SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT:

AZIVENT 500 [Azithromycin Tablets USP 500 mg]

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2. QUALITATIVE AND QUANTITATIVE COMPOSITION :

Each film-coated tablet contains:

Azithromycin Dihydrate BP equivalent to

Anhydrous Azithromycin 500 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

TABLET.

Orange coloured, capsule shaped, biconvex film coated tablets plain on both sides.

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):

- 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
- Infections of the skin and soft tissues of mild to moderate severity e.g. folliculitis, cellulitis, erysipelas.
- Uncomplicated genital infections due to *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.

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

4.2 Posology and method of administration:

Posology

Azithromycin should be given as a single daily dose. Duration of the treatment for the different infection diseases is given below.

Children and adolescents with a body weight above 45 kg, adults and the elderly

The total dose is 1500 mg, administered as 500 mg once daily for 3 days.
Alternatively, the same total dose (1500 mg) can be administered in a period of 5 days, 500 mg on the first day and 250 mg on day 2 to 5.
In the case of uncomplicated *Chlamydia trachomatis* urethritis and cervicitis, the dose is 1000 mg as a single oral dose.

Children and adolescents with a body weight below 45 kg

Azithromycin tablets are not suitable for patients under 45 kg body weight.
Other dosage forms are available for this group of patients.

Elderly patients

For elderly patients the same dose as for adults can be applied. Since elderly patients can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes. (see section 4.4).

Patients with renal impairment:

Dose adjustment is not required in patients with mild to moderate renal impairment (GFR 10-80 ml/min) Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR < 10 ml/min) (see section 4.4 and section 5.2).

Patients with hepatic impairment

Dose adjustment is not required for patients with mild to moderate hepatic dysfunction (see section 4.4).

Method of administration.

Azithromycin should be given as a single daily dose. The tablets can be taken with or without food. The tablets should be taken with ½ glass of water.

4.3 Contraindications:

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

4.4 Special warnings and special precautions for use:

H*ypersensitivity*

As with erythromycin and other macrolides, rare serious allergic reactions, including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalized 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.

Hepatic impairment:

Since the liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life threatening liver failure have been reported with azithromycin (see 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.

Infantile hypertrophic pyloric stenosis (IHPS)

Following the use of azithromycin in neonates (treatment up to 42 days of life), infantile hypertrophic pyloric stenosis (IHPS) has been reported. Parents and are givers should be informed to contact their physician if vomiting or irritability with feeding occurs.

Ergot alkaloids and azithromycin

In patients receiving ergot derivatives, ergotism has been precipitated by co-administration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between 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).

Superinfections:

As with any antibiotic preparation, it is recommended to pay attention to signs of superinfection with nonsusceptible microorganisms like fungi. A superinfection may require an interruption of the azithromycin treatment and initiation of adequate measures.

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

4.4 Special warnings and special precautions for use: [contd]

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C.difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. In case of CDAD anti-peristaltics are contraindicated.

Renal impairment

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

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 acquired 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.

Myasthenia gravis

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

Paediatric population

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

4.4 Special warnings and special precautions for use: [contd]

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.

The selection of azithromycin to treat an individual patient should take into account the appropriateness of using a macrolide antibacterial agent based on adequate diagnosis to ascertain the bacterial etiology of the infection in the approved indications and the prevalence of resistance to azithromycin or other macrolides.

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 requently 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.pallidium* should be excluded.
Neurological or psychiatric diseases:
Azithromycin should be used with caution in patients with neurological or psychiatric disorders.

Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Lactose
Patients with rare hereditary problems of galactose intolerance, total lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and special precautions for use:

Sodium
Azithromycin contains less than 1 mmol (23 mg) of sodium per tablet, that is to say it is essentially 'sodium-free.'

4.5 Interaction with other FPPs and other forms of interaction:

Antacids:
In a pharmacokinetic study investigating the effects of simultaneous administration of antacids with azithromycin, no effect on overall bioavailability was seen, although peak serum levels 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 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.

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.

Didanosins (Dideoxyinosine): Coadministration of 1200 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 (P-gp substrates) and colchicine:
Concomitant administration of macrolide antibiotics, including azithromycin,with P-glycoprotein substrates such as digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate.
Therefore, if azithromycin and P-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered.

4.5 Interaction with other FPPs and other forms of interaction: [contd]

Zidovudine:

Single 1000 mg doses and multiple doses of 600 mg or 1200 mg 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.

Ergotamine derivatives:

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.

Astemizole, alfentanil

There are no known data on interactions with astemizole or alfentanil. Caution is advised in the coadministration of these medicines with Azithromycin because of the known enhancing effect of these medicines when used concurrently with the macrolide antibiotic erythromycin.

Atorvastatin:

Coadministration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase inhibition assay). However, postmarketing 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 zithromycin, 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 postmarketing 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

4.5 Interaction with other FPPs and other forms of interaction: [contd]

to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarintypeoral 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 AUC_{0-5} were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose 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 1200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and halflife of azithromycin were unchanged by the coadministration of fluconazole, however, a clinically insignificant decrease in C_{max} (18%) of azithromycin was observed.

Indinavir:

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

Methylprednisolone:

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

Midazolam:

In healthy volunteers, 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 (1200 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 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).

Sildenafil:

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

4.5 Interaction with other FPPs and other forms of interaction: [contd]

Terfenadine:

Pharmacokinetic studies have reported no evidence of an interaction between azithromycin and terfenadine. There have been rare cases reported where the possibility of such an interaction could not be entirely excluded; however there was no specific evidence that such an interaction had occurred.

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

volunteers. As interactions of other macrolides with theophylline have been reported, alertness to signs that indicate a rise in theophylline levels is advised.

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 1200 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.

Medicinal products known to 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.

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.

4.6 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.

Breastfeeding

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

4.6 Pregnancy and lactation:

Breastfeeding

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 & Use Machines:

No data are available regarding the influence of azithromycin on a patient's ability to drive or operate machinery. However, the possibility of undesirable effects like dizziness and convulsions should be taken into account when performing these activities. Visual impairment

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

4.8 Adverse reactions:

The table below lists the adverse reactions identified through clinical trial 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 (≥ 1/10); Common (≥ 1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥ 1/10,000 to <1/1,000); Very Rare (< 1/10,000); and Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness

4.8 Adverse reactions:

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

Very common ≥1/10	Common ≥1/100 to < 1/10	Uncommon ≥1/1,000 to < 1/100	Rare ≥1/10,000 to <1/1,000	Very rare < 1/10,000	Not known frequency cannot be estimated from available data
Infections and infestations					
		Candidiasis Oral candidiasis Vaginal infection Pneumonia Fungal infection Bacterial infection Pharyngitis Gastroenteritis Respiratory			Pseudo- membranous colitis (see section 4.4)
Very common	**Common**	**Uncommon**	**Rare**	**Very**	**Not known**
>1/10	>1/100 to < 1/10	>1/1,000 to < 1/100	>1/10,000 to <1/1,000	rare < 1/10,000	frequency cannot be estimated from available data
		disorder, Rhinitis			
Blood and lymphatic system disorders					
		Leukopenia Neutropenia Eosinophilia			*Thrombo- cytopenia*, Haemolytic anaemia
Immune system disorders					
		Angioedema Hypersensitivity			Anaphylactic reaction (see section 4.4.)
Metabolism and nutrition disorders					
	Anorexia				
Psychiatric disorders					

		Nervousness, Insomnia	Agitation,		Aggression Anxiety Delirium Hallucination

4.8 Adverse reactions:

Nervous system disorders					
	Headache Dizziness Dysgeusia Paraesthesia	Hypoaesthesia Somnolence			Syncope Convulsion Psychomotor hyperactivity Anosmia Ageusia Parosmia Myasthenia gravis (see section 4.4)
Eye disorders					
	Visual impairment				Blurred vision
Ear and labyrinth disorders					
Very common ≥1/10	**Common** ≥1/100 to < 1/10	**Uncommon** ≥1/1,000 to < 1/100	**Rare** ≥1/10,000 to <1/1,000	**Very rare** < 1/10,000	**Not known** frequency cannot be estimated from available data
	Deafness	Ear disorder Vertigo hearing impaired, tinnitus			
Cardiac disorders					
		Palpitations			Torsades de pointes (see section 4.4) Arrhythmia (see section 4.4) including ventricular tachycardia Electro- cardiogram QT prolonged (see section 4.4)
Vascular disorders					
		Hot flush			Hypotension
Respiratory, thoracic and mediastinal disorders					
		Dyspnoea Epistaxis			

4.8 Adverse reactions:

Gastrointestinal disorders					
Diarrhoea abdominal pain, nausea, flatulence	Vomiting dyspepsia	Constipation Dysphagia Gastritis Abdominal distension Dry mouth Eructation Mouth ulceration Salivary			Pancreatitis, Tongue and teeth discoloration
Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
≥1/10	≥1/100 to < 1/10	≥1/1,000 to < 1/100	≥ 1/10,000 to ≤1/1,000	< 1/10,000	frequency cannot be estimated from available data
		hypersecretion			
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					
	Pruritus *Rash*	Stevens-Johnson, syndrome, photosensitivity reaction, Urticaria Dermatitis Dry skin Hyperhidrosis	Allergic reactions including angioneurotic oedema acute generalised exanthematous pustulosis (AGEP)		Toxic epidermal necrolysis Erythema Multiforme DRESS (Drug reaction with eosinophilia and systemic symptoms
Musculoskeletal and connective tissue disorders					
	Arthralgia	Osteoarthritis Myalgia Back pain Neck pain			

4.8 Adverse reactions: [contd]

Renal and urinary disorders					
		Dysuria Renal pain	Renal failure acute, nephritis interstitial		
Reproductive system and breast disorders					
		Metrorrhagia			

Very common ≥1/10	**Common** ≥1/100 to < 1/10	**Uncommon** ≥1/1,000 to < 1/100	**Rare** ≥1/10,000 to <1/1,000	**Very rare** < 1/10,000	**Not known** frequency cannot be estimated from available data
		Testicular disorder			
General disorders and administration site conditions					
	Fatigue	Oedema Asthenia Malaise Face edema Chest pain Pyrexia Peripheral Pain			

4.8 Adverse reactions: [contd]

Investigations					
	Lymphocyte count decreased Eosinophil count increased Blood bicarbonate decreased Basophils increased Monocytes increased, Neutrophils increased	Aspartate 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			Electrocardiogram QT prolonged (see **section 4.4)**
Injury and poisoning					
		Post procedural complications			

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:

System Organ Class	Adverse reaction	Frequency
Metabolism and Nutrition Disorders	Anorexia	Common
Nervous System Disorders	Dizziness Headache Paraesthesia Dysgeusia	Common
	Hypoesthesia	Uncommon

4.8 Adverse reactions: [contd]

Eye Disorders	Visual impairment	Common
Ear and Labyrinth Disorders	Deafness	Common
	Hearing impaired Tinnitus	Uncommon
Cardiac Disorders	Palpitations	Uncommon
Gastrointestinal Disorders	Diarrhoea Abdominal pain Nausea Flatulence Abdominal discomfort Loose stools	Very common
Hepatobiliary Disorders	Hepatitis	Uncommon
Skin and Subcutaneous Tissue Disorders	Rash Pruritus	Common
	Steven-Johnson syndrome Photosensitivity reaction	Uncommon
Musculoskeletal and Connective Tissue Disorders	Arthralgia	Common
General Disorders and Administration Site Conditions	Fatigue	Common
	Asthenia Malaise	Uncommon

4.9 Overdosage and treatment of overdosage:

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 the event of overdose, general symptomatic and supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES:

5.1 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-9amethyl- 9a-homoerythromycin A. The molecular weight is 749.0.

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

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.

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

5. PHARMACOLOGICAL PROPERTIES: [contd]

5.1 Breakpoints [contd]

EUCAST (European Committee on Antimicrobial Susceptibility Testing) are:

	MIC breakpoint (mg/L)	
Pathogens	**Susceptible (mg/L)**	**Resistant (mg/L)**
Staphylococcus spp.	≤ 1	> 2
Streptococcus spp. (Group A, B, C, G)	≤ 0.25	> 0.5
Streptococcus pneumoniae	≤ 0.25	> 0.5
Haemophilus influenzae	Note[1]	Note[1]
Moraxella catarrhalis	≤ 0.25	> 0.5
Neisseria gonorrhoeae	≤ 0.25	> 0.5

Note1: Clinical evidence for the efficacy of macrolides in H. influenzae respiratory

infections is conflicting due to high spontaneous cure rates. Should there be a need to test any macrolide against this species, the epidemiological cut-offs (ECOFFs) should be used to detect strains with acquired resistance.
The ECOFFs for each agent are: azithromycin 4mg/L.

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.

5. PHARMACOLOGICAL PROPERTIES:

Table of susceptibility

Commonly susceptible species.
Aerobic Gram-negative microorganisms
*Haemophilus influenzae**
*Moraxella catarrhalis**
Other microorganisms
Chlamydophila pneumoniae
Chlamydia trachomatis
Legionella pneumophila
Mycobacterium avium
*Mycoplasma pneumonia**
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
*Staphylococcus aureus**
Streptococcus agalactiae
*Streptococcus pneumoniae**
*Streptococcus pyogenes**
Other microorganisms
Ureaplasma urealyticum

Inherently resistant organisms
Aerobic Gram-positive microorganisms
Staphylococcus aureus – methicillin resistant and erythromycin resistant strains
Streptococcus pneumoniae – penicillin resistant strains
Aerobic Gram-negative microorganisms
Escherichia coli
Pseudomonas aeruginosa
Klebsiella spp.
Anaerobic Gram-negative microorganisms
Bacteroides fragilis-group

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

5.2 Pharmacokinetic properties:

Absorption:
Bioavailability of azithromycin after oral administration is approximately 37%. Peak plasma concentrations are attained after 2-3 hours. The mean maximum concentration observed (C_{max}) after a single dose of 500 mg is approximately 0.4 μg/ml.

Distribution:

Orally administered azithromycin is widely distributed throughout the body.
Pharmacokinetic studies have demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (up to 50 times the maximum observed concentration in plasma) than those measured in plasma. This indicates that the agent strongly binds to tissues (steady-state distribution volume approx. 31 l/kg).

At the recommended dose no accumulation appears in the serum. Accumulation appears in tissues where levels are much higher than in serum. Three days after administration of 500 mg as a single dose or in partial 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 have been measured in resp. lung, prostate, tonsil and serum.

In experimental *in vitro* and *in vivo* studies azithromycin accumulates in phagocytes. Release is stimulated by active phagocytosis. In animal models this process contributes to the accumulation of azithromycin in tissue.

Binding of azithromycin to serum proteins is variable and varies from 50% at 0,05 mg/l to 18% at 0,5 mg/l, depending on the serum concentration.

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

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. Ten metabolites have been identified (formed by N and O demethylation, by hydroxylation of the desosamine and aglycone rings, and by splitting of the cladinose conjugate). Investigations suggest that the metabolites do not play a role in the microbiological activity of azithromycin.

5.2 Pharmacokinetic properties:

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 > 80ml/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.

In elderly volunteers (> 65 years) higher (29%) AUC values have been measured after a 5 day treatment than in younger volunteers (< 45 years). These differences are not regarded as clinically relevant; dose adjustment is therefore not recommended.

Infants, toddlers, children and adolescents:
Pharmacokinetics has 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 25, the C_{max} achieved is slightly lower than in 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 half-life 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.

5.3 Preclinical safety data:[contd]

Mutagenic potential:

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

Reproductive toxicity:

Teratogenic effects were not observed in rat reproductive toxicity studies. In rats, azithromycin doses of 100 and 200 mg/kg body weight/ day led to mild retardation in foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats mild retardations in physical and reflex development were noted following treatment with 50 mg/kg/day azithromycin and above.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Microcrystalline Cellulose, Croscarmellose Sodium, Starch Maize, Sodium Lauryl Sulphate, Magnesium Stearate , Colloidal Anhydrous Silica {Colloidal Silicon Dioxide}, Talc, Colour Sunset Yellow FCF(Lake), Hyperomellose, Titanium Dioxide, Propylene Glycol & Purified Water

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life: 24 MONTHS.

6.4 Special precautions for storage:

Store at a temperature not exceeding 30 °C.

KEEP OUT OF REACH OF CHILDREN.

PROTECT FROM MOISTURE AND LIGHT.

6.5 Nature and contents of container:

Blister pack of 3 tablets. Secondary pack: 10 x3’s;1 x 3’s;10 x1 x 3’s

6.6 Instructions for use and handling:

No special requirements. Any unused product or waste material should be disposed off in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER:

ARISTO PHARMACEUTICALS PRIVATE LIMITED

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Off Veera Desai Road, ANDHERI (W), MUMBAI 400 053, INDIA.
Telephone number: 91 22 2673 9999/26739751/26739749
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8. MA number issued by Ethiopian FDA:

08059/REN/2021

9. Date of first authorization/renewal of the authorization:

19-10-2021

10. DATE OF REVISION OF THE TEXT:

12-07-2023