1. NAME OF THE MEDICINAL PRODUCT

KRISHAT AZITHROMYCIN CAPLET 500MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated caplet contains:
Azithromycin Dihydrate
Eq. to Azithromycin USP ----------500mg.
Excipients----------Q.S
Colour: Approved colour

Excipients with known effect:
Maize Starch, Microcrystalline Cellulose, Sodium Starch Glycolate, P.V.P.K 30, Methyl Paraben, Propyl Paraben, Magnesium Stearate, Purified Talc, Colloidal Silicon Dioxide (Aerosil), Cross Carmelose Sodium, Iso-Propyl Alcohol, Hydroxy Propyl Methyl Cellulose. Protec tab white & Methylene Dichloride
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Caplet
White coloured, oblong shape, film coated caplet embossed with a single line

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Azithromycin is a macrolide antibacterial drug indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below. Recommended dosages and durations of therapy in adult and pediatric patient populations vary in these indications.

Adult Patients

Acute bacterial exacerbations of chronic bronchitis due to Haemophilus influenzae, Moraxella catarrhalis, or Streptococcus pneumoniae
Acute bacterial sinusitis due to Haemophilus influenzae, Moraxella catarrhalis. or Streptococcus pneumoniae
Community-acquired pneumonia due to Chlamydophila pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, or Streptococcus pneumoniae in patients appropriate for oral therapy
Pharyngitis/tonsillitis caused by Streptococcus pyogenes as an alternative to first-line therapy in individuals who cannot use first-line therapy.
Uncomplicated skin and skin structure infections due to Staphylococcus aureus, Streptococcus pyogenes, or Streptococcus agalactiae.
Urethritis and cervicitis due to Chlamydia trachomatis or Neisseria gonorrhoeae
Genital ulcer disease in men due to Haemophilus ducreyi (chancroid). Due to the small number of women included in clinical trials, the efficacy of azithromycin in the treatment of chancroid in women has not been established.

Pediatric Patients

Acute otitis media (>6 months of age) caused by Haemophilus influenzae, Moraxella catarrhalis, or Streptococcus pneumoniae. Community-acquired pneumonia (>6 months of age) due to Chlamydophila pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, or Streptococcus pneumoniae in patients appropriate for oral therapy
Pharyngitis/tonsillitis (>2 years of age) caused by Streptococcus pyogenes as an alternative to first-

line therapy in individuals who cannot use first-line therapy.

4.2 Posology and method of administration

Posology

Adults

For both hypertension and angina the usual initial dose is 5 mg Amlodipine once daily which may be increased to a maximum dose of 10 mg depending on the individual patient's response. In hypertensive patients, Amlodipine has been used in combination with a thiazide diuretic, alpha blocker, beta blocker, or an angiotensin converting enzyme inhibitor. For angina, Amlodipine may be used as mono therapy or in combination with other anti anginal medicinal products in patients with angina that is refractory to nitrates and/or to adequate doses of beta blockers.

No dose adjustment of Amlodipine is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

Special populations

Elderly patients

Amlodipine used at similar doses in elderly or younger patients is equally well tolerated. Normal dosage regimens are recommended in the elderly, but increase of the dosage should take place with care (see sections 4.4 and 5.2).

Patients with hepatic impairment

Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore dose selection should be cautious and should start at the lower end of the dosing range (see sections 4.4 and 5.2). The pharmacokinetics of amlodipine has not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

Patients with renal impairment

Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.

Paediatric population

Children and adolescents with hypertension from 6 years to 17 years of age

The recommended antihypertensive oral dose in paediatric patient’s ages 6-17 years is 2.5 mg once daily as a starting dose, up-titrated to 5 mg once daily if blood pressure goal is not achieved after 4 weeks. Doses in excess of 5 mg daily have not been studied in paediatric patients (see sections 5.1 and 5.2).

Method of administration

Tablet for oral administration

4.3 Contraindications

Hypersensitivity

Azithromycin is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide drug.

Hepatic Dysfunction

Azithromycin is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin.

4.4 Special warnings and precautions for use

Hypersensitivity

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported in patients on azithromycin therapy.

Fatalities have been reported. Cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is presently unknown. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that allergic symptoms may reappear when symptomatic therapy has been discontinued.

Hepatotoxicity

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), IHPS has been reported. Direct parents and caregivers to contact their physician if vomiting or irritability with feeding occurs.

QT Prolongation

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen with treatment with macrolides, including azithromycin. Cases of torsades de pointes have been spontaneously reported during postmarketting surveillance in patients receiving azithromycin. Providers should consider the risk of QT prolongation which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including:

Patients with known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmia or uncompensated heart failure

Patients on drugs known to prolong the QT interval

Patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesaemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents.

Elderly patients may be more susceptible to drug-associated effects on the QT interval.

Clostridium difficile-Associated Diarrhea (CDAD)

Clostridium difficile-associated diarrhea has been reported with use of nearly all antibacterial agents, including AZITHROMYCIN, and may range in severity from mild diarrhea 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 antibacterial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

Exacerbation of Myasthenia Gravis

Exacerbation of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving azithromycin therapy.

Use in Sexually Transmitted Infections

Azithromycin, at the recommended dose, should not be relied upon to treat syphilis. Antibacterial agents used to treat non-gonococcal urethritis may mask or delay the symptoms of incubating syphilis. All patients with sexually transmitted urethritis or cervicitis should have a serologic test for syphilis and appropriate testing for gonorrhoeae performed at the time of diagnosis. Appropriate antibacterial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

Development of Drug-Resistant Bacteria

Prescribing Azithromycin in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Excipients

This medicinal product contains lactose. 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

Nelfinavir

Co-administration of nelfinavir at steady-state with a single oral dose of azithromycin resulted in increased azithromycin serum concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nelfinavir, close monitoring for known adverse reactions of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted.

Warfarin

Spontaneous post marketing reports suggest that concomitant administration of azithromycin may potentiate the effects of oral anticoagulants such as warfarin, although the prothrombin time was not affected in the dedicated drug interaction study with azithromycin and warfarin. Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants concomitantly.

Potential Drug-Drug Interaction with Macrolides

Interactions with digoxin, colchicine or phenytoin have not been reported in clinical trials with azithromycin. No specific drug interaction studies have been performed to evaluate potential drug-drug interaction. However, drug interactions have been observed with other macrolide products. Until further data are developed regarding drug interactions when digoxin, colchicine or phenytoin are used with azithromycin careful monitoring of patients is advised.

4.6 Pregnancy and Lactation

Pregnancy

Available data from published observational studies, case series, and case reports over several decades do not suggest an increased risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes with azithromycin use in pregnant women. Limitations of these data include the lack of randomization and inability to control for confounders such as underlying maternal disease and maternal use of concomitant medications.

Lactation

Azithromycin is present in human milk. Non-serious adverse reactions have been reported in breastfed infants after maternal administration of azithromycin. There are no available data on the effects of azithromycin on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Azithromycin and any potential adverse effects on the breastfed infant from Azithromycin or from the underlying maternal condition.

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

Adults

Multiple-dose regimens: Overall, the most common treatment-related adverse reactions in adult patients receiving multiple-dose regimens of Azithromycin were related to the gastrointestinal system with diarrhea/loose stools (4 to 5%), nausea (3%), and abdominal pain (2 to 3%) being the most frequently reported.

No other adverse reactions occurred in patients on the multiple-dose regimens of Azithromycin with a frequency greater than 1%. Adverse reactions that occurred with a frequency of 1% or less included the following:

Cardiovascular: Palpitations, chest pain.

Gastrointestinal: Dyspepsia, flatulence, vomiting, melena, and cholestatic jaundice.

Genitourinary: Monilia, vaginitis, and nephritis.

Nervous System: Dizziness, headache, vertigo, and somnolence.

General: Fatigue.

Allergic: Rash, pruritus, photosensitivity, and angioedema.

Single 1gram dose regimen:

Overall, the most common adverse reactions in patients receiving a single-dose regimen of 1 gram of Azithromycin were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.

Adverse reactions that occurred in patients on the

single 1-gram dosing regimen of Azithromycin with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), dyspepsia (1%), and vaginitis (1%).

Single 2-gram dose regimen:

Overall, the most common adverse reactions in patients receiving a single 2-gram dose of Azithromycin were related to the gastrointestinal system. Adverse reactions that occurred in patients in this study with a frequency of 1% or greater included nausea (18%), diarrhea/loose stools (14%), vomiting (7%), abdominal pain (7%), vaginitis (2%), dyspepsia (1%), and dizziness (1%). The majority of these complaints were mild in nature.

Pediatric Patients.

Single and Multiple-dose regimens: The types of adverse reactions in pediatric patients were comparable to those seen in adults, with different incidence rates for the dosage regimens recommended in pediatric patients.

Acute Otitis Media: For the recommended total dosage regimen of 30 mg/kg, the most frequent adverse reactions (≥1%) attributed to treatment were diarrhea, abdominal pain, vomiting, nausea, and rash.

Postmarketting Experience

The following adverse reactions have been identified during post-approval use of azithromycin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions reported with azithromycin during the postmarketting period in adult and/or pediatric patients for which a causal relationship may not be established include:

Allergic: Arthralgia, edema, urticaria, and angioedema.

Cardiovascular: Arrhythmias including ventricular tachycardia and hypotension. There have been reports of QT prolongation and torsades de pointes.

Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea, pseudomembranous colitis, pancreatitis, oral candidiasis, pyloric stenosis, and reports of tongue discoloration.

General: Asthenia, paresthesia, fatigue, malaise, and anaphylaxis.

Genitourinary: Interstitial nephritis and acute renal failure and vaginitis.

Hematopoietic: Thrombocytopenia.

Liver/Biliary: Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure.

Nervous System: Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, agitation, and syncope.

Psychiatric: Aggressive reaction and anxiety. Skin/Appendages: Pruritus serious skin reactions including erythema multiforme, AGEP, Stevens - Johnson syndrome, toxic epidermal necrolysis, and DRESS.

Special Senses: Hearing disturbances including hearing loss, deafness and/or tinnitus, and reports of taste/smell perversion and/or loss.

4.9 Overdose

Adverse reactions experienced at higher than recommended doses were similar to those seen at normal doses particularly nausea, diarrhea, and vomiting. In the event of over dosage, general symptomatic and supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Mechanism of Action

Azithromycin acts by binding to the 23S rRNA of the 50S ribosomal subunit of susceptible microorganisms inhibiting bacterial protein synthesis and impeding the assembly of the 50S ribosomal subunit.

Resistance

Azithromycin demonstrates cross resistance with erythromycin. The most frequently encountered mechanism of resistance to azithromycin is modification of the 23S rRNA target, most often by methylation. Ribosomal modifications can determine cross resistance to other macrolides, lincosamides, and streptogramin B (MLSB phenotype).

Antimicrobial Activity

Azithromycin has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections.

Gram-Positive Bacteria

Staphylococcus aureus

Streptococcus agalactiae

Streptococcus pneumoniae

Streptococcus pyogenes

Gram-Negative Bacteria

Haemophilus ducreyi

Haemophilus influenzae

Moraxella catarrhalis

Neisseria gonorrhoeae

Other Bacteria

Chlamydophila pneumoniae

Chlamydia trachomatis

Mycoplasma pneumoniae

The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for azithromycin against isolates of similar genus or organism group. However, the efficacy of azithromycin in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-Positive Bacteria

Beta-hemolytic streptococci (Groups C, F, G)

Viridans group streptococci

Gram-Negative Bacteria

Bordetella pertussis

Legionella pneumophila

Anaerobic Bacteria

Prevotella bivia

Peptostreptococcus species

Other Bacteria

Ureaplasma urealyticum

5.2 Pharmacokinetic properties

Absorption

In a two-way crossover study in which 12 healthy subjects received a single 500 mg dose of azithromycin (two 250 mg tablets) with or without a high fat meal, food was shown to increase Cmax by 23% but had no effect on AUC.

When azithromycin oral suspension was administered with food to 28 adult healthy male subjects, Cmax increased by 56% and AUC was unchanged.

Distribution

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 mcg/mL to 7% at 2 mcg/mL.

The antibacterial activity of azithromycin is pH related and appears to be reduced with decreasing pH; However, the extensive distribution of drug to tissues may be relevant to clinical activity.

Azithromycin has been shown to penetrate into human tissues, including skin, lung, tonsil, and cervix. Extensive tissue distribution was confirmed by examination of additional tissues and fluids (bone, ejaculum, prostate, ovary, uterus, salpinx, stomach, liver, and gallbladder). As there are no data from adequate and well-controlled studies of azithromycin treatment of infections in these additional body sites, the clinical significance of these tissue concentration data is unknown.

Following a regimen of 500 mg on the first day and 250 mg daily for 4 days, very low concentrations were noted in cerebrospinal fluid (less than 0.01 mcg/mL) in the presence of noninflamed meninges.

Metabolism

In vitro and in vivo studies to assess the metabolism of azithromycin have not been performed.

Elimination

Plasma concentrations of azithromycin following single 500 mg oral and IV doses declined in a polyphasic pattern resulting in a mean apparent plasma clearance of 630 mL/min and terminal elimination half-life of 68 hr. The prolonged terminal half-life is thought to be due to extensive uptake and subsequent release of drug from tissues. Biliary excretion of azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

Specific Populations

Patients with Renal Impairment

Azithromycin pharmacokinetics was investigated in 42 adults (21 to 85 years of age) with varying degrees of renal impairment. Following the oral administration of a single 1.0 g dose of azithromycin (4 × 250 mg capsules), mean Cmax and AUC0–120 increased by 5.1% and 4.2%, respectively, in subjects with mild to moderate renal impairment (GFR 10 to 80 mL/min) compared to subjects with normal renal function (GFR >80 mL/min). The mean Cmax and AUC0–120 increased 61% and 35%, respectively, in subjects with severe renal impairment (GFR <10 mL/min) compared to subjects with normal renal function (GFR >80 mL/min).

Patients with Hepatic Impairment

The pharmacokinetics of azithromycin in subjects with hepatic impairment has not been established. Male and Female Patients

There are no significant differences in the disposition of azithromycin between male and female subjects. No dosage adjustment is recommended based on gender.

Geriatric Patients

Pharmacokinetic parameters in older volunteers (65 to 85 years old) were similar to those in young adults (18 to 40 years old) for the 5-day therapeutic regimen. Dosage adjustment does not appear to be

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay. In fertility studies conducted in male and female rats, oral administration of azithromycin for 64 to 66 days (males) or 15 days (females) prior to and during cohabitation resulted in decreased pregnancy rate at 20 and 30 mg/kg/day when both males and females were treated with azithromycin. This minimal effect on pregnancy rate (approximately 12% reduction compared to concurrent controls) did not become more pronounced when the dose was increased from 20 to 30 mg/kg/day (approximately 0.4 to 0.6 times the adult daily dose of 500 mg based on body surface area) and it was not observed when only one animal in the mated pair was treated. There were no effects on any other reproductive parameters, and there were no effects on fertility at 10 mg/kg/day. The relevance of these findings to patients being treated with azithromycin at the doses and durations recommended in the prescribing information is uncertain.

Animal Toxicology and/or Pharmacology

Phospholipidosis (intracellular phospholipid accumulation) has been observed in some tissues of mice, rats, and dogs given multiple doses of azithromycin. It has been demonstrated in numerous organ systems (e.g., eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and/or pancreas) in dogs and rats treated with azithromycin at doses which, expressed on the basis of body surface area, are similar to or less than the highest recommended adult human dose. This effect has been shown to be reversible after cessation of azithromycin treatment. Based on the pharmacokinetic data, phospholipidosis has been seen in the rat (50 mg/kg/day dose) at the observed maximal plasma concentration of 1.3 mcg/mL (1.6 times the observed Cmax of 0.821 mcg/mL at the adult dose of 2 g). Similarly, it has been shown in the dog (10 mg/kg/day dose) at the observed maximal serum concentration of 1 mcg/mL (1.2 times the observed Cmax of 0.821 mcg/mL at the adult dose of 2 g). Phospholipidosis was also observed in neonatal rats dosed for 18 days at 30 mg/kg/day, which is less than the pediatric dose of 60 mg/kg based on the surface area. It was not observed in neonatal rats treated for 10 days at 40 mg/kg/day with mean maximal serum concentrations of 1.86 mcg/mL, approximately 1.5 times the Cmax of 1.27 mcg/mL at the pediatric dose. Phospholipidosis has been observed in neonatal dogs (10 mg/kg/day) at maximum mean whole blood concentrations of 3.54 mcg/mL, approximately 3 times the pediatric dose Cmax. The significance of these findings for animals and for humans is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch, Microcrystalline Cellulose, Sodium Starch Glycolate, P.V.P.K 30, Methyl Paraben, Propyl Paraben, Magnesium Stearate, Purified Talc, Colloidal Silicon Dioxide (Aerosil), Cross Carmelose Sodium, Iso-Propyl Alcohol, Hydroxy Propyl Methyl Cellulose. Protec tab white & Methylene Dichloride

6.2 Incompatibilities

Not Known

6.3 Shelf-life

Blisters: 36 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

The tablets are packed in Alu/Alu blister and inserted in a mono carton.10 Mono carton packed in one outer carton. Pack sizes: 10x10 Captab

6.6 Special precautions for disposal and other handling

No special requirements

7.0 Manufactured by:

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