

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Azithromycin Teva 200 mg/5 ml powder for oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of reconstituted oral suspension contains 200mg azithromycin as dihydrate.

Each 1 ml of reconstituted oral suspension contains 40mg azithromycin as dihydrate.

Excipients

Each 5 ml of reconstituted oral suspension contains 3.78 g of sucrose.

Each 1 ml of reconstituted oral suspension contains 0.756 g of sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral suspension.

White to yellowish-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Azithromycin is indicated for the following bacterial infections induced by micro-organisms susceptible to azithromycin (*see sections 4.4 and 5.1*):

- Infections of the lower respiratory tract: acute bronchitis and mild to moderate community-acquired pneumonia
- Infections of the upper respiratory tract: sinusitis and pharyngitis/tonsillitis
- Acute otitis media
- Infections of the skin and soft tissue of mild to moderate severity *e.g.* folliculitis, cellulites, erysipelas
- Uncomplicated *Chlamydia trachomatis* urethritis and cervicitis.

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

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 5.1*).

4.2 Posology and method of administration

Azithromycin suspension should be given as a single daily dose. The suspension can be taken with or without food. The duration of treatment in each of the infectious diseases is given below.

Children and adolescents over 45 kg body weight, adults and the elderly

The total dosage of azithromycin is 1500 mg which is spread over three days (500 mg once daily). Alternatively, the dosage can be spread over five days (500 mg as a single dose on the first day and thereafter 250 mg once daily).

In uncomplicated *Chlamydia trachomatis* urethritis and cervicitis the dosage is 1000 mg as a single oral dose.

For sinusitis, treatment is aimed at adults and adolescents over 16 years of age.

Other pharmaceutical forms are available to treat patients weighing more than 45 kg.

Children under 45 kg body weight

Azithromycin suspension should be used for children under 45 kg. The following recommendations refer to the reconstituted 40 mg/ml (200 mg/5 ml) suspension.

With as only exception the treatment of *Streptococci* pharyngitis, the total dose in children 1 year and older is 30 mg/kg, to be administered as one single daily dose of 10 mg/kg for three days. As an alternative azithromycin can also be administered over a period of 5 days with one single dose of 10 mg/kg on day 1, followed by one single daily dose of 5 mg/kg on days 2 through 5.

For children with a weight of 10 to 15 kg azithromycin suspension should be measured as accurately as possible with the assistance of the enclosed dosage syringe, which is graduated in 0.5 ml divisions, providing 20 mg of azithromycin in every division.

For children who weigh more than 15 kg, azithromycin suspension should be administered with the assistance of the dosage spoon, which provides 2.5, 3.75 or 5 ml doses, corresponding to 100, 150 or 200 mg of azithromycin, respectively according to the following schedule:

Weight (kg)	3-day treatment*	5-day treatment*	Content bottle
10-15	Once daily 10 mg/kg on days 1 through 3	Once daily 10 mg/kg on day 1, followed by once daily 5 mg/kg on days 2 through 5	15 ml
16-25	Once daily 200 mg (5 ml) on days 1 through 3	Once daily 200 mg (5 ml) on day 1, followed by once daily 100 mg (2.5 ml) on days 2 through 5	15 ml
26-35	Once daily 300 mg (7.5 ml) on days 1 through 3	Once daily 300 mg (7.5 ml) on day 1, followed by once daily 150 mg (3.75 ml) on days 2 through 5	22.5 ml
35-45	Once daily 400 mg (10 ml) on days 1 through 3	Once daily 400 mg (10 ml) on day 1, followed by once daily 200 mg (5 ml) on days 2 through 5	30 ml
>45	Dose as in adults		37.5 ml

* Separate dosage recommendations apply for streptococcal pharyngitis and are described below.

For the treatment of *Streptococci* pharyngitis in children aged 2 years or more: Azithromycin in a single dose of 10 mg/kg or 20 mg/kg for three days, in which the maximum daily dose of 500 mg should not be exceeded. However, penicillin remains the first choice for the treatment of *Streptococcus pyogenes* pharyngitis, among which the prophylaxis for acute rheumatism (see section 4.1).

The maximum dosage in children correlates with the common dosage in adults with 1500 mg azithromycin.

Sinusitis

For the treatment of sinusitis, limited data is available for the treatment of children under 16 years of age.

Elderly

No dose adjustments are required for elderly patients.

Patients with renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min) (see section 4.4).

Patients with hepatic impairment

A dose adjustment is not necessary for patients with mild to moderately impaired liver function (Child-Pugh class A or B) (see sections 4.3 and 4.4).

4.3 Contraindications

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

4.4 Special warnings and precautions for useAllergic reactions

In rare cases azithromycin is reported to have caused serious allergic reactions (rarely fatal) such as angioneurotic oedema and anaphylaxis. Some of these reactions have caused recurrent symptoms and have required longer observation and treatment.

Renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min). Caution is advised in patients with severe renal impairment (GFR < 10 ml/min) as systemic exposure may be increased (33% increases have been observed) (see section 5.2).

Hepatic failure

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 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/ investigations should be performed immediately. Azithromycin administration should be stopped if liver dysfunction has emerged.

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.

QT prolongation

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarisation (see section 4.8). Therefore:

- Azithromycin should not be used in patients with congenital or documented acquired QT prolongation.
- Azithromycin should not be used concurrently with other active substances that prolong QT interval such as antiarrhythmics of classes IA and III, cisapride and terfenadine (see section 4.5).
- Azithromycin should not be used in patients with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- Azithromycin should not be used in patients with clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

The following should be considered before prescribing azithromycin:

Azithromycin powder for oral suspension is not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed.

In areas with a high incidence of erythromycin A resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other antibiotics.

As for other macrolides, high resistance rates of *Streptococcus pneumoniae* (> 30 %) have been reported for azithromycin in some European countries (see section 5.1). 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.

Superinfections

Attention should be paid to possible symptoms of superinfections caused by non-sensitive causal agents such as fungi. A superinfection may require an interruption of the azithromycin treatment and initiation of adequate measures.

Neurological or psychiatric diseases

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

Myasthenia gravis

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

Clostridium difficile –associated diarrhoea

Clostridium difficile–associated diarrhoea (CDAD) has been reported with the 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. A careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Should pseudomembranous colitis be induced by azithromycin, then anti-peristaltics should be contraindicated.

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.

In children aged under 6 months, evidence of the safety of azithromycin is limited.

The safety and efficacy of azithromycin for the prevention or treatment of *Mycobacterium avium* complex (MAC) infection in children have not been established.

Sucrose

This medicinal product contains sucrose.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

The sucrose content should be taken into account in patients with diabetes mellitus.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids

When studying the effect of simultaneously administered antacid on the pharmacokinetics of azithromycin, no overall change has been observed in the bioavailability, although the peak concentrations of azithromycin measured in the plasma did fall by approximately 25 %. Azithromycin should be taken at least 1 hour before or 2 hours after the antacid.

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.

Digoxin

In some patients certain macrolide antibiotics have been reported to have impaired the metabolism of digoxin in the intestine. Consequently, in the case of patients receiving the related azalide azithromycin and digoxin, the possibility of a rise in the digoxin concentrations should be borne in mind.

Zidovudine

1000 mg single doses and 1200 mg or 600 mg multiple doses of azithromycin had only a slight effect upon the pharmacokinetics of zidovudine or its glucuronide metabolite in the plasma or upon excretion in the urine. However, the administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in mononuclear cells in the peripheral circulation. The clinical significance of this finding is unclear, but it may be of benefit to patients.

Didanosine (dideoxyinosine)

Daily dosages of 1200 mg azithromycin co-administered with 400 mg/day didanosine in 6 HIV-positive volunteers appeared to have no effect on the steady-state pharmacokinetics of didanosine compared to placebo.

Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to be subject to the pharmacokinetic interactions seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.

Ergot

The combined use of ergot derivatives and azithromycin may in theory cause ergotism, and consequently their combined use is not recommended (see also section 4.4).

Pharmacokinetic studies have been conducted between azithromycin and the following agents 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 concentration of atorvastatin (based on an HMG-CoA reductase inhibition assay).

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-like oral anticoagulants

In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of 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 prothrombin time monitoring when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Ciclosporin

In a pharmacokinetic study with healthy volunteers given oral azithromycin 500 mg/day for 3 days then 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 agents. If combination treatment is necessary, the ciclosporin levels should be carefully monitored and the dosage should be 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 agent.

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 three days) on the AUC and C_{\max} of sildenafil or its major circulating metabolite.

Terfenadine

In pharmacokinetic studies there are no reports of interactions 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.

Azithromycin should be administered with caution in combination with terfenadine.

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 variables for triazolam compared to triazolam and placebo.

Trimethoprim/sulphamethoxazole

Co-administration of trimethoprim/sulphamethoxazole DS (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 sulphamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies.

Cisapride

Cisapride is metabolized in the liver by the enzyme CYP3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsade de pointes.

Astemizol, alfentanil

No data are available on interactions with astemizol 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.

Substances that prolong the QT interval

Azithromycin should not be used concurrently with other active substances that prolong the QT interval (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well controlled studies in pregnant women. As animal studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

Lactation

There is no data on secretion in breast milk. As many agents are excreted in breast milk, azithromycin should not be used in the treatment of a lactating woman unless the physician feels that the potential benefits justify the potential risks to the infant.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, the possibility of undesirable effects like dizziness and convulsions should be taken into account when performing these activities.

4.8 Undesirable effects

About 13% of patients included in clinical trials reported adverse events, most commonly gastro-intestinal disorders.

<i>System organ class</i>	<i>Very common ≥1/10</i>	<i>Common ≥1/100, <1/10</i>	<i>Uncommon ≥1/1000, ≤1/100</i>	<i>Rare ≥1/10000, ≤1/1000</i>	<i>Not known</i>
<i>Infections and infestations</i>			candidiasis oral candidiasis vaginal infection		
<i>Blood and lymphatic system disorders</i>		lymphocyte count decreased eosinophil count increased blood bicarbonate decreased	leucopenia neutropenia		thrombocytopenia haemolytic anaemia
<i>Immune system disorders</i>			angioedema hypersensitivity		anaphylactic reaction (see section 4.4)
<i>Psychiatric disorders</i>			nervousness	agitation depersonalisation, in elderly patients delirium may occur.	aggression anxiety
<i>Nervous system disorders</i>		dizziness headache paraesthesia dysgeusia	hypoesthesia somnolence insomnia		syncope convulsions psychomotor hyperactivity anosmia parosmia ageusia myasthenia gravis (see section 4.4)
<i>Eye disorders</i>		visual impairment			
<i>Ear and</i>		deafness	hearing impaired	vertigo	

<i>labyrinth disorders</i>			tinnitus		
<i>Cardiac disorders</i>			palpitations		torsades de pointes arrhythmia including ventricular tachycardia (see section 4.4) electrocardiogram QT prolonged (see section 4.4)
<i>Vascular disorders</i>					hypotension
<i>Gastrointestinal disorders</i>	diarrhoea abdominal pain nausea flatulence	vomiting dyspepsia anorexia	gastritis constipation loose stools	discolouration of the teeth	tongue discolouration pancreatitis pseudomembranous colitis (see section 4.4)
<i>Hepatobiliary disorders</i>			hepatitis aspartate aminotransferase increased alanine aminotransferase increased blood bilirubin increased	hepatic function abnormal	hepatic failure which has rarely resulted in death (see section 4.4) hepatitis fulminant hepatic necrosis jaundice cholestatic
<i>Skin and subcutaneous tissue disorders</i>		rash pruritus	Stevens-Johnson syndrome photosensitivity reaction urticaria		maculopapular rash toxic epidermal necrolysis erythema multiforme
<i>Musculoskeletal, connective tissue and bone disorders</i>		arthralgia			
<i>Renal and urinary tract disorders</i>			blood urea increased blood creatinine increased		interstitial nephritis acute renal failure
<i>Reproductive system and breast disorders</i>			vaginitis		
<i>General disorders and administration site conditions</i>		fatigue	chest pain oedema malaise asthenia		pain
<i>Investigations</i>			blood potassium abnormal		

4.9 Overdose

The undesirable effects at dosages in excess of the recommended dosages were similar to those after normal dosages.

Symptoms

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

Treatment

In cases of overdose the administration of medicinal charcoal and general symptomatic treatment and measures to support vital functions are indicated where necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 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 lactone 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.

Mode 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.

(Cross)-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 in both *in vitro* and *in vivo* models is ≤ 1 dilution rise in MICs for *S. pyogenes*, *H. influenzae* and *Enterobacteriaceae* after nine sub-lethal passages of active substance and three dilution increase for *S. aureus* and development of *in vitro* resistance due to mutation is rare.

Breakpoints

Azithromycin susceptibility breakpoints for typical bacterial pathogens:

EUCAST (2008):

- *Staphylococcus* spp.: susceptible ≤ 1 mg/l and resistant >2 mg/l
- *Haemophilus* spp.: susceptible ≤ 0.12 mg/l and resistant > 4 mg/l
- *Moraxella catarrhalis*: susceptible ≤ 0.5 mg/l and resistant > 0.5 mg/l
- *Streptococcus* spp. including groups A, B, C, G and *Streptococcus pneumoniae*: susceptible ≤ 0.25 mg/l and resistant > 0.5 mg/l

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.

Species for which acquired 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: Antibacterial spectrum of azithromycin

Species	
Commonly susceptible species	
Aerobic Gram-positive	
<i>Corynebacterium diphtheriae</i>	
<i>Streptococcus pneumoniae</i>	
Erythromycin-sensitive	
Penicillin-sensitive	
<i>Streptococcus pyogenes</i>	
Erythromycin-sensitive	
Aerobic Gram-negative	
<i>Bordetella pertussis</i>	
<i>Escherichia coli</i> -ETEC	
<i>Escherichia coli</i> -EAEC	
<i>Haemophilus influenzae</i>	
<i>Haemophilus ducreyi</i>	
<i>Legionella</i> spp.	
<i>Moraxella catarrhalis</i>	
Erythromycin-sensitive	
Erythromycin-intermediate	
<i>Pasteurella multocida</i>	
Anaerobic	
<i>Fusobacterium nucleatum</i>	
<i>Fusobacterium necrophorum</i>	
<i>Prevotella</i> spp.	
<i>Porphyromonas</i> spp.	
<i>Propionibacterium</i> spp.	
Other micro-organisms	
<i>Chlamydophila pneumoniae</i>	
<i>Chlamydia trachomatis</i>	
<i>Listeria</i> spp.	
<i>Mycobacterium avium</i> Complex	
<i>Mycoplasma pneumoniae</i>	
<i>Ureaplasma urealyticum</i>	
Species for which acquired resistance may be a problem	
Aerobic Gram-positive	
<i>Staphylococcus aureus</i>	
Methicillin-susceptible	
Coagulase-neg. staphylococci	

Methicillin-susceptible ⁺	
<i>Streptococcus pneumoniae</i>	
Penicillin-intermediate	
Penicillin-resistant	
Erythromycin-intermediate	
<i>Streptococcus pyogenes</i>	
Erythromycin-intermediate	
<i>Streptococci viridans</i> group	
Penicillin-intermediate	
Aerobic Gram-negative	
<i>Moraxella catarrhalis</i>	
Erythromycin-resistant	
Anaerobic	
<i>Peptostreptococcus</i> spp.	
Inherently resistant organisms	
Aerobic Gram positive	
<i>Corynebacterium</i> spp.	
<i>Enterococcus</i> spp.	
<i>Staphylococci</i> MRSA, MRSE	
<i>Streptococcus pneumoniae</i>	
Erythromycin-resistant	
Penicillin & Erythromycin resistant	
<i>Streptococcus pyogenes</i>	
Erythromycin-resistant	
<i>Streptococci viridans</i> group	
Penicillin-resistant	
Erythromycin-resistant	
Aerobic Gram-negative	
<i>Pseudomonas aeruginosa</i>	
Anaerobic	
<i>Bacteroides fragilis</i> group	

⁺ Resistance is greater than 50%.

5.2 Pharmacokinetic properties

Absorption

Following oral administration the bio-availability of azithromycin is approximately 37%. Peak plasma levels are reached after 2-3 hours.

Distribution

Orally administered azithromycin is widely distributed throughout the body. Pharmacokinetic studies have shown considerably higher azithromycin concentrations in the tissues (up to 50 times the maximum concentration observed in the plasma) than in the plasma. This indicates that the substance is extensively bound in the tissues (steady-state volume of distribution approximately 31 l/kg). The mean maximum concentration observed (C_{max}) after a single dose of 500 mg is approximately 0.4 µg/ml, 2-3 hours after administration. 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. Three days after administration of 500 mg as a single dose or in divided doses concentrations of 1.3-4.8 µg/g, 0.6-2.3 µg/g, 2.0-2.8 µg/g and 0-0.3 µg/ml are found in lung, prostate, tonsil and serum respectively.

Mean peak concentrations measured in peripheral leukocytes are higher than the MIC₉₀ of the most common pathogens.

In experimental *in vitro* and *in vivo* studies, azithromycin accumulates in phagocytes; release is promoted by active phagocytosis. In animal models this process appeared to contribute to the accumulation of azithromycin in the 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, depending on the serum concentration.

Metabolism and excretion

The terminal plasma elimination half-life follows the tissue depletion half-life of 2 to 4 days. In elderly volunteers (>65 years), higher (29 %) AUC values were always observed after a 5-day course than in younger volunteers (<45 years). However, these differences are not considered to be clinically relevant; no dose adjustment is therefore recommended. 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). A comparison of HPLC and microbiological determination suggests that the metabolites do not play a role in the microbiological activity of azithromycin.

Pharmacokinetics in special populations

Renal insufficiency

Following a single oral dose of azithromycin 1g, mean C_{\max} and AUC_{0-120} increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 10-80 ml/min) compared with normal renal function (GFR > 80 ml/min). In subjects with severe renal impairment (GFR < 10 ml/min), the mean C_{\max} and AUC_{0-120} increased 61% and 35% respectively compared to normal.

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. 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.

Infants, toddlers, children and adolescents

Pharmacokinetics have been studied 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.

5.3 Preclinical safety data

In animal studies using exposures 40 times those achieved at the clinical therapeutic dosages, azithromycin was found to have caused reversible phospholipidosis, but as a rule there were no associated toxicological consequences. The relevance of this finding to humans receiving azithromycin in accordance with the recommendations is unknown.

Electrophysiological investigations have shown that azithromycin prolongs the QT interval.

Carcinogenic potential

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenic potential

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

Reproductive toxicity

No teratogenic effects were observed in embryotoxicity studies in rats after oral administration of azithromycin. In rats, azithromycin dosages of 100 and 200 mg/kg body weight/day led to mild retardations in fetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardations following treatment with 50 mg/kg/day azithromycin and above were observed.

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

Silica, colloidal anhydrous (E551)
 Sucrose
 Xanthan gum (E415)
 Trisodium phosphate anhydrous
 Hydroxypropyl cellulose
 Cherry flavouring trusil
 Vanilla flavour
 Banana flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened bottles: 2 years
 After reconstitution (for azithromycin 15 ml and 22.5 ml): 5 days
 After reconstitution (for azithromycin 30 ml and 37.5 ml): 10 days
 After reconstitution: store below 25°C

6.4 Special precautions for storage

Unopened bottles: This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE bottles with child-resistant PP closures.
 Pack sizes:
 Azithromycin 600 mg/15 ml
 12.555 g of powder for the preparation of 15 ml suspension
 Each bottle contains an overfill of 5ml to ensure complete dosing

 Azithromycin 900 mg/22.5 ml
 18.8325 g of powder for the preparation of 22.5 ml suspension
 Each bottle contains an overfill of 2.5ml to ensure complete dosing

 Azithromycin 1200 mg/30 ml
 25.110 g of powder for the preparation of 30 ml suspension
 Each bottle contains an overfill of 5ml to ensure complete dosing

Azithromycin 1500 mg/37.5 ml
31.3875 g of powder for the preparation of 37.5 ml suspension
Each bottle contains an overfill of 5ml to ensure complete dosing

Multi-dose polystyrene spoon 2.5 / 5 ml graduated at 3.75 ml.

Polystyrene/polyethylene oral dosing syringe (5 ml). The syringe is graduated at every 0.5 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparing suspension:

First loosen the powder by tapping well.

For 15 ml (600 mg) bottle: add 8 ml water with dosing syringe.

For 22.5 ml (900 mg) bottle: add 9.5 ml water with dosing syringe.

For 30 ml (1200 mg) bottle: add 14.5 ml water with dosing syringe.

For 37.5 ml (1500 mg) bottle: add 16.5 ml water with dosing syringe.

Shake well.

Advice should be given as to whether the dose should be measured using the oral dosing syringe or the spoon provided and on correct usage.

After reconstitution, a yellowish-white suspension will be obtained.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 0749/039/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 September 2007

Date of last renewal: 08 November 2009

10 DATE OF REVISION OF THE TEXT

June 2011