SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
AZITRO 200 mg/5 ml Powder for Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance:
Each 5 ml of suspension contains azithromycin dihydrate equivalent to 200 mg azithromycin.

Excipient(s):
Saccharose 2690.8 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Dry powder for oral suspension
White to off white granular powder, a creamy-white, homogeneous suspension when reconstituted with a characteristic odor.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
AZITRO is indicated for infections due to susceptible organisms, including lower respiratory tract infections such as bronchitis, mild cases of community acquired pneumonia caused by *Streptococcus pneumonia* or *Haemophilus influenza*; skin and soft tissue infections; acute otitis media and upper respiratory tract infections including sinusitis.

It is indicated in pharyngitis/tonsillitis caused by *Streptococcus pyogenes*, in the presence of penicillin allergy.

AZITRO is indicated in sexually transmitted, uncomplicated genital infections in males and females due to *Chlamydia trachomatis.* It is also indicated in soft tissue ulcers due to *Haemophilus ducreyi* and uncomplicated genital infections due to non-multi resistant *Neisseria gonorrhoeae*, but it should be determined that there is no accompanying *Treponema pallidum* infection.

4.2 Posology and method of administration
Posology/frequency and duration of administration:
AZITRO should be given as a single daily dose.
Administration period according to infection is given below.

Adults
The dosage for treatment of sexually transmitted diseases due to *Chlamydia trachomatis*, *Haemophilus ducreyi* or susceptible *Neisseria gonorrhoeae* is 1000 mg as a single oral dose.

In the treatment of *S. pyogenes* tonsillitis/pharyngitis, the total dose is 500 mg on the 1st day and 250 mg per day on the following days (2nd, 3rd, 4th and 5th days) for 5 days.

For all other indications, total dosage is 1500 mg, taken as 500 mg daily for 3 days.

Local treatment guidelines should be followed when prescribing for patients allergic to penicillins and/or cephalosporins.

Method of administration:
For oral use.
The duration of treatment in each of the infectious disease are given below. AZITRO can be taken with or without food.

Preparation
Shake the dry powder in bottle. Afterwards, pour boiled and then cooled water up to the mark on the supplied measuring device, add into the contents of bottle and shake well. 5 ml of the reconstituted suspension contains 200 mg of azithromycin. Shake the bottle before each use.

Using the measuring spoon:
Suspension is administered with double sided (2.5-5 ml) measuring spoon.

Additional information on special populations:
Renal impairment:
No dosage adjustment is recommended for subjects with mild to moderate renal impairment (GFR 10-80 ml/min). Caution should be exercised when azithromycin is administered to subjects with severe renal impairment (GFR<10 ml/min) (see section 4.4).

Hepatic impairment:
Same doses may be administered to patients with mild to moderate hepatic impairment as the patients with normal hepatic functions. As azithromycin is metabolized in the liver and eliminated by the bile, it should not be used in patients with severe hepatic impairment. There are no available studies of Azithromycin use in patients with hepatic impairment (see section 4.4).

Pediatric population
For pediatric patients weighing over 45 kg, adult doses are administered. For indications except tonsillitis/pharyngitis, the recommended total dosage is 1500 mg for 3 days (500 mg once daily).

Except for the treatment of Streptococcal pharyngitis, in children total dose of 30 mg/kg given as 10 mg/kg once daily for 3 days or 10 mg/kg as a single dose on the first day followed by 5 mg/kg/day on days 2-5 alternatively .

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

Weight (kg)	3 days therapy Administered once a day		5 days therapy Administered once a day		Total Dosage
	Day 1	Day 2 - 3	Day 1	Day 2 - 5	
< 15 kg	2,5 ml (100 mg)	2,5 ml (100 mg)	2,5 ml (100 mg)	1,25 ml (50 mg)	30 mg/kg
15-25 kg	5 ml (200 mg)	5 ml (200 mg)	5 ml (200 mg)	2,5 ml (100 mg)	600 mg
26-35 kg	7,5 ml (300 mg)	7,5 ml (300 mg)	7,5 ml (300 mg)	3,75 ml (150 mg)	900 mg
36-45 kg	10 ml (400 mg)	10 ml (400 mg)	10 ml (400 mg)	5 ml (200 mg)	1200 mg
Over 45 kg	Adult dosage				

Efficacy and safety of azithromycin have not been established for infants younger than 6 months of age, therefore it is not recommended.

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 studies comparing these 2 dosage regimens, similar clinical efficacy was observed but greater bacteriologic eradication was evident at the 20 mg/kg per day dose. Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including prophylaxis of rheumatic fever.

Geriatric population:
The same dosage as in adult patients is used in the elderly patients. As elderly patients may have persistent proarrhythmic conditions, special caution is advised for the risk of developing cardiac arrhythmias and *torsades de pointes*.

4.3 Contraindications
The use of this drug is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotics or any of the excipients listed in section 6.1 (see also section 4.4).

4.4 Special warnings and precautions for use
Hypersensitivity
As with erythromycin and other macrolides, serious allergic reactions including angioedema and anaphylaxis (rarely fatal), Stevens Johnson syndrome, toxic epidermal necrosis (rarely fatal), Acute Generalized Exanthematous Pustulosis (AGEP) 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 initiated. The physician should be aware of the possibility of recurrence of allergic symptoms after discontinuation of therapy.

Hepatotoxicity
Because azithromycin is eliminated predominantly via the hepatobiliary pathway, AZITRO should be administered with caution to patients with severe hepatic disease.
Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure (some resulting in death) have been reported with azithromycin therapy (see section 4.8). 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 should be performed. Azithromycin administration should be stopped if liver dysfunction has emerged.

Ergot derivatives
In patients receiving ergot derivatives, ergotism has been precipitated by co-administration of some macrolide antibiotics. There are no data on the interaction between azithromycin and ergot derivatives. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administrated.

Superinfection

As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms including fungi is recommended. In case of superinfection, it may be necessary to discontinue azithromycin therapy and initiate appropriate therapy.

***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 in such a way that *C. difficile* overgrows.

C. difficile producing hypertoxin A and B 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 should be considered in all diarrhea patients on antibiotics. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents. Discontinuation of therapy with azithromycin and the administration of specific treatment for *C. difficile* should be considered.

Renal impairment
In patients with severe renal impairment (GFR <10 ml/min) a 33% increase in systemic exposure to azithromycin was observed (see section 5.2).

Streptococcal infections
Penicillin is usually the first choice for treatment of pharyngitis/tonsillitis due to *Streptococcus pyogenes* and also for prophylaxis of acute rheumatic fever. Azithromycin is in general effective against streptococcus in the oropharynx, but no data are available that demonstrate the efficacy of azithromycin in preventing acute rheumatic fever.

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).

Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade 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). A risk-benefit analysis should be performed when prescribing azithromycin to the following patient groups because of the risk of QT prolongation which may lead to death.

- **Patients with known prolongation of the QT interval, a history of *torsades de pointes*, congenital long QT syndrome, bradyarrhythmias or uncompensated heart failure**
- **Patients on drugs known to prolong the QT interval**
- **Uncorrected hypokalemia or hypomagnesemia, use of class IA (quinidine, procainamide) or class III antiarrhythmic agents (dofetilide, aminodarone, sotalol), cisapride and terfenadine; antipsychotic agents such as pimozide; antidepressants such as citalopram; fluoroquinolones such as moxifloxacin and levofloxacin.**
- **With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency**
- **Female and elderly patients with existing proarrhythmia**

may be more susceptible to drug-related QT interval prolongation.

Myasthenia gravis
Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy (see section 4.8).

This product contains sucrose (saccharose). Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interactions 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 25%. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously.

Cetirizine
In healthy volunteers, co-administration of a 5-day regimen of azithromycin with 20 mg cetirizine at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

Didanosine (Dideoxyinosine)
Co-administration of 1200 mg/day azithromycin with 400 mg/day didanosine in six HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared to placebo.

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.

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 derivatives
Due to the possibility of convulsive ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended (see section 4.4).
Pharmacokinetic studies have been conducted between azithromycin and the following drugs

known to undergo significant cytochrome P450 mediated metabolism.

HMG-CoA reductase inhibitor (statins)
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
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.

Ciclosporin
In a pharmacokinetic study with healthy volunteers who 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 (by 24% and 21% respectively), however no significant changes were seen in $AUC_{0-\infty}$. Consequently, caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

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

Fluconazole
Co-administration of a single dose of 1200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and half-life of azithromycin were unchanged by the co-administration of fluconazole, however, a clinically insignificant decrease in C_{max} (18%) of azithromycin was observed.

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

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

Nelfinavir

Co-administration of 1200 mg azithromycin 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 was required.

Rifabutin
Co-administration of azithromycin and rifabutin did not affect the serum concentrations of either drug.
Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established (see section 4.8).

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.

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

Terfenadine
Although pharmacokinetic studies have shown no interaction between azithromycin and terfenadine, the existence of some reported cases indicates that this possibility cannot be completely excluded. Careful monitoring is recommended when azithromycin and terfenadine are used together.

Triazolam
In 14 healthy volunteers, 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 and placebo.

Trimethoprim/sulfamethoxazole
Co-administration of trimethoprim/sulfamethoxazole (160 mg/800 mg) for 7 days with 1200 mg azithromycin 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.

Coumarin-type oral anticoagulants
In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single dose of 15 mg 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.

Additional information on special populations:
There is no sufficient data regarding drug interactions on special populations.

Pediatric population:
There is no sufficient data regarding drug interactions on the pediatric population.

4.6 Fertility, pregnancy and lactation

General principles
Pregnancy category: B

Women of child-bearing potential/Birth control (Contraception)
Animal studies performed at mild to moderate maternally toxic dose concentrations are insufficient with respect to direct or indirect harmful effects on pregnancy/embryonal/fetal development/ parturition or postnatal development. Therefore, appropriate contraceptive methods should be used in women planning to get pregnant, if pregnancy is suspected, the decision should be made after clarifying whether pregnancy is present or not.

Pregnancy
There are no data from the use of azithromycin in pregnant women. Animal studies are inadequate in terms of effects on pregnancy /and-or/ embryonal/fetal development /and-or/ parturition /and-or/ postnatal development (see section 5.3). The studies showed that azithromycin crossed the placenta and reached the fetus, but there was no evidence of fetal harmful effects. The potential risk to humans is not known. As the safety of azithromycin during pregnancy has not yet been established, it should only be used during pregnancy if absolutely necessary.

Breast-feeding
Azithromycin has been reported to be secreted into human breast milk, however, there are no adequate and controlled studies characterizing the pharmacokinetics of azithromycin excretion in human milk in breastfeeding mothers. 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.

Reproductive ability/ 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.

4.7 Effects on ability to drive and use machines

There is no evidence to suggest that azithromycin may have an effect on patient's ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects are listed according to these categories:
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); unknown (cannot be estimated from the available data).

Infections and infestations
Uncommon : Candidiasis, oral candidiasis, vaginal infection
Unknown : Pseudomembranous colitis (see section 4.4)

Blood and lymphatic system disorders
Uncommon : Leukopenia, neutropenia
Unknown : Thrombocytopenia, hemolytic anemia

Immunity system disorders

Uncommon : Angioedema, hypersensitivity
Unknown : Anaphylactic reactions (see section 4.4)

Metabolism and nutrition disorders
Common : Anorexia

Psychiatric disorders
Uncommon : Nervousness
Rare : Agitation
Unknown : Aggression and anxiety

Nervous system disorders
Common : Headache, drowsiness, paresthesia, dysgeusia
Uncommon : Hypoesthesia, somnolence, insomnia
Unknown : Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis (see section 4.4)

Eye disorders
Common : Visual impairment

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

Cardiac disorders
Uncommon : Palpitation
Unknown : *Torsades de pointes*, arrhythmias including ventricular tachycardia (see section 4.4)

Vascular disorders
Unknown : Hypotension

Respiratory, thoracic and mediastinal disorders
Uncommon : Dyspnea, epistaxis

Gastrointestinal disorders
Very common : Diarrhea, abdominal pain, nausea, flatulence
Common : Vomiting, dyspepsia
Uncommon : Gastritis, constipation
Unknown : Tongue discoloration, pancreatitis

Hepatobiliary disorders
Uncommon : Hepatitis
Rare : Hepatic function abnormalities
Unknown : Hepatic failure (which has rarely resulted in death) (see section 4.4), hepatitis fulminant, hepatic necrosis, cholestatic jaundice

Skin and subcutaneous tissue disorders
Common : Pruritus and rash
Uncommon : Stevens Johnson Syndrome, photosensitivity reactions, urticaria

Rare : Acute Generalized Exanthematous Pustulosis (AGEP)*§, Drug reaction with eosinophilia and systemic symptoms (DRESS)*§
Unknown : Toxic epidermal necrolysis, erythema multiforme

Musculoskeletal, connective tissue disorders
Common : Arthralgia

Renal and urinary disorders
Unknown : Interstitial nephritis and acute renal failure

General disorders and administration site disorders
Common : Fatigue
Uncommon : Edema, chest pain, malaise/weakness, asthenia

Investigations
Common : Decreased lymphocyte count, increased eosinophil count, decreased blood bicarbonate
Uncommon : Increased aspartate aminotransferase, increased alanine aminotransferase, increased blood bilirubin, increased blood urea, increased blood creatinine, abnormal blood potassium
Unknown : Electrocardiogram QT prolonged (see section 4.4)

*ADR identified post-marketing
§ADR frequency represented by the estimated upper limit of the 95% confidence interval calculated using the "Rule of 3".

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions in accordance with local requirements.

4.9 Overdose
Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. The typical symptoms of an overdose include reversible loss of hearing, severe nausea, vomiting and diarrhea. In the event of overdose, the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Macrolide class antibacterials for systemic use
ATC code: J01FA10

Mechanism of action:
Azithromycin is a macrolide antibiotic belonging to the azalide group.

The molecule is constructed by adding a nitrogen atom to the lactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A. The molecular weight is 749.0.
The mechanism of action of azithromycin is based on the suppression of bacterial protein synthesis

by binding to the 23S rRNA portion of the 50S ribosomal subunit and inhibiting the translocation of peptides.

Mechanism of resistance:
Resistance to azithromycin may be inherent or acquired. There are three main mechanisms of resistance in bacteria: target site alteration, alteration in antibiotic transport and modification of the antibiotic.

Azithromycin demonstrates cross resistance with erythromycin resistant gram positive isolates. A decrease in macrolide susceptibility over time has been noted particularly *in Streptococcus pneumoniae* and *Staphylococcus aureus*. Similarly, decreased susceptibility has been observed among *Streptococcus viridans* and *Streptococcus agalactiae* (Group B) streptococcus against other macrolides and lincosamides.

Breakpoints:
Azithromycin susceptibility breakpoints for typical bacterial pathogens published by European Committee on Antimicrobial Susceptibility Testing (EUCAST) are:

Organism	**MIC breakpoints (mg/L)**	
	Susceptible (S≤)	**Resistant (R>)**
Staphylococcus spp.	1	2
Streptococcus groups A, B, C and 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 (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.

Table: Antibacterial spectrum of Azithromycin

Commonly susceptible species
Aerobic Gram-positive microorganisms
Staphylococcus aureus Methycillin-susceptible
Streptococcus pneumoniae Penicillin-susceptible
Streptococcus pyogenes **(Group A)**
Aerobic Gram-negative microorganisms
Haemophilus influenzae *Haemophilus parainfluenzae*
Legionella pneumophila
Moraxella catarrhalis
Neisseria gonorrhoeae
Pasteurella multocida
Anaerobic microorganisms
Clostridium perfringens
Fusobacterium spp.

Prevotella spp.
Porphyromonas spp.
Other microorganisms
Chlamydia trachomatis
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Streptococcus pneumoniae Penicillin-intermediate Penicillin-resistant
Inherently resistant organisms
Aerobic Gram-positive microorganisms
Enterococcus faecalis
Staphylococci MRSA, MRSE*
Anaerobic microorganisms
Bacteroides fragilis group

* Methycillin-resistant staphylococci have a very high prevalence of acquired resistance to macrolides and have been placed here because they are rarely susceptible to azithromycin.

Pediatric population
Following the assessment of studies conducted in children, the use of azithromycin is not recommended for the treatment of malaria, neither as monotherapy nor combined with chloroquine or artemisinin based drugs, as non-inferiority to anti-malarial drugs recommended in the treatment of uncomplicated malaria was not established.

5.2 Pharmacokinetic properties

General properties

Absorption:
Bioavailability after oral administration is approximately 37%. Peak plasma concentrations are attained 2 to 3 hours after taking the medicinal product.

Distribution:
Orally administered azithromycin is widely distributed throughout the body. In pharmacokinetic studies 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. This condition indicates that the agent strongly binds to tissues.

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

Biotransformation:
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. Comparison of the results of liquid chromatography and microbiological analyses has shown that the metabolites of azithromycin are not microbiologically active.

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 experimental models. In animal models this results in high concentrations of azithromycin being delivered to the site of infection.

Elimination:
The terminal plasma elimination half-life closely reflects the elimination half-life (2-4 days) from tissues.

Approximately 12% of an intravenously administered dose of azithromycin is excreted unchanged in urine within the following 3 days.

5.3 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.

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

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

Reproductive toxicity:
In animal studies for embryotoxic effects of the substance, no teratogenic effect was observed in mice and rats. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day led to mild retardation of fetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardation following treatment with 50 mg/kg/day azithromycin and above was observed.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium phosphate, tribasic
Sodium benzoate
Saccharin sodium
Colloidal silicon dioxyde
Hydroxypropyl methylcellulose
Xanthan gum
Banana flavor
Saccharose

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Keep at room temperature below 25°C before reconstitution.
After reconstitution, it is stable at room temperature (below 25°C) for 5 days.

6.5 Nature and contents of container

Nature of packaging material:
Semi-opaque HDPE bottle with white HDPE cap and aluminum seal.

15 ml packaging:
Each cardboard box contains 1 bottle, a double-sided spoon of 5 and 2.5 ml, and a measuring device marked at 12 ml.

30 ml packaging:
Each cardboard box contains 1 bottle, a double-sided spoon of 5 and 2.5 ml, and a measuring device marked at 23 ml.

Presented as 15 ml and 30 ml dry powder for suspension.

6.6 Special precautions for disposal and other handling

Any unused material should be disposed according to local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

DEVA HOLDING A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad.
No: 1 34303 Küçükçekmece/ İSTANBUL/TÜRKİYE
Phone: +90 212 692 92 92
Fax: +90 212 697 00 24
E-posta: deva@devaholding.com.tr

8. MARKETING AUTHORIZATION NUMBER(S)

175/44

9. DATE OF FIRST AUTHORIZATION /RENEWAL OF THE AUTHORIZATION

Date of first authorization : 05.10.1995
Date of last renewal : 22.06.2011

10. DATE OF REVISION OF THE TEXT