PRODUCT NAME

Azithromycin-HEC 250 mg film-coated tablets

- Each film-coated tablet contains 262.05 mg azithromycin dihydrate equivalent to 250 mg azithromycin.

Azithromycin-HEC 500 mg film-coated tablets

- Each film-coated tablet contains 524.1 mg azithromycin dihydrate equivalent to 500 mg azithromycin.

PRODUCT DESCRIPTION

Azithromycin-HEC 250 mg film-coated tablets

White or almost white, capsular shaped film-coated tablets, inscribed "S19" on one side and blank on the other side.

Azithromycin-HEC 500 mg film-coated tablets

White or almost white, capsular shaped film-coated tablets, inscribed "S5" on one side and scored on the other side.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use; macrolides, ATC Code: J01FA10.

Azithromycin is a macrolide antibiotic belonging to the azalide group.

The molecule is constructed by adding a nitrogen atom to the Iactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl-9a-homo-erythromycin A. The molecular weight is 749.0.

Mechanism of action

The action mechanism of azithromycin is based upon the suppression of bacterial protein synthesis, by binding to the 50 S subunit and thus inhibiting the translocation of peptides.

Mechanism of resistance

Generally, the resistance of different bacterial species to macrolides has been reported to occur by three mechanisms associated with target site alteration, antibiotic modification, or altered antibiotic transport (efflux). The efflux in streptococci is conferred by the *mef* genes and results in a macrolide-restricted resistance (M phenotype). Target modification is controlled by *erm* encoded methylases.

A complete cross-resistance exists among erythromycin, azithromycin, other macrolides and lincosamides for *Streptococcus pneumoniae*, beta-haemolytic streptococci of group A, *Enterococcus* spp. and *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA).

Penicillin-sensitive *S. pneumoniae* are more likely to be susceptible to azithromycin than are penicillin-resistant strains of *S. pneumoniae*. Methicillin-resistant *S. aureus* (MRSA) is less likely to be susceptible to azithromycin than methicillin-sensitive *S. aureus* (MSSA).

The induction of significant resistance is ≤1 dilution rise in MICs for *S. pyogenes, H. influenza* and *Enterobacterciae* after nine sub-lethal passages of active substance and three dilution increase for *S. aureus* and development of resistance due to mutation is rare.

Breakpoints:

Azithromycin susceptibility breakpoints for typical bacterial pathogens.

EUCAST (European Committee on Antimicrobial Susceptibility Testing, version 3.1, 11-02-2013)

	MIC breakpoint (mg/L)	
Pathogens	**Susceptible (mg/L)**	**Resistant (mg/L)**
Staphylococcus spp.	≤ 1	> 2
Streptococcus spp. (Group A, B, C, G)	≤ 0.25	> 0.5
Streptococcus pneumoniae	≤ 0.25	> 0.5
Haemophilus influenzae	≤ 0.12	> 4
Moraxella catarrhalis	≤ 0.25	> 0.5
Neisseria gonorrhoeae	≤ 0.25	> 0.5

Susceptibility

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.

Pathogens for which resistance may be a problem: prevalence of resistance is equal to or greater than 10% in at least one country in the European Union.

Table 1: Antibacterial spectrum of azithromycin

Species
Commonly susceptible species
Aerobic Gram-positive
Corynebacterium diphteriae
Streptococcus pneumoniae
Erythromycin-sensitive
Penicillin-sensitive
Streptococcus pyogenes
Erythromycin-sensitive
Aerobic Gram-negative
Bordetella pertussis
Escherichia coli-ETEC
Escherichia coli-EAEC
Haemophilus influenzae *Haemophilus ducreyi*
Legionella spp.
Moraxella catarrhalis
Erythromycin-sensitive
Erythromycin-intermediate
Pasteurella multocida
Anaerobic
Fusobacterium nucleatum *Fusobacterium necrophorum*
Prevotella spp.

Porphyromonas spp.
Propionibacterium spp.
Other micro-organisms
Chlamydia pneumoniae
Chlamydia trachomatis
Listeria spp.
Mycobacterium avium Complex
Mycoplasma pneumoniae
Species for which acquired resistance may be a problem
Aerobic Gram-positive
Staphylococcus aureus
Methicillin-susceptible
Coagulase-neg. staphylococci
Methicillin-susceptible^{+}
Streptococcus pneumoniae
Penicillin-intermediate
Penicillin-resistant
Erythromycin-intermediate
Streptococcus pyogenes
Erythromycin-intermediate
Streptococci viridans group
Penicillin-intermediate
Aerobic Gram-negative
Moraxella catarrhalis Erythromycin-resistant
Anaerobic
Peptostreptococcus spp.
Inherently resistant organisms
Aerobic Gram positive
Corynebacterium spp.
Enterococcus spp.
Staphylococci MRSA, MRSE
Streptococcus pneumoniae
Erythromycin-resistant
Penicillin & Erythromycin resistant
Streptococcus pyogenes
Erythromycin-resistant
Streptococci viridans group
Penicillin-resistant
Erythromycin-resistant
Aerobic Gram-negative

Pseudomonas aeruginosa
Anaerobic
Bacteroides fragilis group

[+] Resistance is greater than 50%.

Pharmacokinetic properties

Absorption

Following oral administration the bio-availability of azithromycin is approximately 37%. Peak plasma levels are reached after 2-3 hours. The mean maximum concentration observed (Cmax) after a single dose of 500 mg is approximately 0.4 μg/ml.

Distribution

Orally administered azithromycin is widely distributed throughout the body. Pharmacokinetic have shown considerably higher azithromycin concentrations in the tissues (up to 50 times the maximum concentration observed in the plasma). This indicates that the substance is extensively bound in the tissues (steady-state volume of distribution approximately 31 l/kg). With the recommended dosage no accumulation in the serum/plasma occurs. Accumulation does occur in the tissues where the levels are much higher than in the serum/plasma. Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC90 for likely pathogens after a single dose of 500 mg.

Azithromycin accumulates in phagocytes; release is promoted by active phagocytosis. This process appears to contribute to the accumulation of azithromycin in tissue.

The binding of azithromycin to plasma proteins is variable and varies from 52% at 0.005 μg/ml to 18% at 0.5 μg/ml.

Biotransformation and Excretion

The terminal plasma elimination half-life follows the tissue depletion half-life of 2 to 4 days.

Approximately 12% of an intravenously administered dose is excreted in unchanged form with the urine over a period of 3 days; the major proportion in the first 24 hours. Concentrations of up to 237 μg/ml azithromycin, 2 days after a 5-day course of treatment, 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 splitting of the cladinose conjugate). Investigations suggests that the metabolites do not play a role in the micro-biological activity of azithromycin.

Pharmacokinetics in special populations

Renal impairment

Following a single oral dose of azithromycin 1g, mean C_{max} and AUC_{0-120} increased by 5.1% and 4.2% respectively, in mild to moderate renal impairment (glomerular filtration rate of 30-80 ml/min/1.73m^2) compared with normal renal function (GFR > 80 ml/min). In severe renal impairment (GFR < 30 ml/min/1.73m^2), the mean C_{max} and AUC_{0-120} increased 61% and 35% respectively compared to normal.

Hepatic impairment

In mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to normal hepatic function. There are no data on azithromycin use in cases of more severe hepatic impairment.

Elderly

The pharmacokinetics of azithromycin in elderly men was similar to that of young adults; however, in elderly women, although higher peak concentrations (increased by 30-50%) were observed, no significant accumulation occurred.

In elderly (>65 years), higher (29 %) AUC values were always observed after a 5-day course than in younger (<45 years). However, these differences are not considered to be clinically relevant; no dose adjustment is therefore recommended.

Paediatric population

In children aged 4 months – 15 years taking capsules, granules or suspension, at 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5, the C_{max} achieved is slightly lower than adults with 224 µg/l in children aged 0.6-5 years and after 3 days dosing and 383 µg/l in those aged 6-15 years. The $t_{1/2}$ of 36h in the older children was within the expected range for adults.

INDICATION

Azithromycin Oral

Azithromycin is indicated for infections caused by susceptible organisms; in lower respiratory tract infections including bronchitis and pneumonia, 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.

RECOMMENDED DOSE

Oral azithromycin should be administered as a single daily dose. The period of dosing with regard to infection is given below.

Azithromycin tablets 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 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 dose by the IV route for at least 2 days. 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 IV azithromycin is 500 mg as a single 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.

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.

In children

The maximum recommended total dose for any treatment is 1500 mg for children.

In general, the total dose in children is 30 mg/kg. Treatment for pediatric streptococcal pharyngitis should be dosed at a different regimen (see below).

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.

For pediatric streptococcal pharyngitis, azithromycin given as a single dose of 10 mg/kg or 20 mg/kg for 3 days has been shown to be effective; however, a daily dose of 500 mg must not be exceeded. In clinical trials comparing these two dosage regimens, similar clinical efficacy was observed but greater bacteriologic eradication was evident at the 20 mg/kg/day dose. However, penicillin is the usual drug of choice for the treatment of Streptococcus pyogenes pharyngitis, including prophylaxis of rheumatic fever.

Azithromycin tablets should only be administered to children weighing more than 45 kg.

Special populations:

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.

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.

ROUTE OF ADMINISTRATION
Azithromycin-HEC 250mg or 500mg film-coated tablets are for oral administration only. The tablets may be taken with or without food.

The tablets should be taken with water.

CONTRAINDICATION
Hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipient.

WARNINGS AND PRECAUTIONS

Hypersensitivity

As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), dermatologic reactions including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) (rarely fatal), and Drug Reaction with Eosinophilia and Systemic 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) [eg. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP)], *Azithromycin-HEC* should be discontinued immediately and appropriate treatment should be urgently initiated.

Renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance > 40 m/min).). In patients with severe renal function impairment (GFR < 10 mL/min), a 33% increase in systemic exposure to azithromycin has been observed (see section Pharmacokinetics).

Hepatic impairment

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. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin (see section Adverse effects). Some patients may have, or have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests/ investigations should be performed immediately. Azithromycin administration should be stopped if liver dysfunction has emerged.

Liver function disorders, hepatitis, cholestatic jaundice, liver necrosis and renal failure have been reported and have been fatal in a number of cases. Discontinue the use of azithromycin if signs and symptoms of hepatitis occur.

Pseudomembranous colitis has been reported following use of macrolide antibiotics. This diagnosis should therefore be taken into consideration in patients who develop diarrhoea after starting treatment with azithromycin.

Infantile hypertrophic pyloric stenosis

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.

Ergot alkaloids and azithromycin

The concurrent use of ergot alkaloids and macrolide antibiotics has been found to accelerate the development of ergotism. The interactions between ergot alkaloids and azithromycin have not been

studied. The development of ergotism is however possible, so that azithromycin and ergot alkaloid derivatives should not be administered simultaneously.

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 (see section 4.8). 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

Myasthenia gravis and azithromycin

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy (see section Adverse effects).

Superinfections

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

Clostridium difficile associated diarrhoea

Clostridium difficile associated diarrhoea (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 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 diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

The following should be considered before prescribing azithromycin:

Azithromycin film-coated tablets are not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed.

As for other macrolides, high resistance rates of *Streptococcus pneumoniae* have been reported for azithromycin in some European countries (see section Pharmacodynamics). This should be taken into account when treating infections caused by *Streptococcus pneumoniae*.

The main causative agent of soft tissue infections, *Staphylococcus aureus*, is frequently resistant to azithromycin. Therefore, susceptibility testing is considered a precondition for treatment of soft tissue infections with azithromycin.

Pharyngitis/tonsillitis

Azithromycin is not the substance of first choice for the treatment of pharyngitis and tonsillitis caused by *Streptococcus pyogenes*. For this and for the prophylaxis of acute rheumatic fever penicillin is the treatment of first choice.

Sinusitis

Often, azithromycin is not the substance of first choice for the treatment of sinusitis.

Acute otitis media

Often, azithromycin is not the substance of first choice for the treatment of acute otitis media.

Infected burn wounds

Azithromycin is not indicated for the treatment of infected burn wounds.

Sexually transmitted disease

In case of sexually transmitted diseases a concomitant infection by *T. pallidum* should be excluded.

Neurological or psychiatric diseases

Azithromycin should be administered with caution to patients suffering from neurological or psychiatric diseases.

Long-term use

There is no experience regarding the safety and efficacy of long-term use of azithromycin for the mentioned indications. In case of rapid recurrent infections, treatment with another antibiotic should be considered.

Due to cross-resistance existing among macrolides, in areas with a high incidence of erythromycin resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other macrolides (see section Pharmacodynamics).

Azithromycin is not the first choice for the empirical treatment of infections in areas where the prevalence of resistant isolates is 10% or more (see section Pharmacodynamics).

Paediatric population

Safety and efficacy for the prevention or treatment of Mycobacterium Avium Complex in children have not been established.

INTERACTION WITH OTHER MEDICINES

Antacids

In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously. Azithromycin should be taken at least 1 hour before or 2 hours after the antacid.

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.

Digoxin (P-gp substrates)

Concomitant administration of 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-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered.

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 (see section warning and precautions).

Astemizole and alfentanil

No data are available on interactions with astemizole and alfentanil. Caution should be exercised with concomitant use of these agents and azithromycin in view of the described potentiation of its effect during concomitant use of the macrolide antibiotic erythromycin.

Atorvastatin

Coadministration 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.

Carbamazepine

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

Cisapride

Cisapride is metabolised in the liver by the enzyme CYP 3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsades de pointes.

Cimetidine

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.

Ciclosporin

The resulting ciclosporin C_{max} and AUC_{0-5} were found to be significantly elevated when administered 500 mg/day oral dose of azithromycin for 3 days and then administered a single 10 mg/kg oral dose of ciclosporin,. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, ciclosporin 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_{max} (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 when 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 (see section Adverse effects).

Sildenafil

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

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.

Triazolam

Coadministration of azithromycin 500 mg 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.

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.

Protease inhibitors

There are no data available about a possible interaction with protease inhibitors.

PREGNANCY AND LACTATION

Pregnancy

There are no adequate data from use of azithromycin in pregnant women. Azithromycin was shown to pass the placenta, but no teratogenic effects were observed. The safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Therefore, azithromycin should only be used during pregnancy if the benefit outweighs the risk.

Breast-feeding

Azithromycin passes into human breast milk, but there are no adequate and well-controlled clinical studies in nursing women that have characterised the pharmacokinetics of azithromycin excretion into human breast milk. Because it is not known whether azithromycin may have adverse effects on the breast-fed infant, nursing should be discontinued during treatment with azithromycin. Among other things diarrhoea, fungus infection of the mucous membrane as well as sensitisation is possible in the nursed infant. It is recommended to discard the milk during treatment and up until 2 days after discontinuation of treatment. Nursing may be resumed thereafter.

ADVERSE EFFECTS

The table below lists the adverse reactions by system organ class and frequency. The frequency grouping is defined using the following convention: Very common; Common; Uncommon; Rare; Very Rare; and Not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

	Very Common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not Known**
Infections and Infestations			Candidiasis, vaginal infection, pneumonia, fungal infection, bacterial			Pseudomembranous colitis

			infection, pharyngitis, gastroenteritis, respiratory disorder, rhinitis, oral candidiasis			
Blood and Lymphatic System Disorders			Leukopenia, neutropenia, eosinophilia			Thrombocytopenia, haemolytic anaemia
Immune System Disorders			Angioedema, hypersensitivity			Anaphylactic reaction
Metabolism and Nutrition Disorders			Anorexia			
Psychiatric Disorders			Nervousness, insomnia	Agitation		Aggression, anxiety, delirium, hallucination
Nervous System Disorders		Headache	Dizziness, somnolence, dysgeusia, paraesthesia			Syncope, convulsion, hypoaesthesia, psychomotor hyperactivity, anosmia, ageusia, parosmia, myasthenia gravis
Eye Disorders			Visual impairment			
Ear and Labyrinth Disorders			Ear disorder, vertigo			Hearing impairment including deafness and/or tinnitus
Cardiac Disorders			Palpitations			Torsades de pointes, arrhythmia including ventricular tachycardia, Electrocardiogram QT prolonged
Vascular Disorders			Hot flushes			Hypotension
Respiratory, thoracic and mediastinal disorders			Dyspnoea, epistaxis			
Gastrointestinal Disorders	Diarrhoea	Vomiting, abdominal pain, nausea,	Constipation, flatulence, dyspepsia, gastritis, dysphagia, abdominal			Pancreatitis, tongue discolouration,

			distension, dry mouth, eructation, mouth ulceration, salivary hypersecretion			
Hepatobiliary Disorders			Hepatitis	Hepatic function abnormal, jaundice cholestatic		Hepatic failure (which has rarely resulted in death) hepatitis fulminant, hepatic necrosis
Skin and Subcutaneous Tissue Disorders			Rash, pruritus, urticaria, dermatitis, dry skin, hyperhidrosis	Photosensitivity reaction	DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms)	Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and Connective Tissue Disorders			Osteoarthritis, myalgia, back pain, neck pain			Arthralgia
Renal and Urinary Disorders			Dysuria, renal pain			Renal failure, acute interstitial nephritis
Reproductive system and breast disorders			Metrorrhagia, testicular disorder			
General Disorders and Administration Site Conditions			Oedema, asthenia, malaise, fatigue, face oedema, chest pain, pyrexia, pain, peripheral oedema			
Investigations		Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased, basophils increased, monocytes increased,	Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal, blood			

		neutrophils increased	alkaline phosphatase increased, chloride increased , glucose increased, platelets increased, haematocrit decreased, bicarbonate increased, abnormal sodium			
Injury, poisoning and procedural complications			Post procedural complication			

Adverse reactions possibly or probably related to Mycobacterium Avium Complex prophylaxis and treatment. These adverse reactions differ from those reported with immediate release or the prolonged release formulations, either in kind or in frequency:

	Very Common	**Common**	**Uncommon**
Metabolism and Nutrition Disorders		Anorexia	
Nervous System Disorders		Dizziness, headache, paraesthesia, dysgeusia	Hypoaesthesia
Eye Disorders		Visual impairment	
Ear and Labyrinth Disorders		Deafness	Hearing impaired, tinnitus
Cardiac Disorders			Palpitations
Gastrointestinal Disorders	Diarrhoea, abdominal pain, nausea, flatulence, abdominal discomfort, loose stools		
Hepatobiliary Disorders			Hepatitis
Skin and Subcutaneous Tissue Disorders		Rash, pruritus	Stevens-Johnson syndrome, photosensitivity reaction
Musculoskeletal and Connective Tissue Disorders		Arthralgia	
General Disorders and Administration Site Conditions		Fatigue	Asthenia, malaise

Skin and Subcutaneous Tissue Disorders:
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).

Post marketing experience:
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)**.

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

Gastrointestinal Disorders: Infantile hypertrophic pyloric stenosis.

SYMPTOMS AND TREATMENT OF OVERDOSE

Symptoms
The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea.

Treatment
In the event of overdose, general symptomatic and supportive measures are indicated as required.

STORAGE CONDITION

Store at temperatures not exceeding 30℃.

DOSAGE FORM AND PACKAGING

Film-coated tablet.
Azithromycin-HEC 250mg film-coated tablets are available in blister packs of 6 tablets
Azithromycin-HEC 500mg film-coated tablets are available in blister packs of 3 tablets and 6 tablets.

Manufacturer
Sunshine Lake Pharma Co., Ltd.
Northern Industry Road 1#,
Song Shan Lake, DongGuan,
GuangDong Province, 523808,
P.R. China

Product Registration Holder
Medispec (M) Sdn Bhd.
55 & 57, Lorong Sempadan 2,
11400 Ayer Itam, Penang,
Malaysia

Date of revision
October 2018