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

℞AZITHRA

Azithromycin for Injection USP, 500 mg/vial, 10 mL Lyo Vial

Description and composition:
A white to off-white lyophilized powder or cake. After reconstitution: A clear, colourless solution, free from visible particulate matter.

Each vial contains 512mg Azithromycin Monohydrate equivalent to 500mg Azithromycin.

Pharmacodynamics:
Mode of action:
Azithromycin is a macrolide antibiotic belonging to the azalide group. The molecule is constructed by adding a nitrogen atom to the lactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A. The molecular weight is 749.0. The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis by means of binding to the ribosomal 50s sub-unit and inhibition of peptide translocation.
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
Azithromycin susceptibility breakpoints for typical bacterial pathogens are:
NCCLS:

- Susceptible ≤ 2mg/l; resistant ≥ 8mg/l
- Haemophilus spp.: susceptible ≤ 4mg/l
- Streptococcus pneumoniae and Streptococcus pyogenes:

Susceptible ≤ 0.5 mg/l; resistant ≥ 2 mg/l
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.

Antibacterial spectrum of Azithromycin
Commonly susceptible species
Aerobic Gram-positive microorganisms
Staphylococcus aureus
Methycillin-susceptible
Streptococcus pneumoniae
Penicillin-susceptible
Streptococcus pyogenes **(Group A)**
Aerobic Gram-negative microorganisms
Haemophilus influenzae
Haemophilus parainfluenzae
Legionella pneumophila
Moraxella catarrhalis
Pasteurella multocida
Anaerobic microorganisms
Clostridium perfringens
Fusobacterium spp.
Prevotella spp.
Porphyromonas spp.
Other microorganisms
Chlamydia trachomatic
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Streptococcus pneumoniae
Penicillin-intermediate
Penicillin-resistant
Inherently resistant organisms
Aerobic Gram-positive microorganisms
Enterococcus faecalis
Staphylococci **MRSA, MRSE** *
Anaerobic microorganisms
Bacteroides fragilis group
• Methycillin-resistant staphylococci have a very high prevalence of acquired resistance to macrolides and have been placed here because they are rarely susceptible to azithromycin.

Pharmacokinetics:
Absorption
Bioavailability after oral administration is approximately 37%. Peak plasma concentrations are attaned 2-3 hours after taking the medicinal product.
Distribution
Orally administered azithromycin is widely distributed throughout the body. In pharmacokinetic studies it has been demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (as much as 50 times) than those measured in plasma, which indicates that the agent strongly binds to tissues. Binding to serum proteins varies according to plasma concentration and ranges from 12% at 0.5 microgram/ml up to 52% at 0.05 microgram azithromycin/ml serum. The mean volume of distribution at steady state (VVss) has been calculated to be 31.1 l/kg.
Elimination
The terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 2-4 days.
Approximately 12% of an intravenously administered dose of azithromycin is excreted unchanged in urine within the following three days. Particularly high concentrations of unchanged azithromycin have been found in human bile. Also in bile, ten metabolites were detected, which were formed through N- and O-demethylation, hydroxylation of desosamine – and aglycone rings and cleavage of cladinose conjugate. Comparison of the results of liquid chromatography and microbiological analyses has shown that the metabolites of azithromycin are not microbiologically active. In animal tests, high concentrations of azithromycin have been found in phagocytes. It has also been established that during active phagocytosis higher concentrations of azithromycin are released from inactive phagocytes. In animal models this results in high concentrations of azithromycin being delivered to the site of infection.

Indication
Azithromycin intravenous (IV) is indicated for the treatment of community acquired pneumonia (CAP) caused by susceptible organisms, including *Legionella pneumophila*, in patients who require initial intravenous therapy.
Azithromycin intravenous (IV) is indicated for the treatment of pelvic inflammatory disease (PID) caused by susceptible organisms (*Chlamydia trachomatis, Neisseria gonorrhoea, Mycoplasma hominis*), in patients who require initial intravenous therapy.

Recommended Dose
After reconstitution and dilution, the recommended route of administration for intravenous azithromycin is by IV infusion only. Do not administer as an intravenous bolus or an intramuscular injection. The infusate concentration and rate of infusion for Azithromycin intravenous (IV) should be either 1 mg/ml over 3 hours or 2 mg/ml over 1 hour. An intravenous dose of 500 mg azithromycin should be infused for a minimum duration of one (1) hour. The safety and efficacy of intravenous azithromycin for the treatment of infections in children has not been established. Safety and efficacy for the prevention or treatment of MAC in children have not been established. Based on pediatric pharmacokinetic data, a dose of 20 mg/kg would be similar to the adult dose of 1200 mg but with a higher C_{max}.
In the elderly: The same dosage as in adult patients is used in the elderly.
In patients with renal impairment: No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10 – 80 ml/min). Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR<10 ml/min)
In patients with Hepatic impairment: The same dosage as in patients with normal hepatic function may be used in patients with mild to moderate hepatic impairment.
Hepatic failure:
Since azythromycin is metabolised in the liver and excreted in the bile, the drug should not be given to patients suffering from severe liver disease. No studies have been conducted regarding treatment of such patients with azithromycin.
Incompatibilities
Other intravenous substances, additives or medications should not be added to
intravenous azithromycin, or infused simultaneously through the same intravenous line.
Mode of Administration
After reconstitution and dilution, the recommended route of administration for intravenous azithromycin is by IV infusion only. Do not administer as an intravenous bolus or an intramuscular injection.

Contraindication
Azithromycin 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.

Warning and precaution
As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic oedema 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.
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. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarisation. As with any antibiotic preparation, there is a possibility that superinfections could occur (e.g. fungal infections). In patients with severe renal impairment (GFR <10 ml/min) a 33% increase in systemic exposure to azithromycin was observed. Azithromycin for injection should be reconstituted and diluted as directed and administered as an intravenous infusion over not less than 60 minutes. Do not administer as an intravenous bolus or an intramuscular injection.

Interaction with other medicaments
Antacids*:* Azithromycin should be taken at least 1 hour before or 2 hours after the antacid.

Carbamazepine*:* Azithromycin had no significant effect on the pharmacokinetics of Carbamazepine.

Cimetidine*:* A single dose of cimetidine administered 2 hours before Azithromycin had no effect on the pharmacokinetics of azithromycin.

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

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.

Methylprednisolone: Azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

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. As with other macrolides, Azithromycin should be administered with caution in combination with terfenadine.

Theophylline: Theophylline levels may be increased.

Coumarin-Type Oral Anticoagulants: Consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used.

Zidovudine: Single 1000mg doses and multiple 1200mg or 600mg doses of azithromycin did not affect 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.

Didanosine: Coadministration of daily doses of 1200mg azithromycin with didanosine did not appear to affect the pharmacokinetics of didanosine.

Rifabutin: Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either drug.

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.
Blood and lymphatic system disorders
Thrombocytopenia
In clinical trials there have been occasional reports of periods of transient, mild neutropenia. However, a causal relationship with azithromycin treatment has not been confirmed.
Psychiatric disorders
Agressiveness, agitation, anxiety and nervousness
Nervous system disorders
Dizziness/vertigo, somnolence, headache, convulsions (which have also been found to be caused by other macrolides), taste perversion, syncope
Paraesthesia and asthenia
Insomnia and hyperactivity
Ear and labyrinth disorders
Macrolide antibiotics have been reported to have caused hearing damage. In some patients receiving azithromycin impaired hearing, deafness and ringing in the ears have been reported. Many of these cases relate to experimental studies in which azithromycin was used at large doses over prolonged periods. According to available follow-up reports, the majority of these problems however were 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.
Vascular disorders
Hypotension
Gastrointestinal disorders
Nausea, vomiting, diarrhoea, abdominal discomfort (pain/cramps) Loose stools, flatulence, digestive disorders, anorexia, dyspepsia Constipation, discoloration of the tongue, pancreatitis Pseudomembranous colitis has been reported
Hepato-biliary disorders
Hepatitis and cholestatic jaundice have been reported, including abnormal liver function test values, as well as rare instances of hepatic necrosis and hepatic dysfunction, which in rare instances have resulted in death
Skin and subcutaneous tissue disorders
Allergic reactions including pruritus and rash Allergic reactions including angioneurotic oedema, urticaria and photosensitivity; serious skin reactions such as erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis ***Musculoskeletal, connective tissue and bone disorders*** Arthralgia
Renal and urinary disorders
Interstitial nephritis and acute renal failure
Reproductive system and breast disorders
Vaginitis
General disorders
Anaphylaxis including oedema (leads in rare cases to death), candidiasis, fatigue, malaise.

Symptoms and treatment of overdose
Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea. In the event of overdose, the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

Instructions for use and handling, and disposal
Reconstitution: Prepare the initial IV solution for infusion by adding 4.8 ml of sterilized water for injection to the 500 mg vial and shaking the vial until all of the drug is dissolved. Since azithromycin IV is supplied under vacuum, it is recommended that a standard 5 ml (non-automated) syringe be used to ensure that the exact amount of 4.8 ml of sterilized water for injection is dispensed. Each ml of reconstituted solution contains 100 mg azithromycin.
Chemical and physical in-use stability of the reconstituted product has been demonstrated for 24 hours at or below 30°C or for 7 days if stored under refrigeration 5°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally be no longer than 24 hours at 2 to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.
Dilute this solution further prior to administration as instructed below:
Dilution: To provide azithromycin over a concentration range of 1.0-2.0 mg/ml, transfer 5 ml of the 100 mg/ml azithromycin solution into the appropriate amount of any of the diluents listed below:

Final Infusion Solution Concentration (mg/ml)	Amount of Diluent (ml)
1.0 mg/ml	500 ml
2.0 mg/ml	250 ml

The reconstituted solution can be diluted with:
Normal Saline (0.9% sodium chloride)
½ Normal Saline (0.45% sodium chloride)
5% Dextrose in water
Lactated Ringer's solution
5% Dextrose in ½ Normal Saline (0.45% sodium chloride) with 20 mEq KCl
5% Dextrose in Lactated Ringer's solution 5% Dextrose in 1/3 Normal Saline (0.3% sodium chloride)
5% Dextrose in ½ Normal Saline (0.45% sodium chloride)
Normosol®-M in 5% Dextrose
Normosol®-R in 5% Dextrose
Parenteral drug products should be inspected visually for particulate matter prior to administration. If particulate matter is evident in reconstituted fluids, the drug solution should be discarded.

Storage condition
Store in a dry place at a temperature not exceeding 30°C, protect from light. Chemical and physical in-use stability of the reconstituted product has been demonstrated for 24 hours at or below 30°C or for 7 days if stored under refrigeration 5°C.

Shelf life
36 months

Presentation
Sterile powder for injection packed in 10 ml clear glass Lyo vial, packed along with package insert.

LEA-xxxxxx-xx

Manufactured by:
Gland Pharma Limited
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Near Gandimaisamma Cross Roads,
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Dimensions: 130 x 295 ± 2 mm