Important information. Please read carefully.

Azytro

Tablet 250 mg

COMPOSITION
Each film-coated tablet contains Azithromycin Dihydrate equivalent to Azithromycin 250 mg.

PHARMACODYNAMICS
Azithromycin is an azalide, derived from the macrolide class of antibiotics. The mode of action of azithromycin is inhibition of protein synthesis in bacteria by binding to the 50s ribosomal subunit and preventing translocation of peptides.

Azithromycin demonstrates activity *in vitro* against a wide variety of Gram-positive and Gram-negative bacteria including: *Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes* (Group A) and other Streptococcal species; *Haemophilus influenzae* and *parainfluenzae*; *Branhamella catarrhalis*; anaerobes including *Bacteroides fragilis*; *Escherichia coli; Bordetella pertussis; Bordetella parapertussis; Borrelia burgdorferi; Haemophilus ducreyi; Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Azithromycin also demonstrates *in vitro* activity against *Legionella pneumophila*, *Mycoplasma pneumoniae* and *hominis*, Campylobacter sp., *Toxoplasma gondii* and *Treponema pallidum*.

PHARMACOKINETICS
Following oral administration in humans, azithromycin is widely distributed throughout the body; bioavailability is approximately 37%. The time taken to peak plasma levels is 2-3 hours. The plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days.

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 drug is heavily tissue bound. Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC90 for likely pathogens after a single dose of 500mg.

Following a single dose of azithromycin 1 gram orally, the pharmacokinetics in subjects with mild to moderate renal impairment (GFR 10 - 80 ml/min) were not affected. Statistically significant differences in AUC 0-120 (8.8 µg•hr/ml vs. 11.7 µg•hr/ml), Cmax (1.0 µg/ml vs. 1.6 µg/ml) and CLr (2.3 ml/min/kg vs. 0.2 ml/min/kg) were observed between the group with normal renal function and the group with severe renal impairment (GFR < 10 ml/min).

INDICATIONS
Azytro is indicated for infections caused by susceptible organisms; in lower respiratory tract infections including bronchitis and pneumonia, in skin and soft tissue infections, in otitis media and in upper respiratory tract infections including sinusitis and pharyngitis/tonsillitis. (Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. Azithromycin is generally effective in the eradication of streptococci from the oropharynx, however, data establishing the efficacy of azithromycin and the subsequent prevention of rheumatic fever are not available at present.)

In sexually transmitted diseases in men and women, **Azytro** is indicated in the treatment of uncomplicated genital infections due to *Chlamydia trachomatis*. It is also indicated in the treatment of uncomplicated genital infection due to non-multiresistant *Neisseria gonorrhoea*, concurrent infection with *Treponema pallidum* should be excluded.

Azytro is indicated, either alone or in combination with rifabutin, for prophylaxis against *Mycobacterium avium – intracellulare complex* (MAC) infection, an opportunistic infection prevalent in patients with advanced human immunodeficiency virus (HIV).

DOSAGE AND ADMINISTRATION
To be administered orally.
Azytro should be given as a single daily dose. The period of dosing with regard to infection is given below.

Azytro can be taken with food.

In adults – For the treatment of sexually transmitted diseases caused by *Chlamydia trachomatis*, or susceptible *Neisseria gonorrhoea*, 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.

According to the 1999 USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus, the optimal criteria for discontinuing MAC prophylaxis remain to be defined. However, a reasonable option would be to consider discontinuing prophylaxis in patients with a CD4+ T-lymphocyte count greater than 100 cells/microlitre for a sustained period (eg.greater than 3-6 months.)

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 500 mg given on day 1, then 250 mg daily on days 2 to 5.

In the elderly: The same dose range as in younger patients may be used in elderly.

In patients with renal impairment: No dose adjustment is necessary in patients with mild to moderate (GFR 10 - 80 ml/min) or severe (GFR < 10 ml/min) renal impairment (see section Warnings and Precautions).

In patients with hepatic impairment: See section Warnings and Precautions.

In children: With the single exception of the treatment of streptococcal pharyngitis, the total dose in children is 30 mg/kg which should be given as a single daily dose of 10 mg/kg daily for 3 days or as an alternative, given 5 days with a single daily dose of 10 mg/kg on day 1, then 5 mg/kg on days 2-5.

Treatment of acute otitis media in children may be given as either a single dose of 30 mg/kg or as 10 mg/kg daily for 3 days.

Azytro Tablet should only be administered to children weighing more than 45 kg.

Safety and efficacy for the prevention of MAC in children have not been established. Based on pediatric pharmaceutic data, a dose of 20 mg/kg would be similar to the adult dose of 1200 mg but with higher Cmax.

For pediatric streptococcal pharyngitis, azithromycin given as a single dose of 10 mg/kg or 20 mg/kg for 3 days has been shown to be effective; however, do not exceed a daily dose of 500 mg. In clinical trials comparing these two dosage regimens, similar clinical efficacy was observed but greater bacteriologic eradication was evident at the 20 mg/kg/day dose. However, penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including prophylaxis of rheumatic fever.

CONTRAINDICATIONS
Azytro is contra-indicated in patients with a known hypersensitivity to azithromycin or any of the macrolide antibiotics.

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

WARNINGS AND PRECAUTIONS
Hypersensitivity
As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), dermatologic reactions including 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.
In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalized exanthematous pustulosis (AGEP)], **Azytro** should be discontinued immediately and appropriate treatment should be urgently initiated. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Prolongation of the QT Interval
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 (see section Side Effects). Prescribers 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 congenital or documented QT prolongation
- Patients currently receiving treatment with other active substances known to prolong QT interval, such as antiarrhythmics of Classes IA and III, antipsychotic agents, antidepressants, and fluoroquinolones
- Patients with electrolyte disturbance, particularly in cases of hypokalemia and hypomagnesemia
- Patients with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency
- Elderly patients: elderly patients may be more susceptible to drug-associated effects on the QT interval

Infantile hypertrophic pyloric stenosis (IHPS)
Infantile hypertrophic pyloric stenosis (IHPS) has been reported following the use of azithromycin in infants (treatment up to 42 days of life). Parents and caregivers should be informed to contact their physician if vomiting and/ or irritability with feeding occurs.

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

Use in hepatic impairment: As the liver is the principal route of excretion of azithromycin, it should not be used in patients with hepatic disease.

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

DRUG INTERACTIONS
Antacids: In patients receiving azithromycin and antacids, azithromycin should be taken at least 1 hour before or 2 hours after the antacid.

Cyclosporin: Caution should be exercised before considering coadministration of azithromycin and cyclosporin. If coadministration is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Digoxin: Some of the macrolide antibiotics have been reported to impair the metabolism of digoxin (in the gut) in some patients. Therefore, in patients receiving concomitant azithromycin and digoxin the possibility of raised digoxin levels should be borne in mind, and digoxin levels monitored.

Ergot derivatives: Because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be coadministered.

Terfenadine: As with other macrolides, azithromycin should be administered with caution in combination with terfenadine.

Theophylline: Theophylline levels may be increased in patients taking azithromycin.

Coumarin-Type Oral Anticoagulants: Consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Zidovudine: To be used with caution as 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.

PREGNANCY AND LACTATION
Use in pregnancy: Animal reproduction studies have demonstrated that azithromycin crosses the placenta, but have revealed no evidence of harm to the foetus. There are no adequate and well controlled studies in pregnant women. Since animal studies are not always predictive of human response, azithromycin should be used during pregnancy only if adequate alternatives are not available.

Use in lactation: No data on secretion of azithromycin in breast milk are available, so that azithromycin should only be used in lactating women where adequate alternatives are not available.

SIDE EFFECTS
Azithromycin is well tolerated with a low incidence of side effects.

Infections and Infestations: Moniliasis and vaginitis

Blood and Lymphatic System Disorders: Thrombocytopenia. Transient mild reductions in neutrophil counts have occasionally been observed in clinical trials.

Immune system disorders: Anaphylaxis (rarely fatal) (see section Warnings and Precautions)

Metabolism and nutrition disorders: Anorexia

Psychiatric Disorders: Aggressive reaction, nervousness, agitation and anxiety.

Nervous System Disorders: Dizziness, convulsions (as seen with other macrolides), headache, somnolence, parasthesia, hyperactivity and syncope. There have been rare reports of taste perversion.

Ear and Labyrinth Disorders: Vertigo, hearing impairment has been reported with macrolide antibiotics. There have been reports of hearing impairment, including hearing loss, deafness and/or tinnitus 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 were available the majority of these events was reversible.

Cardiac Disorders: Palpitations and arrythmias including ventricular tachycardia (as seen with macrolides) have been reported. There have been rare reports of QT prolongation and torsades de pointes (see section Warnings and Precautions).

Vascular Disorders: Hypotension

Gastrointestinal Disorders: Nausea, vomiting/diarrhoea (rarely resulting in dehydration), loose stools, dyspepsia, abdominal discomfort (pain/cramps), constipation, flatulence, infantile hypertrophic pyloric stenosis, pseudomembranous colitis, pancreatitis and rare reports of tongue discoloration.
Hepatobiliary Disorders: Abnormal liver function including 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 (frequency not known): Allergic reactions including pruritus, rash, photosensitivity, oedema, urticaria and angioedema.
Severe cutaneous adverse reactions (SCARs) including erythema multiforme, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalized exanthematous pustulosis (AGEP) have occurred. (see section Warnings and Precautions).

Musculoskeletal and Connective Tissue Disorders: Arthralgia

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

General Disorders and Administration Site Conditions: Asthenia, fatigue and malaise have been reported.

SYMPTOMS AND TREATMENT OF 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.

STORAGE CONDITION
Store below 30°C.

SHELF LIFE
The expiry date is indicated on the packaging.

PRODUCT DESCRIPTION, DOSAGE FORM AND PACKAGING
White, oval shaped, film coated tablet engraved with "AV" on one side and plain on the other side. Available in blister pack of 6's in packs of 30's.

KEEP OUT OF REACH OF CHILDREN
JAUHI DARI KANAK-KANAK

For further information, please consult your pharmacist or physician.

Revision Date: 19-Feb-2020

Manufactured by
Xepa-Soul Pattinson (Malaysia) Sdn Bhd
1-5 Cheng Industrial Estate, 75250 Melaka, Malaysia.

Product Registration Holder
Apex Pharmacy Marketing Sdn Bhd
2, Jalan SS13/5 47500 Subang Jaya, Malaysia.