

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Azomax 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg azithromycin (as azithromycin monohydrate)

Excipient(s) with known effect:

Each tablet contains 0.36 mg soya lecithin.

Each tablet contains 0.407 mg sodium (0.018 mmol).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

500 mg film-coated tablets:

white to off-white, oblong, film-coated, deep break line on one side and scoreline on other side. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Azomax 500 mg film-coated tablets can be applied for the treatment of the following infections, when caused by microorganisms sensitive to azithromycin (see sections 4.4 and 5.1):

- acute bacterial sinusitis (adequately diagnosed)
- acute bacterial otitis media (adequately diagnosed)
- pharyngitis, tonsillitis
- acute exacerbation of chronic bronchitis (adequately diagnosed)
- mild to moderately severe community acquired pneumonia
- skin and soft tissue infections
- uncomplicated *Chlamydia trachomatis* urethritis and cervicitis

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

4.2 Posology and method of administration

Posology

Adults

In uncomplicated *Chlamydia trachomatis* urethritis and cervicitis the dose is 1,000 mg as a single oral dose).

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

Elderly people

The same dose as in adult patients is used for older people. Since elderly people 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).

Paediatric population

Azomax 500 mg film-coated tablets should only be administered to children weighing more than 45 kg when normal adult dose should be used. For children under 45 kg other pharmaceutical forms of azithromycine, e.g. suspensions, may be used.

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

In patients with hepatic impairment: A dose adjustment is not necessary for patients with mild to moderately impaired liver function (see section 4.4).

Method of administration

Azomax film coated tablets should be given as a single daily dose. The tablets may be taken with food.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hypersensitivity

As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

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

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.

In patients receiving ergotamine derivatives, ergotism has been precipitated by coadministration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergotamine derivatives and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered (see section 4.5).

Cardiovascular events

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 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) 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), cisapride and terfenadine; antipsychotic agents such as pimozide; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
 - With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

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

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. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antimicrobial agents. In case of CDAD anti-peristaltics are contraindicated.

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).

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

The following should be considered before prescribing azithromycin:

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

Azithromycin is not the first choice for the empiric treatment of infections in areas where the prevalence of resistant isolates is 10% or more (see section 5.1).

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*.

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.

Skin and soft tissue infections

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.

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. palladium* should be excluded.

Neurological or psychiatric diseases

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

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

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

Azomax contains soya lecithin which might be a source of soya protein and should therefore not be taken in patients allergic to soya or peanut due to the risk of hypersensitivity reactions.

Azomax contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on azithromycin:

Antacids

In a pharmacokinetic study investigating the effects of simultaneous administration of antacids and azithromycin, no effect on overall bioavailability was seen, although the peak serum concentrations were reduced by approximately 25%. In patients receiving both azithromycin and antacids, the

medicinal products should not be taken simultaneously. Azithromycin must be taken at least 1 hour before or 2 hours after the antacids.

Co-administration 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.

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.

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.

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Rifabutin

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

Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established (see section 4.8).

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.

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.

Effect of azithromycin on other medicinal products:

Ergotamine derivatives

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

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.

Coumarin-Type Oral Anticoagulants

In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15-mg dose of warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to co-administration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Cyclosporin

In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of cyclosporin, the resulting cyclosporin C_{max} and AUC₀₋₅ were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Theophylline

There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are co-administered to healthy volunteers. As interactions of other macrolides with theophylline have been reported, alertness to signs that indicate a rise in theophylline levels is advised.

Trimethoprim/sulfamethoxazole

Co-administration 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.

Zidovudine

Single 1,000 mg doses and multiple 1,200 mg or 600 mg doses of azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients.

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

Astemizole, alfentanil

There are no known data on interactions with astemizole or alfentanil. Caution is advised in the co-administration of these medicines with azithromycin because of the known enhancing effect of these medicines when used concurrently with the macrolid antibiotic erythromycin.

Atorvastatin

Co-administration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase inhibition assay). However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.

Carbamazepine

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

Cisapride

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

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.

Didanosins (Dideoxyinosine)

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

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.

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.

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.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of azithromycin in pregnant women. In reproduction toxicity studies in animals azithromycin was shown to pass the placenta, but no teratogenic effects were observed (see section 5.3). The safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Therefore azithromycin should only be used during pregnancy if the benefit outweighs the risk.

Breast-feeding

Azithromycin 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.

Because it is not known whether azithromycin may have adverse effects on the breast-fed infant, nursing should be discontinued during treatment with azithromycin. Among other things diarrhoea, fungus infection of the mucous membrane as well as sensitisation is possible in the nursed infant. It is recommended to discard the milk during treatment and up until 2 days after discontinuation of treatment. Nursing may be resumed thereafter.

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 a patient's ability to drive or operate machinery. Visual impairment and vision blurred may have an effect on a patient's ability to drive or operate machinery (section 4.8).

4.8 Undesirable effects

The table below lists the adverse reactions identified through clinical experience and post-marketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in italics. The frequency grouping is defined using the following convention: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available

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

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

<u>System Organ Class</u>	<u>Frequency</u>	<u>Adverse reaction</u>
<u>Infections and infestations</u>	<u>Uncommon</u>	<u>Candidiasis</u> <u>Vaginal infection</u> <u>Pneumonia</u> <u>Fungal infection</u> <u>Bacterial infection</u> <u>Pharyngitis</u> <u>Gastroenteritis</u> <u>Respiratory disorder</u> <u>Rhinitis</u> <u>Oral candidiasis</u>
	<u>Not known</u>	<u>Pseudomembranous colitis (see section 4.4)</u>
<u>Blood and lymphatic system disorders</u>	<u>Uncommon</u>	<u>Leukopenia</u> <u>Neutropenia</u> <u>Eosinophilia</u>
	<u>Not known</u>	<u>Thrombocytopenia</u> <u>Haemolytic anaemia</u>
<u>Immune system disorders</u>	<u>Uncommon</u>	<u>Angioedema</u> <u>Hypersensitivity</u>
	<u>Not known</u>	<u>Anaphylactic reaction (see section 4.4)</u>
<u>Metabolism and nutrition disorders</u>	<u>Uncommon</u>	<u>Anorexia</u>
<u>Psychiatric disorders</u>	<u>Uncommon</u>	<u>Nervousness</u> <u>Insomnia</u>
	<u>Rare</u>	<u>Agitation</u> <u>Depersonalisation</u>
	<u>Not known</u>	<u>Aggression</u> <u>Anxiety</u> <u>Delirium</u> <u>Hallucination</u>
<u>Nervous system disorders</u>	<u>Common</u>	<u>Headache</u>
	<u>Uncommon</u>	<u>Dizziness</u> <u>Somnolence</u> <u>Dysgeusia</u> <u>Paraesthesia</u>
	<u>Not known</u>	<u>Syncope, convulsion</u>

<u>System Organ Class</u>	<u>Frequency</u>	<u>Adverse reaction</u>
		<u>Hypoaesthesia</u> <u>Psychomotor hyperactivity</u> <u>Anosmia</u> <u>Ageusia</u> <u>Parosmia</u> <u>Myasthenia gravis (see section 4.4).</u>
<u>Eye disorders</u>	<u>Uncommon</u>	<u>Visual impairment</u>
	<u>Not known</u>	<u>Blurred vision</u>
<u>Ear and labyrinth disorders</u>	<u>Uncommon</u>	<u>Ear disorder</u> <u>Vertigo</u>
	<u>Not known</u>	<u>Hearing impairment including deafness and/or tinnitus</u>
<u>Cardiac disorders</u>	<u>Uncommon</u>	<u>Palpitations</u>
	<u>Not known</u>	<u>Torsades de pointes (see section 4.4)</u> <u>Arrhythmia (see section 4.4) including ventricular tachycardia</u> <u>electrocardiogram QT prolonged (see section 4.4)</u>
<u>Vascular disorders</u>	<u>Uncommon</u>	<u>Hot flush</u>
	<u>Not known</u>	<u>Hypotension</u>
<u>Respiratory, thoracic and mediastinal disorders</u>	<u>Uncommon</u>	<u>Dyspnoea</u> <u>Epistaxis</u>
<u>Gastrointestinal disorders</u>	<u>Very common</u>	<u>Diarrhoea</u>
	<u>Common</u>	<u>Vomiting</u> <u>Abdominal pain</u> <u>Nausea</u>
	<u>Uncommon</u>	<u>Constipation</u> <u>Flatulence</u> <u>Dyspepsia</u> <u>Gastritis</u> <u>Dysphagia</u> <u>Abdominal distension</u> <u>Dry mouth</u> <u>Eructation</u> <u>Mouth ulceration</u> <u>Salivary hypersecretion</u>
	<u>Not known</u>	<u>Pancreatitis</u> <u>Tongue discolouration</u>
<u>Hepatobiliary disorders</u>	<u>Uncommon</u>	<u>Hepatitis</u>
	<u>Rare</u>	<u>Hepatic function abnormal</u> <u>Jaundice cholestatic</u>
	<u>Not known</u>	<u>Hepatic failure (which has rarely resulted in death) (see section</u>

<u>System Organ Class</u>	<u>Frequency</u>	<u>Adverse reaction</u>
		4.4)* <u>Hepatitis fulminant</u> <u>Hepatic necrosis</u>
<u>Skin and subcutaneous tissue disorders</u>	<u>Uncommon</u>	<u>Rash</u> <u>Pruritus</u> <u>Urticaria</u> <u>Dermatitis</u> <u>Dry skin</u> <u>Hyperhidrosis</u>
	<u>Rare</u>	<u>Photosensitivity reaction</u> <u>Acute generalised exanthematous pustulosis (AGEP)</u>
	<u>Not known</u>	<u>Steven-Johnson syndrome</u> <u>Toxic epidermal necrolysis</u> <u>Erythema multiforme</u>
<u>Musculoskeletal and connective tissue disorders</u>	<u>Uncommon</u>	<u>Osteoarthritis</u> <u>Myalgia</u> <u>Back pain</u> <u>Neck pain</u>
	<u>Not known</u>	<u>Arthralgia</u>
<u>Renal and urinary disorders</u>	<u>Uncommon</u>	<u>Dysuria</u> <u>Renal pain</u>
	<u>Not known</u>	<u>Renal failure acute</u> <u>Nephritis interstitial</u>
<u>Reproductive system and breast disorders</u>	<u>Uncommon</u>	<u>Metrorrhagia</u> <u>Testicular disorder</u>
<u>General disorders and administration site conditions</u>	<u>Uncommon</u>	<u>Oedema</u> <u>Asthenia</u> <u>Malaise</u> <u>Fatigue</u> <u>Face oedema</u> <u>Chest pain</u> <u>Pyrexia</u> <u>Pain</u> <u>Peripheral oedema</u>
<u>Investigations</u>	<u>Common</u>	<u>Lymphocyte count decreased</u> <u>Eosinophil count increased</u> <u>Blood bicarbonate decreased</u> <u>Basophils increased</u> <u>Monocytes increased</u> <u>Neutrophils increased</u>
	<u>Uncommon</u>	<u>Aspartate aminotransferase increased</u> <u>Alanine aminotransferase</u>

<u>System Organ Class</u>	<u>Frequency</u>	<u>Adverse reaction</u>
		<u>increased</u> <u>Blood bilirubine increased</u> <u>Blood urea increased</u> <u>Blood creatinine increased</u> <u>Blood potassium abnormal</u> <u>Blood alkaline phosphatase increased</u> <u>Chloride increased</u> <u>Glucose increased</u> <u>Platelets increased</u> <u>Hematocrit decreased</u> <u>Bicarbonate increased</u> <u>Abnormal sodium</u>
<u>Injury and poisoning</u>	<u>Uncommon</u>	<u>Post procedural complication</u>

* which has rarely resulted in death

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:

<u>System Organ Class</u>	<u>Frequency</u>	<u>Adverse reaction</u>
<u>Metabolism and nutrition disorders</u>	<u>Common</u>	<u>Anorexia</u>
<u>Nervous system disorders</u>	<u>Common</u>	<u>Dizziness</u> <u>Headache</u> <u>Paraesthesia</u> <u>Dysgeusia</u>
	<u>Uncommon</u>	<u>Hypoaesthesia</u>
<u>Eye disorders</u>	<u>Common</u>	<u>Visual impairment</u>
<u>Ear and labyrinth disorders</u>	<u>Common</u>	<u>Deafness</u>
	<u>Uncommon</u>	<u>Hearing impaired</u> <u>Tinnitus</u>
<u>Cardiac disorders</u>	<u>Uncommon</u>	<u>Palpitations</u>
<u>Gastrointestinal disorders</u>	<u>Very common</u>	<u>Diarrhoea</u> <u>Abdominal pain</u> <u>Nausea</u> <u>Flatulence</u> <u>Abdominal discomfort</u> <u>Loose stools</u>
<u>Hepatobiliary disorders</u>	<u>Uncommon</u>	<u>Hepatitis</u>
<u>Skin and subcutaneous tissue disorders</u>	<u>Common</u>	<u>Rash</u> <u>Pruritus</u>
	<u>Uncommon</u>	<u>Steven-Johnson syndrome</u> <u>Photosensitivity reaction</u>

<u>System Organ Class</u>	<u>Frequency</u>	<u>Adverse reaction</u>
<u>Musculoskeletal and connective tissue disorders</u>	<u>Common</u>	<u>Arthralgia</u>
<u>General disorders and administration site conditions</u>	<u>Common</u>	<u>Fatigue</u>
	<u>Uncommon</u>	<u>Asthenia</u> <u>Malaise</u>

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 drug.safesty@novartis.com

4.9 Overdose

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. In the event of overdosage general symptomatic and general supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

General properties

Pharmacotherapeutic group: antibacterials for systemic use; macrolids; azithromycin, ATC code: J01FA10

Mode of action

Azithromycin is an azalide, a sub-class of the macrolid antibiotics. By binding to the 50S-ribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented.

PK/PD relationship

For azithromycin the AUC/MIC is the major PK/PD parameter correlating best with the efficacy of azithromycin.

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.

Complete cross resistance exists among *Streptococcus pneumoniae*, beta-haemolytic streptococcus of group A, *Enterococcus faecalis* and *Staphylococcus aureus*, including methicillin resistant *S. aureus* (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

Breakpoints

EUCAST (European Committee on Antimicrobial Susceptibility Testing)

Pathogens	susceptible (mg/l)	resistant (mg/l)
<i>Staphylococcus</i> spp.	≤ 1	> 2
<i>Streptococcus</i> spp. (Group A, B, C, G)	≤ 0.25	> 0.5
<i>Streptococcus pneumoniae</i>	≤ 0.25	> 0.5
<i>Haemophilus influenzae</i>	≤ 0.12	> 4
<i>Moraxella catarrhalis</i>	≤ 0.5	> 0.5
<i>Neisseria gonorrhoeae</i>	≤ 0.25	> 0.5

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

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

Table of susceptibility

Commonly susceptible species
Aerobic Gram-negative microorganisms
<i>Haemophilus influenzae</i> *
<i>Moraxella catarrhalis</i> *
Other microorganisms
<i>Chlamydophila pneumoniae</i>
<i>Chlamydia trachomatis</i>
<i>Legionella pneumophila</i>
<i>Mycobacterium avium</i>
<i>Mycoplasma pneumoniae</i> *
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
<i>Staphylococcus aureus</i> *
<i>Streptococcus agalactiae</i>
<i>Streptococcus pneumoniae</i> *
<i>Streptococcus pyogenes</i> *
Other microorganisms
<i>Ureaplasma urealyticum</i>
Inherently resistant organisms
Aerobic Gram-positive microorganisms
<i>Staphylococcus aureus</i> – methicillin resistant and erythromycin resistant strains
<i>Streptococcus pneumoniae</i> – penicillin resistant strains

Aerobic Gram-negative microorganisms
<i>Escherichia coli</i> <i>Pseudomonas aeruginosa</i> <i>Klebsiella</i> spp.
Anaerobic Gram-negative microorganisms
<i>Bacteroides fragilis</i> group

* Clinical effectiveness is demonstrated by sensitive isolated organisms for approved clinical indications.

5.2 Pharmacokinetic properties

Absorption

After oral administration the bioavailability of azithromycin is approximately 37%. Peak plasma levels are reached after 2-3 hours (C_{max} after a single dose of 500 mg orally was approximately 0.4 mg/l).

Distribution

Kinetic studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the active substance is heavily tissue bound (steady state distribution volume of approximately 31 l/kg). Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC_{90} for likely pathogens after a single dose of 500 mg.

In experimental *in vitro* and *in vivo* studies azithromycin accumulates in the phagocytes, freeing is stimulated by active phagocytosis. In animal studies this process appeared to contribute to the accumulation of azithromycin in the tissue.

In serum the protein binding of azithromycin is variable and depending on the serum concentration varies from 50% in 0.05 mg/l to 12% in 0.5 mg/l.

Excretion

Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. About 12% of an intravenously administered dose is excreted in the urine unchanged over a period of 3 days; the majority in the first 24 hours. Biliary excretion of azithromycin, predominantly in unchanged form, is a major route of elimination.

The identified metabolites (formed by N- and O- demethylising, by hydroxylising of the desosamine and aglycone rings, and by the splitting of the cladinose conjugate) are microbiologically inactive. After a 5 day treatment slightly higher (29%) AUC values were seen in the elderly volunteers (>65 years of age) compared to the younger volunteers (< 45 years of age). However these differences are not regarded as clinically relevant; therefore a dose adjustment is not recommended.

Pharmacokinetics in special populations

Renal insufficiency

Following a single oral dose of azithromycin 1 g, 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, the mean C_{max} and AUC_{0-120} increased 61% and 33% 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.

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 ug/l in children aged 0.6-5 years and after 3 days dosing and 383 ug/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 high-dose animal studies, giving active substance concentrations 40 fold higher than those expected in clinical practice, azithromycin has been noted to cause reversible phospholipidosis, generally without discernible toxicological consequences. There is no evidence that this is of relevance to the normal use of azithromycin in humans.

Carcinogenic potential:

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

Mutagenic potential:

Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay.

Reproductive toxicity:

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Microcrystalline cellulose
Pregelatinised maize starch
Sodium starch glycolate Type A
Colloidal anhydrous silica
Sodium laurilsulfate
Magnesium stearate

Coating:

Polyvinyl alcohol
Titanium dioxide (E 171)
Talc
Soya Lecithin
Xanthan Gum.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blister

Pack sizes:

4, 6, 12, 24, 50, and 100 film-coated tablets
2, 3, 6, 12, 24, 30, 50, and 100 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sandoz Pharmaceuticals d.d
Verovskova 57, 1000 Ljubljana,
Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

Date of latest renewal: {DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]