Zithrodose
100 mg / 5 ml powder for oral suspension

Active ingredients: ***Azithromycin Dihydrate 104.8 mg equivalent to 100 mg Azithromycin base***

In active ingredients:

Cream flavor powder, aspartame, microcrystalline cellulose and carboxymethylcellulose sodium, xanthan gum, colloidal anhydrous silica, sodium phosphate tribasic anhydrous, mannitol powder, banana flavor powder, strawberry flavor powder, sucrose.

FULL PRESCRIBING INFORMATION

1- **INDICATIONS AND USAGE**

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZITHRODOSE (azithromycin) and other antibacterial drugs, ZITHRODOSE (azithromycin) should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

ZITHRODOSE (azithromycin) is a macrolide antibacterial drug indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below. Recommended dosages and durations of therapy in adult and pediatric patient populations vary in these indications.

1.1 **Adult Patients**

- Acute bacterial exacerbations of chronic bronchitis due to Haemophilus influenza, Moraxella catarrhalis, or Streptococcus pneumonia.

- Acute bacterial sinusitis due to Haemophilus influenzae, Moraxella catarrhalis. or Streptococcus pneumoniae.

• Community-acquired pneumonia due to Chlamydophila pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, or Streptococcus pneumoniae in patients appropriate for oral therapy.

• Pharyngitis/tonsillitis caused by Streptococcus pyogenes as an alternative to first-line therapy in individuals who cannot use first-line therapy.

• Uncomplicated skin and skin structure infections due to Staphylococcus aureus, Streptococcus pyogenes, or Streptococcus agalactiae.

• Urethritis and cervicitis due to Chlamydia trachomatis or Neisseria gonorrhoeae.

• Genital ulcer disease in men due to Haemophilus ducreyi (chancroid). Due to the small number of women included in clinical trials, the efficacy of azithromycin in the treatment of chancroid in women has not been established.

1.2 Pediatric Patients

• Acute otitis media (>6 months of age) caused by Haemophilus influenzae, Moraxella catarrhalis, or Streptococcus pneumoniae

• Community-acquired pneumonia (>6 months of age) due to Chlamydophila pneumoniae, Haemophilus influenzae, Mycoplasma pneumonia, or Streptococcus pneumoniae in patients appropriate for oral therapy.

• Pharyngitis/tonsillitis (> 2 years of age) caused by Streptococcus pyogenes as an alternative to first-line therapy in individuals who cannot use first-line therapy.

1.3 Limitations of Use

Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following:

● patients with cystic fibrosis

● patients with nosocomial infections

● patients with known or suspected bacteremia

● patients requiring hospitalization

● elderly or debilitated patients, or

● Patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

2- DOSAGE AND ADMINISTRATION

2.1 Pediatric Patients

Infection*	**Recommended Dose/Duration of Therapy**
Acute otitis media	30 mg/kg as a single dose or 10 mg/kg once daily for 3 days or 10 mg/kg as a single dose on Day 1 followed by 5 mg/kg/day on Days 2 through 5.
Acute bacterial sinusitis	10 mg/kg once daily for 3 days.

Community-acquired pneumonia	10 mg/kg as a single dose on Day 1 followed by 5 mg/kg once daily on Days 2 through 5.
Pharyngitis/tonsillitis	12 mg/kg once daily for 5 days.
*DUE TO THE INDICATED ORGANISMS	

ZITHRODOSE for oral suspension can be taken with or without food.

PEDIATRIC DOSAGE GUIDELINES FOR OTITIS MEDIA, ACUTE BACTERIAL SINUSITIS, AND COMMUNITYACQUIRED PNEUMONIA (Age 6 months and above, Based on Body Weight

OTITIS MEDIA AND COMMUNITY-ACQUIRED PNEUMONIA: (5-Day Regimen)*					
Dosing Calculated on 10 mg/kg/day Day 1 and 5 mg/kg/day Days 2 to 5.					
Weight		**100 mg/5 mL**		**Total mL per Treatment Course**	**Total mg per Treatment Course**
Kg	**Lbs.**	**Day 1**	**Days 2-5**		
5	11	2.5 mL; (½ tsp)	1.25 mL;(¼ tsp)	7.5 mL	150 mg
10	22	5 mL; (1tsp)	2.5 mL; (½ tsp)	15 mL	300 mg

* Effectiveness of the 3-day or 1-day regimen in pediatric patients with community-acquired pneumonia has not been established.

OTITIS MEDIA AND ACUTE BACTERIAL SINUSITIS: (3-Day Regimen)*					
Dosing Calculated on 10 mg/kg/day.					
Weight		**100 mg/5 mL Days 1-3**		**Total mL per Treatment Course**	**Total mg per Treatment Course**
Kg	**Lbs.**	**Day 1**	**Days 2-5**		
5	11	2.5 mL; (½ tsp)	1.25 mL;(¼ tsp)	7.5 mL	150 mg
10	22	5 mL; (1tsp)	2.5 mL; (½ tsp)	15 mL	300 mg

*Effectiveness of the 5-day or 1-day regimen in pediatric patients with acute bacterial sinusitis has not been established.

3- DOSAGE FORMS AND STRENGTHS

ZITHRODOSE for oral suspension after constitution contains a flavored suspension. ZITHRODOSE for oral suspension is supplied to provide 100 mg/5 mL suspension in bottles.

4- Contraindications

4.1 Hypersensitivity

ZITHRODOSE is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide drug.

4.2 Hepatic Dysfunction

ZITHRODOSE is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin.

Discontinue Zithrodose immediately if signs and symptoms of hepatitis occur.

ZITHRODOSE have been associated with cardiovascular effects, especially prolongation of the QT interval can lead to Torsades of points (TdP).

5- WARNINGS AND PRECAUTIONS

This drug should not be used in patients with phenyl ketone urea. And patient with sugar intolerance as it contain sugar.

5.1 Hypersensitivity

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported in patients on azithromycin therapy.

Fatalities have been reported. Cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is presently unknown.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that allergic symptoms may reappear when symptomatic therapy has been discontinued.

5.2 Hepatotoxicity

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur.

5.3 QT Prolongation

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen with treatment with macrolides, including azithromycin. Cases of torsades de pointes have been spontaneously reported during post marketing surveillance in patients receiving azithromycin. Providers 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 known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmias or uncompensated heart failure
- patients on drugs known to prolong the QT interval
- Patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesaemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents.

Elderly patients may be more susceptible to drug-associated effects on the QT interval.

***5.4 Clostridium difficile*-Associated Diarrhea (CDAD)**

Clostridium difficile-associated diarrhea has been reported with use of nearly all antibacterial agents, including ZITHRODOSE, and may range in severity from mild diarrhea 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 antibacterial 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.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.5 Exacerbation of Myasthenia Gravis

Exacerbation of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving azithromycin therapy.

5.6 Use in Sexually Transmitted Infections

ZITHRODOSE, at the recommended dose, should not be relied upon to treat syphilis. Antibacterial agents used to treat non-gonococcal urethritis may mask or delay the symptoms of incubating syphilis. All patients with sexually transmitted urethritis or cervicitis should have a serologic test for syphilis and appropriate testing for gonorrhea performed at the time of diagnosis. Appropriate antibacterial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

5.7 Development of Drug-Resistant Bacteria

Prescribing ZITHRODOSE in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

6- ADVERSE REACTIONS

6.1 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.

Pediatric Patients

Single and Multiple-dose regimens: The types of adverse reactions in pediatric patients were comparable to those seen in adults, with different incidence rates for the dosage regimens recommended in pediatric patients.

Acute Otitis Media: For the recommended total dosage regimen of 30 mg/kg, the most frequent adverse reactions (≥1%) attributed to treatment were diarrhea, abdominal pain, vomiting, nausea, and rash.

Community-Acquired Pneumonia: For the recommended dosage regimen of 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5, the most frequent adverse reactions attributed to treatment were diarrhea/loose stools, abdominal pain, vomiting, nausea, and rash.

Pharyngitis/Tonsillitis: For the recommended dosage regimen of 12 mg/kg on Days 1-5, the most frequent adverse reactions attributed to treatment were diarrhea, vomiting, abdominal pain, nausea, and headache.

With any of the treatment regimens, no other adverse reactions occurred in pediatric patients treated with Azithromycin with a frequency greater than 1%. Adverse reactions that occurred with a frequency of 1% or less included the following:
Cardiovascular: Chest pain.
Gastrointestinal: Dyspepsia, constipation, anorexia, enteritis, flatulence, gastritis, jaundice, loose stools, and oral moniliasis.
Hematologic and Lymphatic: Anemia and leukopenia.
Nervous System: Headache (otitis media dosage), hyperkinesia, dizziness, agitation, nervousness, and insomnia.
General: Fever, face edema, fatigue, fungal infection, malaise, and pain.
Allergic: Rash and allergic reaction.
Respiratory: Cough, pharyngitis, pleural effusion, and rhinitis.
Skin and Appendages: Eczema, fungal dermatitis, pruritus, sweating, urticaria, and vesiculobullous rash.
Special Senses: Conjunctivitis.

6.2 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 post marketing 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 torsades de pointes. Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea, pseudomembranous colitis, pancreatitis, oral candidiasis, pyloric stenosis, and reports of tongue discoloration. General: Asthenia, paresthesia, fatigue, malaise, and anaphylaxis Genitourinary: Interstitial nephritis and 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 serious skin reactions including erythema multiforme, 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.

6.3 Laboratory Abnormalities

Pediatric Patients:
One, Three, and Five Day Regimens Laboratory data collected from comparative clinical trials employing two 3-day regimens (30 mg/kg or 60 mg/kg in divided doses over 3 days), or two 5-day regimens (30 mg/kg or 60 mg/kg in divided doses over 5 days) were similar for regimens of azithromycin and all comparators combined, with most clinically significant laboratory abnormalities occurring at incidences of 1-5%. Laboratory data for patients receiving 30 mg/kg as a single dose were collected in one single center trial. In that trial, an absolute neutrophil count between 500-1500 cells/mm3 was observed in 10/64 patients receiving 30 mg/kg as a single dose, 9/62 patients receiving 30 mg/kg given over 3 days, and 8/63 comparator patients. No patient had an absolute neutrophil count <500 cells/mm3.

In multiple-dose clinical trials involving approximately 4700 pediatric patients, no patients discontinued therapy because of treatment-related laboratory abnormalities.

7- DRUG INTERACTIONS

7.1 Nelfinavir

Co-administration of nelfinavir at steady-state with a single oral dose of azithromycin resulted in increased azithromycin serum concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nelfinavir, close monitoring for known adverse reactions of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted.

7.2 Warfarin

Spontaneous post marketing reports suggest that concomitant administration of azithromycin may potentiate the effects of oral anticoagulants such as warfarin, although the prothrombin time was not affected in the dedicated drug interaction study with azithromycin and warfarin. Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants concomitantly.

7.3 Potential Drug-Drug Interactions with Macrolides

Interactions with digoxin or phenytoin have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interactions. However, drug interactions have been observed with other macrolide products. Until further data are developed regarding drug interactions when digoxin or phenytoin are used concomitantly with azithromycin careful monitoring of patients is advised.

8- USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose concentrations (i.e., 200 mg/kg/day). These daily doses in rats and mice, based on body surface area, are estimated to be 4 and 2 times, respectively, an adult daily dose of 500 mg. In the animal 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 clearly needed.

8.2 Nursing Mothers

Azithromycin has been reported to be excreted in human breast milk in small amounts. Caution should be exercised when azithromycin is administered to a nursing woman.

8.3 Pediatric Use

Safety and effectiveness in the treatment of pediatric patients with acute otitis media, acute bacterial sinusitis and community-acquired pneumonia under 6 months of age have not been established. Use of ZITHRODOSE for the treatment of acute bacterial sinusitis and community-acquired pneumonia in pediatric patients (6 months of age or greater) is supported by adequate and well-controlled trials in adults

Pharyngitis/Tonsillitis: Safety and effectiveness in the treatment of pediatric patients with pharyngitis/tonsillitis under 2 years of age have not been established.

8.4 Geriatric Use

In multiple-dose clinical trials of oral azithromycin, 9% of patients were at least 65 years of age (458/4949) and 3% of patients (144/4949) were at least 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Elderly patients may be more susceptible to development of torsades de pointes arrhythmias than younger patients.

9- OVERDOSAGE

Adverse reactions experienced at higher than recommended doses were similar to those seen at normal doses particularly nausea, diarrhea, and vomiting. In the event of over dosage, general symptomatic and supportive measures are indicated as required.

10- CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Azithromycin is a macrolide antibacterial drug.

10.2 Pharmacodynamics

Based on animal models of infection, the antibacterial activity of azithromycin appears to correlate with the ratio of area under the concentration-time curve to minimum inhibitory concentration (AUC/MIC) for certain pathogens (S. pneumonia and S. aureus). The principal pharmacokinetic/pharmacodynamics

parameter best associated with clinical and microbiological cure has not been elucidated in clinical trials with azithromycin.

Cardiac Electrophysiology

QTc interval prolongation was studied in a randomized, placebo-controlled parallel trial in 116 healthy subjects who received either chloroquine (1000 mg) alone or in combination with oral azithromycin (500 mg, 1000 mg, and 1500 mg once daily). Co-administration of azithromycin increased the QTc interval in a dose-and concentration-dependent manner. In comparison to chloroquine alone, the maximum mean (95% upper confidence bound) increases in QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with the co-administration of 500 mg, 1000 mg and 1500 mg azithromycin, respectively.

10.3 **Pharmacokinetics**

Absorption

When azithromycin oral suspension was administered with food to 28 adult healthy male subjects, Cmax increased by 56% and AUC was unchanged.

Distribution

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 mcg/mL to 7% at 2 mcg/mL.

The antibacterial activity of azithromycin is pH related and appears to be reduced with decreasing pH, However, the extensive distribution of drug to tissues may be relevant to clinical activity.

Azithromycin has been shown to penetrate into human tissues, including skin, lung, tonsil, and cervix. Extensive tissue distribution was confirmed by examination of additional tissues and fluids (bone, ejaculum, prostate, ovary, uterus, salpinx, stomach, liver, and gallbladder). As there are no data from adequate and well-controlled studies of azithromycin treatment of infections in these additional body sites, the clinical significance of these tissue concentration data is unknown.

Metabolism

In vitro and in vivo studies to assess the metabolism of azithromycin have not been performed.

Elimination

Plasma concentrations of azithromycin following single 500 mg oral and IV doses declined in a polyphasic pattern resulting in a mean apparent plasma clearance of 630 mL/min and terminal elimination half-life of 68 hr. The prolonged terminal half-life is thought to be due to extensive uptake and subsequent release of drug from tissues. Biliary excretion of azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

Specific Populations

Hepatic Insufficiency

The pharmacokinetics of azithromycin in subjects with hepatic impairment has not been established.

Geriatric Patients

Pharmacokinetic parameters in older volunteers (65 to 85 years old) were similar to those in young adults (18 to 40 years old) for the 5-day therapeutic regimen. Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen.

Pediatric Patients

In two clinical studies, azithromycin for oral suspension was dosed at 10 mg/kg on day 1, followed by 5 mg/kg on days 2 through 5 in two groups of pediatric patients (aged 1-5 years and 5-15 years, respectively). The mean pharmacokinetic parameters on day 5 were Cmax=0.216 mcg/mL, Tmax=1.9 hr, and AUC0-24=1.822 mcg·hr/mL for the 1 to 5-year-old group and were Cmax=0.383 mcg/mL, Tmax=2.4 hr, and AUC0-24=3.109 mcg·hr/mL for the 5 to 15-year-old group.

Single dose pharmacokinetics of azithromycin in pediatric patients given doses of 30 mg/kg have not been studied.

11 Storage conditions:

Store at room temperature.

12 Package:

Carton box contains glass bottle to make 15 - 30 – 45 - 60 ml suspension + inner leaflet.

Produced by Averroes pharma for pharmaceutical industries
Block No.6048, 6th industrial zone, Sadat city, Egypt.