

# PACKAGE INSERT TEMPLATE FOR AZITHROMYCIN POWDER FOR INTRAVENOUS (IV) SOLUTION

## Brand or Product Name

[Product name] Powder for IV Solution 500mg

## Name and Strength of Active Substance(s)

Azithromycin dihydrate ....mg equivalent to azithromycin 500mg

## Product Description

[Visual description of the appearance of the product (eg colour, odour etc)

eg White to off-white caked powder. Upon reconstitution, azithromycin powder yields a white to off white solution]

## Pharmacodynamics

Azithromycin is the first of a subclass of macrolides 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 mode of action of azithromycin is inhibition of protein synthesis in bacteria by binding to the 50s ribosomal subunit and preventing translocation of peptides.

Azithromycin demonstrates activity in vitro against a wide range of bacteria including:

### Gram-positive Aerobic Bacteria

*Staphylococcus aureus*, *Streptococcus pyogenes* (group A beta-hemolytic streptococci), *Streptococcus pneumoniae*, *alpha-hemolytic streptococci* (viridans group) and other streptococci, and *Corynebacterium diphtheriae*. Azithromycin demonstrates cross-resistance with erythromycin-resistant Gram-positive strains, including *Streptococcus faecalis* (enterococcus) and most strains of methicillin-resistant staphylococci.

### Gram-negative Aerobic Bacteria

*Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Acinetobacter* species, *Yersinia* species, *Legionella pneumophila*, *Bordetella pertussis*, *Bordetella parapertussis*, *Shigella* species, *Pasteurella* species, *Vibrio cholerae* and *parahaemolyticus*, *Plesiomonas shigelloides*. Activities against *Escherichia coli*, *Salmonella enteritidis*, *Salmonella typhi*, *Enterobacter* species, *Aeromonas hydrophila* and *Klebsiella* species are variable and susceptibility tests should be performed. *Proteus* species, *Serratia* species, *Morganella* species, and *Pseudomonas aeruginosa* are usually resistant.

### Anaerobic Bacteria

*Bacteroides fragilis* and *Bacteroides* species, *Clostridium perfringens*, *Peptococcus* species and *Peptostreptococcus* species, *Fusobacterium necrophorum* and *Propionibacterium acnes*.

### Organisms of Sexually Transmitted Diseases

Azithromycin is active against *Chlamydia trachomatis* and also shows good activity against *Treponema pallidum*, *Neisseria gonorrhoeae*, and *Haemophilus ducreyi*.

### Other Organisms

*Borrelia burgdorferi* (Lyme disease agent), *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Campylobacter* species and *Listeria monocytogenes*.

### Opportunistic Pathogens Associated with HIV Infections

*Mycobacterium avium-intracellulare* complex, *Pneumocystis carinii* and *Toxoplasma gondii*.

Commonly susceptible species :

Aerobic Gram-positive bacteria:

*Staphylococcus aureus*, *Streptococcus agalactiae*, 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 pneumonia* and *Ureaplasma urealyticum*.

Species for which acquired resistance :

Aerobic Gram-positive bacteria: *Streptococcus pneumoniae*, *Streptococcus pyogenes*

Note: Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive strains.

Inherently resistant organisms : Enterobacteriaceae, *Pseudomonas*

## **Pharmacokinetics**

### *Absorption*

Following oral administration in humans, azithromycin is widely distributed throughout the body; bioavailability is approximately 37%. The time taken to peak plasma levels is 2-3 hours.

### *Distribution*

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 tissue 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.

### *Elimination*

Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 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. Very high concentrations of unchanged drug have been found in human bile, together with 10 metabolites, formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by 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.

## Pharmacokinetics in Special Patient Groups

### *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.

### *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 one gram dose of immediate release azithromycin. Statistically significant differences in AUC 0-120 (8.8 µg·hr/ml vs. 11.7 µg·hr/ml), C<sub>max</sub> (1.0 µg/ml vs. 1.6 µg/ml) and CL<sub>r</sub> (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.

### *Hepatic Impairment*

In patients with mild to moderate 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.

### **Indication**

Azithromycin intravenous (IV) is indicated for the treatment of community acquired pneumonia (CAP) caused by susceptible organisms, including *Legionella pneumophila*, in patients who require initial intravenous therapy.

Azithromycin intravenous (IV) is indicated for the treatment of pelvic inflammatory disease (PID) caused by susceptible organisms (*Chlamydia trachomatis*, *Neisseria gonorrhoea*, *Mycoplasma hominis*), in patients who require initial intravenous therapy.

### **Recommended Dosage**

#### Adults

For the treatment of adult patients with CAP due to the indicated organisms, the recommended dose of intravenous azithromycin is 500 mg as a single daily dose by the IV route for at least two days. Intravenous therapy should be followed by oral azithromycin as a single daily dose of 500 mg to complete a 7 to 10 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.

For the treatment of adult patients with PID due to the indicated organisms, the recommended dose of intravenous azithromycin is 500 mg as a single dose by the IV route for one or two days. Intravenous therapy should be followed by azithromycin by the oral route 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.

#### *Intravenous Administration*

After reconstitution and dilution, the recommended route of administration for intravenous azithromycin is by IV infusion only. Do not administer as an intravenous bolus or an intramuscular injection. The infusate concentration and rate of infusion for azithromycin intravenous (IV) should be either 1 mg/ml over 3 hours or 2 mg/ml over 1 hour. An intravenous dose of 500 mg azithromycin should be infused for a minimum duration of one (1) hour.

#### Children

The safety and efficacy of intravenous azithromycin for the treatment of infections in children has not been established.

## Elderly

The same dosage as in adult patients is used in the elderly.

## Patients with Renal Impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10 - 80 ml/min). Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR < 10 ml/min).

## 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.

## **Mode of Administration**

Intravenous infusion

## **Contraindications**

The use of this product is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic.

## **Warnings and Precautions**

As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

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.

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 coadministered.

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

*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C difficile*.

*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 diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

In patients with severe renal impairment (GFR <10 ml/min) a 33% increase in systemic exposure to azithromycin was observed.

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides. A similar effect with

azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarization.

#### *Intravenous Administration*

Azithromycin for injection should be reconstituted and diluted as directed and administered as an intravenous infusion over not less than 60 minutes. Do not administer as an intravenous bolus or an intramuscular injection.

#### *Effects on Ability to Drive and Use Machines*

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

### **Interactions with Other Medicaments**

#### *Antacids*

No effect on overall bioavailability was seen although peak serum concentrations were reduced by approximately 25%. In patients receiving both oral azithromycin and antacids, the drugs should not be taken simultaneously.

#### *Cetirizine*

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

#### *Didanosine (Dideoxyinosine)*

Coadministration of 1200 mg/day azithromycin with 400 mg/day didanosine in HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

#### *Digoxin*

Some of the macrolide antibiotics have been reported to impair the microbial metabolism of digoxin in the gut in some patients. In patients receiving concomitant azithromycin, a related azalide antibiotic, and digoxin the possibility of raised digoxin levels should be borne in mind.

#### *Zidovudine*

Single 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin had little effect on 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.

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.

#### *Ergot*

Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended.

Pharmacokinetic studies have been conducted between azithromycin and the following drugs known to undergo significant cytochrome P450 mediated metabolism.

### *Atorvastatin*

Coadministration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin.

### *Carbamazepine*

No significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

### *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*

There have been reports 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.

### *Cyclosporin*

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

### *Efavirenz*

Coadministration of a 600 mg single dose of azithromycin and 400 mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions.

### *Fluconazole*

Coadministration of a single dose of 1200 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<sub>max</sub> (18%) of azithromycin was observed.

### *Indinavir*

Coadministration of a single dose of 1200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

### *Methylprednisolone*

Azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

### *Midazolam*

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

### *Nelfinavir*

Coadministration of azithromycin (1200 mg) 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 is required.

### *Rifabutin*

Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either drug.

Neutropenia was observed in subjects receiving concomitant treatment of 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*

There was no evidence of an effect of azithromycin (500mg daily for 3 days) on the AUC and Cmax, of sildenafil or its major circulating metabolite.

### *Terfenadine*

Pharmacokinetic studies have reported no evidence of an interaction between azithromycin and terfenadine. There have been rare cases reported where the possibility of such an interaction could not be entirely excluded; however, there was no specific evidence that such an interaction had occurred.

### *Theophylline*

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

### *Triazolam*

Coadministration of azithromycin with 0.125 mg triazolam 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 azithromycin 1200 mg 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.

## **Statement on Usage During Pregnancy and Lactation**

Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of harm to the fetus due to azithromycin was found. 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.

There are no data on secretion in breast milk. As many drugs are excreted in human milk, azithromycin should not be used in the treatment of a lactating woman unless the physician feels that the potential benefits justify the potential risks to the infant.

## **Adverse Effects / Undesirable Effects**

Azithromycin is well tolerated with a low incidence of side effects.

### *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.

### *Ear and Labyrinth Disorders*

Hearing impairment (including hearing loss, deafness and/or tinnitus) has been reported in some patients receiving azithromycin. Many of these have been associated with prolonged use of high doses in

investigational studies. In those cases where follow-up information was available the majority of these events were reversible.

#### *Gastrointestinal Disorders*

Nausea, vomiting, diarrhea, loose stools, abdominal discomfort (pain/cramps), and flatulence.

#### *Hepatobiliary Disorders*

Abnormal liver function.

#### *Skin and Subcutaneous Tissue Disorders*

Allergic reactions including rash and angioedema.

#### *General Disorders and Administration Site Conditions*

Local pain and inflammation at the site of infusion.

The following undesirable effects have been reported in association with DMAC prophylaxis and treatment:

The most frequent adverse reactions in HIV-infected patients receiving azithromycin for prophylaxis for DMAC were diarrhea, abdominal pain, nausea, loose stools, flatulence, vomiting, dyspepsia, rash, pruritus, headache, and arthralgia.

When azithromycin 600 mg is given daily for the treatment of DMAC infection for prolonged periods, the most frequently reported treatment-related side effects are abdominal pain, nausea, vomiting, diarrhea, flatulence, headache, abnormal vision, and hearing impairment.

In post-marketing experience, the following additional undesirable effects have been reported:

#### *Infections and Infestations*

Moniliasis and vaginitis.

#### *Blood and Lymphatic System Disorders*

Thrombocytopenia.

#### *Immune System Disorders*

Anaphylaxis (rarely fatal)

#### *Metabolism and Nutrition Disorders*

Anorexia.

#### *Psychiatric Disorders*

Aggressive reaction, nervousness, agitation, and anxiety.

#### *Nervous System Disorders*

Dizziness, convulsions (as seen with other macrolides), headache, hyperactivity, hypoesthesia, paresthesia, somnolence, and syncope. There have been rare reports of taste/smell perversion and/or loss. However, a causal relationship has not been established.

#### *Ear and Labyrinth Disorders*

Vertigo.

### *Cardiac Disorders*

Palpitations and arrhythmias including ventricular tachycardia (as seen with other macrolides) have been reported. There have been rare reports of QT prolongation and torsades de pointes. A causal relationship between azithromycin and these effects has not been established.

### *Vascular Disorders*

Hypotension

### *Gastrointestinal Disorders*

Vomiting/diarrhea (rarely resulting in dehydration), dyspepsia, constipation, pseudomembranous colitis, pancreatitis, and rare reports of tongue discoloration.

### *Hepatobiliary Disorders*

Hepatitis and cholestatic jaundice have been reported, as well as rare cases of hepatic necrosis and hepatic failure, which have rarely resulted in death. However, a causal relationship has not been established.

### *Skin and Subcutaneous Tissue Disorders*

Allergic reactions including pruritus, rash, photosensitivity, edema, urticaria, and angioedema. Rarely, serious skin reactions including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported.

### *Musculoskeletal and Connective Tissue Disorders*

Arthralgia.

### *Renal and Urinary Disorders*

Interstitial nephritis and acute renal failure.

### *General Disorders and Administration Site Conditions*

Asthenia has been reported, although a causal relationship has not been established; fatigue, and malaise.

## **Overdose and Treatment**

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

## **Incompatibilities**

Other intravenous substances, additives or medications should not be added to intravenous azithromycin, or infused simultaneously through the same intravenous line.

## **Instructions for Use**

### **IV Solution Preparation for IV Administration**

#### *Reconstitution*

Prepare the initial IV solution for infusion by adding 4.8 ml of sterilized Water for Injection 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 sterilized Water for Injection 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 100mg/ml azithromycin solution into the appropriate amount of any of the diluents listed below:

<u>Final Infusion Solution Concentration (mg/ml)</u>	<u>Amount of Diluent (ml)</u>
1.0 mg/ml	500 ml
2.0 mg/ml	250 ml

The reconstituted solution can be diluted with:

Normal Saline (0.9% sodium chloride)  
1/2 Normal Saline (0.45% sodium chloride)  
5% Dextrose in Water

#### Lactated Ringer's Solution

5% Dextrose in 1/2 Normal Saline (0.45% sodium chloride) with 20 mEq KCl  
5% Dextrose in Lactated Ringer's Solution  
5% Dextrose in 1/3 Normal Saline (0.3% sodium chloride)  
5% Dextrose in 1/2 Normal Saline (0.45% sodium chloride)  
Normosol®-M in 5% Dextrose  
Normosol®-R in 5% Dextrose

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

Azithromycin IV powder for solution for infusion should not be given as a bolus or an intramuscular injection.

### **Storage Conditions**

Finished product - Store below ....°C

Reconstituted product (if applicable) - Store below ....°C for .... hours.

\* If not, please include this statement - For single use only. Discard any unused portion after opening

### **Dosage Forms and Packaging Available**

[ *Packaging type & pack size* ]

### **Name and Address of Manufacturer**

[ *Name & full address of manufacturer* ]

### **Name and Address of Marketing Authorization Holder**

[ *Name & full address of marketing authorization holder* ]

### **Date of Revision of Package Insert**

[ *day/month/year* ]