1.3

PRODUCT INFORMATION

1.3.1

Summary of Product Characteristics

Enclosed

1. Name of the Medicinal Product

1.1 Product Name: KLARICIN 250

1.2 Generic Name: Azithromycin Tablets USP 250mg

1.3 Strength: 250mg

1.4 Pharmaceutical Dosage Form: Film Coated Tablets

2. Qualitative & Quantitative Composition

Each film coated tablet contains:

Azithromycin USP..... 250mg

Excipients..... q.s.

Colour:(Yellow)Titanium Dioxide

Qualitative –Quantitative formula

Batch Size: 1,00,000 Tablets

Sr. No.	Ingredients	Specification	Rationale	Label Claim (in mg)	Overages (%)	Qty/Per Tablet (in mg, ml)	Qty/ (1,00,000 Tablets) (in kg, ltr)
1.	Azithromycin	USP	Active	250.00	---	250.00	25.000
2.	Maize Starch	BP	Diluent	---	---	110.00	11.000
3.	Dibasic Calcium Phosphate	BP	Diluent	---	---	59.00	5.900
4.	Sodium Lauryl Sulphate	BP	Surfactant	---	---	4.00	0.400
5.	Povidone (PVPK-30)	BP	Binder	---	---	10.00	0.100
6.	Purified Talc	BP	Glidant	---	---	11.00	1.100
7.	Magnesium Stearate	BP	Lubricant	---	---	7.00	0.700
8.	Sodium Starch Glycolate	BP	Disintegrant	---	---	2.00	0.200
9.	Pellcoat White	IHS	Colour	---	---	25.80	2.580
10	Isopropyl Alcohol*	BP	Solvent	---	---	165.10	16.510
11.	Dichloromethane*	BP	Solvent	---	---	411.7	41.17
12.	Purified Water*	BP	Vehicle	---	---	120.0	12.00
			TOTAL			**728.8**	**72.88**

Note: *Not present in final product

3. Pharmaceutical form

Film Coated Tablets

4. Clinical Particulars

4.1 Therapeutic Indications

Azithromycin tablets can be applied for the treatment of the following infections, when caused by microorganisms sensitive to Azithromycin

− 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:

Adults:

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

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

Elderly people:

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

Paediatric population:

Azithromycin tablets should only be administered to children weighing more than 45Kg when normal adult dose should be used. For children under 45kg other pharmaceutical forms of Azithromycin, e.g. suspensions, may be used.

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

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

Method of administration:

Azithromycin Tablets should be given as a single daily dose. The tablets may be taken with food.

4.3 Contraindications

Hypersensitivity to the active substance, erythromycin, any macrolide or ketolide antibiotic, soya lecithin or to any of the excipient.

4.4 Special warning and precautions for use

Hypersensitivity:

As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute 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 symptomsand required a longer period of observation and treatment.

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

Hepatoxicity:

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

In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests / investigations should be performed immediately. Azithromycin administration should be stopped if liver dysfunction has emerged.

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue Azithromycin immediately if signs and symptoms of hepatitis occur.

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 caregivers should be informed to contact their physician if vomiting or irritability with feeding occurs.

Pseudomembranous colitis:

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

Ergot derivatives:

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

Cross resistance:

Cross-resistance exists between Azithromycin and other macrolides (erythromycin, clarithromycin, roxithromycin), lincosamides and streptogramin B (MLSB phenotype). Concomitant use of several medicinal products from the same or related group of antibacterial agents is not recommended.

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 arrhytmias (including torsade de pointes) which can lead to cardiac arrest, Azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients:

- With congenital or documented QT prolongation.
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of class IA (quinidine and procainamide) and class III (dofetilide, amiodarone and sotalol), cisapride and terfenadine; antipsychotic agents such as pimozide; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin.
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

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

Clostridoides difficile associated diarrhoea

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

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

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.

The following should be considered before prescribing Azithromycin:

Serious infections:

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

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

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

As for other macrolides, high resistance rates of Streptococcus pneumoniae (>30%) have been reported for Azithromycin in some European countries (see section 5.1). This should be taken into account when treating infections caused by Streptococcus pneumoniae.

Pharyngitis/ tonsillitis:

Azithromycin is not the substance of first choice for the treatment of pharyngitis and tonsillitis caused by Streptococcus pyogenes. For this and for the prophylaxis of acute rheumatic fever penicillin is the treatment of first choice.

Sinusitis:

Often, Azithromycin is not the substance of first choice for the treatment of sinusitis.

Acute otitis media:

Often, Azithromycin is not the substance of first choice for the treatment of acute otitis media.

Skin and soft tissue infections:

The main causative agent of soft tissue infections, Staphylococcus aureus, is frequently resistant to Azithromycin. Therefore, susceptibility testing is considered a precondition for treatment of soft tissue infections with Azithromycin.

Infected burn wounds:

Azithromycin is not indicated for the treatment of infected burn wounds.

Sexually transmitted disease:

In case of sexually transmitted diseases a concomitant infection by T. palladium should be excluded.

Neurological or psychiatric diseases:

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

Superinfection:

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

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).

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

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

4.5 Interaction with other medicinal products and other forms of interactions

Effects of other medicinal products on Azithromycin:

Antacids:

In a pharmacokinetic study investigating the effects of simultaneous administration of antacids and azithromycin, no effect on overall bioavailability was seen, although the peak serum concentrations were reduced by approximately 24%. In patients receiving both azithromycin and antacids, the medicinal products should not be taken simultaneously. Azithromycin must be takenat least 1 hour before or 2 hours after the antacids.

Co-administration of azithromycin prolonged-release granules for oral suspension with a single 20ml dose of co-magaldrox (aluminium hydroxide and magnesium hydroxide) did not affect the rate and extent of azithromycin absorption.

Efavirenz:

Co-administration of a 600mg single dose of azithromycin and 400mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions.

Fluconazole:

Co-administration of a single dose of 1,200mg azithromycin did not alter the pharmacokinetics of a single dose of 800mg fluconazole. Total exposure and half-life of azithromycin were unchanged by the co-administration of fluconazole, however, a clinically insignificant decrease in Cmax (18%) of azithromycin was observed.

Nelfinavir:

Co-administration of azithromycin (1,200mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment is required.

Rifabutin:

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

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

Terfenadine:

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

Cimetidine:

In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.

Effect of Azithromycin on other medicinal products:

Ergot derivatives:

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

Digoxin and colchicine (P-gp substrates):

Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-gp substrates such as digoxin are

administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered.

Coumarin-Type Oral Anticoagulants:

In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15-mg dose of warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to co- administration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoringprothrombin 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 co-administration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Theophylline:

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

Trimethoprim/sulfamethoxazole:

Co-administration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with azithromycin 1,200 mg on Day 7 had no significant effect on peak concentrations total exposure or urinary excretion of either trimethoprim or sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies.

Zidovudine:

Single 1,000 mg doses and multiple 1,200 mg or 600 mg doses of azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated

zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients.

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

Astemizole, alfentanil:

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

Atorvastatin:

Co-administration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase inhibition assay).

However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.

Carbamazepine:

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

Cisapride:

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

Cetirizine:

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

Didanosins (Dideoxyinosine):

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

Efavirenz:

Co-administration of a 600 mg single dose of azithromycin and 400 mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions.

Indinavir:

Co-administration of a single dose of 1,200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

Methylprednisolone:

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

Midazolam:

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

Sildenafil:

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

Triazolam:

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

Medicinal products known to prolong the QT interval

Azithromycin should not be used co-administered with other medicinal products, known to prolong the QT interval (see section 4.4).

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.

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 pharmacokineticsof 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 machine

There is no evidence to suggest that azithromycin may have an effect: on a patient's ability to drive or operate machinery. Visual impairment and vision blurred may have an effect on a patient's ability to drive or operate machinery (section 4.8).

4.8 Undesirable effects

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

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

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Uncommon	Candidiasis Vaginal infection Pneumonia Fungal infection Bacterial infection Pharyngitis Gastroenteritis Respiratory disorder Rhinitis Oral candidiasis
	Not known	*Pseudomembranous colitis* (see section 4.4)
Blood and lymphatic system disorders	Uncommon	Leukopenia Neutropenia Eosinophilia
	Not known	Thrombocytopenia Haemolytic anaemia
Immune system disorders	Uncommon	Angioedema Hypersensitivity
	Not known	*Anaphylactic reaction* (see section 4.4)
Metabolism and nutrition disorders	Uncommon	Anorexia
Psychiatric disorders	Uncommon	Nervousness Insomnia
	Rare	Agitation Depersonalisation
	Not known	*Aggression* *Anxiety*

		Delirium Hallucination
Nervous system disorders	Common	Headache
	Uncommon	Dizziness Somnolence Dysgeusia Paraesthesia
	Not known	*Syncope, convulsion* Hypoaesthesia *Psychomotor hyperactivity* *Anosmia* *Ageusia* *Parosmia* *Myasthenia gravis* (see section 4.4).
Eye disorders	Uncommon	Visual impairment
Ear and labyrinth disorders	Uncommon	Ear disorder Vertigo
	Not known	Hearing impairment including deafness and/or tinnitus
Cardiac disorders	Uncommon	Palpitations
	Not known	*Torsades de pointes* (see section 4.4) *Arrhythmia* (see section 4.4) *including ventricular tachycardia* *Electrocardiogram QT prolonged*
Vascular disorders	Uncommon	Hot flush
	Not known	*Hypotension*
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea Epistaxis
Gastrointestinal disorders	Very common	Diarrhoea
	Common	Vomiting Abdominal pain

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		Nausea
	Uncommon	Constipation Flatulence Dyspepsia Gastritis Dysphagia Abdominal distension Dry mouth Eructation Mouth ulceration Salivary hypersecretion
	Not known	*Pancreatitis* *Tongue discolouration*
Hepatobiliary disorders	Uncommon	Hepatitis
	Rare	Hepatic function abnormal Jaundice cholestatic
	Not known	*Hepatic failure* (which has rarely resulted in death) (see section 4.4)* *Hepatitis fulminant* *Hepatic necrosis*
Skin and subcutaneous tissue disorders	Uncommon	Rash Pruritus Urticaria Dermatitis Dry skin Hyperhidrosis
	Rare	Photosensitivity reaction
	Not known	Steven-Johnson syndrome *Toxic epidermal necrolysis* *Erythema multiforme*
Musculoskeletal and	Uncommon	Osteoarthritis

connective tissue disorders		Myalgia Back pain Neck pain
	Not known	Arthralgia
Renal and urinary disorders	Uncommon	Dysuria Renal pain
	Not known	Renal failure acute Nephritis interstitial
Reproductive system and breast disorders	Uncommon	Metrorrhagia Testicular disorder
General disorders and administration site conditions	Uncommon	Oedema Asthenia Malaise Fatigue Face oedema Chest pain Pyrexia Pain Peripheral oedema
Investigations	Common	Lymphocyte count decreased Eosinophil count increased Blood bicarbonate decreased Basophils increased Monocytes increased Neutrophils increased
	Uncommon	Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubine 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	Uncommon	Post procedural complication

* Which has rarely resulted in death

Adverse reactions possibly or probably related to Mycobacterium Avium Complex prophylaxis and treatment based on clinical trial experience and post-marketing surveillance. These adverse reactions differ from those reported with immediate release or the prolonged release formulations, either in kind or in frequency:

System Organ Class	Frequency	Adverse reaction
Metabolism and nutrition disorders	Common	Anorexia
Nervous system disorders	Common	Dizziness Headache Paraesthesia Dysgeusia
	Uncommon	Hypoaesthesia
Eye disorders	Common	Visual impairment
Ear and labyrinth disorders	Common	Deafness
	Uncommon	Hearing impaired Tinnitus
Cardiac disorders	Uncommon	Palpitations
Gastrointestinal disorders	Very common	Diarrhoea Abdominal pain Nausea

		Flatulence Abdominal discomfort Loose stools
Hepatobiliary disorders	Uncommon	Hepatitis
Skin and subcutaneous tissue disorders	Common	Rash Pruritus
	Uncommon	Steven-Johnson syndrome Photosensitivity reaction
Musculoskeletal and connective tissue disorders	Common	Arthralgia
General disorders and administration site conditions	Common	Fatigue
	Uncommon	Asthenia Malaise

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 Pharmacodynamics properties

General properties

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

Mode of action:

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

PK/PD relationship:

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

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.

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 Pharmacokinetc properties

Absorption:

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

Distribution:

Kinetic studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the active substance is heavily tissue bound (steady state distribution volume of approximately 31 l/kg). Concentrations intarget tissues such as lung, tonsil, and prostate exceed the MIC90 for likely pathogens after a singledose of 500 mg.

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

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

Excretion:

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

The identified metabolites (formed by N- and O- demethylising, by hydroxylising of the desosamine and aglycone rings, and by the splitting of the cladinose conjugate) are microbiologically inactive.

After a 5 day treatment slightly higher (29%) AUC values were seen in the elderly volunteers (>65 years of age) compared to the younger volunteers (< 45 years of age). However these differences are not regarded as clinically relevant; therefore a dose adjustment is not recommended.

Pharmacokinetics in special populations:

Renal insufficiency:

Following a single oral dose of azithromycin 1 g, mean 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 > 80 ml/min). In subjects with

severe renal impairment, the mean Cmax and AUC0-120 increased 61% and 33% respectively compared to normal.

Hepatic insufficiency:

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

Elderly:

The pharmacokinetics of azithromycin in elderly men was similar to that of young adults; however, in elderly women, although higher peak concentrations (increased by 30-50%) were observed, no significant accumulation occurred.

Infants, toddlers, children and adolescents:

Pharmacokinetics have been studied in children aged 4 months – 15 years taking capsules, granules or suspension.. At 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5, the Cmax achieved is slightly lower than adults with 224 ug/l in children aged 0.6-5 years and after 3 days dosing and 383 ug/l in those aged 6-15 years. The t1/2 of 36 h in the older children was within the expected range for adults.

5.3 Preclinic Safety data

In high-dose animal studies, giving active substance concentrations 40 fold higher than those expected in clinical practice, azithromycin has been noted to cause reversible phospholipidosis, generally without discernible toxicological consequences. There is no evidence that this is of relevance to the normal use of azithromycin in humans.

Carcinogenic potential:

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

Mutagenic potential:

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

Reproductive toxicity:

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

6. Pharmaceutical Particulars

6.1 List of Excipients

Maize Starch

Dibasic Calcium Phosphate

Sodium Lauryl Sulphate

Povidone (PVPK-30)

Purified Talc

Magnesium Stearate

Sodium Starch Glycolate

Pellcoat white

Isopropyl Alcohol

Dichloromethane

Purified Water

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 Months

6.4 Special Precautions for storage

Store below 30°C, in a dry place, protected from light & moisture.

6.5 Nature and content of container

3 Tablets packed in Alu-PVC Blister & Single blister to be packed in a carton.

7. Authorization Holder

NORRIS MEDICINES LIMITED.
Plot No. 901/4-5, GIDC Estate,
Ankleshwar 393002. Gujarat, INDIA.
Tel.: (02646) 223462, 227530
Fax: 0091-2646-250126
E mail: njpatelnoris@yahoo.comc Website:
www.norrismedicines.com

8. Marketing Authorization Number

CIFAX EXIM LIMITED

9. Date of first authorization/ renewal of the authorization

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10. Date of Revision of the text

April 2022

Klaricn

Azithromycin Oral Suspension

Azithromycin For Oral Suspension USP 200mg

COMPOSITION:

Each bottle contains:

1) Azithromycin For Oral Suspension USP 200mg/5ml
Each 5ml (A Measurement) contains:
Azithromycin (Anhydrous) USP ... 200mg

MECHANISM OF ACTION: Azithromycin is an analogue or subclass of the macrolides. It retains the spectrum of activity of erythromycin against gram-positive and Gram-negative pathogens and has increased activity against many Gram-negative and atypical strains. It has greater acid stability than erythromycin. It acts by suppressing bacterial protein synthesis by binding to the 23S ribosomal subunit.

INDICATIONS: Indicated in pediatric patients for treatment of the following:

Acute otitis media caused by *Haemophilus influenzae, Moraxella catarrhalis* or *Streptococcus pneumoniae*.

Community- acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae* or *Streptococcus pneumoniae* in patients for Oral therapy.

Pharyngitis/tonsillitis caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy.

CONTRAINDICATIONS: is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin or any macrolide antibiotic.

DOSAGE: Routes For Oral Administration

Pediatric Dose

Acute Otitis media and community- Acquired Pneumonia: The recommended dose of Azithromycin For Oral Suspension for the treatment of children with acute otitis media and community-acquired pneumonia is 10 mg/kg as a single dose on the first day (not to exceed 500mg/day) followed by 5mg/kg on days 2 through 5 (not to exceed 250mg/day).

WARNING: Caution should be exercised when azithromycin is administered to patient with impaired renal & hepatic function, with prolonged QT interval & with previous history of arrhythmias. Patients should be cautioned to take Azithromycin oral suspension at least one hour prior to a meal or at least two hours after a meal. These medications should not be taken with food. The patient should be directed to discontinue azithromycin immediately and contact a physician if any signs of an allergic reaction occur.

PRECAUTION: General: Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patient with impaired hepatic function. There are no data regarding azithromycin usage in patients with renal impairment, thus caution should events have not been reported when prescribing azithromycin in these patient. The following adverse events have not been reported with macrolide products: ventricular arrhythmias including ventricular tachycardia and torsades de pointes. In individuals with prolonged QT intervals.

There has been a spontaneous report from the post-marketing experience of a patient with previous history of arrhythmia who experienced torsades de pointes and subsequent myocardial infarction following a course of azithromycin therapy.

Information for patients: patient should be cautioned to take Azithromycin oral suspension at least an hour prior to a meal or at least two hours after a meal. These medications should not be taken with food. Patients should also be cautioned not to take aluminum and magnesium containing antacids and azithromycin simultaneously.

The patient should be directed to discontinue azithromycin immediately and contact a physician if any signs of an allergic reaction occur. Teratogenic Effects: Pregnancy Category.

Reproduction studies have been performed in rats and mice at doses up to approximately maternally toxic dose levels (i.e. 250mg/kg/day). These doses, based on a mg/m² basis, are equivalent to the 4 and 2 times, respectively, the human daily dose of 500 mg. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnancy women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

Pediatric Use

Acute Otitis Media (dosage regimen: 10mg/kg on day 1 followed by 5 mg/kg on Days 2-5): Safety and effectiveness in the treatment of children with middle ear fluid under 6 months of age have not been established.

Community-Acquired Pneumonia (dosage regimen: 10mg/kg on Day 1 followed by 5 mg/kg on Day 2-5): Safety and effectiveness in the treatment of children with community-acquired pneumonia under 6 months of age have not been established. Safety and effectiveness for pneumonia due to *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* were documented in pediatric clinical trials. Safety and effectiveness for pneumonia due to *Haemophilus influenzae* and *Streptococcus pneumoniae* were not documented bacteriologically in the pediatric clinical trial due to difficulty in obtaining specimens. Use of azithromycin for these two microorganisms is supported, however, by evidence from adequate and well controlled studies in adults. Pharyngitis/Tonsillitis (Dosage Regimen: 12 mg/kg on Days 1-5): Safety and effectiveness in the treatment of children with Pharyngitis/Tonsillitis (dosage regimen: 12mg/kg on Days 1-5) Safety and effectiveness in the treatment of children with pharyngitis/tonsillitis under 2 years of age has not been established. Studies evaluating the use of repeated courses of therapy have not been conducted.

SIDE EFFECTS: Some of the commonly observed side effect associated with the use of Azithromycin Oral Suspension are Nausea, vomiting, abdominal pain, diarrhoea, dyspepsia, flatulence, dizziness, headaches, vertigo. Potentially serious side effects of angioedema and cholestatic jaundice were reported rarely.

DRUG INTERACTIONS: Aluminum and magnesium containing antacids reduce the peak serum levels (rate) but not the AUC (extent) of azithromycin absorption.

Macrolides and theophylline: increases in the serum concentration of theophylline.

Warfarin: Increases anticoagulant effects.

Digoxin-elevated digoxin levels.

Ergotamine or dihydroergocarnine- acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia. Triazolam: decrease the clearance of triazolam and thereby increase the pharmacologic effect of triazolam.

Drugs metabolized by the cytochrome P 450 system –elevations of serum carbamazepine, terfenadine, cyclosporine, hexobarbital and phenytoin levels.

OVERDOSAGE: Emesis, Gastric lavage, administration activated charcoal. General supportive and symptomatic treatment. Dialysis is of no help.

Keep all medicine out of reach of children.

STORAGE: Store in a cool place below 30°C.

Protected from light and keep away from children.

Presentation: Bottle pack of 30ml.

NAFDAC. REG. NO:

Manufactured by India by:
NOAHS MEDICINES LIMITED
Plot No. 803/P & 923/4-5, Gidc Estate
Ankleshwar 393002(GUJ) INDIA.

Marketed By:
Cilas Farm Limited
20, Medal Street, Ikeja
Lagos, NIGERIA.

Exported by:
SYNERCARE
Mumbai-India
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