pharmaniaga®

Zithrolide

500mg Powder for Solution for Infusion

COMPOSITION:
Each vial contains Azithromycin dihydrate 524.03 mg equivalent to 500.0 mg of azithromycin base.

DESCRIPTION:
Before reconstitution: Hygroscopic, white to off-white solid.
After reconstitution: A clear solution.

PHARMACODYNAMICS:
Mode 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 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
Co-administration of azithromycin 500 mg, 1000 mg, 1500 mg with chloroquine (1000mg) increases 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, 1500 mg with chloroquine (1000mg) 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 (*E. coli* numbering system) of the 23S-rRNA by methylases encoded by *erm* (erythromycin *r*ibosome *m*ethylase) genes.
Ribosomal modifications often determine cross resistance (MLS_B phenotype) to other classes of antibiotics whose ribosomal binding sites overlap that 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 influenza* (where they may determine intrinsically higher MICs) and staphylococci. In streptococci and enterococci, an efflux pumps that recognizes 14- and 15-membered macrolides (which include, respectively erythromycin and Azithromycin) is encoded by *mef* (A) genes.

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): *Staphylococcus aureus, Streptococcus agalactiae*, Streptococcus pneumoniae*, Streptococcus pyogenes*,* other β-hemolytic 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 *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae* (PRSP).
Aerobic and facultative gram-negative bacteria: *Bordetella pertussis, Haemophilus ducreyi*, Haemophilus influenzae*, 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 pneumoniae*, Mycoplasma pneumoniae*, Treponema pallidum, and Ureaplasma urealyticum.*
Opportunistic pathogens associated with HIV infection: Eukaryotic microorganisms *Pneumocystis jirovecii* and *Toxoplasma gondii*.
*The efficacy of azithromycin against the indicated species has been demonstrated in clinical trials.

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 to 3 hours.

Distribution
High azithromycin concentrations have been observed in phagocytes. Higher concentrations of azithromycin are released during active phagocytosis than from non-stimulated phagocytes. This results in high concentrations of azithromycin being delivered to the site of infection.
Pharmacokinetics 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 MIC_{90} 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, 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 to be 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 $AUC_{0\text{-}120}$ (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 the group with severe renal impairment (GFR<10 ml/min) and the group with normal renal function.

Hepatic impairment
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 clearance of azithromycin appears to increase, perhaps to compensate for reduced hepatic clearance.

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

ROUTE OF ADMINISTRATION
Parenteral (Intravenous infusion only)

RECOMMENDED DOSAGE:
Pharmaniaga Zithrolide 500mg Powder for Solution for Infusion should not be given as a bolus or an intramuscular injection.

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 intravenous (IV) route for at least two days. Intravenous (IV) 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 (IV) azithromycin is 500 mg as a single dose by the intravenous (IV) route for one or two days. Intravenous (IV) therapy should be followed 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.
For all other indications in which the oral formulation is administered, the total dosage of 1500 mg should be given as 500 mg daily for 3 days. As an alternative, the same total dose can be given over 5 days with 500 mg given on Day 1, then 250 mg daily on Days 2 to 5.

Intravenous Administration
After reconstitution and dilution, the recommended route of administration for intravenous (IV) azithromycin is by IV infusion only. **Do not administer as an intravenous (IV) 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 (IV) dose of 500 mg azithromycin should be infused for a minimum duration of one (1) hour.

Special Populations:
In the Elderly:
The same dosage as in adult patients is used in the elderly. Elderly patients may be more susceptible to development of torsades de pointes arrhythmia than younger patients.

In 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).

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.

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

Reconstitution
Prepare the initial intravenous (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 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 of azithromycin.
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 refrigerator at 2-8°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally be no longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

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 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

The reconstitution 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% Dextrose in 0.45% Sodium Chloride

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.

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

WARNINGS/PRECAUTIONS:
Hypersensitivity
As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), have been reported. Dermatologic reactions including Stevens - Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) (rarely fatal), and Drug Reaction with Eosinophilia and Systematic Symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.
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.

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP)], Pharmaniaga Zithrolide 500mg Powder for Solution for Infusion should be discontinued immediately and appropriate treatment should be urgently initiated.

Hepatotoxicity
Since the liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease.
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 co-administration 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 coadministrated.

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

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

Clostridium difficile associated diarrhea
Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agent 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 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.

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

Prolongation of the QT Interval
Prolonged cardiac repolarisation 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 benefits 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 substance known to prolong 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 hypomagnesemia
- Patients with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency
- Elderly patients: elderly patients may be more susceptible to drug-associated effects on the QT interval.

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

Azithromycin for injection should be reconstituted and diluted as directed and administered as an intravenous infusion over not less 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 MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Antacids: No effect on overall bioavailability was seen although peak serum concentrations were reduced by approximately 24%. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously.

Cetirizine: Co-administration 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*): Co-administration 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: Concomitant administration macrolide antibiotics including azithromycin, with P-glycoprotein substrates such as digoxin has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-glycoprotein substrates such as digoxin are administered concomitantly, the possibility of elevated serum digoxin concentrations should be considered. Clinical monitoring, and possibly serum digoxin levels, during treatment with azithromycin and after its discontinuation are necessary.

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

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

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

Cimetidine: No alteration of azithromycin pharmacokinetics was seen.

Coumarin-Type Oral Anticoagulants: There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to co-administration 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 these drugs. If co-administration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Efavirenz: Co-administration 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: Co-administration 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 co-administration of fluconazole, however a clinically insignificant decrease in C_{max} (18%) of azithromycin was observed.

Indinavir: Co-administration 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: Co-administration 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: Co-administration of azithromycin (1200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased of azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment is required.

Rifabutin: Co-administration 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 (500 mg daily dose 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: Co-administration of azithromycin 500 mg on Day 1 and 250 mg on Day 2 with 0.125 mg triazolam no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

Trimethoprim/Sulfamethoxazole: Co-administration 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.

INCOMPATIBILITIES
Intravenous: Other intravenous (IV) substances, additives or other medications should not be added to intravenous azithromycin or infused simultaneously through the same intravenous line.

FERTILITY, PREGNANCY AND LACTATION
Pregnancy
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, 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.

Lactation

Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in nursing women that have characterized the pharmacokinetics of azithromycin excretion into human breast milk.

Fertility
In fertility studies conducted in rat, reduced pregnancy rates were noted following administration of azithromycin. The relevance of this finding to humans is unknown.

ADVERSE EFFECTS/UNDESIRABLE EFFECTS
Azithromycin is well tolerated with a low incidence of side effects.

In clinical trials, the following undesirable effects have been reported:

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.

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

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 reports of taste/smell perversion and/or loss. However, a causal relationship has not been established.

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. 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, rare reports of tongue discoloration and infantile hypertrophic pyloric stenosis.

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. Frequency not known: severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP).

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.

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

INSTRUCTION FOR USE:
Instructions for use, handling and disposal
The solution should be used immediately after opening of the vial. Any remaining solution should be discarded. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

STORAGE CONDITIONS
Before reconstitution: Store below 30°C.
After reconstituted: 7 days when stored at 2°C to 8°C or 24 hours when stored at below 30°C.

Do not freeze. Retain in carton until time of use.

See Section **Recommended Dosage** for storage information after reconstitution.

SHELF LIFE:
Before reconstitution: 3 years.
After reconstitution: 7 days when stored at 2°C to 8°C or 24 hours when stored at below 30°C.

Solution	Storage condition
Reconstituted solution (after reconstitution with water for injection)	i) 24 hours (below 30°C) ii) 7 days (2 - 8°C)
Mixed solution (after reconstitution and dilution with IV solution)	

The reconstitution solution will remain stable within 24 hours at below 30°C and 7 days at 2°C to 8°C after diluted with respective infusion solution as below:
- Normal Saline (0.9% sodium chloride)
- ½ Normal Saline (0.45% sodium chloride)
- 5% Dextrose in Water
- Lactated Ringer's Solution
- 5% Dextrose in 0.45% Sodium Chloride

DOSAGE FORMS AND PACKAGING AVAILABLE:
- 1 x 10mL vial (10R clear glass vial) of Zithrolide 500mg Powder for Solution for Infusion. 1 vial per unit PVC tray were packed in paper carton.
- 10 x 10mL vial (10R clear glass vial) of Zithrolide 500mg Powder for Solution for Infusion. 10 vials per unit PVC tray were packed in paper carton.

PRODUCT REGISTRATION HOLDER /MANUFACTURER
PHARMANIAGA LIFESCIENCE SDN BHD (198201002939)
Lot 7, Jalan PPU 3,
Taman Perindustrian Puchong Utama,
47100 Puchong, Selangor Darul Ehsan, Malaysia
2002236
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