For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

Azithromycin Oral Suspension I.P.

Aziclass®-100

Liquid

COMPOSITION
Each ml contains :
Azithromycin I.P. equivalent to
Anhydrous Azithromycin 20 mg
In a flavoured base q.s.
Colour : Quinoline Yellow WS

Aziclass®-200

Liquid

COMPOSITION
Each ml contains :
Azithromycin I.P. equivalent to
Anhydrous Azithromycin 40 mg
In a flavoured base q.s.
Colour : Sunset Yellow FCF

INDICATION
For susceptible infections including community acquired pneumonia pelvic inflammatory disease.

DOSAGE AND ADMINISTRATION
The recommended dose of Azithromycin in children is 10 mg/kg once daily for three days, or over a period of five days starting with a single dose of 10 mg/kg on the first day, followed by doses of 5 mg/kg per day for the following 4 days, or as directed by the Physician.
There is no information on children under six months of age. The duration of therapy is 3 days or as depending upon the severity of infection.
Method of administration: For oral administration only.
Azithromycin should be given in a single daily dose. After taking the suspension a bitter after-taste can be avoided by drinking fruit juice directly after swallowing. It may be taken together with food.

CONTRAINDICATIONS
Azithromycin is contraindicated in patients with known hypersensitivity to Azithromycin or any of the macrolide antibiotics.
Azithromycin and ergot derivatives should not be co-administrated.
Azithromycin should not be used in hepatic disease.

SPECIAL WARNINGS 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 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 medicinal product should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.
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. 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 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 superinfection with non- susceptible organisms, including fungi is recommended.
Clostridium 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 antibacterial agents.
In patients with severe renal impairment (GFR <10 ml/min) a 33% increase in systemic exposure to azithromycin was observed.
Cardiovascular Events
Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with 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 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 hypomagnesemia
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.
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 in children have not been established.

DRUG INERACTIONS
Antacids: Azithromycin should be taken at least one hour before or 2 hours after the antacids.
Cyclosporin: Cyclosporin levels should be monitored and dose adjusted accordingly.
Digoxin: No interactions have been reported, any way raised digoxin levels should be borne in mind.
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.
Ergot derivatives: Azithromycin and ergot derivatives should not be co-administered.
No interaction with the following drugs were reported when used concomitantly with: Carbamazepine, Cimetidine, Methyl prednisolone, Theophylline and Wafarin.

PREGNANCY, LACTATION AND INFERTILITY
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.
Breastfeeding
Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in breastfeeding women that have characterized the pharmacokinetics of azithromycin excretion into human breast milk.
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
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.

ADVERSE DRUG REACTIONS / UNDESIRABLE EFFECTS.
Azithromycin induced Acute generalized Exanthematosus Pustulosis (AGEP).
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
In clinical trials, most of the reported adverse reactions were mild to moderate in severity and were reversible upon discontinuation of the drug. Approximately 0.7% of the patients from the multiple-dose clinical trials discontinued Azithromycin therapy because of treatment-related adverse reactions. Serious adverse reactions included angioedema and cholestatic jaundice. Most of the adverse reactions leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, or abdominal pain.
Multiple-dose regimen
Overall, the most common adverse reactions in adult patients receiving a multiple-dose regimen of Azithromycin were related to the gastrointestinal system with diarrhea/loose stools (5%), nausea (3%), and abdominal pain (3%) being the most frequently reported.
No other adverse reactions occurred in patients on the multiple-dose regimen of Azithromycin with a frequency greater than 1%. Adverse reactions that occurred with a frequency of 1% or less included the following:
Cardiovascular: Palpitations and 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, photosensitivity, and angioedema.
Chronic therapy with 1200 mg weekly regimen
The nature of adverse reactions seen with the 1200 mg weekly dosing regimen for the prevention of Mycobacterium avium infection in severely immunocompromised HIV-infected patients were similar to those seen with short-term dosing regimens.
Chronic therapy with 600 mg daily regimen combined with ethambutol
The nature of adverse reactions seen with the 600 mg daily dosing regimen for the treatment of Mycobacterium avium complex infection in severely immunocompromised HIV-infected patients were similar to those seen with short term dosing regimens. Five percent of patients experienced reversible hearing impairment in the pivotal clinical trial for the treatment of disseminated MAC in patients with AIDS. Hearing impairment has been reported with macrolide antibiotics, especially at higher doses. Other treatment related adverse reactions occurring in >5% of subjects and seen at any time during a median of 87.5 days of therapy include: abdominal pain (14%), nausea (14%), vomiting (13%), diarrhea (12%), flatulence (5%), headache (5%), and abnormal vision (5%). Discontinuations from treatment due to laboratory abnormalities or adverse reactions considered related to study drug occurred in 8 of 88 (9.1%) of subjects.
Single 1-gram dose regimen
Overall, the most common adverse reactions in patients receiving a single-dose regimen of 1 gram of azithromycin tablets 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%).
Postmarketing 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 postmarketing 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 torsade's de pointes.
Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting / diarrhea pseudomembranous colitis, pancreatitis, oral candidiasis, pyloric stenosis, and tongue discoloration.
General: Asthenia, paresthesia, fatigue, malaise, and anaphylaxis.
Genitourinary: Interstitial nephritis, 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, and 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.
Laboratory Abnormalities
Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows:
With an incidence of 1-2%, elevated serum creatine phosphokinase, potassium, ALT (SGPT), GGT, and AST (SGOT).
With an incidence of less than 1%, leukopenia, neutropenia, decreased platelet count, elevated serum alkaline phosphatase, bilirubin, BUN, creatinine, blood glucose, LDH, and phosphate.
When follow-up was provided, changes in laboratory tests appeared to be reversible.
In multiple-dose clinical trials involving more than 3000 patients, 3 patients discontinued therapy because of treatment-related liver enzyme abnormalities and 1 because of a renal function abnormality.
In a phase 1 drug interaction study performed in normal volunteers, 1 of 6 subjects given the combination of azithromycin and rifabutin, 1 of 7 given rifabutin alone, and 0 of 6 given azithromycin alone developed a clinically significant neutropenia (<500 cells/mm3). Laboratory abnormalities seen in clinical trials for the prevention of disseminated Mycobacterium avium disease in severely immunocompromised HIV-infected patients.
Chronic therapy (median duration: 87.5 days, range: 1-229 days) that resulted in laboratory abnormalities in >5% of subjects with normal baseline values in the pivotal trial for treatment of disseminated MAC in severely immunocompromised HIV-infected patients treated with azithromycin 600 mg daily in combination with ethambutol include: a reduction in absolute neutrophils to <50% of the lower limit of normal (10/52, 19%) and an increase to ve times the upper limit of normal in alkaline phosphatase (3/35, 9%). These ndings in subjects with normal baseline values are similar when compared to all subjects for analyses of neutrophil reductions (22/75, 29%) and elevated alkaline phosphatase (16/80, 20%). Causality of these laboratory abnormalities due to the use of study drug has not been established.

OVERDOSAGE
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.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamics Properties
Pharmacotherapeutic group: antibacterials for systemic use; macrolides; azithromycin.
Azithromycin is an azalide, a sub-class of the macrolide antibiotics. By binding to the 50S-ribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other. It prevents bacteria from growing by interfering with their protein synthesis. Azithromycin binds to the 50S subunit of the bacterial ribosome, and thus inhibits translation of mRNA. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented.
Azithromycin demonstrates activity against a wide range of Gram-positive and Gram-negative bacteria including: staphylococcus aureus, strepto¬coccus pneumoniae, streptococcus pyogenes (Group A) and other strepto¬coccal species, haemophilus influenzae and parainfluenzae, moraxella catarrhalis, anaeorobes including bacteroides fragilis, E. coli, bordetella parapertussis, borrelia burgdorferi, haemophilus ducreyi, neisseria gonor¬rhea and chlamydia trachomatis. Azithromycin also demonstrates activity against legionella pneumophila, mycoplasma pneumoniae and hominis, campylobacter sp., toxoplasma gondii and treponema pallidum.
Pharmacokinetics Properties
Absorption
The biological availability of azithromycin after oral administration is approximately 37%. Peak plasma levels are achieved 2-3 hours after taking the medicinal product.
Distribution
After oral administration, azithromycin is distributed throughout the entire body. The protein binding of azithromycin in serum is variable and varies, depending on the serum concentration, from 52% at 0.05 mg/l to 12% at 0.5 mg/l. The steady state distribution volume is 31.1 l/kg.
Elimination
The terminal plasma-elimination half-life closely follows the tissue depletion half-life from 2 to 4 days.
Pharmacokinetic studies have shown clearly higher azithromycin levels in the tissues than in the plasma (up to 50 times the maximum observed concentration in plasma). This indicates that the substance is bound in the tissues in considerable quantities. Concentrations in the infected tissues, such as lungs, tonsil and prostate are higher than the MRC90 of the most frequently occurring pathogens after a single dose of 500 mg.

INCOMPATIBILITIES
Not applicable.

STORAGE
Store at temperatures not exceeding 30°C. Protect from light and moisture.
KEEP OUT OF REACH OF CHILDREN

apex®

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