Zithromax®

Azithromycin

200 mg/5ml Powder for Oral Suspension

Reference Market: UK

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zithromax 200 mg in 5 ml suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zithromax Powder for Oral Suspension is a dry blend of azithromycin dihydrate 209.60 mg per 5 ml, containing the equivalent of 200 mg azithromycin base, on reconstitution with water.

Excipients with known effect:
Also contains 3.87 g sucrose per 5 ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for Oral Suspension
A dry powder which reconstitutes with water to give a cherry/banana flavoured suspension with a slight vanilla odour.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Azithromycin is indicated for the treatment of the following infections when known or likely to be due to one or more susceptible microorganisms (see section 5.1):

- bronchitis
- community-acquired pneumonia
- sinusitis
- pharyngitis/tonsillitis (see section 4.4 regarding streptococcal infections)
- otitis media
- skin and soft tissue infections
- uncomplicated genital infections due to *Chlamydia trachomatis and Neisseria gonorrhoeae.*

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

4.2. Posology and method of administration

Posology
Zithromax should be given as a single daily dose.

Zithromax Suspension can be taken with or without 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. For susceptible *Neisseria gonorrhoeae* the recommended dose is 1000 mg or 2000 mg of azithromycin in combination with 250 mg or 500 mg ceftriaxone according to local clinical treatment guidelines. For patients who are allergic to penicillin and/or cephalosporins, prescribers should consult local treatment guidelines.

Paediatric population:
In children under 45 kg body weight: Zithromax 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, Zithromax Suspension should be administered using the spoon provided according to the following guidance:

15-25 kg (3-7 years): 5 ml (200 mg) given as 1 x 5 ml spoonful, once daily for 3 days.

26-35 kg (8-11 years): 7.5 ml (300 mg) given as 1 x 7.5 ml spoonful, once daily for 3 days.

36-45 kg (12-14 years): 10 ml (400 mg) given as 1 x 10 ml spoonful, once daily for 3 days.

Over 45 kg: Dose as per adults.
See section 6.5 for appropriate pack size to use depending on age/body weight of child.

The specially supplied measure should be used to administer Zithromax suspension to children.

Renal impairment:
No dose adjustment is necessary in patients with GFR 10 – 80 ml/min. Caution should be exercised when azithromycin is administered to patients with GFR < 10 ml/min (see section 4.4 and section 5.2).

Hepatic impairment:
Since azithromycin 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 (see section 4.4).

Method of administration
Zithromax Suspension is for oral administration only.

4.3. Contraindications

Zithromax is contra-indicated in patients with a known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients (listed in section 6.1).

4.4. Special warnings and precautions for use

Hypersensitivity
As with erythromycin and other macrolides, serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), Acute Generalized Exanthematous Pustulosis (AGEP) 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.

Hepatotoxicity
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 4.8). 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.

Ergot derivatives
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.

Prolongation of the QT interval
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 (see section 4.8); 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 hypokalaemia and hypomagnesemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Superinfection
As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms including fungi is recommended.

Clostridium difficile associated diarrhoea
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. 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 diarrhoea during or subsequent to the administration of any antibiotics. Careful medical history is necessary since CDAD has been reported to occur over 2 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.

Renal impairment
In patients with GFR <10 ml/min a 33% increase in systemic exposure to azithromycin was observed (see section 5.2).

Myasthenia gravis
Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy (see section 4.8).

Hydroxychloroquine or chloroquine
Carefully consider the balance of benefits and risks before prescribing azithromycin for any patients

taking hydroxychloroquine or chloroquine, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality (see section 4.5).

Diabetes
Caution in diabetic patients: 5 ml of reconstituted suspension contains 3.87 g of sucrose.

Excipients information
Zithromax suspension contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Zithromax suspension contains less than 1 mmol sodium (23 mg) per 5 ml of reconstituted suspension, that is to say essentially 'sodium-free'.

Zithromax Suspension is for oral administration only.

4.5. Interactions with other medicinal products and other forms of interaction

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 24%. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously.

Cetirizine: In healthy volunteers, co-administration of a 5-day regimen of azithromycin with 20 mg cetirizine 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 six HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared to placebo.

Digoxin and colchicine: concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-glycoprotein substrates such as digoxin are administered concomitantly, the possibility of elevated serum digoxin concentrations should be considered. Clinical monitoring, and possibly serum digoxin levels, during treatment with azithromycin and after its discontinuation are necessary.

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).

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 dose of 15 mg 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 who 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 AUC_{0-5} were found to be significantly elevated (by 24% and 21% respectively), however no significant changes were seen in $AUC_{0-\infty}$. 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 single dose of 600mg 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 500 mg/day azithromycin for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single dose of 15 mg 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 was 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 4.8.).

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*:* In 14 healthy volunteers, co-administration of 500 mg azithromycin on Day 1 and 250 mg on Day 2 with 0.125 mg triazolam on Day 2 had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

Trimethoprim/sulfamethoxazole: Co-administration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with 1200 mg azithromycin on Day 7 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.

Hydroxychloroquine or chloroquine: Observational data have shown that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Carefully consider the balance of benefits and risks before prescribing azithromycin for any patients taking hydroxychloroquine. Similar careful consideration of the balance of benefits and risk should also be undertaken before prescribing azithromycin for any patients taking chloroquine, because of the potential for a similar risk with chloroquine.

Medicinal products which are known to prolong the QT interval (see section 4.4): Azithromycin should be used with caution in patients receiving medicines known to prolong the QT interval with potential to induce cardiac arrhythmia, e.g. hydroxychloroquine.

4.6. Fertility, pregnancy and lactation

Pregnancy

Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of harm to the foetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women.

There is a large amount of data from observational studies performed in several countries on exposure to azithromycin during pregnancy, compared to no antibiotic use or use of another antibiotic during the same period (> 7,300 first trimester exposures). While most studies do not suggest an association with adverse foetal effects such as major congenital malformations or cardiovascular malformations, there is limited epidemiological evidence of an increased risk of miscarriage following azithromycin exposure in early pregnancy. Therefore, azithromycin should only be used during pregnancy if clinically needed and the benefit of treatment is expected to outweigh any small increased risks which may exist.

Breast-feeding

Limited information available from published literature indicates that azithromycin is present in human milk at an estimated highest median daily dose of 0.1 to 0.7 mg/kg/day. No serious adverse effects of azithromycin on the breast-fed infants were observed. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7. Effects on ability to drive and use machines

There is no evidence to suggest that Zithromax may have an effect on a patient's ability to drive or operate machinery.

4.8. Undesirable effects

Zithromax is well tolerated with a low incidence of side effects.

The section below lists the adverse reactions identified through clinical trial experience and postmarketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in italics. The frequency grouping is defined using the following convention: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 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.

Adverse reactions possibly or probably related to azithromycin based on clinical trial experience and post-marketing surveillance:

Infections and Infestations
Uncommon *(≥ 1/1,000 to < 1/100)*
Candidiasis, oral candidiasis, vaginal infection
Not known *(cannot be estimated from available data)*
Pseudomembranous colitis (see section 4.4)

Blood and Lymphatic System Disorders
Uncommon *(≥ 1/1,000 to < 1/100)*
Leukopenia, neutropenia
Not known *(cannot be estimated from available data)*
Thrombocytopenia, haemolytic anaemia

Immune System Disorders
Uncommon *(≥ 1/1,000 to < 1/100)*
Angioedema, hypersensitivity
Not known *(cannot be estimated from available data)*
Anaphylactic reaction (see section 4.4)

Metabolism and Nutrition Disorders
Common *(> 1/100 < 1/10)*
Anorexia

Psychiatric Disorders
Uncommon *(≥ 1/1,000 to < 1/100)*
Nervousness
Rare *(> 1/10,000 < 1/1,000)*
Agitation
Not known *(cannot be estimated from available data)*
Aggression, anxiety

Nervous System Disorders
Common *(> 1/100 < 1/10)*
Dizziness, headache, paraesthesia, dysgeusia

Uncommon *(≥ 1/1,000 to < 1/100)*
Hypoaesethesia, somnolence, insomnia
Not known *(cannot be estimated from available data)*
Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, *Myasthenia gravis* (see section 4.4)

Eye Disorders
Common *(> 1/100 < 1/10)*
Visual impairment

Ear and Labyrinth Disorders
Common *(> 1/100 < 1/10)*
Deafness
Uncommon *(≥ 1/1,000 to < 1/100)*
Hearing impaired, tinnitus
Rare *(> 1/10,000 < 1/1,000)*
Vertigo

Cardiac Disorders
Uncommon *(≥ 1/1,000 to < 1/100)*
Palpitations
Not known *(cannot be estimated from available data)*
Torsades de pointes (see section 4.4), arrhythmia (see section 4.4) including ventricular tachycardia

Vascular Disorders
Not known *(cannot be estimated from available data)*
Hypotension

Gastrointestinal Disorders
Very common *(≥ 1/10)*
Diarrhoea, abdominal pain, nausea, flatulence
Common *(> 1/100 < 1/10)*
Vomiting, dyspepsia
Uncommon *(> 1/1,000 < 1/100)*
Gastritis, constipation
Not known *(cannot be estimated from available data)*
Pancreatitis, tongue discolouration

Hepatobiliary Disorders
Uncommon *(> 1/1,000 < 1/100)*
Hepatitis
Rare *(> 1/10,000 < 1/1,000)*
Hepatic function abnormal
Not known *(cannot be estimated from available data)*
Hepatic failure (see section 4.4), which has rarely resulted in death, hepatitis fulminant, hepatic necrosis, jaundice cholestatic

Skin and Subcutaneous Tissue Disorders
Common *(> 1/100 < 1/10)*
Pruritus and rash
Uncommon *(> 1/1,000 < 1/100)*
SJS, photosensitivity reaction, urticaria
Rare *(≥ 1/10,000 to < 1/1,000)*
Acute Generalized Exanthematous Pustulosis (AGEP)*§

Drug reaction with eosinophilia and systemic symptoms (DRESS)*§
Not known *(cannot be estimated from available data)*
TEN, erythema multiforme

Musculoskeletal, Connective Tissue Disorders
Common *(> 1/100 < 1/10)*
Arthralgia

Renal and Urinary Disorders
Not known *(cannot be estimated from available data)*
Renal failure acute, nephritis interstitial

General disorders and Administration Site Conditions
Common *(> 1/100 < 1/10)*
Fatigue
Uncommon *(> 1/1,000 < 1/100)*
Chest pain, oedema, malaise, asthenia

Investigations
Common *(> 1/100 < 1/10)*
Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased
Uncommon *(> 1/1,000 < 1/100)*
Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal
Not known *(cannot be estimated from available data)*
Electrocardiogram QT prolonged (see section 4.4)

*ADR identified post-marketing
§ADR frequency represented by the estimated upper limit of the 95% confidence interval calculated using the "Rule of 3".

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after marketing authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions according to their local requirements

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 diarrhoea. 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
Pharmacotherapeutic group: Antibacterials for systemic use. ATC code: J01FA10

Mode of action
Zithromax 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.

Azithromycin demonstrates cross resistance with erythromycin resistant gram positive isolates. A decrease in macrolide susceptibility over time has been noted particularly in Streptococcus pneumoniae and Staphylococcus aureus. Similarly, decreased susceptibility has been observed among Streptococcus viridans and Streptococcus agalactiae (Group B) streptococcus against other macrolides and lincosamides.

Breakpoints
Azithromycin susceptibility breakpoints for typical bacterial pathogens published by EUCAST are:

Organism	**MIC breakpoints (mg/L)**	
	Susceptible (S≤)	**Resistant (R>)**
Staphylococcus spp.	1	2
Streptococcus groups A, B, C and G	0.25	0.5
Streptococcus pneumoniae	0.25	0.5
Haemophilus influenzae	0.12	4
Moraxella catarrhalis	0.25	0.5
Neisseria gonorrhoeae	0.25	0.5

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.

Table: 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
Neisseria gonorrhoeae
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 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.

Paediatric population
Following the assessment of studies conducted in children, the use of azithromycin is not recommended for the treatment of malaria, neither as monotherapy nor combined with chloroquine or artemisinin based drugs, as non-inferiority to anti-malarial drugs recommended in the treatment of uncomplicated malaria was not established.

5.2. Pharmacokinetic properties

Absorption
Bioavailability after oral administration is approximately 37%. Peak plasma concentrations are attained 2 to 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 to 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.

5.3. Preclinical safety data

Phospholipidosis (intracellular phospholipid accumulation) has been observed in several tissues (e.g. eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and/or pancreas) of mice, rats, and dogs given multiple doses of azithromycin. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs. The effect has been shown to be reversible after cessation of azithromycin treatment. The significance of the finding for animals and humans is unknown.

Carcinogenic potential
Long-term studies in animals have not been performed to evaluate carcinogenic potential as the drug is indicated for short-term treatment only and there were no signs indicative of carcinogenic activity.

Mutagenic potential
There was no evidence of a potential for genetic and chromosome mutations in in-vivo and in-vitro test models.

Reproductive toxicity
In animal studies for embryotoxic effects of the substance, no teratogenic effect was observed in mice and rats. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day led to mild retardation of foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardation following treatment with 50 mg/kg/day azithromycin and above was observed.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Hydroxypropylcellulose
Sodium phosphate tribasic anhydrous
Sucrose
Xanthan gum
Flavours:
Artificial banana
Artificial cherry
Artificial creme de vanilla.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Do not use Zithromax after the expiry date which is stated on the carton/ vial label after EXP:. The expiry date refers to the last day of that month.

6.4. Special precautions for storage

Before reconstitution Store below 30°C.

After reconstitution, the oral suspension is stable for 5 days at 30°C.

6.5. Nature and contents of container

Zithromax Powder for Oral Suspension is available as:

600 mg (15 ml) Pack: (Recommended for use in children up to 7 years (25 kg)).
Packs of powder equivalent to 600 mg azithromycin in a High-Density Polyethylene bottle (opaque) with child resistant screw cap (with or without a tamper evident seal), in a carton box. Pack contains a double-ended multi-dosing spoon[1] and 10 ml oral dosing syringe with detachable adaptor. Reconstitute with 9 ml of water to give 15 ml suspension.

900 mg (22.5 ml) Pack: (Recommended for use in children aged from 8-11 years (26-35 kg)).
Packs of powder equivalent to 900 mg azithromycin in a High-Density Polyethylene bottle (opaque) with child resistant screw cap (with or without a tamper evident seal), in a carton box. Pack contains a double-ended multi-dosing spoon[1]. Reconstitute with 12 ml of water to give 22.5 ml suspension.

1200 mg (30 ml) Pack: (Recommended for use in children aged from 12-14 years (36-45 kg)).
Packs of powder equivalent to 1200 mg azithromycin in High-Density Polyethylene bottle (opaque) with child resistant screw cap (with or without a tamper evident seal) in a carton box. Pack contains a double-ended multi-dosing spoon[1]. Reconstitute with 15 ml of water to give 30 ml suspension.

Multi-dosing spoon delivers doses as follows:

Small end to graduation	2.5 ml (100 mg)
brimful	5 ml (200 mg)
Large end to graduation	7.5 ml (300 mg)
brimful	10 ml (400 mg)

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Keep out of the sight and reach of children.

When dispensing the 15 ml pack, advice should be given as to whether the dose should be measured using the oral dosing syringe

or the spoon provided and on correct usage. If the dose is to be given using the oral dosing syringe, before dispensing the syringe adaptor should be detached from the syringe and inserted into the bottle neck and the cap replaced.

When dispensing 22.5 ml and 30 ml packs, advice should be given as to the correct usage of the multi-

dosing spoon.

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

7. FUTHER INFORMATION

MARKETING AUTHORISATION HOLDER.
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United Kingdom

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8. DATE OF REVISION OF THE TEXT
August 2023

THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep all medicaments out of reach of children

Council of Arab Health Ministers
Union of Arabic Pharmacists