1.3 PRODUCT INFORMATION

1.3.1 Summary of product Characteristics (SmPC)

The Summary of Product Characteristics of MACROSAFE 250 (Azithromycin Tablets USP 250 mg) are enclosed in the following pages.

SMPC

SUMMARY OF PRODUCT CHARACTERISTICS

MACROSAFE 250/500 (AzithromycinTablets USP 250/500 mg)

1. Name of the medicinal product

MACROSAFE 250/500 (Azithromycin Tablets USP 250/500 mg)

2.Qualitative and quantitative composition

MACROSAFE 250
Each film coated tablet contains:
Azithromycin USP (As Dihydrate)
Equivalent toAzithromycinAnhydrous 250 mg

MACROSAFE 500
Each film coated tablet contains:
Azithromycin USP (As Dihydrate)
Equivalent toAzithromycinAnhydrous 500 mg

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Film coated Tablets.
250 mg: Round shaped white colored, film coated tablets with plain on both sides.
500 mg: Caplet shaped white colored, film coated tablets with plain on both sides.

4. Clinical particulars

4.1 Therapeutic indications

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

- 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 Chlamydia trachomatis urethritis and cervicitis

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.

Adults, children and adolescents with a body weight of 45 kg or over:

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 dosage 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) (see section 4.4).

Patients with hepatic impairment:

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

Method of administration

The tablets can be taken with or without food.

The tablets should be taken with ½ glass of water

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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 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.

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.

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 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 non-susceptible micro-organisms 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.

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

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.

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 (MAC) in children have not been established.

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 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.

In bacterial pharyngitis the use of azithromycin is recommended only in cases where first line therapy with beta-lactams is not possible.

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. 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 Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products 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%. Azithromycin must be taken at least 1 hour before or 2 hours after antacids.

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):

Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin, 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 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 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: Coadministration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase-inhibition assay). However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.

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

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.

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 coumarintype 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 Cmax and AUC0-5 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 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 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 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.

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.

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

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.

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. 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.

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 disorder, rhinitis.			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					
	Dizziness, headache, paraesthesia, dysgeusia	Hypoaesthesia somnolence			Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis (see section 4.4)
Eye disorders					
	Visual impairment				
Ear and labyrinth disorders					
	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. Electrodiogram QT prolonged (see section 4.4)
Vascular disorders					

		Hot flush			Hypotension
Respiratory, thoracic and mediastinal disorders					
		Dyspnoea, epistaxis			
Gastrointestinal disorders					
Diarrhoea, abdominal pain, nausea, flatulence	Vomiting, dyspepsia	Gastritis, constipation, dysphagia, abdominal distension, dry mouth, eructation, mouth ulceration, salivary hypersecretion			Pancreatitis, tongue and teeth discoloration
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	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			
Renal and urinary disorders					
		Dysuria, renal pain	Renal failure acute, nephritis interstitial		
Reproductive system and breast disorders					
		Metrorrhagia, testicular disorder			
General disorders and administration site conditions					
	Fatigue	Chest pain, face oedema, pyrexia,			

		peripheral pain, oedema malaise asthenia			
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 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
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 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 the event of overdose, 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-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 50Sribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side ofthe ribosome to the other. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented.

Pharmacokinetic/pharmacodynamic 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, betahaemolytic 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)

	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	≤ 0.125	> 4
Moraxella catarrhalis	≤ 0.25	> 0.5
Neisseria gonorrhoeae	≤ 0.25	> 0.5

Susceptibility:

The prevalence of acquired resistance may vary geographically and with time for selected species 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
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 (Cmax) 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 andin 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 52% 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 half-life 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.

<u>Pharmacokinetics in Special populations:</u>

Renal Insufficiency:

Following a single oral dose of azithromycin 1 g, mean Cmax and AUC0-120 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 Cmax and AUC0-120 increased 61% and 35% respectively compared to normal.

Hepatic insufficiency:

In patients with mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to normal hepatic function. In these patients, urinary recovery of azithromycin appears to increase perhaps to compensate for reduced hepatic clearance.

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 2-5, the Cmax 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.

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 dosages of 100 and 200 mg/kg bodyweight/ 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, Sodium Lauryl Sulfate, Croscarmellose Sodium,
Hydroxy Propyl Cellulose, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate and Instacoat Universal White IC-U-1308.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

PVC/PVdC blisters: Do not store above 30C. Protect from light and moisture.Keep out of reach of children.

6.5 Nature and contents of container

For Azithromycin Tablets USP 250 mg:

6 tablets of Macrosafe 250 (Azithromycin Tablets USP 250 mg) are sealed with PVC/PVdC film on one side and Printed aluminium foil on the other side in the form of a blister pack and 1 such blister pack is further packed in a printed carton along with instructions for use.

For Azithromycin Tablets USP 500 mg:

3 tablets of Macrosafe 500 (Azithromycin Tablets USP 500 mg) are sealed with PVC/PVdC film on one side and Printed aluminium foil on the other side in the form of a blister pack and 1 such blister pack is further packed in a printed carton along with instructions for use.

6.6 Special precautions for disposal and other handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER:
MSN LABORATORIES LIMITED
MSN House, Plot No. : C-24, Industrial Estate,
Sanath Nagar, Hyderabad – 500 018
Telangana, India

8. Date of revision of the text

AUGUST 2019

1.3.2 Labelling (outer & inner labels)

The artworks of container label, carton & Pack Insert for MACROSAFE 250 (Azithromycin Tablets USP 250 mg) are enclosed in the following pages.

℞ **MACROSAFE 250**

Azithromycin Tablets USP 250 mg

Each film coated tablet contains:
Azithromycin USP (As Dihydrate)
Equivalent to
Azithromycin anhydrous 250 mg

DOSAGE : As directed by the Physician.

Do not store above 30°C.
Protect from light and moisture.

Keep out of reach of children.

NAFDAC Reg No.: B4-4572

Manufactured by:
MSN Laboratories Private Limited
(Formulations divisions) Plot No 42,
Anrich Industrial Estate, Bollaram,
Sanagareddy District - 502 325,
Telangana, INDIA.
Mfg. Lic. No.: 38/MD/AP/2007/F/CC

Marketed and Distributed by:
Phillips Pharmaceuticals (Nigeria) Ltd,
122-132 Afprint Industrial Estate,
Iyana-Isolo,Lagos, Nigeria

℞ **MACROSAFE 250**

Azithromycin Tablets USP 250 mg

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Azithromycin USP (As Dihydrate)
Equivalent to
Azithromycin anhydrous 250 mg

DOSAGE : As directed by the Physician.

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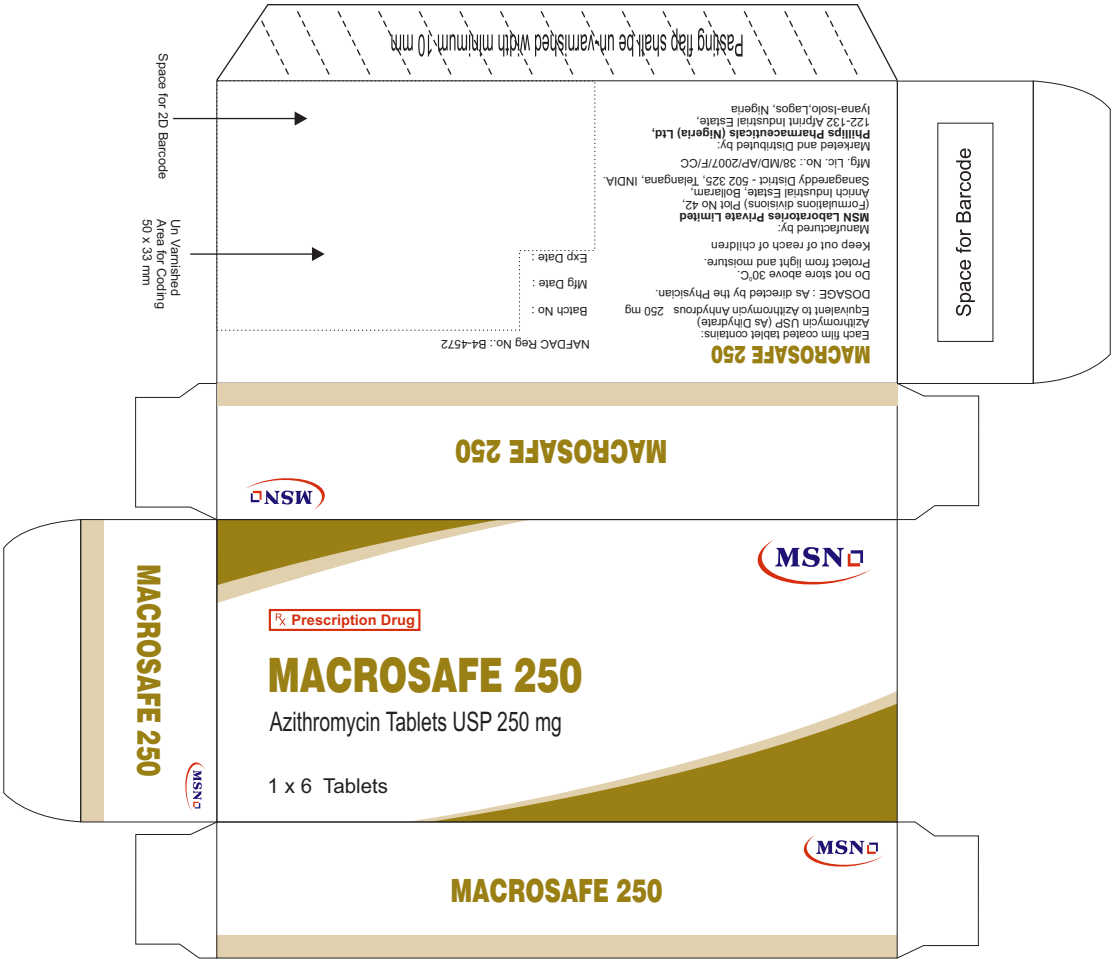
BLACK

Foil Width 176 mm
Alu Blister Size 84 x 36mm (Repeat 1.2)

Blister Foil

Test	Specification
1. Description	Printed hard tampered aluminium foil with VMCH coating on the sealing side.
2. Thickness of Aluminium	0.018 to 0.022 mm
3. Width	176 ± 1.0 mm (175 – 177 mm)
4. Aluminium foil GSM VMCH Coating GSM	49.86 to 58.54 GSM 4 to 6 GSM
5. Pin Holes	Nil
6. Ink Adhesion Test	No Ink Lifting
7. Inner Core Diameter	76 ± 1 mm



PANTONE 456 C PANTONE 273 C PANTONE 485 C Black

Dimension : 90 x 18 x 40 mm

Box style : Reverse tuck in style

Board : Cyber XL board with 300 GSM
Varnish : UV Varnish except over printing area

Renal and urinary disorders					
		Dysuria, renal pain	Renal failure acute, nephritis interstitial		
Reproductive system and breast disorders					
		Metrorrhagia, testicular disorder			
General disorders and administration site conditions					
	Fatigue	Chest pain, face oedema, pyrexia, peripheral pain, oedema malaise asthenia			
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 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
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

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

PHARMACEUTICAL PARTICULARS

List of excipients

Microcrystalline cellulose, Sodium Lauryl sulphate, Croscarmellose sodium, Hydroxy propyl cellulose, Colloidal silicon dioxide, Magnesium stearate.

Coating: Hypromellose, Polyethylene glycol, Talc & Titanium dioxide.

Incompatibilities
Not applicable.

Special precautions for storage
Do not store above 30°C. Protect from light & moisture.
Keep out of reach of children.

Nature and contents of container
250 mg: Blister Pack of 6 Tablets
500 mg: Blister Pack of 3 Tablets

NAFDAC Reg.No.
Macrosafe 250: B4-4572
Macrosafe 500: B4-4573

Manufactured by:
MSN Laboratories Private Limited
Plot No. 42, Anrich Industrial Estate,
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Prescription only medication

MACROSAFE

(Azithromycin Tablets USP 250 mg & 500 mg)

QUALITATIVE AND QUANTITATIVE COMPOSITION

MACROSAFE 250
Each film coated tablet contains:
Azithromycin USP (As Dihydrate)
Equivalent to Azithromycin Anhydrous 250 mg

MACROSAFE 500
Each film coated tablet contains:
Azithromycin USP (As Dihydrate)
Equivalent to Azithromycin Anhydrous 500 mg
For excipients, Please refer Pharmaceutical particulars.

PHARMACEUTICAL FORM

Film coated Tablets.
250 mg: Round shaped white colored, film coated tablets with plain on both sides.
500 mg: Caplet shaped white colored, film coated tablets with plain on both sides.

PHARMACOLOGICAL PROPERTIES

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-homoerythromycin A. The molecular weight is 749.0.

Mode of action

Azithromycin is an azalide, a sub-class of the macrolide antibiotics. By binding to the 50Sribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side ofthe 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, betahaemolytic 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)

	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	≤ 0.125	> 4
Moraxella catarrhalis	≤ 0.25	> 0.5
Neisseria gonorrhoeae	≤ 0.25	> 0.5

Susceptibility:

The prevalence of acquired resistance may vary geographically and with time for selected species 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
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.

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 (Cmax) 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 52% at 0,05 mg/l to 18% at 0,5 mg/l, depending on the serum concentration.

Excretion:

The terminal plasma elimination half-life closely reflects the elimination half-life 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.

Pharmacokinetics in Special populations:

Renal Insufficiency:
Following a single oral dose of azithromycin 1 g, mean Cmax and AUC0-120 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 Cmax and AUC0-120 increased 61% and 35% respectively compared to normal.

Hepatic insufficiency:

In patients with mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to normal hepatic function. In these patients, urinary recovery of azithromycin appears to increase perhaps to compensate for reduced hepatic clearance.

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 2-5, the Cmax 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.

CLINICAL PARTICULARS

Therapeutic Indications

Azithromycin is indicated for the following bacterial infections induced by micro-organisms susceptible to azithromycin:

Dimensions : 280 x 350 mm
Folded Dimensions : 35 x 58 mm
BIBLE PAPER 40 GSM
Version: 00

- 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 Chlamydia trachomatis urethritis and cervicitis

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

Posology and Method of Administration

Azithromycin should be given as a single daily dose. Duration of the treatment for the different infection diseases is given below.
The tablets can be taken with or without food.
The tablets should be taken with ½ glass of water.

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 dosage 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.

Patients with renal impairment:

Dose adjustment is not required in patients with mild to moderate renal impairment (GFR 10-80 ml/min).

Patients with hepatic impairment:

Dose adjustment is not required for patients with mild to moderate hepatic dysfunction.

Contraindications

The use of this product is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipient listed in section 6.1.

Special warnings and precautions for use

As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.
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. 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 ergot 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.

Superinfections:

As with any antibiotic preparation, it is recommended to pay attention to signs of superinfection with non-susceptible micro-organisms 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.
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 patients with severe renal impairment (GFR < 10 ml/min) a 33% increase in systemic exposure to azithromycin was observed.
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. 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.

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy.
Safety and efficacy for the prevention or treatment of Mycobacterium Avium Complex (MAC) in children have not been established.

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 have been reported for azithromycin in some European countries. This should be taken into account when treating infections caused by Streptococcus pneumoniae.
In bacterial pharyngitis the use of azithromycin is recommended only in cases where first line therapy with beta-lactams is not possible.

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. 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 Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.

Interaction with other medicinal products 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%. Azithromycin must be taken at least 1 hour before or 2 hours after antacids.

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):
Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin, 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 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.
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 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: Coadministration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase-inhibition assay). However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.

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

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.

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 coumarintype 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 Cmax and AUC0-5 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 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 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 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.

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.

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.

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. 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.

Effects on ability to drive and 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.

Undesirable effects

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.
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 disorder, rhinitis.			Pseudomembranous colitis
Blood and lymphatic system disorders					
		Leukopenia, neutropenia, eosinophilia			Thrombocytopenia, haemolytic anaemia
Immune system disorders					
		Angioedema hypersensitivity			Anaphylactic reaction
Metabolism and nutrition disorders					
	Anorexia				
Psychiatric disorders					
		Nervousness, insomnia	Agitation, depersonalisation		Aggression, anxiety, delirium, hallucination
Nervous system disorders					
	Dizziness, headache, paraesthesia, dysgeusia	Hypoaesthesia somnolence			Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis
Eye disorders					
	Visual impairment				
Ear and labyrinth disorders					
	Deafness	Ear disorder, vertigo, hearing impaired, tinnitus			
Cardiac disorders					
		Palpitations			Torsades de pointes arrhythmia including ventricular tachycardia. Electrodiogram QT prolonged
Vascular disorders					
		Hot flush			Hypotension
Respiratory, thoracic and mediastinal disorders					
		Dyspnoea, epistaxis			
Gastrointestinal disorders					
Diarrhoea, abdominal pain, nausea, flatulence	Vomiting, dyspepsia	Gastritis, constipation, dysphagia, abdominal distension, dry mouth, eructation, mouth ulceration, salivary hypersecretion			Pancreatitis, tongue and teeth discoloration
Hepatobiliary disorders					
		Hepatitis,	Hepatic function abnormal, jaundice cholestatic		Hepatic failure (which has rarely resulted in death) *, hepatitis fulminant, hepatic necrosis,
Skin and subcutaneous tissue disorders					
	Rash, pruritus	Stevens-Johnson syndrome, photosensitivity reaction, urticaria, dermatitis, dry skin, hyperhidrosis	Allergic reactions including angioneurotic oedema		Toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders					
	Arthralgia	Osteoarthritis, myalgia, back pain, neck pain			

1.3.3 Package Insert (also known as patient information PIL)

Patient Information leaflet for MACROSAFE 250 (Azithromycin Tablets USP 250 mg) has been enclosed in the following pages.

PATIENT INFORMATION LEAFLET
FOR
AZITHROMYCIN TABLETS USP 250 mg

Read all of this leaflet carefully before you start taking this medicine

• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Azithromycin is and what it is used for

Azithromycin is one of a group of antibiotics called macrolides. It is used to treat infections caused by certain bacteria and other micro-organisms, which include:
• Chest, throat or nasal infections (such as bronchitis, pneumonia, tonsillitis, sore throat (pharyngitis) and sinusitis)
• ear infections
• skin and soft tissue infections (such as an abscess or boil)
• sexually transmitted diseases caused by an organism called chlamydia

2. Before you take Azithromycin

Do not take Azithromycin if:
• you are allergic to Azithromycin or any other macrolide antibiotic such as erythromycin or clarithromycin or any of the ingredients listed in section 6. An allergic reaction may cause skin rash or wheezing
• you are taking any ergot derivatives such as ergotamine (used to treat migraine) as these medicines should not be taken together with Azithromycin.

Take special care with Azithromycin

Your doctor needs to know before you take Azithromycin if you have or have had any of the following conditions:

• kidney problems

• heart conditions

• liver problems: your doctor may need to monitor your liver function or stop the treatment

• and if you are taking any ergot derivatives such as ergotamine (used to treat migraine) as these medicines should not be taken together with Azithromycin.

Tell your doctor immediately if you feel your heart beating in your chest or have an abnormal heartbeat, or get dizzy or faint or suffer from any muscle weakness when taking Azithromycin.

If you develop diarrhoea or loose stools during or after treatment, tell your doctor at once.
Do not take any medicine to treat your diarrhoea without first checking with your doctor.
If your diarrhoea continues, please inform your doctor.

Taking other medicines

Tell your doctor before taking Azithromycin, if you are taking any of the medicines listed below:

• ergot or ergotamine – see 'Take special care' section

• warfarin or any similar medicine to prevent blood clots

• ciclosporin (used to suppress the immune system to prevent and treat rejection of a transplanted organ or bone marrow)

• antacids (for indigestion)

• digoxin (used to treat heart failure)

• terfenadine (for hay fever or a skin allergy)

You should always tell your doctor if you are taking or have recently taken any other medicines including those obtained without a prescription.

Taking Azithromycin with food and drink

You should take Azithromycin either 1 hour before a meal or 2 hours after a meal.

Pregnancy and breast-feeding

If you are pregnant, trying to get pregnant or are breast-feeding you should not take Azithromycin without discussing it with your doctor first.

Driving and using machines

Azithromycin is not expected to affect your ability to drive or use machines.

3. How to take Azithromycin

Always take Azithromycin exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The capsules should be swallowed whole.

The usual dose in adults and children over 7 stones (45 kg) is 500mg (2 Tablets) taken together, once a day, for 3 days. For some diseases such as Chlamydia the dose is 1g (4 Tablets) taken all together on one day only.

Azithromycin capsules should not be taken by children weighing less than 45kg.

You should tell your doctor if you have kidney or liver problems as your doctor may need to alter the normal dose.

Doctors sometimes prescribe different doses to these. The label on the pack will tell you which dose you should take. If you are still not sure, ask your doctor or pharmacist.

Always continue with the course even if you feel better. If your infection gets worse or you do not start to feel better within a few days or a new infection develops, go back and see your doctor.

If you take more Azithromycin than you should

If you take too much Azithromycin you may feel unwell. Tell your doctor or contact your nearest hospital casualty department immediately.

If you forget to take Azithromycin

If you forget to take Azithromycin take it as soon as you can. Take your next dose at the right time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Azithromycin

If you stop taking Azithromycin too soon, the infection may return. Take the capsules for the full time of treatment, even when you begin to feel better.

If you have any further questions about the use of this product, ask your doctor or pharmacist for advice.

4. Possible side effects

Like all medicines Azithromycin can cause side effects although not everybody gets them.

Tell your doctor immediately if you experience any of the following symptoms after taking this medicine as the symptoms can be severe.

sudden wheeziness, difficulty in breathing, swelling of eyelids, face or lips, rash or itching (especially affecting the whole body)

- severe or prolonged diarrhoea, which may have blood or mucus in it, during or after treatment with Azithromycin as this may be a sign of serious bowel inflammation
- severe skin rash causing redness and flaking
- rapid or irregular heartbeat
- low blood pressure

The most common side effects that occur when taking Azithromycin are listed below. These may go away during treatment as your body adjusts to the medicine. Tell your doctor if any of these side effects continue to bother you.

Very common side effects (occurring in at least 1 in 10 people taking Azithromycin):

• stomach cramps, feeling sick, diarrhoea, wind

Common side effects (likely to occur in less than 1 in 10 people)

• dizziness, headache
• numbness or pins and needles
• being sick, indigestion
• loss of appetite, taste disturbance
• visual disturbances, deafness
• skin rash and /or itching
• joint pain
• low numbers of lymphocytes (type of white blood cells), higher number of eosinophils (type of white blood cells)
• low blood bicarbonate
• tiredness or weakness

Uncommon side effects that occur in less than 1 in 100 people taking Azithromycin are:

• yeast infections of the mouth and vagina (thrush)
• low numbers of leukocytes (type of white blood cells), low number of neutrophils (type of white blood cells)
• allergic reactions of various severity
• blistering of the skin, mouth, eyes and genitals
• skin more sensitive to sunlight than normal
• feeling nervous
• reduced sense of touch or sensation (hypoesthesia)
• sleepiness or sleeplessness (insomnia)
• poor hearing or ringing in the ears
• heart palpitations, chest pain
• constipation, stomach pain associated with diarrhoea and fever

• inflammation of the liver (hepatitis), changes in liver enzymes
• general loss of strength
• swelling
• general discomfort
• abnormal laboratory test values (e.g. blood or liver tests).

Rare side effects that occur in less than 1 in 1,000 people taking Azithromycin are:
• agitation
• vertigo
• changes in liver function

Other side effects that have been reported, but it is not known how frequently they occur:
• fits or fainting
• aggression or anxiety
• feeling hyperactive
• localised muscle weakness
• loss of smell or altered sense of smell, loss of taste
• tongue discolouration
• inflammation of the pancreas (pancreatitis)
• inflammation of the kidney or kidney failure
• yellowing of the skin or eyes (jaundice) or liver failure (rarely life-threatening)
• bruising or prolonged bleeding after injury
• blistering of the skin, severe skin reaction
• abnormal electrocardiogram (EEG)

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Azithromycin

Keep all medicines out of the sight and reach of children

This medicine does not require any special storage conditions.

Do not take this medicine after the expiry date stamped on the pack after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What Azithromycin contains

The active substance is azithromycin (250mg).

The other ingredients are Microcrystalline cellulose PH 101, Sodium lauryl sulphate, Croscarmellose sodium, Hydroxy propyl cellulos, Colloidal silicon dioxide, Magnesium stearate & Instacoat universal white IC-U-1308.

What Azithromycin looks like and contents of the pack

6 tablets of Azithromycin Tablets USP 250 mg are sealed with PVC/PVdC film on one side and Printed aluminium foil on the other side in the form of a blister pack and 1 such blister pack is further packed in a printed carton along with instructions for use.

Marketing Authorisation Holder

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