UNILAB

AZITHROMYCIN MONOHYDRATE

ZENITH® 500 mg Film-coated Tablet
ANTIBACTERIAL

FORMULATION
Each film-coated tablet contains:
Azithromycin (as monohydrate)..500 mg

PHARMACEUTICAL FORM
White to off-white oblong film-coated tablet, deep break line on one side, score line on the other side

CLINICAL PARTICULARS
Therapeutic indications
For the treatment of the following infections caused by microorganisms sensitive to azithromycin (see Special warnings and precautions for use and Pharmacodynamic properties):
- Mild to moderate community-acquired pneumonia, in particular pneumonia caused by *Mycoplasma pneumoniae*, *Chlamydophila psittaci* (ornithosis) or *Chlamydophila pneumoniae* (TWAR)
- Acute exacerbation of chronic bronchitis (adequately diagnosed)
- Acute bacterial sinusitis (adequately diagnosed)
- Tonsillitis, pharyngitis and acute otitis media in patients with hypersensitivity to beta-lactam antibiotics or when such treatment is not suitable for other reasons
- Skin and soft tissue infections such as furunculosis, pyoderma, impetigo and erysipelas in patients with hypersensitivity to beta-lactam antibiotics or when such treatment is not suitable for other reasons
- Uncomplicated genital infections caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae* (non-multidrug-resistant strains)

Considerations should be given to official guidance on the appropriate use of antibacterial agents.

Dosage and method of administration
Azithromycin differs from other antibiotics by its high tissue affinity. Azithromycin reaches levels up to 50 times higher in tissue than in plasma and tissue elimination half-life ranges between 2 to 4 days. Thus, azithromycin dose regimen differs from that of other antibiotics.

Dosage
Adults
In uncomplicated genital infections due to *Chlamydia trachomatis* or sensitive *Neisseria gonorrhoeae*, the dose is 1,000 mg azithromycin (given as a single oral dose).

For all other indications the dose is 1,500 mg, to be administered as 500 mg per day for three consecutive days. As an alternative, the same total dosage (1,500 mg) can also be administered over a period of five days with 500 mg on the first day and then 250 mg on the second to the fifth day.

A 5-day treatment regimen of azithromycin was shown to have sufficient efficacy in the treatment of pneumonia. In most cases, use of a 3-day treatment regimen also seems to be sufficient.

Older people
The same dose as in adult patients is used in older people. Since older patients can be patients with ongoing proarrhythmic conditions, a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes (see Special warnings and precautions for use).

Paediatric population
Azithromycin tablets should only be administered to children weighing more than 45 kg when normal adult dose should be used. For children under 45 kg, other pharmaceutical forms of azithromycin, e.g. suspensions, may be used.

In patients with renal impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 mL/min) (see Special warnings and precautions for use and Pharmacokinetic properties).

In patients with hepatic impairment
A dose adjustment is not necessary for patients with mild to moderately impaired liver function (see Special warnings and precautions for use and Pharmacokinetic properties).

Method of administration
Azithromycin should be swallowed whole with liquid as a single daily dose. The tablets may be taken with food.

Contraindications
Hypersensitivity to the active substance, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients.

Special warnings and precautions for use
Hypersensitivity
As with erythromycin and other macrolides, rare serious allergic reactions, including angioneurotic oedema and anaphylaxis (rarely fatal), and dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome, 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 medicinal product 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.

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. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin (see Undesirable effects). Some patients may 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.

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.

Infantile hypertrophic pyloric stenosis (IHPS)
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.

Pseudomembranous colitis
Pseudomembranous colitis has been reported with the use of macrolide antibiotics. This diagnosis should therefore be considered in patients who get diarrhoea after starting treatment with azithromycin.

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.

Cross resistance
Because of existing cross-resistance with erythromycin-resistant gram-positive strains and most strains of methicillin resistant staphylococci, use of azithromycin is not recommended.
Local epidemiology and susceptibility patterns should be taken into consideration.

Serious infections
Azithromycin is not intended to treat suitable severe infections where fast high blood concentrations of antibiotic have to be achieved.

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.

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

Cardiovascular events
Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides including azithromycin (see Undesirable effects). Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including torsades de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients:
- With congenital or documented QT prolongation
- Currently receiving treatment with other active substances that prolong QT interval such as antiarrhythmics of classes IA (quinidine and procainamide) and class III (dofetilide, amiodarone and sotalol), cisapride and terfenadine; antipsychotic agents such as pimozide; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including azithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing azithromycin.

Myasthenia gravis

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

Paediatric population

Safety and efficacy for the prevention or treatment of *Mycobacterium avium* complex in children have not been established.

Long-term use

There is no experience on safety and effectiveness of long-term use of azithromycin in indications mentioned before. At fast recurrent infections, treatment with other antibiotics should be considered.

Neurological and psychiatric disorders

Azithromycin should be used with caution in patients with neurological and psychiatric disorders.

Interaction with other medicinal products and other forms of interaction

Antacids

In a pharmacokinetic study investigating the effects of simultaneous administration of antacid with azithromycin, no effect on overall bioavailability was seen although peak serum concentrations were reduced by approximately 24%. In patients receiving both azithromycin and antacids, the medicinal products should not be taken simultaneously.

Cetirizine

In healthy volunteers, 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 1,200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

Digoxin and colchicine (P-gp substrates)

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

Ergot derivatives

Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended (see Special warnings and precautions for use).

Zidovudine

Single 1,000 mg doses and multiple 1,200 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.

Pharmacokinetic studies have been conducted between azithromycin and the following medicinal products 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 a HMG CoA-reductase inhibition assay). However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.

Carbamazepine

In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

Cimetidine

In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.

Coumarin-type oral anticoagulants

In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15 mg dose of warfarin administered to healthy volunteers. 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.

Ciclosporin

In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of ciclosporin, the resulting ciclosporin C_{max} and AUC_{0-5} were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these medicinal products. If co-administration of these medicinal products is necessary, ciclosporin 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 1,200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg Fluconazole. Total exposure and half-life of azithromycin were unchanged by the 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 1,200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

Methylprednisolone

In a pharmacokinetic interaction study in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

Midazolam

In healthy volunteers, 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 (1,200 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

Co-administration of azithromycin and rifabutin did not affect the serum concentrations of either medicinal product.

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 (see Undesirable effects).

Sildenafil

In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC and C_{max} of sildenafil or its major circulating metabolite.

Terfenadine

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

In 14 healthy volunteers, co-administration 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 variable for triazolam compared to triazolam and placebo.

Trimethoprim/sulfamethoxazole

Co-administration of trimethoprim/sulfamethoxazole (160 mg/800 mg) for 7 days with azithromycin 1,200 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.

Other antibiotics

On a possible co-resistance between macrolide antibiotics and azithromycin (e.g. erythromycin) as well as lincomycin and clindamycin is to look at. Concomitant use of several medicinal products from the same group of substances is not recommended.

Medicinal products known to prolong the QT interval

Azithromycin should not be co-administered with other medicinal products known to prolong the QT interval (see Special warnings and precautions for use).

Pregnancy and lactation

Pregnancy

There are no adequate data from the use of azithromycin in pregnant women. In reproduction toxicity studies in animals, 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.

Breastfeeding

Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in breastfeeding women that have characterised 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.

Effects on ability to drive and use machines

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

However, certain adverse reactions, visual impairment and vision blurred may have an effect on a patient's ability to drive or operate machinery (see Undesirable effects).

Undesirable effects

Below the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency are listed.
The frequency grouping is defined using the following convention:

Very common	(≥1/10)
Common	(≥1/100 to <1/10)
Uncommon	(≥1/1,000 to <1/100)
Rare	(≥1/10,000 to <1/1,000)
Very rare	(<1/10,000)
Not known	(cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Approximately 13% of the patients in clinical trials reported adverse events, wherein gastrointestinal disorders were the most common.

Adverse reactions possibly or probably related to azithromycin based on clinical trial experience and post-marketing surveillance:

Infections and infestations
Uncommon: Candidiasis, vaginal infection, pneumonia, fungal infections, bacterial infection, pharyngitis, gastroenteritis, respiratory disorder, rhinitis, oral candidiasis
Not known: Pseudomembranous colitis (see Special warnings and precautions for use)

Blood and lymphatic system disorders
Uncommon: Leukopenia, neutropenia, eosinophilia
Not known: Thrombocytopenia, haemolytic anaemia

Immune system disorders
Uncommon: Angioedema, hypersensitivity reaction
Not known: Severe (partly fatal) anaphylactic reaction e.g. anaphylactic shock (see Special warnings and precautions for use)

Metabolism and nutrition disorders:
Uncommon: Anorexia

Psychiatric disorders
Uncommon: Nervousness, insomnia
Rare: Agitation
Not known: Aggression, anxiety, delirium, hallucination

Nervous system disorders
Common: Headache
Uncommon: Dizziness, somnolence, dysgeusia, paraesthesia
Not known: Syncope, convulsion, hypoaesthesia, psychomotor hyperactivity, anosmia, ageusia, parosmia, myasthenia gravis (see Special warnings and precautions for use)

Eye disorders
Uncommon: Visual impairment
Not known: Blurred vision

Ear and labyrinth disorders
Uncommon: Ear disorder, vertigo
Not known: Hearing impairment including deafness and/or tinnitus

Cardiac disorders
Uncommon: Palpitations
Not known: Torsades de pointes (see Special warnings and precautions for use), arrhythmia (see Special warnings and precautions for use) including ventricular tachycardia, electrocardiogram QT prolonged (see Special warnings and precautions for use)

Vascular disorders
Uncommon: Hot flush
Not known: Hypotension

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea, epistaxis

Gastrointestinal disorders
Very common: Diarrhoea
Common: Vomiting, abdominal pain, nausea
Uncommon: Constipation, flatulence, dyspepsia, gastritis, dysphagia, abdominal distension, dry mouth, eructation, mouth ulceration, salivary hypersecretion
Not known: Pancreatitis, tongue discoloration

Hepatobiliary disorders
Rare: Hepatic function abnormal, jaundice cholestatic
Not known: Hepatic failure (which has rarely resulted in death) (see Special warnings and precautions for use), hepatitis fulminant, hepatic necrosis

Skin and subcutaneous disorders
Uncommon: Rash, pruritus, urticaria, dermatitis, dry skin, hyperhidrosis
Rare: Photosensitivity reaction, acute generalised exanthematous pustulosis (AGEP)
Very rare: DRESS (drug reaction with eosinophilia and systemic symptoms)*
Not known: Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme

*Frequency estimated with the "rule of three"

Musculoskeletal and connective tissue disorders
Uncommon: Osteoarthritis, myalgia, back pain, neck pain
Not known: Arthralgia

Renal and urinary disorders
Uncommon: Dysuria, renal pain
Not known: Renal failure acute, nephritis interstitial

Reproductive system and breast disorders
Uncommon: Metrorrhagia, testicular disorder

General disorders and administration site conditions
Uncommon: Oedema, asthenia, malaise, fatigue, face oedema, chest pain, pyrexia, pain, peripheral oedema

Investigations
Common: Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased, basophils increased, monocytes increased, neutrophils increased
Uncommon: Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal, blood alkaline phosphatase increased, chloride increased, glucose increased, platelets increased, haematocrit decreased, bicarbonate increased, abnormal sodium

Injury and poisoning
Uncommon: Post procedural complication

Adverse reactions possibly or probably related to *Mycobacterium avium* complex prophylaxis and treatment based on clinical trial experience and post-marketing surveillance. These adverse reactions differ from those reported with immediate release or the prolonged release formulations, either in kind or in frequency:

Metabolism and nutrition disorders
Common: Anorexia

Nervous system disorders
Common: Dizziness, headache, paraesthesia, dysgeusia
Uncommon: Hypoaesthesia

Eye disorders
Common: Visual impairment

Ear and labyrinth disorders
Common: Deafness
Uncommon: Hearing impaired, tinnitus

Cardiac disorders
Uncommon: Palpitations

Gastrointestinal disorders
Very common: Diarrhoea, abdominal pain, nausea, flatulence, abdominal discomfort, loose stools

Hepatobiliary disorders
Uncommon: Hepatitis

Skin and subcutaneous tissue disorders
Common: Rash, pruritus
Uncommon: Stevens-Johnson syndrome, photosensitivity reaction

Musculoskeletal and connective tissue disorders
Common: Arthralgia

General disorders and administration site conditions

Common:	Fatigue
Uncommon:	Asthenia, malaise

Overdose

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea.

In the event of overdose, the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, macrolide, lincosamides and streptogramins
ATC code: J01FA10

Mode of action

Azithromycin is an azalide, a sub-class of the macrolide antibiotics. By binding to the 50S-ribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other. Azithromycin acts as a bacteriostatic.

PK/PD relationship

The efficacy of azithromycin is best described by the relationship AUC/MIC, where AUC describes the area under the curve and MIC represents the mean inhibitory concentration of the microbe concerned.

Mechanism of resistance

Resistance to azithromycin may be natural or acquired. There are 3 main mechanisms of resistance affecting azithromycin:

- Efflux: resistance may be due to an increase in the number of efflux pumps on the cell membrane. In particular, 14- and 15-link macrolides are affected. (M-phenotype)
- Alterations of the cell structure: methylisation of the 23s rRNS may reduce the affinity of the ribosomal binding sites, which can result in microbial resistance to macrolides, lincosamides and group B streptogramins (SB) (MLS_B-phenotype).
- Enzymatic deactivation of macrolides is only of limited clinical significance.

In the presence of the M-phenotype, complete cross resistance exists between azithromycin and clarithromycin, erythromycin and roxithromycin. With the MLS_B***-phenotype, additional cross resistance exists with clindamycin and streptogramin B. A partial cross resistance exists with spiramycin.***

Breakpoints

Testing of azithromycin is done by using the usual dilution series. The following minimum inhibitory concentrations for susceptible and resistant germs were determined:

EUCAST (European Committee on Antimicrobial Susceptibility Testing)

Pathogens	**S≤ (mg/L)**	**R> (mg/L)**
Staphylococcus spp.	1 [a]	2 [a]
Streptococcus spp. (groups A, B, C, G)	0.25 [a]	0.5 [a]
Streptococcus pneumoniae	0.25 [a]	0.5 [a]
Haemophilus influenzae	Note [b]	Note [b]
Moraxella catarrhalis	0.25 [a]	0.5 [a]
Neisseria gonorrhoeae	0.25	0.5
Campylobacter jejuni and *coli*	Note [c]	Note [c]
Kingella kingae	Note [c]	0.25 [d]
Viridans group streptococci	IE	IE
PK-PD (non-species related) breakpoints	IE	IE

[a] Erythromycin can be used to determine susceptibility to azithromycin, clarithromycin and roxithromycin.
[b] Clinical evidence for the efficacy of macrolides in H. influenzae respiratory infections is conflicting due to high spontaneous cure rates. Should there be a need to test any macrolide against this species, the epidemiological cut-offs (ECOFFs) should be used to detect strains with acquired resistance. The ECOFFs for each agent are: azithromycin 4 mg/L, clarithromycin 32 mg/L, erythromycin 16 mg/L and telithromycin 8 mg/L. There are insufficient data available to establish an ECOFF for roxithromycin.
[c] Erythromycin can be used to determine susceptibility to azithromycin and clarithromycin.
[d] Susceptibility can be inferred from erythromycin susceptibility.
IE Indicates that there is insufficient evidence that the organism or group is a good target for therapy with the agent. An MIC with a comment but without an accompanying S, I or R categorisation may be reported

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.

Microbiological diagnosis with detection of the pathogen and its susceptibility to azithromycin should be attempted, particularly in the case of serious infections or treatment failures.

Table of susceptibility

Commonly susceptible species
Aerobic Gram-positive microorganisms
Mycobacterium avium [0]
Streptococcus pyogenes
Aerobic Gram-negative microorganisms
Haemophilus influenza [$]
Legionella pneumophila [0]
Moraxella catarrhalis
Neisseria gonorrhoeae
Other microorganisms
Chlamydia trachomatis [0]
Chlamydophila pneumoniae [0]
Mycoplasma pneumoniae [0]
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Staphylococcus aureus (methicillin-sensitive)
Staphylococcus aureus (methicillin-resistant) *
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
Streptococcus agalactiae
Streptococcus pneumoniae [Ω]
Inherently resistant organisms
Aerobic Gram-negative microorganisms
Escherichia coli
Klebsiella spp.
Pseudomonas aeruginosa

[0] There were no current data available at the time of publishing this table. Susceptibility is assumed in the primary literature, standard works and therapeutic recommendations.
[$] The natural sensitivity of most isolates lies in the intermediate range
[+] Rate of resistance is over 50% in at least one region.
[Ω] In isolates of invasive disease the rate of resistance is <10%.

Pharmacokinetic properties

Absorption

After oral administration, peak plasma levels are reached after 2 to 3 hours; plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. After a 5 day treatment, slightly higher AUC values were seen in the elderly patients (>65 years of age) compared to the younger patients (<40 years of age). However these differences are not regarded as clinically relevant; therefore a dose adjustment is not recommended.

In animal tests, high concentrations of azithromycin have been found in phagocytes. It has also been established that during active phagocytosis higher concentrations of azithromycin are released from inactive phagocytes. In animal models, this results in high concentrations of azithromycin being delivered to the site of infection.

Non-linearity

Study data suggest non-linear pharmacokinetics of azithromycin in the therapeutic range.

Distribution

It has been demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (as much as 50 times) than those measured in plasma which indicates that the agent strongly binds to tissues. Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC_{90} for likely pathogens after a single dose of 500 mg.

Binding to serum proteins varies according to plasma concentration and ranges from 12% at 0.5 µg/mL up to 52% at 0.05 µg azithromycin/mL serum. The mean volume of distribution at steady state (VV_{ss}) has been calculated to be 31.1 L/kg.

Elimination

About 12% of an intravenously administered dose is excreted unchanged within 3 days; the majority is excreted in the first 24 hours. Particularly high concentrations of unchanged azithromycin have been found in human bile. Also in bile, 10 metabolites were detected, which were formed through N- and O-demethylation, hydroxylation of desosamine and aglycone rings and cleavage of cladinose conjugate. Corresponding studies indicate that the metabolites of azithromycin are not microbiologically active.

Pharmacokinetics in special populations

Renal insufficiency

Following a single oral dose of azithromycin 1 g, pharmacokinetics were unchanged in subjects with a glomerular filtration rate <10 mL/min, there were statistically significant differences compared with subjects with normal renal function (GFR >80 mL/min) in $\text{AUC}_{0\text{-}120}$ (8.8 µg x h/mL vs. 11.7 µg x h/mL), C_{max} (1.0 µg/mL vs. 1.6 µg/mL) and CLr (2.3 mL/min/kg vs. 0.2 mL/min/kg).

Hepatic insufficiency

In patients with mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to normal hepatic function. In these patients, urinary recovery of azithromycin appears to increase perhaps to compensate for reduced hepatic clearance.

Preclinical safety data

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

Electrophysiological studies have shown that azithromycin prolongs the QT interval.

There was no evidence of a potential for genetic and chromosome mutations in *in-vivo* and *in-vitro* test models.

Long-term studies in animals have not been performed to evaluate carcinogenic potential as the medicinal product is indicated for short-term treatment only and there were no signs indicative of carcinogenic activity.

No teratogenic effects were observed in animal studies of embryotoxicity in mice and rats. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day led to mild retardations in fetal ossification and in maternal weight gain. In peri-/postnatal studies in rats, mild retardations following treatment with 50 mg/kg/day azithromycin and above were observed (retardation in physical development and reflex behaviour).

In neonatal studies, rats and dogs did not show higher sensitivity to azithromycin than adult animals of the respective species.

PHARMACEUTICAL PARTICULARS

Incompatibilities

Not applicable.

STORAGE

Store at temperatures not exceeding 30°C.

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY

Box of 30's (10 blister packs x 3's)

ADVERSE DRUG REACTION REPORTING STATEMENT

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at +632-8-**UNILAB**-1 (+632-8-**864522**-1) for Metro Manila or toll-free +1-800-10-UNILAB-1 for provinces, or e-mail productsafety@unilab.com.ph.

By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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RETAIL PRICE NOT TO EXCEED Php. 151.43
UNDER DRUG PRICE REGULATION

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