SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Azithromycin 200 mg/5 ml powder for oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Excipients with known effect:

Benzyl alcohol: 0.65 microgram/5 ml (equivalent to 0.13 microgram/ml)
Sodium: 35.2 mg/5 ml (equivalent to 7.1 mg/ml)
Sucrose: 3.75 g/5 ml (equivalent to 0.75 g/ml)
Sulphites: 0.74 microgram/5 ml (equivalent to 0.148 microgram/ml)
Sulphur dioxide: 0.11 microgram/5 ml (equivalent to 0.02 microgram/ml)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral suspension

White to yellowish-white powder
After reconstitution: Yellowish-white suspension

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Azithromycin is indicated for the following bacterial infections induced by microorganisms 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, cellulitis, 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

Posology

The duration of treatment in each of the infectious diseases is given below.

Paediatric population over 45 kg body weight, adults

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.

Paediatric population 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.

The azithromycin suspension should be measured as accurately as possible with the assistance of the enclosed dosing syringe, which is graduated in 0.1 ml and 0.25 ml divisions. 0.25 ml of the azithromycin suspension providing 10 mg of azithromycin.
The azithromycin should be administered 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
36-45	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

Weight (kg)	*3-day treatment**	*5-day treatment**	*Content bottle*
>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 treament of children under 16 years of age.

Elderly

The same dosage as recommended for adult patients is used in the elderly. Since elderly 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 section 4.4).

Renal impairment

No dose adjustment is necessary in patients with a glomerular filtration rate (GFR) between 10 and 80 mL/min (see section 4.4).

Hepatic impairment

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

Method of administration
Azithromycin should be given as a single daily dose. The suspension can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance, erythromycin, any macrolide or ketolide antibiotic or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Allergic reactions
As with erythromycin and other macrolides, serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), drug reaction with eosinophilia and systemic symptoms (DRESS) and severe dermatologic reactions such as acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson-syndrome and toxic epidermal necrolysis (TEN) have

been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Renal impairment
No dose adjustment is necessary in patients with a GFR between 10 and 80 mL/min. Caution is advised in patients with GFR < 10 mL/min because in these patients a 33% increase in systemic exposure of azithromycin was observed (see section 5.2).

Hepatic impairment
Since liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin (see section 4.8). Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

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.

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
In patients receiving ergot derivatives, ergotism has been precipitated by coadministration 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 coadministered.

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 including azithromycin (see section 4.8). 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 known to prolong QT interval such as antiarrhythmics of class IA (quinidine and procainamide) and class III (dofetilide, amiodarone and sotalol), hydroxychloroquine, 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 hypomagnesemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

The following should be considered before prescribing azithromycin:

Azithromycin 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.

Pneumonia
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*.

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

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).

Clostridioides difficile-associated diarrhoea
Clostridiioides 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.

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

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.

Mycobacterium Avium Complex (MAC) infection in children
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.

Excipients

Benzyl alcohol
Benzyl alcohol may cause allergic reactions.
Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called “gasping syndrome”) in young children.
Must not be used for more than a week in young children (less than 3 years old), because of an increased risk due to accumulation.

Sodium
This medicinal product contains 35.2 mg sodium per 5 ml of reconstituted suspension, equivalent to 1.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Sucrose
This medicinal product contains sucrose (3.75 g/5 ml of reconstituted suspension).
This should be taken into account in patients with diabetes mellitus.Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Sulphites and sulphur dioxide
May rarely cause severe hypersensitivity reactions and bronchospasm.

4.5 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 25%. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously. Azithromycin should be taken at least 1 hour before or 2 hours after the antacid.
Coadministration of azithromycin prolonged-release granules for oral suspension with a single 20 ml dose of co-magaldrox (aluminium hydroxide and magnesium hydroxide) did not affect the rate and extent of azithromycin absorption.

Cetirizine

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

Didanosine (Dideoxyinosine)
Coadministration of 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.

Zidovudine
Single 1000 mg dose 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.

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

Ergot
Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended (see section 4.4).

Pharmacokinetic studies have been conducted between azithromycin and the following drugs known to undergo significant cytochrome P450 mediated metabolism.

Atorvastatin
Coadministration 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). 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 coadministration 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
Coadministration of a 600 mg single dose of azithromycin and 400 mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions.

Fluconazole
Coadministration of a single dose of 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 coadministration of fluconazole, however, a clinically insignificant decrease in Cmax (18%) of azithromycin was observed.

Indinavir
Coadministration 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 conducted in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

Midazolam
In healthy volunteers, coadministration of azithromycin 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam.

Nelfinavir
Coadministration of azithromycin (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
Coadministration 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 Cmax, 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.

As with other macrolides,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 coadministered to healthy volunteers.

Triazolam
In 14 healthy volunteers, coadministration of azithromycin 500 mg on day 1 and 250 mg on day 2 with 0.125 mg triazolam on day 2 had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

Trimethoprim/sulfamethoxazole
Coadministration of trimethoprim/sulfamethoxazole 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 sulfamethoxazole. 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 torsades de pointes.

Astemizole, alfentanil
No data are available on interactions with astemizole and alfentanil. Caution should be exercised with concomitant use of these drugs 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 be used with caution in patients receiving medicines known to prolong the QT interval with potential to induce cardiac arrhythmia, e.g. hydroxychloroquine (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
In reproduction toxicity studies in animals azithromycin was shown to pass the placenta, but no teratogenic effects were observed. There is a large amount of data from observational studies performed in several countries on exposure to azithromycin during pregnancy, compared to no antibiotic use or use of another antibiotic during the same period. While most studies do not suggest an association with adverse fetal effects such as major congenital malformations or cardiovascular malformations, there is limited epidemiological evidence of an increased risk of miscarriage following azithromycin exposure in early pregnancy.
Azithromycin should only be used during pregnancy if clinically needed and the benefit of treatment is expected to outweigh any small increased risks which may exist.

Breast-feeding
Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in nursing women that have characterized the pharmacokinetics of azithromycin excretion into human breast milk. No serious adverse effects of azithromycin on the breast-fed infants were observed. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

Azithromycin has no or negligible influence on the ability to drive and use machines. However, the possibility of undesirable effects like dizziness and convulsions should be taken into account when performing these activities.

4.8 Undesirable effects

The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
About 13% of patients included in clinical trials reported adverse events, most commonly gastro-intestinal disorders.

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

System organ class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very rare (<1/10000)**	**Not known (cannot be estimated from the available data)**
Infections and infestations			Candidiasis Vaginal infection Pneumonia Fungal infection Bacterial infection Pharyngitis Gastroenteritis Respiratory disorder Rhinitis Oral candidiasis			Pseudomembranous colitis (see section 4.4)

Blood and lymphatic system disorders			Leukopenia Neutropenia Eosinophilia			Thrombocytopenia Haemolytic anaemia
Immune system disorders			Angioedema Hypersensitivity			Anaphylactic reaction (see section 4.4)
Metabolism and nutrition disorders			Anorexia			
Psychiatric disorders			Nervousness Insomnia	Agitation Depersonalisation		Aggression Anxiety Delirium Hallucination
Nervous system disorders		Headache	Dizziness Somnolence Dysgeusia Paraesthesia			Syncope Convulsion Hypoaesthesia Psychomotor hyperactivity Anosmia Ageusia Parosmia Myasthenia gravis (see section 4.4)
Eye disorders			Visual impairment			
Ear and labyrinth disorders			Ear disorder Vertigo			Hearing impairment including deafness and/or tinnitus
Cardiac disorders			Palpitations			Torsades de pointes (see section 4.4) Arrhythmia (see section 4.4) including ventricular tachycardia Electrocardiogram QT prolonged (see section 4.4)
Vascular disorders			Hot flush			Hypotension

Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis			
Gastrointestinal disorders	Diarrhoea	Vomiting Abdominal pain Nausea	Gastritis Constipation Flatulence Dyspepsia Dysphagia Abdominal distension Dry mouth Eructation Mouth ulceration Salivary hypersecretion Loose stools	Discolouration of the teeth		Pancreatitis Tongue Discolouration
Hepatobiliary disorders			Hepatitis	Hepatic function abnormal Jaundice cholestatic		Hepatic failure which has rarely resulted in death (see section 4.4) Hepatitis fulminant Hepatic necrosis
Skin and subcutaneous tissue disorders			Rash Pruritus Urticaria Dermatitis Dry skin Hyperhidrosis	Photosensitivity reaction, acute generalised exanthematous pustulosis (AGEP)	Drug reaction with eosinophilia and systemic symptoms (DRESS)	Stevens-Johnson syndrome Toxic epidermal necrolysis Erythema multiforme Maculopapular rash
Musculoskeletal and connective tissue disorders			Osteoarthritis Myalgia Back pain Neck pain			*Arthralgia*
Renal and urinary disorders			Dysuria Renal pain			*Acute renal failure* *Interstitial nephritis*
Reproductive system and breast disorders			Metrorrhagia Testicular disorder Vaginitis			

General disorders and administration site conditions			Oedema Asthenia Malaise Fatigue Face oedema Chest pain Pyrexia Pain Peripheral oedema			
Investigations		Lymphocyte count decreased Eosinophil count increased Blood bicarbonate decreased Basophils increased Monocytes increased Neutrophils increased	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 Hematocrit decreased Bicarbonate increased Abnormal sodium			
Injury, poisoning and procedural complications			Post procedural complication			

Adverse reactions possibly or probably related to Mycobacterium Avium Complex prophylaxis and treatment 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:

	Very Common (≥1/10)	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to <1/100)**
Metabolism and nutrition disorders		Anorexia	
Nervous system disorders		Dizziness Headache Paraesthesia Dysgeusia	Hypoaesthesia
Eye disorders		Visual impairment	
Ear and labyrinth disorders		Deafness	Hearing impaired Tinnitus
Cardiac disorders			Palpitations
Gastrointestinal disorders	Diarrhoea Abdominal pain Nausea Flatulence Abdominal discomfort Loose stools		
Hepatobiliary disorders			Hepatitis
Skin and subcutaneous tissue disorders		Rash Pruritus	Stevens-Johnson syndrome Photosensitivity reaction
Musculoskeletal and connective tissue disorders		Arthralgia	
General disorders and administration site conditions		Fatigue	Asthenia Malaise

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses.

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 and supportive measures are indicated as required.

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.

Mechanism of action

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

(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 $\leq$1 dilution rise in MICs for *S. pyogenes, H. influenzae* and *Enterobacterciae* 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.

Susceptibility testing breakpoints
MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for azithromycin and are listed here:
https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

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.

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 micro-organisms
Corynebacterium diphteriae
Streptococcus pneumoniae Erythromycin-sensitive Penicillin-sensitive
Streptococcus pyogenes Erythromycin-sensitive
Aerobic Gram-negative micro-organisms
Bordetella pertussis
Escherichia coli-ETEC
Escherichia coli-EAEC
Haemophilus influenzae
Haemophilus ducreyi
Legionella spp.
Moraxella catarrhalis
Erythromycin-sensitive
Erythromycin-intermediate
Pasteurella multocida
Anaerobic micro-organisms
Fusobacterium nucleatum

Fusobacterium necrophorum
Prevotella spp.
Porphyromonas spp.
Propionibacterium spp.
Other micro-organisms
Chlamydophila pneumoniae
Chlamydia trachomatis
Listeria spp.
Mycobacterium avium Complex
Mycoplasma pneumoniae
Ureaplasma urealyticum
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms
Staphylococcus aureus Methicillin-susceptible
Coagulase-neg. Staphylococci Methicillin-susceptible[+]
Streptococcus pneumoniae
Penicillin-intermediate
Penicillin-resistant
Erythromycin-intermediate
Streptococcus pyogenes
Erythromycin-intermediate
Streptococci viridans group
Penicillin-intermediate
Aerobic Gram-negative micro-organisms
Moraxella catarrhalis Erythromycin-resistant
Anaerobic micro-organisms
Peptostreptococcus spp.
Inherently resistant organisms
Aerobic Gram positive micro-organisms
Corynebacterium spp.
Enterococcus spp.
Staphylococci MRSA, MRSE
Streptococcus pneumoniae
Erythromycin-resistant
Penicillin- & Erythromycin-resistant
Streptococcus pyogenes Erythromycin-resistant
Streptococci viridans group
Penicillin-resistant
Erythromycin-resistant
Aerobic Gram-negative micro-organisms
Pseudomonas aeruginosa
Anaerobic micro-organisms
Bacteroides fragilis group

+ Resistance is greater than 50%.

Paediatric 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

Absorption
Following oral administration the bioavailability 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 MIC_{90} 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.

Biotransformation and elimination
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 micro-biological activity of azithromycin.

Pharmacokinetics in special populations

Renal impairment
Following a single oral dose of 1 g azithromycin, C_{max} and AUC_{0-120} increased by 5.1% and 4.2%, respectively, in patients with GFR between 10 and 80 mL/min) compared to patients with GFR > 80 mL/min). In patients with GFR < 10 mL/min), the mean C_{max} and AUC_{0-120} increased by 61% and 33% respectively, compared to patients with GFR >80 mL/min.

Hepatic impairment
In patients with mild to moderate hepatic impairment, there is no evidence of apparent changes 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.

Paediatric population
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 36 h 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 foetal 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 (contains benzyl alcohol and sulphur dioxide E220)
Vanilla flavour (contains sulphites)
Banana flavour (contains sulphites)

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: Store below 25°C

For storage conditions after reconstitution of the medicinal product, see section 6.3

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 includes an overfill of 5 ml 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 includes an overfill of 2.5 ml to ensure complete dosing.

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

Oral dosing syringe (5 ml). The syringe is graduated at every 0.1 ml and 0.25 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Preparation of the suspension:
First loosen the powder by tapping well.
For 15 ml (600 mg) bottle: add 9.5 ml water with dosing syringe.
For 22.5 ml (900 mg) bottle: add 12.0 ml water with dosing syringe.
For 30 ml (1200 mg) bottle: add 16.5 ml water with dosing syringe.
For 37.5 ml (1500 mg) bottle: add 20.0 ml water with dosing syringe.
Shake well.
Advice should be given on preparation of suspension and correct usage of the oral dosing syringe.

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited,
Ridings Point,
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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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