ZITHROMAX

Azithromycin

500 mg powder for solution for infusion

Reference Market: Italy

AFME markets using the same LPD: Saudi Arabia

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zithromax IV 500 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:

Active substance:

Azithromycin dihydrate	524.1 mg
equivalent to Azithromycin base	500 mg

Excipient with known effects:
ZITHROMAX 500 mg powder for solution for infusion contains 114 mg sodium in each vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZITHROMAX powder for solution for infusion is indicated in the treatment of community-acquired pneumonia caused by susceptible organisms, including *Legionella pneumophila*, in patients who require an initial therapy intravenously.

ZITHROMAX powder for solution for infusion is indicated in the treatment of pelvic inflammatory disease caused by susceptible organisms, in patients who require an initial therapy intravenously.

4.2 Posology and method of administration

In the treatment of community-acquired pneumonia, the recommended dosage for an adult is 500 mg of ZITHROMAX powder for solution for infusion in a single daily dose intravenously for at least two days. Intravenous therapy must be followed by oral therapy with a dose of 500 mg once-daily dosing regimen for a total period of treatment of 7-10 days. The time it takes to make the transition to oral therapy must be decided by the physician depending on the clinical response.
In the treatment of pelvic inflammatory disease, the recommended dosage for an adult is 500 mg of ZITHROMAX powder for solution for infusion in a single daily dose intravenously for one or two days. Intravenous therapy must be followed by oral therapy with a dose of 250 mg once-daily dosing regimen for a total period of treatment of 7 days. The time it takes to make the transition to oral therapy must be decided by the physician depending on the clinical response.

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

Paediatric population
The efficacy and tolerability of ZITHROMAX powder for solution for infusion in the treatment of infections in children and adolescents under the age of 16 years have not been established. In controlled clinical trials azithromycin by oral administration was administered to paediatric patients (aged from 6 months to 16 years).

For information on the use of azithromycin in the treatment of paediatric patients, see the Summary of Product Characteristics of the oral formulations of the azithromycin.

Renal Impairment
No dose adjustment is required for patients with a glomerular filtration rate (GFR) of 10 - 80 mL/min; however, caution is necessary for patients with a GFR of < 10 mL/min (see Sections 4.4 and 5.2).

Hepatic Impairment
No dose adjustment is required for patients with mild to moderate hepatic impairment (see Sections 4.4 and 5.2).

Method of administration
ZITHROMAX powder for solution for infusion after reconstitution and dilution should be administered by intravenous infusion.
The concentration of the solution and the duration of the infusion must be equal to: 1 mg/mL in 3 hours or 2 mg/mL in 1 hour.

ZITHROMAX powder for solution for infusion should not be administered as a bolus or intramuscularly (see Sections 4.4 and 6.6).

PREPARATION OF THE SOLUTION FOR INTRAVENOUS ADMINISTRATION (see also Section 6.6)

Reconstitution
The initial solution must be prepared by adding 4.8 mL of water for injections in the vial containing the powder. Shake the vial until the powder has completely dissolved. Using a standard 5-mL syringe is recommended to take the exact volume of 4.8 mL of sterile water for injections. 1 mL of reconstituted solution contains 100 mg of azithromycin.
The drugs to be administered via parenteral route must be carefully controlled to exclude the presence of particulate in the solution. If suspended particles can be seen, the solution should be discarded.
The reconstituted solution must be diluted prior to administration by following the instructions below.

Dilution
In order to obtain a concentration of azithromycin equal to 1.0-2.0 mg/mL, remove 5 mL of the reconstituted solution from the vial (concentration of 100 mg/mL), adding it to the appropriate volume of one of the solvents mentioned in Section 6.6.

Final concentration of the solution for infusion	Solvent volume
1.0 mg/mL	500 mL
2.0 mg/mL	250 mL

The intravenous administration of a 500 mg dose of azithromycin, diluted according to the instructions must be performed within a period of not less than 60 minutes.

4.3 Contraindications

Hypersensitivity to the active ingredient, to erythromycin, any other macrolide or ketolide antibiotics, or any other excipients listed in paragraph 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity
As for erythromycin and other macrolides serious rare allergic reactions have been reported, including angioneurotic oedema and anaphylaxis (rarely fatal), dermatological reactions including acute generalized exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and rash with eosinophilia and systemic symptoms (DRESS). Some of these reactions associated with Zithromax have caused recurring symptoms and have required an observation period and prolonged treatment.

If there is an allergic reaction, the administration of the medicinal product must be discontinued and adequate therapy started. Physicians should be aware of the fact that when the symptomatic therapy is suspended allergic symptoms may occur.

Hepatotoxicity

Azithromycin must be used with caution in patients with serious liver disease since its primary route of elimination is the liver. With azithromycin, there have been reports of hepatic impairment, hepatitis, cholestatic jaundice, hepatic necrosis and fulminant hepatic failure, potentially caused by hepatic impairment, some of which had fatal results (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)

As a result of the use of azithromycin in infants (treatment up to 42nd day of life), infantile hypertrophic pyloric stenosis (IHPS) has been reported. Parents and health operators must be told to contact their physician if vomiting or irritability occurs after eating.

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. The strains of *C. difficile* that produce excess toxins cause an increase in morbidity and mortality rates as these infections are usually refractory to antibacterial therapy and often require a colectomy. The possibility of diarrhoea associated with *C. difficile* must be considered in all patients who develop diarrhoea after a treatment with antibiotics. A detailed patient history is also necessary because cases of diarrhoea associated with *C. difficile* have been reported over two months after the administration of antibiotics.

Renal Impairment

In patients with a GFR of < 10 mL/min a 33% increase in systemic exposure to azithromycin was observed (see Section 5.2).

Prolonged QT interval

In treatment with macrolides, including azithromycin, a prolonged cardiac repolarisation and QT interval were found using ECG, with the risk of developing cardiac arrhythmia and torsade de pointes (see Section 4.8). Therefore, given that the following situations can cause an increase in the risk of ventricular arrhythmias (including torsade de pointes) that can lead to cardiac arrest, azithromycin should be administered with caution in patients who have concomitant proarrhythmic conditions (especially women and elderly patients).
Prescribers must take into account the risk of the prolongation of the QT interval, which can be fatal, in assessing the risks and benefits of azithromycin in groups of patients at risk, 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 anti-arrhythmics (dofetilide, amiodarone and sotalol), 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 being treated with azithromycin, there have been reports of exacerbation in symptoms of myasthenia gravis and initial development of myasthenic syndrome (see paragraph 4.8).

The safety and efficacy of azithromycin for intravenous administration in the treatment of paediatric infections have not been established.

ZITHROMAX powder for solution for infusion has to be reconstituted and diluted by following the instructions and must be administered with infusions lasting at least 60 minutes. **Not for bolus injection or intramuscularly (see Sections 4.2 and 6.6).**

ZITHROMAX 500 mg powder for solution for injection contains 114 mg of sodium per each vial, equivalent to 5,7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
Zithromax 500 mg /5 ml powder for solution for infusion may be further prepared for administration with sodium-containing solutions (see section 6.6) and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

4.5 Interactions with other medicinal products and other forms of interaction

Antacids
In a pharmacokinetic study on the effects caused by co-administration of antacids and oral azithromycin, no effects were detected on the bioavailability of azithromycin, even though a decrease of approximately 25% was observed in maximum serum concentrations. Therefore, patients being treated with oral azithromycin and antacids containing magnesium and aluminium must not take the two drugs concomitantly. The administration of oral antacids should not alter the characteristics of azithromycin administered intravenously.

Cetirizine
In healthy volunteers, the concomitant administration of a 5-day regimen of azithromycin and 20 mg of steady state cetirizine did not show any pharmacokinetic interactions or significant alterations in the QT interval.

Didanosine
It was observed that co-administration of daily doses of azithromycin 1,200 mg/day and didanosine 400 mg/day 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)
There have been reports that the administration of macrolide antibiotics, including azithromycin with P-glycoprotein substrates such as digoxin, has caused an increase in the blood serum levels of P-glycoprotein substrates. Therefore, the possibility of an increase in digoxin blood serum levels must be carefully considered when co-administering azithromycin and P-glycoprotein substrates, such as digoxin. Clinical monitoring is required both during and after interruption of azithromycin treatment, as well as monitoring for possible increases in digoxin levels.

Zidovudine
The administration of individual 1,000 mg doses and multiple 1,200 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 importance of this data is not clear, but it may still render benefits to the patient.

Azithromycin does not significantly interact with the cytochrome P450 hepatic 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, for which significant metabolic activity was noted and mediated by cytochrome P450.

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 have been reported in patients treated with azithromycin and statins.

Carbamazepine
During an interaction study conducted in healthy volunteers, no significant effects were observed on plasma levels of carbamazepine or its active metabolite in patients who were taking azithromycin concomitantly.

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

Cyclosporine
In a pharmacokinetic study conducted in healthy volunteers administered an oral dose of 500 mg/day of azithromycin for 3 days and then a single oral dose of 10 mg/kg 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 as needed.

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

Fluconazole
Co-administration of a single dose of azithromycin (1,200 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 (1,200 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 (1,200 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 was necessary.

Rifabutin

Concomitant administration of azithromycin and rifabutin does not change 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 ruled out; however, there is no scientific evidence that the interaction occurred.

Triazolam
In 14 healthy volunteers, concomitant administration of 500 mg of azithromycin on Day 1 and 250 mg on Day 2 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 trimetoprim/sulfamethoxazole (160 mg/800 mg) and azithromycin (1,200 mg) for 7 days, no significant effect was found on peak concentrations, exposure time, or urinary excretion of both trimetoprim and sulfamethoxazole on Day 7. 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.
During the post-marketing phase, cases of increased anticoagulant action were reported following co-administration of azithromycin and coumarin-type oral anticoagulants. Even though 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

Pregnancy
Animal reproduction studies have been conducted using scaled doses to reach moderately toxic maternal 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 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. While most studies do not suggest an association with adverse fetal 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.
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.

Breastfeeding
The limited information available from the published literature, indicates that azithromycin is present in human milk in a highest median daily dose estimated to be between 0.1 and 0.7 mg/kg/day. No side effects have been observed in breast-fed infants.

It must be decided whether to discontinue breastfeeding or discontinue/refrain from therapy with azithromycin taking into consideration the benefits of breastfeeding for the child and that 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 machines.

4.8 Undesirable effects

The table below lists the side effects 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 (frequency cannot be defined based on available data). Possible 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 par. 4.4)	Not known
Blood and lymphatic system disorders	Leukopaenia, neutropaenia, eosinophilia	Uncommon
	Thrombocytopaenia, haemolytic anaemia	Not known
Immune system disorders	*Angiooedema, 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 and Labyrinth Disorders	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 par. 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 Mediastinal Disorders	Dyspnoea, epistaxis	Uncommon
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 generalised exanthematous pustulosis (AGEP)§,* *Drug rash with eosinophilia and systemic symptoms (DRESS)§*	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, asthaenia, malaise, fatigue, facial oedema, chest pain, pyrexia, pain, peripheral oedema	Uncommon
	Pain at injection site*, inflammation at injection site*	Common
Diagnostic tests	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

§ Frequency ADR 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 <u>differ</u> 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 Headache 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 marketing authorisation of the medicinal product is important. It allows constant monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

To Report side effects

- **Saudi Arabia**

National Pharmacovigilance Centre (NPC)

- SFDA Call center: 19999
- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa/

- **Other GCC States**

- *Please contact the relevant competent authority.*

4.9 Overdose

Side effects 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 agents for systemic use: macrolides, ATC code: J 01FA10.

Azithromycin is the first drug 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-homoerithromycin A. The 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 study in parallel groups on 116 healthy subjects who either took chloroquine (1,000 mg) alone or in combination with azithromycin (500 mg, 1,000 mg, 1,500 mg once a day). The coadministration with azithromycin resulted in an increase in QTc interval in a dose- and concentration-dependent way. Maximum increases in the QTcF compared with chloroquine monotherapy (whose differences observed with respect to the placebo vary in the range of between 18.4 and 35 ms) were on average (upper limit of the 95% confidence interval) 5 (10 ms), 7 (12 ms) and 9 (14) ms following the concomitant administration of 500 mg, 1,000 mg, 1,500 mg of 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 (MLSBphenotype) 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 large 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 minimum 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
Haemolytic β streptococcus [a]	≤ 0.25	> 0.5
Haemophilus influenzae	≤ 0.12	> 4
Moraxella catarrhalis	≤ 0.25	> 0.5

Susceptibility breakpoints for azithromycin

	MIC (mg/L)	
	Susceptible	**Resistant**
Neisseria gonorrhoeae	≤ 0.25	> 0.5

[a] includes groups A, B, C, G.
EUCAST = *European Committee on Antimicrobial Susceptibility Testing*; MIC = Minimum 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 the Type B streptogramins (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 (erithromycin-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

CLINICAL PHARMACOLOGY

Treatment of community-acquired pneumonia
In a non-comparative, open-label study carried out on patients suffering from community-acquired pneumonia, subjects were administered azithromycin for intravenous infusion (for 2-5 days) followed by azithromycin orally (to complete a total treatment period of 7-10 days). Among evaluable patients, the clinical success rates (recovery and improvement) were equal to 88% (74/84) after 10-14 days from the end of the therapy and 86% (73/85) after 4 to 6 weeks.

In a randomised, open-label, comparative study between azithromycin (intravenously followed by oral therapy) and cefuroxime (intravenously followed by oral therapy, in combination with erythromycin or not) in community-acquired pneumonia therapy, no statistically significant differences were observed between the two treatments.

In these two studies an overall recovery percentage of 84% (16/19) was found in patients with positive serology for *Legionella pneumophila.* Furthermore, in an open-label, non-comparative study, patients with *Legionella pneumophila* (serogroup 1) with the diagnosis made by a specific urinary antigen test were treated with azithromycin intravenously followed by azithromycin orally positive. After 10-14 days of therapy, clinical recovery was achieved in 16 of 17 of the evaluable patients and after 4-6 weeks, 20 patients out of 20 had recovered.

Treatment of pelvic inflammatory disease
The results of an open-label study indicate that three therapeutic regimens of pelvic inflammatory disease (azithromycin vs. azithromycin/metronidazole and vs. doxycycline, metronidazole, cefoxitin and probenecid) are comparable both from the point of view of efficacy and safety. In another open-label, comparative study, patients suffering from pelvic inflammatory disease were treated with azithromycin IV/oral vs. azithromycin IV in combination with metronidazole IV/oral and vs. doxycycline in combination with amoxicillin - clavulanic acid IV/oral. These regimens were shown to be comparable in terms of efficacy and safety. The data reported from these studies show overall clinical success (recovery and improvement) ≥ 97% in all treatment groups, with a ≥ 96% percentage of pathogens eradicated at the end of the therapy. In the follow-up, the percentage of pathogens eradicated was ≥ 90%.

Paediatric population

Following the assessment of studies conducted on children, because non-inferiority has not been established with respect to the antimalarial drugs recommended in the treatment of uncomplicated malaria, the use of azithromycin is not recommended for the treatment of malaria, either as monotherapy or in combination with chloroquine or artemisinin-based drugs.

5.2 Pharmacokinetic properties

Absorption/Distribution
In humans after oral administration, azithromycin spreads quickly and extensively throughout the body with a bioavailability of about 37%. The time required to obtain peak plasma levels is 2-3 hours.
In hospitalised patients with community-acquired pneumonia who received a once-daily dosing regimen of 500 mg of azithromycin for infusion (for 1 hour, concentration equal to 2 mg/mL) for 2-5 days, the average C_{max} reached was 3.63 ± 1.60 μg/mL, the threshold level reached after 24 hours was 0.20 ± 0.15 μg/mL and the AUC_{24} was equal to 9.60 ± 4.80 μg h/mL.
In healthy volunteers who received 500 mg of azithromycin for infusion (for 3 hours, concentration equal to 1 mg/mL), the average C_{max} reached was 1.14 ± 0.14 μg/mL, the threshold level reached after 24 hours was 0.18 ± 0.02 μg/mL and the AUC_{24} was equal to 8.03 ± 0.86 μg h/mL.
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 phenomena 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 bound to tissues. Concentrations in tissues such as lung, tonsil, and prostate, exceed MIC_{90} values for common pathogens after a single administration of 500 mg of azithromycin.
High concentrations of azithromycin have been found in gynaecological tissues 96 hours after a single oral administration of 500 mg.

Biotransformation/Elimination
The terminal plasma half-life time closely reflects the tissue depletion half-life time (from 2 to 4 days). In a study with multiple doses conducted on 12 healthy volunteers with a dosage of 500 mg intravenously (1 mg/mL in an hour) for 5 days, the amount of unchanged azithromycin eliminated in the urine in 24 hours was equal to about 11% after the 1st dose and approximately 14% after the 5th dose. These values are higher than the rate

of 6% of unchanged drug reported for azithromycin administered orally. Biliary elimination is the primary route of unchanged drug elimination 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 glyconic 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 powder for solution for infusion.

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 a GFR of 10 - 80 mL/min. However, statistically significant differences were found in AUC $values_{0-120}$ (8.8 µg-h/mL vs. 11.7 µg-h/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 the group with a GFR of < 10 mL/min and a GFR of > 80 ml/min.

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 azithromycin caused reversible phospholipidosis, generally without true toxicological consequences. The effect proved to be reversible with discontinuation of the azithromycin treatment. The significance of these results for animals as well as for humans is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, sodium hydroxide.

6.2 Incompatibility

The reconstituted solution of azithromycin powder for solution for infusion should be diluted according to the instructions and with the compatible infusion solutions indicated in Section 6.6.

6.3 Shelf life

3 years.

The reconstituted solution is chemically and physically stable for 24 hours if stored at temperatures no higher than 30°C. However, from a microbiological point of view, the product should be used immediately. If the solution is not used immediately, the people who use it need to check the storage times and conditions. However, it is advisable not to exceed 24 hours at temperatures of between 2 and 8°C, unless the reconstitution/dilution has taken place under validated and controlled aseptic conditions.

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of the container

A white to off-white cake powder in type I 10-mL glass vial with a closure comprising grey bromobutyl rubber stoppers and aluminium seal, containing 500 mg of active substance.
Each pack contain 1 vial.

6.6 Special precautions for disposal and other handling

Keep out of the sight and reach of children.

ZITHROMAX powder for solution for infusion is contained in a disposable vial. The contents of the vial should be reconstituted with 4.8 mL of sterile water for injections (100 mg/mL of azithromycin). For administration, the required volume of the reconstituted solution is added to the compatible solution for infusion in order to obtain a solution of azithromycin with a concentration equal to 1.0-2.0 mg/mL.

The drugs to be administered via parenteral route must be carefully controlled to exclude the presence of particulate in the solution. If suspended particles can be seen, the solution should be discarded.

The chemical and physical stability after reconstitution has been demonstrated for 24 hours at 30°C. Once diluted according to the instructions, the solution is stable from a chemical and physical point of view for 24 hours at temperatures equal to or lower than 30°C or for 7 days if stored in a refrigerator (5°C).
However, from a microbiological point of view, the product should be used immediately. If the suspension is not used immediately, the people who use it need to check the storage times and conditions that would normally not be longer than 24 hours at temperatures of between 2 and 8°C, unless the reconstitution/dilution has taken place under validated and controlled aseptic conditions.

The reconstituted solution must be diluted with one of the following solutions for infusion:

Physiological solution (0.9% sodium chloride)
Physiological solution (0.45% sodium chloride)
Ringer's lactate
Glucose 5% in water
Glucose 5% in physiological solution (0.45% sodium chloride) with 20 mEq KCl
Glucose 5% in physiological solution (0.45% sodium chloride)
Glucose 5% in physiological solution (0.30% sodium chloride)
Glucose 5% in Ringer's lactate

The intravenous administration of a 500 mg dose of azithromycin, diluted according to the instructions must take place within a period of not less than 60 minutes.

ZITHROMAX powder for solution for infusion should not be administered as a bolus or intramuscularly.

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

7. FURTHER INFORMATION

MARKETING AUTHORISATION HOLDER
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Via Isonzo 71,
04100 Latina,
Italy

MANUFACTURER

Manufacturing and Packaging:
Pharmacia Upjohn Company LLC, Kalamazoo, United States

Labelling, secondary packaging, and release:
Fareva Amboise, Amboise, France

8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20-Aug-2003Most recent renewal date:

9. DATE OF REVISION OF THE TEXT

October 2023