1.3 Product Information

1.3.1 Summary of Product Characteristics

1. Name of the medicinal product

Azithromycin film-coated tablets 500mg

2. Qualitative and quantitative composition

Each film-coated tablet contains 500 mg azithromycin.

3. Pharmaceutical form

Film-coated tablet.

4. Clinical particulars

4.1 Therapeutic indications

Approved Indication (CPR): For the treatment of infections from respiratory pathogens (e.g. S. pyogenes, S. pneumonia, M. catarrhalis, C. trachomatis, Legionella sp, Mycoplasma pneumonia, S. aureus, and H. influenza). Treatment of C. pneumoniae and M. avium infection, uncomplicated chlamydial urethritis, cervicitis or pharyngitis. An alternative drug for multi-drug resistant Salmonella typhi infection outside the CNS.

4.2 Posology and method of administration

Oral azithromycin should be administered as a single daily dose. The period of dosing with regard to infection is given below.

Azithromycin tablets can be taken with or without food.

In Adults- For the treatment of sexually transmitted diseases caused by Chlamydia trachomatis, Haemophilus ducreyi, or susceptible Neisseria gonorrhea, the dose is 1000 mg as a single oral dose.

For prophylaxis_ against MAC infections in patients infected with the human immunodeficiency virus (HIV), the dose is 1200 mg once per week.

For the treatment of Disseminated MAC (DMACL infections in patients with advanced HIV infections, the recommended dose is 600 mg once a day. Azithromycin should be administered in combination with other antimycobacterial agents that have shown in vitro activity against MAC, such as ethambutol at the approved dose.

For all other indications, the total dosage of 1500 mg should be given as 500 mg daily for 3 days. As an alternative, the same total dose can be given over 5 days with 50 mg given on day 1, then 250 mg daily on days 2 to 5.

The maximum recommended total dose for any treatment is 1500 mg for children.

Azithromycin tablets should only be administered to children weighing more than 45 kg.

In the Elderly: The same dosage as in adult patients used in the elderly.

4.3 Contraindications

The use of this product is contraindicated in patients with hypersensitivity to azithromycin, erythromycin or ketolide antibiotic.

4.4 Special warnings and precautions for use

As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema 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 liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease.

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 ergot and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be coadministered.

As with any antibiotic preparation, observation for signs of super infection with non-susceptible organism, including fungi is recommended.

Clostridium difficile associated diarrhea (CDAD) have been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild to diarhea 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 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. In patients with severe renal impairment (GFR<10ml/min) a 33% increase in systematic exposure to azithromycin was observed.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids: In pharmacokinetic study investigating the effects of simultaneous administration of antacid with azithromycin, no effects on overall bioavailability was seen although peek serum concentrations were reduce by up to 30%. In patients receive both azithromycin and antacids, the drugs should not be taken simultaneously.

Cetirizine

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

Didanosine

Coadministration of macrolide 1200 mg/day azithromycin with 400 mg/day didanosine in HIV-positive subjects did not appear to affect the steady-state pharmacokinetic of didanosine as compared with placebo.

Digoxin:

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

Zidovudine:

Single 1000 mg doses and multiple 1200 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.

Ergot:

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 medicinal products known to undergo significant cytochrome P450 mediated metabolism.

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).

Carbamazepine

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

Cimetidine:

In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of 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 coumarin type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

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.

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 Pregnancy and lactation

Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if deary needed.

There are no data on secretion in breast milk. AS many drugs are excreted in human milk, azithromycin should not be used in the treatment of lactating woman unless the physcian feels that the potential benefits justify the potential risk to the infant.

4.7 Effects on ability to drive and use machines

There is no evidence to suggest that azithromycin may have an effect on a patient's ability to drive or operate machinery.

4.8 Undesirable effects

Azithromycin is well tolerated with low incidence of side effects. In clinical trials, the following undesirable effects have been reported.

Blood and Lymphatic_ System_ Disorders: Transient episodes of mild neutopenia have occasionally been observed in clinical trials.

Ear and Labyrinth Disorders: Hearing impairment (including hearing loss, deafness and /or tinnitus) has been reported in some patients receiving azithromycin. Many of these have been associated with prolonged use of high doses in investigational studies. In those cases where follow-up information was available the majority of these events were reversible.

Gastrointestinal Disorders: Nausea, vomiting, diarrhea, loose stools, abdominal discomfort (pain/cramps), and flatulence.

Hepatobiliary Disorders: Abnormal liver function.

Skin and Subcutaneous Tissue Disorders: Allergic reactions including rash and angioedema.

General Disorders and Administration Site Conditions: Local pain and inflammation at the site of infusion.

The following undesirable DMAC prophylaxis and treatment clinical trials:

The most frequent (>5% in any treatment group) averse reactions in HIV-infected patients receiving azithromycin for prophylaxis for DMAC were diarrhea, abdominal pain, nausea, loose stools, flatulence, vomiting, dyspepsia, rash, pruritus, headache, and arthralgia.

When azithomycin 600 mg is given daily for the treatment of DMAC infection for prolonged periods, the most frequently reported treatment related side effects are abdominal pain, nausea, vomiting, diarrhea, flatulence, headache, abnormal vision, and hearing impairment.

In post-marketing experience, the following additional undesirable effects have been reported:

Infections and Infestations: Moniliasis and vaginitis.

Blood and Lymphatic System Disorders: Thrombocytopenia.

Immune system Disorders: Anaphylaxis.

Metabolism and Nutrition Disorders: Anorexia.

Psychiatric Disorders: aggressive reactions, nervousness, agitation, and anxiety.

Nervous system Disorders: Dizziness, convulsion, headache, hyperactivity, hypoesthesia, paresthesia, somnolence, and syncope. There have been rare reports of taste/smells perversion and/or loss.

Ear and Labyrinth Disorders: Vertigo.

Cardiac Disorders: Palpitations and arrhythmias including ventricular tachycardia have been reported. There have been rare reports of QT prolongation and torsades de pointes.

Vascular Disorders: Hypertension.

Gastrointestinal

Disorders:Vomiting/diarrhea (rarely resulting in dehydration), dyspepsia, constipation, pseudomembranous colitis, pancreatitis, and rare reports of tongue discoloration.

Hepatobiliary Disorders: Hepatitis and cholestatic jaundice have been reported, as well as rare cases of hepatic necrosis and hepatic failure, which have rarely resulted in death.

Skin and Subcutaneous Tissue Disorders: Allergic reactions including pruritus, rash, photosensitivity, edema, urticaria, and angioedema. Rarely, serious skin reactions including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported.

Musculoskeletal and Connective Tissue Disorders: Arthralgia.

Renal and Urinary Disorders: Interstitial nephritis and acute renal failure.

General Disorders and Administration site Conditions: Asthenia has been reported; fatigue, and malaise.

4.9 Overdose

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. In the event of overdosage, general symptomatic and 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 the first of a class of antibiotics designated chemically as azalides. Chemically it is derived by insertion of a nitrogen atom into the lactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza-methyl-9a-homoerythromycin A. The molecular weight is 749.0. The mode of action of azithromycin is inhibition of protein synthesis in bacteria by biding to the 50s ribosomal subumit and preventing translocation of peptides.

Antibacterial Spectrum:

The susceptibility of bacterial species to azithromycin is shown below:

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when local prevalence or resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species

Aerobic Gram-positive bacteria:

Streptococci (Group C, F, G) and Viridans group streptococci.

Aerobic Gram-negative bacteria:

Bordetella pertussis, Haemophilus ducreyi, Haemophilus influenzae** Haemophilus parainfluenzae*, Legionella pneumophila, Moraxella catarrhalis * and Neisseria gonorrhoeae.

5.2 Pharmacokinetic properties

Absorption

Following oral administration in humans, azithromycin is widely distributed throughout the body; bio-availability is approximately 37%.

Administration of azithromycin capsules following a substantial meal reduces bio-availability by at least 50%. The time taken to peak plasma level is 2-3 hours.

Distribution

In animal studies, high azithromycin concentrations have been observed in phagocytes. In experimental models, higher concentrations of azithromycin are released during active phagocytosis than from non-stimulated phagocytes. In animal models this results in high concentration in azithromycin being delivered to the site of infection.

Pharmacokinetics studies in humans have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the drug is heavily tissue bound. Concentrations in target tissues, such as ling, tonsil and prostate exceed the MIC_{90} for likely pathogens after a single dose of 500 mg.

Following oral administration of daily doses 600mg azithromycin, mean maximum plasma concentration (C_{max}) was 0.33 ug/ml (±33%) for 24 hours at steady-state.

Pharmacokinetics in Special Patients Groups

Elderly

In Elderly volunteers (>65 years), slightly higher AUC values were seen after a 5-day regimen than in young volunteers (<40 years), but these are not considered clinically significant, and hence no dose adjustment is recommended.

Renal Impairment

The pharmacokinetics of azithromycin in subjects with mild to moderate renal impairment (GFR 10 - 80 ml/min) were not affected following a single one gram dose of immediate release azithromycin. Statistically significant differences in AUC 0-120 (8.8μgxhr/ml vs. 11.7μg x hr/ml),C max (1.0 ug/ml vs. 1.6 μg/ml) and CLr (2.3ml/min/kg Vs. 0.2 ml/min/kg) were observed between the group with severe renal impairment (GFR< 10ml/min) and the group with normal renal function.

Hepatic Impairment

In patients with mid (class A) to moderate (class B) hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to those with normal hepatic

function. In these patients urinary clearance of azithromycin appears to increase, perhaps to compensate for reduced hepatic clearance.

5.3 Preclinical safety data

Phospholipidosis (intracellular phospholipid accumulation) has been observed in several tissues (e.g. eye, dorsal root ganglia, liver gallbladder, kidney, spleen, and/or pancreas) of mice, rats, and dogs given multiple doses of azithromycin. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs. The effect has been shown to be reversible after cessation of azithromycin treatment. The significance of the finding for animal and for human is unknown.

6. Pharmaceutical particulars

6.1 List of excipients

The excipients include low-substituted hydroxypropyl cellulose, maize starch, 15% maize starch paste, magnesium stearate, dry talc, white coating powder.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Film-Coated Tablets: Store at temperature not exceeding 30°C.

6.5 Nature and contents of container

PA/Al/PVC Cold-formed Foil/Aluminium foil blister pack.

6.6 Special precautions for disposal and other handling

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

7. Manufacturer

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