Zithromax®

Azithromycin

200 mg/5ml Powder for Oral Suspension

Reference Market: Italy

AfME Markets using same as LPD
Bahrain, Iran, Jordan, Kuwait, Oman, Qatar, Sudan, UAE, Yemen, Iraq

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ZITHROMAX 200 mg/5 mL powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZITROMAX powder for oral suspension – 600 mg vial
The reconstituted suspension contains 40 mg of azithromycin per ml (200 mg for a 5 ml dose).
100 grams of powder contains:
Active ingredient
Azithromycin dihydrate 5.01 g
equivalent to Azithromycin base4.78 g

ZITHROMAX powder for oral suspension – 900 mg vial
The reconstituted suspension contains 40 mg of azithromycin per ml (200 mg for one dose of 5 ml).
100 grams of powder contains:
Active ingredient:
Azithromycin dihydrate 5.01 g
Equivalent to Azithromycin base 4.78 g

ZITHROMAX powder for oral suspension – 1200 mg vial
The reconstituted suspension contains 40 mg of azithromycin per ml (200 mg for one dose of 5 ml).
The composition per 100 grams of powder contains:
Active ingredient:
Azithromycin dihydrate 5.01 g
equivalent to Azithromycin base 4.78 g
Excipients with known effects: the medicine contains sucrose.
For the complete list of excipients, see Section 6.1.

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For the complete list of excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Powder for oral suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of infections caused by azithromycin-susceptible bacteria.
- infections of the upper respiratory tract (sinusitis, tonsillitis, and pharyngitis);
- infections of the lower respiratory tract (including bronchitis and pneumonia);
- middle ear infections (acute otitis media);
- odontostomatological infections;
- skin and soft tissue infections.

4.2 Posology and method of administration

Adults
For the treatment of upper and lower respiratory tract infections, skin and soft tissue infections and oral and dental infections: 500 mg per day taken once daily, for three consecutive days.

Elderly
The same dosage regimen can be applied to elderly patients.
Since elderly patients are more susceptible to the development of cardiac arrhythmia, particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes (see section 4.4).

Paediatric population
10 mg/kg/day for 3 consecutive days.
For children weighing 45 kg or more, the adult dose can be used (500 mg/day for three consecutive days).

Weight (kg)	**Dosage regimen**
< 15	10 mg/kg/day for 3 days
15-25	200 mg (5 mL)/day for 3 days
26-35	300 mg (7.5 mL)/day for 3 days
36-45	400 mg (10 mL)/day for 3 days
> 45	500 mg/day for 3 days (same dosage as adults)

For the treatment of acute otitis media in children, the recommended dose is 10 mg/kg/day for 3 consecutive days or 30 mg/kg in a single dose.

For the treatment of streptococcal pharyngitis in children efficacy has been observed with a 10 mg/kg dose as well as 20 mg/kg, both in a single administration and for three consecutive days; however, a daily dose of 500 mg should not be exceeded. Similar efficacy has been observed in clinical studies on the two dosages, although greater bacterial eradication was found with the 20 mg/kg/day dosage. However, penicillin is the medicine of choice for the treatment of pharyngitis caused by *Streptococcus pyogenes* and for the prophylaxis of rheumatic fever.

The total maximum dosage recommended for any paediatric treatment is 1500 mg.

The drug must always be administered in a single daily dose.

ZITHROMAX (azithromycin) oral suspension may be taken any time whether on an empty stomach or after meals. Eating before administration of this drug may mitigate any adverse gastrointestinal side effects caused by azithromycin.

Method of administration: For instructions on reconstitution and administration, see section 6.6.

Renal impairment
No dose adjustment is required for patients with mild to moderate renal impairment (GFR 10-80 mL/min); however, caution is necessary in those seriously compromised (GFR < 10 mL/min) (see sections 4.4 and 5.2).

Hepatic impairment
The same dosage used in patients with normal hepatic function may be used in patients with a mild to moderate change in hepatic function (see sections 4.4 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substance, erythromycin, any other macrolide or ketolide antibiotics, 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, rare serious allergic reactions, including angioneurotic oedema and

anaphylaxis (rarely fatal), dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these reactions with Zithromax have resulted in recurrent symptoms and required a longer period of observation and treatment.

If an allergic reaction occurs, the drug should be discontinued, and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Hepatotoxicity

Since liver it's the principal route of elimination for azithromycin, the use of azithromycin in patients with serious hepatic diseases must be undertaken with caution . With azithromycin, there have been reports of hepatic impairment, hepatitis, cholestatic jaundice, hepatic necrosis and fulminant hepatitis, potentially causing liver failure, some of which have resulted in death (see section 4.8). A few patients may have had previous hepatic diseases or may have taken other hepatotoxic medicinal products. If signs and symptoms of hepatic dysfunction develop, such as rapid appearance of asthaenia associated with jaundice, dark urine, bleeding or hepatic encephalopathy, diagnostic analysis/exams must be run on hepatic function immediately. Immediately suspend treatment with azithromycin if any signs of hepatic dysfunction develop.

Infantile hypertrophic pyloric stenosis (IHPS)

Following the use of azithromycin in newborns (treatment until 42nd day of life), infantile hypertrophic pyloric stenosis (IHPS) has been reported. Parents and caregivers should be advised to contact their doctor if vomiting or irritability occurs as a result of food intake.

Ergotamine derivatives

Co-administration of macrolide antibiotics in patients being treated with ergotamine derivatives has precipitated convulsive ergotism. There are no data currently available on the possibility of interaction between ergotamine and azithromycin. However, due to the theoretical possibility of ergotism, azithromycin and ergotamine must not be co-administered.

As with all other antibiotic preparations, it is recommended to carefully monitor for any development of super infections with resistant micro-organisms including fungi.

Diarrhoea associated with *Clostridium difficile*

As with almost all antibiotics, including azithromycin, there have been reports of diarrhoea associated with *Clostridium difficile* (CDAD), the severity of which can vary from mild diarrhoea to fatal colitis. Treatment with antibiotics alters the normal flora of the colon and results in excessive growth of *C. difficile.*

C. difficile produces toxins A and B, which contribute to the development of diarrhoea. *C. difficile* strains that produce excess toxins cause an increase in morbidity and mortality rates since these infections are generally refractory to antibiotic treatment and often require a colectomy. The possibility of diarrhoea associated with *C. difficile* must be considered in all patients who present with diarrhoea after a treatment with antibiotics. A detailed patient history is also necessary because cases of diarrhoea associated with *C. difficile* have been also reported over two months after the administration of antibiotics.

In patients with seriously compromised renal function (GFR < 10 mL/min) a 33% increase in systemic exposure to azithromycin was observed (see section 5.2).

Prolongation of the QT Interval

In treatment with macrolides, including azithromycin, a prolonged cardiac repolarisation and QT interval have been observed on ECGs, with the risk of developing cardiac arrhythmia and torsade de pointes (see section 4.8). Therefore, since the following situations may result in an increased risk of ventricular arrhythmias (including torsade de pointes), which may lead to cardiac arrest, azithromycin must be administered with caution to patients with concomitant conditions of proarrhythmia (especially in women and elderly patients).

Prescribing doctors must take into account the risk of prolonging the QT interval, which may be fatal, when evaluating the risk-benefit ratio of azithromycin in groups of at risk patients, such as:

- Patients with congenital or documented prolonged QT interval;
- Patients under treatment with other active ingredients that prolong the QT interval such as class IA (quinidine and procainamide) and class III (dofetilide, amiodarone and sotalol) anti-arrhythmics, cisapride and terfenadine, antipsychotic drugs such as pimozide, antidepressants such as citalopram, fluoroquinolones such as moxifloxacin, levofloxacin and chloroquine;
- Patients with electrolyte changes, especially in cases of hypopotassaemia and hypomagnesaemia;
- Patients with clinically significant bradycardia, cardiac arrhythmia or severe heart failure;
- Women and elderly patients who may demonstrate greater sensitivity to the (drug-related) effects of alteration of the QT interval.

In patients receiving azithromycin therapy, there have been reports of exacerbation in symptoms of myasthenia gravis and initial development of myasthenic syndrome (see section 4.8).

Zithromax 200 mg/5 mL powder for oral suspension contains 3,87 g of **sucrose** (sugar) in 5 mL of reconstituted suspension. This should be taken into account in patients with diabetes mellitus.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids
In a pharmacokinetic study investigating the effects of co-administration of antacids and azithromycin, no effect was detected on the bioavailability of azithromycin, although a decrease *of approximately 25%* was observed in maximum serum concentrations. Therefore, patients receiving both azithromycin and antacids should not take the two drugs concomitantly.

Cetirizine
In healthy volunteers, the co-administration of a 5-day regimen of azithromycin with 20 mg cetirizine at *steady state* did not show any pharmacokinetic interactions or significant changes in the QT interval.

Didanosine
It was observed that co-administration of daily doses of 1200 mg/day azithromycin and 400 mg/day didanosine in six HIV-positive patients did not have any effect on the *steady state* pharmacokinetics of didanosine compared to placebo.

Digoxin and colchicine (P glycoprotein substrates)
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 substrates. 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 the treatment with azithromycin and after its discontinuation, are necessary.

Zidovudine
The administration of individual 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin did not substantially modify the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, the administration of azithromycin resulted in increased concentrations of phosphorylated zidovudine, its clinically active metabolite, in the peripheral blood mononuclear cells. The clinical significant of this finding is unclear, but it may be of benefit to patient.

Azithromycin does not significantly interact with the hepatic cytochrome P450 system. It is not deemed to be involved in pharmacokinetic interactions as found with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.

Ergotamine
Due to the potential onset of convulsive ergotism, concomitant use of azithromycin and ergotamine derivatives is not recommended (see section 4.4).

Pharmacokinetic studies have been conducted between azithromycin and the following drugs, known to have significant cytochrome P450 mediated metabolic activity.

HMG-CoA Reductase Inhibitors (Statins)
The concomitant administration of atorvastatin (10 mg/day) and azithromycin (500 mg/day) did not alter the plasma concentrations of atorvastatin (based on an HMG-CoA reductase inhibition assay) and thus did not cause alterations of HMG-CoA reductase activity. However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin and statins have been reported.

Carbamazepine
During an interactive study conducted in healthy volunteers, no significant effects were observed on plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

Cimetidine
During a pharmacokinetic study conducted to evaluate the effects of a single dose of cimetidine administered 2 hours after azithromycin, no alterations in azithromycin pharmacokinetics were detected.

Cyclosporine
In a pharmacokinetic study conducted in 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 cyclosporine, significant increases in the C_{max} and AUC_{0-5} values for cyclosporine were observed. Therefore, any co-administration of these two drugs requires caution. If co-administration of these two drugs is absolutely necessary, cyclosporine levels must be closely monitored and the dose of cyclosporine must be adjusted accordingly.

Efavirenz
Co-administration of a single daily dose of azithromycin (600 mg) and efavirenz (400 mg) for 7 days did not cause any clinically significant pharmacokinetic interactions.

Fluconazole
Co-administration of a single dose of azithromycin (1200 mg) did not alter the pharmacokinetics of a single dose of fluconazole (800 mg). The total exposure time and half-life of azithromycin were not influenced by co-administration of fluconazole, although there was a clinically insignificant decrease in C_{max} (18%).

Indinavir
Concomitant administration of a single dose of azithromycin (1200 mg) did not show a statistically significant effect on the pharmacokinetics of indinavir administered three times a day for 5 days at doses of 800 mg.

Methylprednisolone
A pharmacokinetic study conducted on healthy volunteers showed that azithromycin does not significantly influence methylprednisolone pharmacokinetics.

Midazolam
In healthy volunteers, concomitant administration of azithromycin 500 mg/day for 3 days did not cause any clinically significant changes in the pharmacokinetics or pharmacodynamics of a single dose of midazolam 15 mg.

Nelfinavir
Co-administration of azithromycin (1200 mg) and *steady state* nelfinavir (750 mg three times per day) caused an increase in the concentrations of azithromycin. No clinically significant adverse reactions were observed, and no dose adjustment is necessary.

Rifabutin
Concomitant administration of azithromycin and rifabutin does not affect the serum concentrations of the two drugs.
Cases of neutropenia have been observed in some patients taking the two drugs concomitantly; although it is known that rifabutin can cause neutropenia, it is not possible to verify a causal relation between the aforementioned episodes of neutropenia and the association of rifabutin and azithromycin (see section 4.8).

Sildenafil
In healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg/day for 3 days) on the AUC and C_{max} of sildenafil or its major circulating metabolite.

Theophylline
Co-administration of azithromycin and theophylline to healthy volunteers did not show any clinically significant interaction between the two drugs.

Terfenadine
Pharmacokinetic studies did not show any interactions between azithromycin and terfenadine. Some rare cases were reported in which the possibility of this interaction could not be completely excluded; however, there is no scientific evidence that such an interaction had occurred.

Triazolam
In 14 healthy volunteers, concomitant administration of 500 mg of azithromycin on the 1st day and 250 mg on the 2nd day and 0.125 mg of triazolam on Day 2 did not have significant effects on the pharmacokinetic variables of triazolam compared to triazolam and placebo.

Trimethoprim/Sulfamethoxazole
After concomitant administration of trimethoprim/sulfamethoxazole (160 mg/800 mg) and azithromycin (1200 mg) for 7 days, no significant effect was found on peak concentrations, exposure time, or urinary excretion of both trimethoprim and sulfamethoxazole on the 7th day. Azithromycin serum concentrations were similar to those found in other studies.

Coumarin-type Oral Anticoagulants
In a pharmacokinetic study conducted on healthy volunteers, it was observed that azithromycin did not modify the anticoagulant effect of a single 15 mg dose of warfarin.
There have been reports received in the post-marketing period of potentiated anticoagulation subsequent co administration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, it is recommended to re-evaluate the frequency of monitoring prothrombin time when administering azithromycin to patients receiving coumarin-type anticoagulants.

4.6 Fertility, pregnancy and lactation

There are insufficient data for the use of azithromycin in pregnant women. The safety of azithromycin during pregnancy has not been verified. Therefore, azithromycin must only be used during pregnancy if the benefits outweigh the risks.

Pregnancy
Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. No evidence of foetal risk due to azithromycin has emerged from these studies. In animal reproductive toxicology studies, there is evidence that azithromycin crosses the placenta, but no teratogenic effects have been observed. There are no adequate and well-controlled studies available in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin must only be used during pregnancy if absolutely necessary.

Breastfeeding
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 breastfed 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.

Fertility
In fertility studies conducted in rats, a reduction in the fertility rate following administration of azithromycin was observed. The significance of these results in humans is unknown.

4.7 Effects on ability to drive and use machines

There is no evidence that azithromycin affects the ability of patients to drive vehicles or use machinery.

4.8 Undesirable effects

The table below lists the adverse reactions identified during clinical studies and post-marketing surveillance, and they are subdivided based on system organ class and frequency. The possible adverse reactions identified during post-marketing surveillance are shown in italics. Frequency is defined using the following parameters: Very common (≥ 1/10); Common (≥ 1/100, <1/10); Uncommon (≥1/1,000, <1/100); Rare (≥ 1/10,000, < 1/1,000); Very Rare (< 1/10,000); Not Known (cannot be estimated from the available data). Side effects are listed in order of decreasing severity within each frequency classification.

Adverse reactions with possible or probable correlation to azithromycin based on the results of clinical studies and post-marketing surveillance.

System Organ Class	Adverse reaction	Frequency
Infections and Infestations	Candidiasis, vaginal infection, pneumonia, fungal infection, bacterial infection, pharyngitis, gastroenteritis, respiratory disorders, rhinitis, oral candidiasis	Uncommon
	Pseudomembranous colitis (see sec. 4.4)	Not known
Blood and lymphatic system disorders	Leucopenia, neutropenia, eosinophilia	Uncommon
	Thrombocytopenia, haemolytic anaemia	Not known
Immune system disorders	*Angio-oedema, hypersensitivity*	Uncommon
	Anaphylactic reaction (see sec. 4.4)	Not known
Metabolism and nutrition disorders	Anorexia	Uncommon
Psychiatric Disorders	Nervousness, insomnia	Uncommon
	Agitation	Rare
	Aggression, anxiety, delirium, hallucinations	Not known
Nervous System Disorders	Headache	Common
	Dizziness, somnolence, dysgeusia, paraesthesia	Uncommon
	Syncope, convulsions, hypoaesthesia, *psychomotor hyperactivity, anosmia, ageusia, parosmia,* *Myasthenia gravis* (see sec. 4.4)	Not known
Eye Disorders	Vision impairment	Uncommon
	Ear disorders, vertigo	Uncommon
	Hearing impairment including deafness and/or tinnitus	Not known
Cardiac disorders	Palpitations	Uncommon
	Torsade de pointes (see sec. 4.4), *arrhythmia* (see sec. 4.4*) including ventricular tachycardia, prolonged QT interval on the electrocardiogram* (see sec. 4.4)	Not known
Vascular disorders	Hot flashes	Uncommon
	Hypotension	Not known
Respiratory, thoracic and	Dyspnoea, epistaxis	Uncommon

mediastinal disorders		
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting, abdominal pain, nausea	Common
	Constipation, flatulence, dyspepsia, gastritis, dysphagia, abdominal distension, dry mouth, eructation, mouth ulceration, salivary hypersecretion	Uncommon
	Pancreatitis, tongue discolouration	Not known
Hepatobiliary disorders	Impaired hepatic function, *cholestatic jaundice*	Rare
	Hepatic failure (rarely fatal) (see sec. 4.4), *fulminant hepatitis, hepatic necrosis*	Not known
Skin and subcutaneous tissue disorders	Rash, pruritus, urticaria, dermatitis, dry skin, hyperhidrosis	Uncommon
	Photosensitivity reaction, *Acute Generalized Exanthematous Pustulosis (AGEP)*[§]	Rare
	Drug reaction with eosinophilia and systemic symptoms (DRESS)	Very rare
	Stevens-Johnson syndrome, *toxic epidermal necrolysis, erythema multiforme*	Not known
Musculoskeletal and connective tissue disorders	Osteoarthritis, myalgia, back pain, neck pain	Uncommon
	Arthralgia	Not known
Renal and urinary disorders	*Dysuria, renal pain*	Uncommon
	Acute renal insufficiency, interstitial nephritis	Not known
Reproductive System and Breast Disorders	Metrorrhagia, testicular disorders	Uncommon
General disorders and administration site conditions	Oedema, asthenia, malaise, fatigue, facial oedema, chest pain, pyrexia, pain, peripheral oedema	Uncommon
	Pain at injection site*, inflammation at injection site*	Common
Investigations	Decrease in lymphocyte count, increase in eosinophil count, decrease in blood bicarbonate, increase in basophils, increase in monocytes, increase in neutrophils	Common
	Increase in aspartate aminotransferase (AST), increase in alanine aminotransferase (ALT), increase in blood bilirubin, increase in blood urea, increase in blood creatinine, abnormal blood potassium, increase in blood alkaline phosphatase, increase in chloride levels, increase in glucose, increase in platelets, decrease in haematocrit, increase in blood bicarbonate, abnormal sodium levels	Uncommon
Injury and Poisoning	Post-procedural complications	Uncommon

[§] ADR frequency represented by the estimated upper limit of the 95% confidence interval calculated using the "Rule of 3."

* only for the powder for solution for infusion

Adverse reactions possibly or probably related to Mycobacterium Avium Complex prophylaxis and treatment based on clinical trial experience and post-marketing surveillance. These adverse reactions differ from those reported with immediate release or prolonged release formulations, in kind or in frequency:

	Very common (≥ 1/10)	Common (≥ 1/100, < 1/10)	Uncommon (≥ 1/1,000, < 1/100)
Metabolism and nutrition disorders		Anorexia	
Nervous system disorders		Dizziness Migraine Paraesthesia Dysgeusia	Hypoesthesia
Eye Disorders		Vision impairment	
Ear and Labyrinth Disorders		Deafness	Impaired hearing Tinnitus
Cardiac disorders			Palpitations
Gastrointestinal disorders	Diarrhoea Abdominal pain Nausea Flatulence Abdominal discomfort Loose stools		
Hepatobiliary disorders			Hepatitis
Skin and subcutaneous tissue disorders		Rash Pruritus	Stevens-Johnson syndrome Photosensitivity reaction
Musculoskeletal and connective tissue disorders		Arthralgia	
General disorders and administration site conditions		Fatigue	Asthaenia Malaise

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after 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 reactions reported with doses greater than those recommended were similar to those reported with normal doses. In case of overdose, the appropriate general symptomatic and support measures are indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial for systemic use - Macrolides, ATC code: J01FA10.

Azithromycin is first in a sub-class of macrolide antibiotics called azalides and is chemically different from erythromycin. It is chemically derived from the insertion of a nitrogen atom into the lactone ring of the erythromycin A. Its chemical name is: 9-deoxy-9a-aza-9a-methyl-9a-omoerithromycin A. Its molecular weight is 749.0.

Mechanism of action
Azithromycin binds to the 23S rRNA of 50S ribosomal subunit. Azithromycin blocks protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit.

Cardiac electrophysiology
The prolongation of the QT interval was studied in a randomized, placebo-controlled, parallel group study with 116 healthy subjects taking either chloroquine (1000 mg) as monotherapy or in combination with azithromycin (500 mg, 1000 mg, 1500 mg a once a day). Co-administration with azithromycin resulted in an

increase in the QTc interval in correlation with the dose and concentration. The maximum increases in QTcF compared to chloroquine as monotherapy (for which the differences observed compared to placebo ranged between 18.4 ms to 35 ms) were on average (upper limit of 95% confidence interval) of 5 (10) ms, 7 (12) ms and 9 (14) ms following concomitant administration of 500 mg, 1000 mg, 1500 mg azithromycin, respectively.

Mechanism of resistance

The two most frequently encountered mechanisms of resistance to macrolides, including azithromycin, are target modification (very often due to methylation of 23S rRNA) and active efflux. The occurrence of these resistance mechanisms varies from species to species, and within each species the frequency of resistance varies depending on the geographical location.

The most important ribosomal modification that determines reduced binding of macrolides is post-transcriptional (N)- 6 demethylation of adenine at nucleotide A2058 (*E.coli* numbering system) of the 23S rRNA by the methylases codified by *erm* (erithromycin ribosomal methylase) genes.

Ribosomal modifications often determine cross resistance (MLS_Bphenotype) to other classes of antibiotics whose ribosomal binding sites overlap that of the macrolides: the lincosamides (including clindamycin), and the Type B streptogramins (which include, for example, the quinupristin component of quinupristin/dalfopristin). Different *erm* genes are present in different bacterial species, in particular streptococci and staphylococci. Susceptibility to macrolides can also be affected by less frequently encountered mutational changes in nucleotides A2058 and A2059, and at some other positions of 23S rRNA or in the larger subunit ribosomal proteins L4 and L22.

Efflux pumps occur in a number of species, including Gram-negatives, such as *Haemophilus influenzae* (where they may determine intrinsically higher minimal inhibitory concentrations [MICs]) and staphylococci. In streptococci and in enterococci, an efflux pump that recognizes macrolides measuring 14 and 15 atoms (including, respectively, erythromycin and azithromycin) is codified by *mef* (A) genes.

Method for determining in vitro susceptibility of bacteria to azithromycin

Susceptibility testing should be conducted using standardised laboratory methods such as those described by the *Clinical and Laboratory Standards Institute* (CLSI). These include dilution methods (MIC determination) and disk susceptibility methods.

Both the CLSI and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) provide interpretative criteria for these methods.

Based on a number of studies, it is recommended that the *in vitro* activity of azithromycin be tested in ambient air to ensure physiological pH of the growth medium. Elevated CO_2 pressures, such as those used for streptococci and anaerobic bacteria, and occasionally for other species, results in a reduction in the pH of the medium. This has a greater adverse effect on the apparent potency of azithromycin than on that of other macrolides.

EUCAST has also established the susceptibility breakpoints for azithromycin based on MIC determination. The EUCAST susceptibility criteria are listed in the following table.

Susceptibility breakpoints for azithromycin

	MIC (mg/L)	
	Susceptible	**Resistant**
Staphylococcus spp.	≤ 1	> 2
Streptococcus pneumoniae	≤ 0.25	> 0.5
Haemolyticβ streptococcus[a]	≤ 0.25	> 0.5
Haemophilus influenzae	≤ 0.12	> 4
Moraxella catarrhalis	≤ 0.25	> 0.5
Neisseria gonorrhoeae	≤ 0.25	> 0.5

[a] includes groups A, B, C, G.

EUCAST = *European Committee on Antimicrobial Susceptibility Testing*; MIC = Minimal inhibitory concentration.

Antibacterial spectrum
The prevalence of acquired resistance may vary geographically and over time for selected species, and it is helpful to have local information on resistances, in particular when treating serious infections. If necessary, expert advice should be requested if the local prevalence of resistant strains is such that the usefulness of agents, at least in certain types of infections, is disputable.

Azithromycin shows cross resistance with erythromycin resistant gram-positive germs. As described above, some ribosomal modifications determine cross resistance with other classes of antibiotics whose ribosomal binding sites overlap that of the macrolides: the lincosamides (including clindamycin), and streptogramins B (which include, for example, the quinupristin component of quinupristin/dalfopristin). Over the course of time, a decrease has been noted in macrolide susceptibility, in particular in *Streptococcus pneumoniae* and in *Staphylococcus aureus,* and has also been observed in *viridans* group streptococci and in *Streptococcus agalactiae.*

Organisms that are commonly susceptible to azithromycin include:

Aerobic and facultative gram-positive bacteria (erythromycin-susceptible isolates): *S. aureus*, *Streptococcus agalactiae**, *S. pneumoniae**, *Streptococcus pyogenes**, other haemolytic β streptococci (groups C, F, G), *viridans* group streptococci. Macrolide-resistant germs are found relatively frequently among aerobic and facultative gram-positive bacteria, in particular among methicillin-resistant *S. aureus* (MRSA) and penicillin-resistant S. *pneumoniae* (PRSP).

Aerobic and facultative gram-negative bacteria: *Bordetella pertussis*, *Campylobacter jejuni*, *Haemophilus ducreyi**, *Haemophilus influenzae**, *Haemophilus parainfluenzae**, *Legionella pneumophila*, *Moraxella catarrhalis**, and *Neisseria gonorrhoeae**. *Pseudomonas* spp. and the majority of *Enterobacteriaceae* are inherently resistant to azithromycin, although azithromycin has been used to treat *Salmonella enterica* infections.

Anaerobes: *Clostridium perfringens, Peptostreptococcus* spp. and *Prevotella bivia*.

Other bacterial species: *Borrelia burgdorferi*, *Chlamydia trachomatis*, *Chlamydophila pneumoniae**, *Mycoplasma pneumoniae**, *Treponema pallidum*, and *Ureaplasma urealyticum*.

Opportunistic pathogens associated with HIV infection. MAC*, and the eukaryote micro-organisms *Pneumocystis jirovecii* and *Toxoplasma gondii*.

*The efficacy of azithromycin against the described species has been demonstrated in clinical studies

5.2 Pharmacokinetic properties

Absorption
Azithromycin is more stable at gastric pH compared to erythromycin.
In humans, following oral administration, azithromycin spreads quickly and fully to the entire body; the time required to achieve peak plasma levels is 2-3 hours.

Distribution
In animal studies, high concentrations of azithromycin were observed inside phagocyte cells. In experimental models, higher concentrations of azithromycin were released by activated phagocytes than by non-activated phagocytes. In the animal model, this phenomenon causes high concentrations of azithromycin at the infection site.
Pharmacokinetic studies in humans have shown higher azithromycin tissue levels compared to plasma levels (up to 50 times the maximum concentrations observed in plasma) indicating, therefore, that the drug is highly linked to tissues. Concentrations in tissues such as lung, tonsil, and prostate, exceed MIC_{90} values for the most common pathogens after a single oral administration of 500 mg.

Elimination
The terminal plasma half-life time closely reflects the tissue depletion half-life time (from 2 to 4 days). Approximately 12% of an IV dose is eliminated in urine as an unchanged drug after 3 days, the majority during the first 24 hours. Biliary elimination constitutes the main route of elimination for unchanged drug after oral administration. Very elevated concentrations of unchanged drug were found in human bile along with 10 metabolites formed by the N- and O-demethylation processes, by hydroxylation of the desosamine and the agliconic ring and by cleavage of the cladinosium-conjugates. Comparison of HPLC and microbiological assays in tissues suggests that metabolites play no part in the microbiological activity of azithromycin.

Pharmacokinetics in special patient populations

Elderly
A study conducted in healthy volunteers highlighted that after a treatment period of 5 days, AUC values were slightly higher in elderly patients (> 65 years) compared to younger patients (< 40 years); however, because this data is not clinically significant, no dose adjustment is required.

Renal impairment
Following single oral administration of 1 gram of azithromycin, no pharmacokinetic effects were found in patients with slight to moderate renal impairment (GFR 10-80 mL/min). However, statistically significant differences were found in AUC_{0-120} (8.8 μg-hr/mL vs. 11.7 μg-hr/mL), C_{max} (1.0 μg/mL vs. 1.6 μg/mL) and CLr (2.3 mL/min/kg vs. 0.2 mL/min/kg) among those with severe renal impairment (GFR < 10 mL/min) and those with normal renal function.

Hepatic impairment
In patients with mild (Class A) and moderate (Class B) hepatic impairment, there was no evidence of significant changes in the blood pharmacokinetics of the azithromycin compared to patients with normal hepatic function. In these patients, elimination of azithromycin through urine seemed to increase, probably as compensation for reduced hepatic clearance.

5.3 Preclinical safety data

In animal studies conducted with elevated doses that exceeded 40 times the maximum dose used in clinical practice, it was found that the azithromycin caused reversible phospholipidosis, generally without true toxicological consequences. The effect was found to be reversible with interruption of azithromycin treatment. The significance of these results for animals as well as for humans is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous tribasic calcium phosphate, hydroxypropyl cellulose, xanthan gum, cherry fragrance, cream of vanilla, banana fragrance, **saccharose**.

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.

Once reconstituted, the powder for oral suspension can be stored for 10 days at room temperature.

6.4 Special precautions for storage

Before reconstitution Store below 30C.

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

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

ZITHROMAX 200 mg/5 ml powder for oral suspension – 600 mg vial
High density polyethylene vial containing 600 mg of the active substance with childproof closure and measuring tool.
ZITHROMAX 200 mg/5 ml powder for oral suspension – 900 mg vial
High density polyethylene vial containing 900 mg of the active substance with childproof closure and measuring tool.
ZITHROMAX 200 mg/5 ml powder for oral suspension – 1200 mg vial
High density polyethylene vial containing 1200 mg of the active substance with childproof closure and measuring tool.

Once reconstituted, the suspension contains 200 mg/5 ml.

6.6 Special precautions for disposal and other handling

Keep out of the sight and reach of children

INSTRUCTIONS FOR PREPARING AND ADMINISTERING THE SUSPENSION
- Shake the bottle containing the powder before adding water.
- Using the measuring spoon on the package lid, fill with water up to the line (corresponding to 9 ml) only once.
- Pour the water from the measuring spoon into the bottle.
- Shake well until all of the powder becomes a suspension.

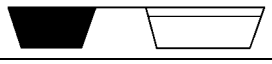
One ml of reconstituted suspension contains 40 mg of azithromycin (equal to 200 mg for a dose of 5 ml).
Always shake the suspension before using.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment
The reconstituted suspension must be administered using one of the two measuring spoons included in the package:

1. **"Two sided" measuring spoon**
   For use in children weighing from 15 kg to 45 kg. The measuring spoon consists of a teaspoon (capacity 5 ml) on one side and a tablespoon (capacity 10 ml) on the other

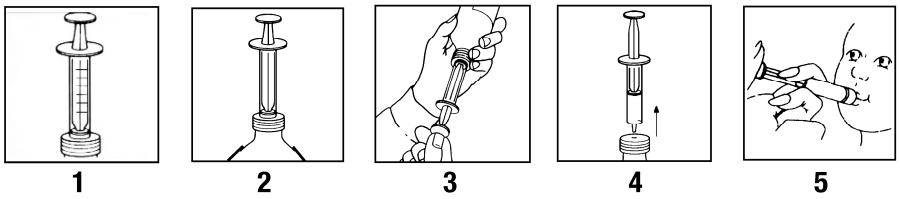
2. **"syringe" measurer**
   For use in children weighing less than 15 kg.

1) INSTRUCTIONS FOR USING THE "DOUBLE TEASPOON" GRADUATED DOSING DEVICE

CHILD WEIGHT	ONLY ONCE A DAY FOR 3 DAYS	MEDICINE QUANTITY
from 15 kg to 25 kg	 Teaspoon filled all the way	200 mg

from 26 kg to 35 kg		Tablespoon filled to the line	300 mg
from 36 kg to 45 kg		Tablespoon filled all the way	400 mg

2) HOW TO USE THE "MEASURING DEVICE SYRINGE"



1. The syringe is calibrated for mg and ml of the medicine and weight (in kg) of the child.
2. Twist off the plastic cap and insert the syringe, with the adaptor, into the bottle.
3. Draw the prescribed quantity of suspension.
4. Remove the syringe from the adaptor
5. Using the syringe, administer the suspension directly into the child's mouth.

Close the bottle using its lid. Rinse the measuring syringe used.

N.B.
To treat acute otitis media in children who weigh less than 15 kg, the dosage of 30 mg/kg can be taken in a single administration, filling the measuring "syringe" as many times as needed to reach the prescribed dose.

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

7.FUTHER INFORMATION

MARKETING AUTHORISATION HOLDER

Pfizer Limited-Ramsgate Road, Sandwich Kent CT13 9NJ- United Kingdom

MANUFACTURER

Haupt Pharma Latina S.r.l.: S.S. 156, Km 47,600 – Borgo San Michele, 04100 Latina

8. DATE OF REVISION OF THE TEXT

October 2018

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