodium hydroxide (pH adjusting agent)

6.2 Incompatibilities

Azithromycin-AFT may be diluted using the instructions and compatible infusion solutions provided in **Section 4.2 Dose and administration, Method of administration**. Other IV 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: refer to outer carton for shelf life.

In-use shelf life: 24 hours when stored between 2 – 8 °C (see **Section 4.2 Dose and method of administration, Method of administration, Dilution).**

6.4 Special precautions for storage

Store below 30 °C (see section 4.2 for storage information after reconstitution)

6.5 Nature and contents of container

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

Pack size: 5 vials

6.6 Special precautions for disposal

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

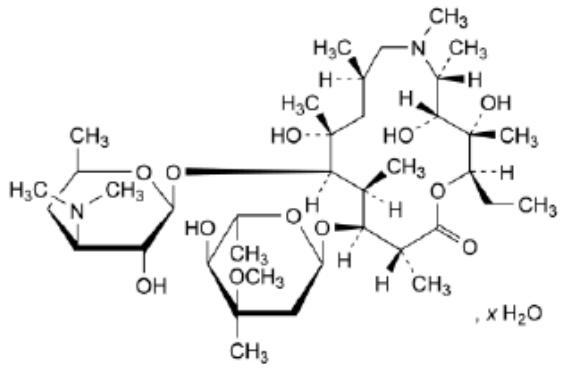
6.7 Physicochemical properties

Chemical structure

Azithromycin is the first of a class of antibiotics designated chemically as azalides, a subclass of macrolides. Chemically it is derived by insertion of a nitrogen atom into the lactone ring of erythromycin A.

The chemical name of azithromycin is 9-deoxy-9*a*-aza-9*a*-methyl-9*a*-homoerythromycin A. The

structural formula is:



Azithromycin has a chemical formula of $C_{38}H_{72}N_2O_{12}$ and a molecular weight of 749.0.

pKa: 8.74 at 25 °C

Solubility: Practically insoluble in water, freely soluble in ethanol and in methylene chloride

Partition coefficient:

Property	Value
Water solubility	5.14^{e-01} g/L
log P	3.03
log P	2.44

pH of reconstituted solution: Between 6.4 and 6.8 on reconstitution with 4.8 mL of WFI

CAS number:
117772-70-0

7. FORENSIC CLASSIFICATION

Prescription Only Medicine

8. PRODUCT OWNER

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

Product registration number: SIN 16605P

9. DATE OF FIRST APPROVAL

21 September 2022

10. DATE OF REVISION

Not applicable