(L)297mm

(W)210mm

pharmaniaga®

Zithrolide

Azithromycin 250 mg
Azithromycin 500 mg

TABLET DESCRIPTION

Zithrolide Tablet 250mg
White to off white, oblong, biconvex film coated tablet with Pharmaniaga icon on one side and scored on the other.

Zithrolide Tablet 500mg
White to off white, oblong, biconvex film coated tablet with Pharmaniaga icon on one side and plain on the other

COMPOSITION

Zithrolide Tablet 250mg
Each film coated tablet contains: Azithromycin dihydrate equivalent to Azithromycin 250mg.

Zithrolide Tablet 500mg
Each film coated tablet contains: Azithromycin dihydrate equivalent to Azithromycin 500mg.

PHARMACODYNAMICS

Pharmacotherapeutic group: Macrolides, ATC code J01FA10

Mode of action
Azithromycin is the first of a subclass of macrolide antibiotics which belongs to azalide group, 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-9ahomoerythromycin 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.

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:

Table 1

CLSI Dilution Susceptibility Interpretive Criteria

	Broth microdilution MIC (mg/L)		
Organism	**Susceptible**	**Intermediate**	**Resistant**
Haemophilus species	≤4	-	-[b]
Moraxella catarrhalis	≤0.25	-	-
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:

Table 2

CLSI Disk Zone Interpretive Criteria

	Disk inhibition zone diameter (mm)		
Organism	**Susceptible**	**Intermediate**	**Resistant**
Haemophilus species	≥12	-	-
Moraxella catarrhalis	≥26	-	-
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:

Table 3

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:

Table 4

EUCAST Susceptibility Breakpoints for Azithromycin

	MIC (mg/L)	
	Susceptible	**Resistant**
Staphylococcus species	≤1	>2
Streptococcus pneumoniae	≤0.25	>0.5
β-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 Website.
EUCAST Clinical Breakpoint Table v. 8.0, valid from 2018-01-01
www.eucast.org/.../EUCAST.../Breakpoint_tables/v_8.0_Breakpoint_Tables.pdf

Antibacterial Spectrum
The prevalence of a 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. Some ribosomal modifications determine cross-resistance with other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin), and the streptogramin B (which include, for example, the quinupristin component of quinupristin/dalfopristin). A decrease in macrolide susceptibility over time has been noted in particular in *Streptococcus pneumoniae* and *Staphylococcus aureus*, and has also been observed in *viridans streptococci* and *Streptococcus agalactiae*.

Organisms that are commonly susceptible to azithromycin include:

Aerobic and facultative gram: positive bacteria (erythromycin-susceptible isolates) - S. *aureus*, *Streptococcus agalactiae*,* *S. pneumoniae*, * *Streptococcus pyogenes*,* other ⊠-hemolytic *streptococci* (Groups C, F, G) and viridans *streptococci*. Macrolide-resistant isolates are encounteredrelatively frequently among aerobic and facultative gram-positive bacteria, in particular among methicillin-resistant S. *aureus* (MRSA) and penicillin-resistant S. *pneumoniae* (PRSP).

Aerobic and facultative gram-negative bacteria: *Bordetella pertussis*, *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 studies

PHARMACOKINETICS

Absorption
Azithromycin is widely distributed throughout the body following oral administration in humans; bioavailability is approximately 37%. The time taken to peak plasma levels is 2 to 3 hours.

Distribution
Available data shows that 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. 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 after 3 days as the parent drug, the majority in the first 24 hours. Major route of elimination for unchanged drug following oral administration is through biliary excretion. 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.

Pharmacokinetics in special patient groups

Elderly
In elderly volunteers (>65 years), slightly higher AUC values were seen after a 5-day regimen compared to 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 1 gram dose of immediate-release azithromycin. Statistically significant differences in AUC0-120 (8.8 µg⊠h/ml vs. 11.7 µg⊠h/ml), Cmax (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 is indicated for infections caused by susceptible organisms; in lower respiratory tract infection including bronchitis and pneumonia – skin and soft tissue infections – acute otitis media – upper respiratory tract infections including sinusitis and pharyngitis/tonsillitis. (Penicillin is the usual drug of choice in the treatment of *Streptococcus pyrogenes* 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 disease in men and women, azithromycin is indicated in the treatment on uncomplicated genital infections due to *Chlamydia trachomatis*. It is also indicated in the treatment of Chancroid due to *H.ducreyi* and uncomplicated genital infection due to non-multiresistant *Neisseria gonorrhoea*, concurrent infection with *Treponema pallidum* should be excluded.

CONTRAINDICATIONS

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

RECOMMENDED DOSAGE

Azithromycin should be administered as a single daily dose. The period of dosing with regard to infection given below. Azithromycin tablet can be taken with or without food.

In adults - For the treatment of sexually transmitted diseases caused by Chlamydia trachomatis and Haemophilus ducreyi, or susceptible Neisseria gonorrhoeae, the dose is 1000 mg as a single oral dose.

For patients who are allergic to penicillin and/or cephalosporins, prescribers should consult local treatment guidelines.

For the treatment of adult patients with community-acquired pneumonia (CAP) due to indicated organisms, IV azithromycin therapy should be followed by oral azithromycin at 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 pelvic inflammatory disease (PID) due to the indicated organisms, IV azithromycin 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.

For all other indications, the total dosage of 1500 mg should be given as 500 mg daily for 3 days, or can be given over 5 days with 500 mg given on day 1, then 250 mg daily on days 2-5.

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

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.

In children - Azithromycin tablets should only be administered to children weighing more than 45 kg. The maximum recommended total dose for any treatment is 1500 mg for children. In general, the total dose in children is 30 mg/kg.

The total dose of 30 mg/kg should be given as a single daily dose of 10 mg/kg daily for 3 days, or given over 5 days with a single daily dose of 10 mg/kg on Day 1, then 5 mg/kg on Days 2-5.

As an alternative to the above dosing, treatment for children with acute otitis media can be given as a single dose of 30 mg/kg.

WARNINGS AND PRECAUTIONS

Hypersensitivity
As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), Dermatologic reactions including Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) (rarely fatal), and Drug Reaction with Eosinophilia and Systemic Symptoms

attn	customer **Pharmaniaga Manufacturing Berhad**	date **01.06.2022**
1 colours	process colours: **Black**	**Please Chop & Sign For Approval**
size description	(L)**297 x** (W)**210mm** **Zithrolide Insert - Front (PRP 0469.2/ PRP 0563.2 270422)**	material **60gm simili**
FocusPrint SDN BHD	t: 603-8766 6030 f: 603-8766 6033 (Factory) website: www.focusprint.com.my	
artwork prepared by: cynthia yap	email: graphic@focusprint.info (graphic Dept)	**date:**

IMPORTANT ! **Please note that this colour print is for visual purpose only. Output colour might differ in actual production.**

ARTWORK LOG

Revision no.	Date	Reason for Change
01	31.12.18	- New artwork received.
02	14.01.19	- Amend artwork
03	11.03.19	- Amend artwork
04	24.04.19	- Amend artwork
05	26.04.19	- Amend artwork
06	09.05.19	- Amend artwork
07	21.05.19	- Amend TM to ®
08	04.04.2020	- Amend wording
09	06.04.2020	- Amendment made in (Cardiac disorders)
10	07.04.2020	- Amendment made in (Cardiac disorders)
11	30.06.2020	- Amend PRP date.
12	23.12.2020	- Amend wording, PRP and date of revision.
13	14.01.2021	- Amend from V12 (30/6/2020), amend wording and PRP no.
14	28.01.2021	- Amend wording and date of revision.
15	08.03.2021	- Amend wording and date of revision.
16	18.04.2022	- Amend wording and date of revision.
17	27.04.2022	- Amend Insert size from 250x200mm to 297x210mm
18	18.05.2022	- Amend wording, PRP and date of revision.
19	01.06.2022	- Amend wording.

(L)297mm

(W)210mm

(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) & acute generalised exanthematous pustulosis (AGEP)], Zithrolide Tablet should be discontinued immediately and appropriate treatment should be urgently initiated.

Hepatotoxicity
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.

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 co-administered.

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

Clostridium difficile-associated diarrhea
Clostridium difficile-associated diarrhea (CDAD) has been reported with the 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 2 months after the administration of antibacterial agents.

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

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

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 QT interval, such as antiarrhythmics of Classes IA and III, antipsychotic agents, antidepressants, and fluoroquinolones
- Patients with electrolyte disturbance, particularly in cases of hypokalemia 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

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

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.

PREGNANCY AND LACTATION
Use in pregnancy: No evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Since reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

Used 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 to 0.7 mg/kg/day. No serious adverse effects of azithromycin on the breast-fed infants were observed.

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.

INTERACTIONS WITH OTHER MEDICAMENTS
Antacids: In a pharmacokinetic study investigating the effects of simultaneous administration of antacid with azithromycin, no effects on overall bioavailability was seen although peak serum concentrations were reduced by up to 24%. In patients receiving both azithromycin and antacids, the drug should not be taken simultaneously.

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.

Cimetidine: A single dose of cimetidine administered 2 hours before Zithrolide had no effect on the pharmacokinetics of azithromycin.

Cyclosporin Administration of a 500 mg/day oral dose of azithromycin for 3 days and administration of a single 10 mg/kg oral dose of cyclosporin resulting significantly elevated cyclosporin Cmax and AUC0-5. Consequently, 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.

Digoxin and colchicine Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates, such as digoxin and colchicine, 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 derivatives: Because of the theoretical possibility of ergotism, Zithrolide and ergot derivative should not be co-administered.

Methylprednisolone: In a pharmacokinetics interaction study in healthy volunteers, Zithrolide had no significant effect on the pharmacokinetics of methylprednisolone.

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 interaction had occurred.

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

Coumarin-Type Oral Anticoagulants: In a pharmacodynamic interaction study, azithromycin did not alter the anticoagulant effect of a single 15mg dose of warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulant subsequent to co-administered of azithromycin and coumarin-type oral anticoagulants. Although a casual 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.

Zidovudine: Single 1000mg doses and multiple 1200mg or 600mg 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.

Didanosine (Dideoxyinosine): Coadministration of 1200 mg/day azithromycin with 400 mg/day didanosine in HIV-positive patients did not appear to affect the steady-state pharmacokinetics of didanosine.

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 casual relationship to combination with azithromycin has not been established.

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.

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

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 coadministration of fluconazole, however a clinically insignificant decrease in Cmax (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.

Nelfinavir: Co-administration 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.

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.

Triazolam: Co-administration 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.

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.

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

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

Blood and Lymphatic Disorders: Transient episodes of mild neutropenia have occasionally been observed in clinical trials.

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, diarrhoea, loose stools, abdominal discomfort (pain/cramps), and flatulence.

Hepatobiliary Disorders: Abnormal liver function.

Skin and Subcutaneous Tissue Disorders:
Allergic reactions including rash and angiodema.

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) & acute generalised exanthematous pustulosis (AGEP).

General Disorders and Administration Site Conditions: Local pain and inflammation at the site of infusion.

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, headache, hyperactivity, hypoesthesia, paresthesia, simnolence, and 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 **Warnings and Precautions**).

Vascular Disorders: Hypotension.

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

Skin and Subcutaneous Tissue Disorders: Allergic reactions including pruritus, rash, photosensitivity, edema, urticaria, and angioedema. Rarely, serious cutaneous adverse reactions including erythema multiforme, AGEP, SJS, TEN and DRESS 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, 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.

STORAGE CONDITIONS
Store below 30°C.
Protect from light.

ROUTE OF ADMINISTRATION
Oral

SHELF-LIFE
Products should not be used beyond the expiry date imprinted on the product packaging.

PRESENTATION
Zithrolide Tablet 250mg
In blisters of 6 tablets.

Zithrolide Tablet 500mg
In blisters of 3 tablets.

Date of revision: 18th May 2022
PRODUCT REGISTRATION HOLDER/ MANUFACTURER:
PHARMANIAGA MANUFACTURING BERHAD (198001006232)
No.11A, Jalan P/1, Kawasan Perusahaan Bangi,
43650 Bandar Baru Bangi, Selangor Darul Ehsan, Malaysia.

PRP 0469.3/ PRP 0563.3 180522

attn	customer **Pharmaniaga Manufacturing Berhad**	date **01.06.2022**
1 colours	process colours: **Black**	**Please Chop & Sign For Approval**
size / description	(L)**297 x** (W)**210mm** **Zithrolide Insert - Back (PRP 0469.2/ PRP 0563.2 270422)**	material **60gm simili**
FocusPrint SDN BHD	t: 603-8766 6030 f: 603-8766 6033 (Factory) website: www.focusprint.com.my	
artwork prepared by: cynthia yap	email: graphic@focusprint.info (graphic Dept)	**date:**

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07	21.05.19	- Amend TM to ®
08	04.04.2020	- Amend wording
09	06.04.2020	- Amendment made in (Cardiac disorders)
10	07.04.2020	- Amendment made in (Cardiac disorders)
11	30.06.2020	- Amend PRP date.
12	23.12.2020	- Amend wording, PRP and date of revision.
13	14.01.2021	- Amend from V12 (30/6/2020), amend wording and PRP no.
14	28.01.2021	- Amend wording and date of revision.
15	08.03.2021	- Amend wording and date of revision.
16	18.04.2022	- Amend wording and date of revision.
17	27.04.2022	- Amend Insert size from 250x200mm to 297x210mm
18	18.05.2022	- Amend wording, PRP and date of revision.
19	01.06.2022	- Amend wording.