

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Epizithro 500mg capsules

2. Qualitative and quantitative composition

Each hard gelatin capsule contains: Azithromycin dehydrate 524 mg
Equivalent to Azithromycin 500 mg

Excipients with known effect

Each tablet contains anhydrous Lactose.

For excipients see section 6.1

3. Pharmaceutical form

Hard gelatin capsule with dark blue cap and white body containing white or almost white powder.

4. Clinical particulars

4.1 Therapeutic indications

Therapeutic Indications:

Epizithro is indicated for the treatment of the following infections when known or likely to be due to one or more susceptible microorganisms (see Pharmacodynamic properties):

- Bronchitis.
- Community-acquired pneumonia.
- Sinusitis.
- Pharyngitis/tonsillitis.
- Otitis media.
- Skin and soft tissue infections.
- Uncomplicated genital infections due to Chlamydia trachomatis.

Considerations should be given to official guidance regarding the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Method of administration:

Epizithro should be given as a single daily dose. In common with many other antibiotics Epizithro Capsules should be taken at least 1 hour before or 2 hours after food, but Epizithro suspension can be taken with food. Children over 45 kg body weight and adults, including elderly patients: The total dose of azithromycin is 1500 mg which should be given over three days (500 mg once daily). In uncomplicated genital infections due to Chlamydia trachomatis, the dose is 1000 mg as a single oral dose. In children under 45 kg body weight:

Epizithro Suspension should be used for children under 45 kg. There is no information on children less than 6 months of age. The dose in children is 10 mg/kg as a single daily dose for 3 days:

Up to 15 kg (less than 3 years): Measure the dose as closely as possible using the 10 ml oral dosing syringe provided. The syringe is graduated in 0.25 ml divisions, providing 10 mg of azithromycin in every graduation. For children weighing more than 15 kg: Epizithro should be administered using the following guidance: 15-25 kg (3-7 years): 200 mg (5 ml), once daily for 3 days. 26-35 kg (8-11 years): 300 mg (7.5 ml), once daily for 3 days. 36-45 kg (12-14 years): 400 mg (10 ml), once daily for 3 days. Renal failure: 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). Hepatic failure: Since azithromycin is metabolized 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 (see Special warnings and Precautions for use). Epizithro Capsules and Dry Mix are for oral administration only. Reconstitution of Epizithro Dry Mix: Shake the bottle to loosen the powder, add 10 ml pure water to make 15 ml suspension or 20 ml pure water to make 30 ml suspension to the content of bottle and shake well. Shake well before use.

4.3 Contraindications

Epizithro is contraindicated in patients with a known hypersensitivity to azithromycin or any of the macrolide or ketolide antibiotics, erythromycin, or to any other excipients in the product. Epizithro is contraindicated in patients with a history of cholestatic jaundice/ hepatic dysfunction associated with prior use of Epizithro.

4.4 Special warnings and precautions for use

As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic edema 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. Hepatotoxicity: Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue Epizithro immediately if signs and symptoms of hepatitis occur. Since the 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 (see Section Undesirable effects). 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. Epizithro have been associated with cardiovascular effects, prolongation of the QT interval. Prolongation of the QT interval can lead to Torsades de points. Prolonged cardiac repolarization 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 repolarization (see Section Undesirable effects); therefore, caution is required when treating patients:

- With congenital or documented QT prolongation.
- Currently receiving treatment with other active substance known to prolong QT interval such as antiarrhythmics of classes Ia and III, cisapride and terfenadine.
- With electrolyte disturbance, particularly in case of hypokalemia and hypomagnesemia.

- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency. In patients receiving ergot derivatives, ergotism has been precipitated by co- administration 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 co-administrated. As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms including fungi is recommended. Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhea to fatal colitis. Strains of C. difficile producing hypertoxin A and B 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. Therefore, CDAD must be considered in patients who present with diarrhea during or subsequent to the administration of any antibiotics. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Discontinuation of therapy with azithromycin and the administration of specific treatment for C. difficile should be considered. Streptococcal infections: Penicillin is usually the first choice for treatment of pharyngitis/tonsillitis due to Streptococcus pyogenes and also for prophylaxis of acute rheumatic fever. Azithromycin is in general effective against streptococcus in the oropharynx, but no data are available that demonstrate the efficacy of azithromycin in preventing acute rheumatic fever. Use in renal impairment: In patients with severe renal impairment (GFR <10

ml/min) a 33% increase in systemic exposure to azithromycin was observed. 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 prevention or treatment of MAC in children have not been established. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Caution in diabetic patients: 5 ml of reconstituted suspension contains sucrose. Due to the sucrose content, this medicinal product is not indicated for persons with fructose intolerance (hereditary fructose intolerance), glucose-galactose malabsorption or saccharase-isomaltase deficiency.

4.5 Interaction with other medicinal products

Antacids: In a pharmacokinetic study investigating the effects of simultaneous administration of antacid with azithromycin, no effect on overall bioavailability was seen, although peak serum concentrations were reduced by approximately 25%. In patients receiving azithromycin and antacids, the drugs should not be taken simultaneously. **Cetirizine:** In healthy volunteers, co-administration of a 5 - day regimen of azithromycin with cetirizine 20 mg at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval. **Didanosine (Dideoxyinosine):** Co-administration of 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo. **Digoxin:** Some of the macrolide antibiotics have been reported to impair the microbial metabolism of digoxin in the gut in some patients. In patients receiving concomitant azithromycin, a related azalide antibiotic, and digoxin the possibility of raised digoxin levels should be borne in mind. **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 derivatives:** Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended. (See Section

4.4 Special warnings and precautions for use).

Pharmacokinetic studies have been conducted between azithromycin and the following drugs known to undergo significant cytochrome P450 mediated

metabolism. Atorvastatin: Co-administration 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 co-administration 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. Ciclosporin: In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of ciclosporin, the resulting ciclosporin C_{max} and AUC₀₋₅ were found to be significantly elevated (by 24% and 21% respectively), however no significant changes were seen in AUC_{0-∞}. Consequently, caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly. Efavirenz: Co-administration 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: Co-administration 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 co-administration of fluconazole, however, a clinically insignificant decrease in C_{max} (18%) of azithromycin was observed. Indinavir: Co-administration 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, co-administration 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: Co-administration 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: Co-administration 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 (see Section Undesirable effects). 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 C_{max}, 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: Co-administration of azithromycin with triazolam had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo. Trimethoprim/sulfamethoxazole: Co-administration of trimethoprim/sulfamethoxazole with azithromycin 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 Fertility, pregnancy and lactation

There are 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 clearly 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 a lactating woman unless the physician feels that the potential benefits justify the potential risks 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 to operate machinery.

4.8 Undesirable effects

Epizithro is well tolerated with a low incidence of side effects. The frequency grouping for the undesirable effects are defined using the following convention: Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very Rare ($< 1/10,000$); and Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and Infestations:

Uncommon: Candidiasis, oral candidiasis, vaginal infection. Not known: Pseudomembranous colitis.

Blood and Lymphatic System Disorders:

Uncommon: Leukopenia, neutropenia. Not known: Thrombocytopenia, hemolytic anemia.

Immune System Disorders:

Uncommon: Angioedema, hypersensitivity. Not known: Anaphylactic reaction.

Metabolism and Nutrition Disorders:

Common: Anorexia.

Psychiatric Disorders:

Uncommon: Nervousness. Rare: Agitation. Not known: Aggression, anxiety.

Nervous System Disorders:

Common: Dizziness, headache, paraesthesia, dysgeusia. Uncommon: Hypoesthesia, somnolence, insomnia. Not known: Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis.

Eye Disorders:

Common: Visual impairment.

Ear and Labyrinth Disorders:

Common: Deafness. Uncommon: Impaired hearing, tinnitus. Rare: Vertigo.

Cardiac Disorders:

Uncommon: Palpitations. Not known: Torsades de pointes, arrhythmia including ventricular tachycardia.

Vascular Disorders:

Not known: Hypotension.

Gastrointestinal Disorders:

Very common: Diarrhea, abdominal pain, nausea, flatulence. Common: Vomiting, dyspepsia. Uncommon: Gastritis, constipation. Not known: Pancreatitis, tongue discoloration.

Hepatobiliary Disorders:

Uncommon: Hepatitis. Rare: abnormal hepatic function. Not known: Hepatic failure, which has rarely resulted in death, fulminant hepatitis, hepatic necrosis, cholestatic jaundice.

Skin and Subcutaneous Tissue Disorders:

Common: Pruritus and rash. Uncommon: Stevens-Johnson syndrome, photosensitivity reaction, urticaria. Not known: Toxic epidermal necrolysis, erythema multiforme.

Musculoskeletal, Connective Tissue Disorders:

Common: Arthralgia.

Renal and Urinary Disorders:

Not known: Acute renal failure, interstitial nephritis.

General disorders and Administration Site Conditions:

Common: Fatigue.

Uncommon: Chest pain, edema, malaise, asthenia.

Investigations:

Common: Decreased lymphocyte count, increased eosinophil count, decreased blood bicarbonate. **Uncommon:** Increased aspartate aminotransferase, increased alanine aminotransferase, increased blood bilirubin, increased blood urea, increased blood creatinine, abnormal blood potassium. **Not known:** Electrocardiogram QT prolonged.

Post marketing experience:

Liver/Biliary: Adverse reaction related to hepatic dysfunction have been reported in post marketing experience with azithromycin.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS)
<https://pv.pharmacyboardkenya.org>

4.9 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 diarrhea. In the event of overdose, the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

5. Pharmacological properties

5.1 Pharmacodynamic properties

General properties: Antibacterials for systemic use. Mode of action: Epizithro 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, beta hemolytic streptococcus of group A, *Enterococcus faecalis* and *Staphylococcus aureus*, including methicillin resistant *S. aureus* (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides. 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 (Methicillin-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 trachomatis.

Species for which acquired resistance may be a problem:

Aerobic Gram-positive microorganisms:

Streptococcus pneumoniae (Penicillin-intermediate).

Inherently resistant organisms:

Aerobic Gram-positive microorganisms:

Enterococcus faecalis. *Staphylococci* MRSA, MRSE*.

Anaerobic microorganisms:

Bacteroides fragilis group. * Methicillin-resistant staphylococci have a very high prevalence of acquired resistance to macrolides and have been placed here because they are rarely susceptible to azithromycin.

5.2 Pharmacokinetic properties

Absorption: Bioavailability after oral administration is approximately 37%. Peak plasma concentrations are attained 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.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose anhydrous, pre-gelatinized starch, talc purified, sodium lauryl sulphate, magnesium stearate, colloidal silicon dioxide, gelatin, titanium dioxide, brilliant blue, erythrosine.

6.2 Incompatibilities

None.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a dry place at a temperature not exceeding 25°C.

6.5 Nature and contents of container

Carton box containing (Aluminum / opaque PVC) strips each of 3 hard gelatin capsules and inner leaflet.

6.6 Special precautions for disposal and other handling

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

7. Marketing authorization holder

Egyptian International Pharmaceutical Industries Company (EIPICO)

P. O. Box 149, Egypt

8. Marketing Authorization Number

H2025/CTD11080/23028

9. Date of first authorization/renewal of the authorization

13/08/2025

10. Date of revision of the text

June 2017