Zithromax IV®

500mg

Powder for solution for infusion

Azithromycin

Reference Market: Austria

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zithromax® IV 500 mg Powder for Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains 500 mg azithromycin (as dihydrate) for preparation of a 100 mg/ml solution for further dilution.
Excipient with known effect: Sodium hydroxide (198.3 mg per vial)
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White powder for solution for infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zithromax® IV 500 mg Powder for Solution for Infusion is indicated for the treatment of the following infections caused by azithromycin-susceptible microorganisms (see sections 4.4 and 5.1):

Treatment of community acquired pneumonia requiring hospitalisation, caused by susceptible organisms, including *Legionella pneumophila,* in patients who require initial intravenous therapy (see section 4.2).
Pneumonia caused by gram-negative organisms other than Haemophilus or *Moraxella catarrhalis* was excluded from the clinical trials.

This preparation should be used by specialists only.

Official recommendations for the appropriate use of antibiotics should be considered.

Zithromax® IV 500 mg – Powder for Solution for Infusion is used in adults.

4.2 Posology and method of administration

Use in Adults

The recommended daily dose for the treatment of community acquired pneumonia requiring hospitalisation in adults is 500 mg as a single daily intravenous dose for at least 2 days.
The timing of the conversion from intravenous to oral therapy with Zithromax 500 mg should be done at the discretion of the treating physician based on clinical response.
The total duration of therapy should be decided by the treating physician based on clinical response and should be 7-10 days.

Use in Children and Adolescents

The safety and effectiveness of intravenous azithromycin in the treatment of infections in children and adolescents have not been established.

Method of administration

Zithromax IV is **for intravenous use (infusion) after reconstitution and dilution**.

Do not administer Zithromax IV as intravenous bolus or as intramuscular injection (see section 4.4).

The infusion must be given at a concentration of either 1 mg/ml for 3 hours or of 2 mg/ml for 1 hour.

Preparation of the solution for infusion

Reconstitution

For preparing the solution for infusion, add 4.8 ml sterile Water for Injection to the 500 mg vial (using a standard 5 ml syringe to ensure that the exact amount of 4.8 ml water is dispensed) and shake vial until all of the powder is completely dissolved. Each ml of the reconstituted solution contains 100 mg azithromycin. If particulate matter is detected upon visual inspection of the reconstituted solution, the solution should not be used.

Prior to administration the solution must be diluted as described below.

Dilution of the solution for infusion

To obtain a concentration of 1.0 mg/ml, 5 ml of the 100 mg/ml solution must be diluted to 500 ml with one of the diluents listed below.

To obtain a concentration of 2.0 mg/ml, 5 ml of the 100 mg/ml solution must be diluted to 250 ml with one of the diluents listed below.

Solvents for dilution

Normal saline (0.9 % NaCl)
½ Normal saline (0.45 % NaCl)
5 % Dextrose in water
Lactated Ringer's solution
5 % Dextrose in 0.45 % NaCl with 20 mEq KCl
5 % Dextrose in lactated Ringer's solution
5 % Dextrose in 0.3 % NaCl
5 % Dextrose in 0.45 NaCl

The 500 mg dose of azithromycin diluted as described above should be infused over a period of at least 60 minutes.

Special dosage recommendations

Use in patients with renal impairment

No dose adjustment is necessary in patients with a glomerular filtration rate (GFR) of 10-80 ml/min. Caution should be exercised when azithromycin is administered to patients with a GFR of < 10 ml/min (see sections 4.4 and 5.2).

Use in patients with hepatic impairment

In patients with mild to moderate hepatic impairment the same dosage as in patients with normal hepatic function can be used with caution.
Since azithromycin is primarily excreted via the liver, its use in patients with severe hepatic impairment is not recommended (see section 4.4).

Use in patients with renal and hepatic impairment

Due to lack of data, the use of Zithromax IV in patients with renal and hepatic impairment is not recommended.

Use in patients on dialysis

Due to lack of data, the use of Zithromax IV in patients on dialysis is not recommended.

Use in elderly patients

In elderly patients no dosage adjustment is necessary. Because elderly patients may suffer from proarrhythmic disorders, special caution is advised because of the risk for development of cardiac arrhythmia and Torsades de pointes (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any excipient listed in section 6.1, or to erythromycin, or to any macrolide and ketolide antibiotic

4.4 Special warnings and precautions for use

Hypersensitivity

As with erythromycin and other macrolides in rare cases serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), and skin reactions, including Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson syndrome (SJS),toxic epidermal necrolysis (TEN; fatal in individual cases) 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.
If an allergic reaction occurs, the medicinal product must be discontinued and suitable treatment initiated. Physician must be aware that allergic symptoms may recur when the symptomatic treatment is discontinued.

Paediatric population
Safety and efficacy for the prevention or treatment of Mycobacterium Avium Complex in children have not been established.

Hepatotoxicity

Since liver is the principal route of biotransformation and elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease.
Impairment of the hepatic function, hepatitis, cholestatic jaundice, hepatic necrosis and hepatic failure, in some cases fatal, have been reported (see section 4.8). Some patients may have had a pre-existing liver disorder or treatment with other hepatotoxic medicinal products.
If symptoms of hepatic impairment occur, such as fast progressing weakness with jaundice, darkening of urine, bleeding tendency or hepatic encephalopathy, a hepatic function test/investigation must be done immediately. In case of hepatic function impairment treatment with azithromycin must be discontinued.

Infantile hypertrophic pyloric stenosis (IHPS)

Following the use of azithromycin in neonates (treatment up to 42 days of life), infantile hypertrophic pyloric stenosis (IHPS) has been reported. Parents and caregivers should be informed to contact their physician if vomiting or irritability with feeding occurs.

Ergot derivatives

In patients receiving ergotamine or ergot derivatives, ergotism has been precipitated by coadministration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergot

derivatives and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be coadministered.

Resistance

As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms, including fungi is recommended. If resistance or selection of organisms occur, a different antibiotic has to be used.

It should be noted that there is a cross-resistance between erythromycin-resistant grampositive strains and most strains of methicillin-resistant staphylococci.
Furthermore there are cross-resistances to lincosamides (including clindamycin), and the streptogramins B (which include, for example, the quinupristin component of quinupristin/dalfopristin).

Clostridioides difficile associated diarrhea

Clostridioides difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *Clostridioides difficile*.

Clostridioides difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *Clostridioides difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

In cases of severe and persisting diarrhea therapy should be discontinued immediately and an appropriate treatment (e.g. oral Vancomycin) be initiated. Peristalsis inhibiting drugs are contraindicated.

Renal function disorder

In patients with a GFR of < 10 ml/min a 33 % increase in systemic exposure to azithromycin was observed, therefore caution should be exercised when prescribing azithromycin in these cases (see section 5.2).

Prolongation of the QT interval

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides, including azithromycin (see section 4.8). The circumstances listed below may lead to an increased risk of ventricular arrhythmia including Torsades the pointes, which may be fatal. Therefore extreme caution is advised in the use of azithromycin in patients with pre-existing proarrhythmic disorders (especially women and elderly patients), as for example in patients:

- with congenital or documented QT prolongation
- who are being treated with other active substances that prolong the QT interval such as antiarrhythmics of class IA (quinidine and procainamide) and class III (dofetilide, amiodarone and sotalol), cisapride and terfenadine. Antipsychotics such as pimozide; antidepressants such as citalopram and fluoroquinolones such as moxifloxacin and levofloxacin,
- with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesemia
- with clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency
- elderly patients: elderly patients may be more susceptible to drug-associated effects on the QT interval

Myasthenia

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).

Intravenous Administration

The efficacy and safety of Zithromax IV in the treatment of infections in children and adolescents has not been investigated.

Zithromax IV should be reconstituted and diluted as described in section 4.2 and administered over a period of at least 60 minutes. **Do not administer Zithromax IV as intravenous bolus or as intramuscular injection (**see **section 4.2** and **section 6.6)**.

Other components

Each vial contains 198.3 mg sodium hydroxide (equivalent to 114 mg or 4.96 mmol sodium), equivalent to 5,7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction 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 (2 - 3 hours time distance).

Cetirizine: In healthy volunteers, coadministration 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): Coadministration of 1 200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

Digoxin 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 substrate. Therefore, if azithromycin and P-glycoprotein substrates such as digoxin are administered concomitantly, the possibility of elevated serum levels of the substrate should be considered.
Clinical monitoring, and possibly serum digoxin levels, during treatment with azithromycin and after its discontinuation are necessary.

Ergot derivatives: There is a theoretical possibility of interaction between azithromycin and ergot derivatives (see section 4.4).

Zidovudine: Single 1 000 mg doses and multiple 1 200 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.

Interactions associated with the cytochrome P450 system: 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.

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

Atorvastatin: Coadministration 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). However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin in combination with statins have been reported.

Carbamazepine: In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

Cimetidine: In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.

Coumarin-Type Oral Anticoagulants: In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15-mg dose of warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to coadministration 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.

Cyclosporin: In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of cyclosporin, the resulting cyclosporin C_{max} and AUC_{0-5} were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Efavirenz: Coadministration of a 600 mg single dose of azithromycin and 400 mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions.

Fluconazole: Coadministration of a single dose of 1 200 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 coadministration of fluconazole, however, a clinically insignificant decrease in C_{max} (18 %) of azithromycin was observed.

Indinavir: Coadministration of a single dose of 1 200 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, coadministration of azithromycin 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam

Nelfinavir: Coadministration of azithromycin (1 200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment is required.

Rifabutin: Coadministration 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 (500mg 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, coadministration of azithromycin 500 mg 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-trimoxazole): Coadministration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with azithromycin 1 200 mg 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Reproduction studies in animals demonstrated, that azithromycin is distributed into the placenta, however, 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.
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.

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 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.

Fertility

In fertility studies conducted on rats, reduced pregnancy rates were noted following administration of azithromycin. The relevance of this finding to humans is not known.

4.7 Effects on ability to drive and use machines

There are no study results available on the effects on the ability to drive and use machines. There is no evidence to suggest that azithromycin may have an effect on a patient's ability to drive or operate machinery.
However, Zithromax may impair alertness due to potential side effects. Therefore, caution is recommended in driving or operating machinery.

4.8 Undesirable effects

The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. 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:

	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)**	**Not known**
Infections and Infestations			Candidiasis Vaginitis Vaginal infections Pneumonia Fungal infections Bacterial infections Pharyngitis Gastroenteritis Respiratory disorder Rhinitis Oral candidiasis		Pseudomembranous colitis (see section 4.4)
Blood and lymphatic system disorders			Leukopenia Neutropenia Eosinophilia		Thrombocytopenia Haemolytic anaemia
Immune system disorders			Angioedema Hypersensitivity		Anaphylactic reactions (see section 4.4)
Metabolism and nutrition disorders			Anorexia		
Psychiatric disorders			Nervousness Insomnia	Agitation	Aggression Anxiety Delirium Hallucinations
Nervous system disorders		Headache	Dizziness Sleepiness Dysgeusia Paraesthesia		Syncopes Convulsions Hypoaesthesia, Psychomotor hyperactivity AnosmiaAgeusia Parosmia Myasthenia gravis (see section 4.4)
Eye disorders			Sight disorder		
Ear and labyrinth disorders			Ear disorder Vertigo		Hearing impairment including deafness and/or tinnitus

	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)	Not known
Cardiac disorders			Palpitation		Torsades de pointes (see section 4.4) Arrhythmia (see section 4.4) including ventricular tachycardia QT interval prolonged in ECG (see section 4.4)
Vascular disorders			Hot flushes		Hypotension
Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis		
Gastrointestinal disorders	Diarrhoea	Vomiting Abdominal pain Nausea	Obstipation Flatulence Dyspepsia Gastritis Dysphagia Distended abdomen Dry mouth Eructation Mouth ulcers Excessive salivation		Pancreatitis Tongue discolouration
Hepatobiliary disorders			Hepatitis	Liver function disorder Cholestatic jaundice	Hepatic failure (fatal in rare cases) (See section 4.4) Fulminant hepatitis Hepatic necrosis
Skin and subcutaneous tissue disorders			Erythema Rash Pruritus Urticaria Dermatitis Dry skin Hyperhidrosis	Acute Generalized Exanthematous Pustulosis (AGEP) Photosensitivity reaction Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	Stevens-Johnson syndrome (SJS) Toxic epidermal necrolysis (TEN) Erythema multiforme
Musculoskeletal and connective tissue disorders			Osteoarthritis Myalgia Back pain Neck pain		Arthralgia
Renal and urinary disorders			Dysuria Renal pain		Acute renal failure Interstitial nephritis
Reproductive system and breast disorders			Metrorrhagia Testicular disorder		

	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)	Not known
General disorders and administration site conditions			Oedema Asthenia Malaise Fatigue Face oedema Chest pain Fever Pain Peripheral oedema		
Investigations		Lymphocyte count decreased Eosinophil count increased Blood bicarbonate decreased Basophils increased monocytes increased, neutrophils increased	Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubin increased Blood urea increased Blood creatinine increased Blood potassium abnormal Blood alkaline phosphatase increased Chloride increased Glucose increased Platelets increased Haematocrit decreased Bicarbonate increased Abnormal sodium		
Injury, poisoning and procedural complications			Post surgery complications		

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. In the event of overdosage, general symptomatic and supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Macrolides, Lincosamides and Streptogramins, Macrolides
ATC code: J01F A10

Azithromycin is a semi-synthetic azalide derivative with a 15-membered lactone ring of the group of macrolide antibiotics.

Mechanism of action

Azithromycin binds to 23S-rRNA, a 50-S subunit of the bacterial ribosome. It blocks the protein synthesis by inhibiting the transpeptisation/translocation step of protein synthesis and by inhibition of protein biosynthesis by binding to the 50S subunit of the ribosome, thus mostly causing a bacteriostatic effect.

Relationship between pharmacokinetics and pharmacodynamics

Efficacy mainly depends on the ratio of AUC (area under the curve, area under the concentration-time curve) and MIC of the pathogen.

Mechanism of resistance

Resistance to azithromycin may be due to the following mechanisms:

- Efflux: resistance may be caused by an increase in the number of efflux pumps in the cytoplasma membrane, of which only 14- and 15-membered macrolides are affected (so called M phenotype).
- Change of target structure: by methylation of the 23S rRNA, the affinity to ribosomal binding sites is reduced thus resulting in resistance to macrolides (M), lincosamides (L) and type B streptogramins (SB) (so-called MLSB phenotype).
- Enzymatic inactivation of macrolides is of minor clinical importance only.

The M phenotype involves complete cross-resistance of azithromycin to clarithromycin, erythromycin and roxithromycin. The MLSB phenotype additionally implies cross-resistance to clindamycin and streptogramin B. Partial cross-resistance exists to the 16-membered macrolide spiramycin.

Methodology for determining the in vitro susceptibility of bacteria to azithromycin

Susceptibility testing should be conducted using standardized 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 CLSI and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) provide interpretive 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 tensions, as often used for streptococci and anaerobes, 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.

European Committee on Antimicrobial Susceptibility Testing (EUCAST) has set susceptibility breakpoints, based on MIC determination. The EUCAST susceptibility criteria are listed in the table below.

EUCAST susceptibility breakpoints for azithromycin

	MIC (mg/l)

Pathogen	susceptible	resistant
Staphylococcus spp	≤ 2	> 2
Streptococcus pneumoniae	≤ 0.25	> 0.25
ß-haemolytic streptococci (Groups A, B, C, G) [1]	≤ 0.25	> 0.25
Haemophilus influenzae	*	*
Moraxella catarrhalis	0.25	> 0.25
Neisseria gonorrhoeae	**	**
Campylobacter jejuni und C. coli	***	***

**Clinical evidence for the efficacy of macrolides in H. influenzae respiratory infections is conflicting due to high spontaneous cure rates. Should there be a need to test any macrolide against this species, the epidemiological cut-offs (ECOFFs) should be used to detect strains with acquired resistance. The ECOFFs for each agent are: azithromycin 4 mg/L, clarithromycin 32 mg/L, erythromycin 16 mg/L and telithromycin 8 mg/L. There are insufficient data available to establish an ECOFF for roxithromycin.*
***Azithromycin is always used in conjunction with another effective agent. For testing purposes with the aim of detecting acquired resistance mechanisms, the ECOFF is 1 mg/L.*
****Susceptibility to azithromycin and clarithromycin can be inferred from erythromycin (Erythromycin sensitivity: C. jejuni ≤ 4 mg/l; C. coli ≤ 8 mg/l).*
EUCAST = European Committee on Antimicrobial Susceptibility Testing
MIC = Minimum inhibitory concentration
Source: EUCAST Web site; EUCAST Clinical Breakpoint Table v. 13.0

Antibacterial Spectrum

The prevalence of acquired resistance may vary geographically and over the course of time for individual species. Therefore, local information on the resistance situation is desirable, particularly for treatment of severe infections. Expert advice on therapy should be sought if the local prevalence of resistance is such that the efficacy of azithromycin seems questionable at least in some forms of infections.

Azithromycin demonstrates cross resistance with erythromycin-resistant gram-positive isolates. As already mentioned some ribosomal modifications cause cross resistance to other classes of antibiotics whose ribosomal binding sites overlap that of the macrolides: the lincosamides (including clindamycin), and the streptogramins B (which include, for example, the quinupristin component of quinupristin/dalfopristin).

A decrease in macrolide susceptibility over time has been noted in particular in *Streptococcus pneumoniae* and *Staphylococcus aureus,* and has also been observed in *viridans streptococci* and in *Streptococcus agalactiae*.

Organisms that are commonly susceptible to azithromycin and prevalence of acquired resistance in Germany based on data from national resistance surveillance projects and studies of the past 5 years (status: April 2022):

Commonly susceptible species
Aerobic gram-positive microorganisms
Mycobacterium avium°
Streptococcus pyogenes
Aerobic gram-negative microorganisms
Legionella pneumophila °
Moraxella catarrhalis
Neisseria gonorrhoeae
Other microorganisms
Chlamydia trachomatis°
Chlamydophila pneumoniae°
Mycoplasma pneumoniae°
Species for which acquired resistance may represent a problem in usage
Aerobic gram-positive microorganisms
Staphylococcus aureus (methicillin-susceptible)
Staphylococcus aureus (methicillin-resistant)$^{+}$
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
Streptococcus agalactiae
Streptococcus pneumoniae$^{\Omega}$
Inherently resistant species
Aerobic gram-negative microorganisms
Escherichia coli
Klebsiella spp.
Pseudomonas aeruginosa

° When tables were published, no up-to-date data were available. In primary literature, textbooks and treatment recommendations a susceptibility of pathogens is assumed.

$^{+}$ In at least one region the resistance rate is above 50 %.

$^{\Omega}$ Among isolates from invasive disease the resistance rate is below 10 %.

Cardiac electrophysiology

QTc interval prolongation was studied in a randomised, placebo-controlled parallel study in 116 healthy volunteers who received either chloroquine (1 000 mg) alone or in combination with azithromycin (500 mg, 1 000 mg, and 1 500 mg once daily). Co-administration of azithromycin led to a prolongation of the QTc interval in a dose- and concentration-dependent manner. In comparison to chloroquine alone, the maximum mean (95 % upper confidence bound) increases in QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with the co-administration of 500 mg, 1 000 mg and 1 500 mg azithromycin, respectively.

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

Distribution

Azithromycin is widely distributed throughout the body, the concentration in tissue being up to 50 times the level observed in plasma. This mode of distribution, which is rather untypical for antibiotics, is due to a high concentration of azithromycin in lysosomes. In animal studies, high azithromycin concentrations have been observed in phagocytes, which resulted in high concentrations of azithromycin being delivered to the site of infection. Pharmacokinetic studies have shown markedly higher concentration in tissue than in plasma (up to the 50-fold of the maximum concentration observed in plasma) indicating that azithromycin is highly tissue bound. The concentrations in target tissues such as lung, tonsils and prostate exceed the MIC_{90} for likely pathogens after a single dose of 500 mg. High concentrations of azithromycin were found in gynecological tissue 96 hours after an oral 500 mg dose. Very high concentrations of the antibiotic are also reached in the bile.

The serum protein binding of azithromycin is concentration-dependent with values of 12 % at 0.5 µg/ml and 52 % at 0.05 µg azithromycin/ml serum. The mean volume of distribution in the steady state (Vss) was calculated to be 31.1 l/kg.

Biotransformation and elimination

Azithromycin is widely metabolised but does not form metabolites with a significant antimicrobial activity. Only about 12 % of an intravenously administered dose is excreted renally as the unchanged drug, the majority during the first 24 hours. Elimination half-life is 2 - 4 days.

In a multiple-dose study in 12 normal subjects with a daily 3-hour infusion of 500 mg (1 mg/ml), for 5 days, the amount of the administered azithromycin dose excreted in urine within 24 hours was about 11 % after the first and about 14 % after the fifth dose. These values are approximately 6 % higher than after oral dosing.

Non-linearity

Study data suggest non-linear pharmacokinetics of azithromycin in the therapeutic range.

Pharmacokinetic/pharmacodynamic relationships

In patients with community acquired pneumonia who received a daily 1-hour intravenous infusion of 500 mg azithromycin at a concentration of 2 mg/ml for 2 to 5 days, the mean C_{max} was 3.63 ± 1.60 µg/ml, the AUC_{24} was 9.60 ± 4.80 µg x h/ml.
In subjects receiving a 3-hour intravenous infusion of 500 mg azithromycin at a concentration of 1 mg/ml, the mean C_{max} and AUC_{24} values were 1.14 ± 0.14 µg/ml and 8.03 ± 0.86 µg x h/ml, respectively.

Pharmacokinetic properties in special clinical situations

Pharmacokinetic studies in elderly persons (> 65 years of age) have shown that AUC values were higher on an average by 29 % and T_{max} values by 37.5 % than in younger volunteers (< 40 years). Since these differences are not considered clinically significant, no dose adjustment is required.

Hepatic impairment: In patients with mild to moderate hepatic impairment, the serum pharmacokinetics of azithromycin after a single dose did not significantly differ from those seen with normal hepatic function. There are no data on multiple dose administration. In these patients renal azithromycin clearance appears

to increase, perhaps to compensate for reduced hepatic clearance. Since the liver is the principal route of elimination for azithromycin, its use is not recommended in patients with severe hepatic impairment.

Renal impairment: The pharmacokinetics of azithromycin in subjects with a GFR of 10 – 80 ml/min were not affected following a single one gram dose of immediate release azithromycin. Statistically significant differences 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) were observed between the groups with a GFR of < 10 ml/min and a GFR of > 80 ml/min.

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 for humans is unknown.

Electrophysiological studies showed that azithromycin prolongs the QT interval.

In vivo and *in vitro* studies for the detection of gene and chromosome mutations showed no evidence of mutagenic potential.

Carcinogenicity studies with azithromycin were not conducted, as only short-term use is intended and there is no evidence of mutagenic or carcinogenic properties.

No teratogenic effects were observed in animal experiments on embryotoxicity in mice and rats. In rats, doses of 100 and 200 mg/kg bw/day caused slight delays in maternal body weight gain and fetal ossification. In the peri- and postnatal study, rats showed slight retardation from 50 mg/kg bw/day (delays in physical development and reflex behavior).

In neonatal studies, rats and dogs showed no greater sensitivity to azithromycin than adult animals of the respective species.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid
Sodium hydroxide

6.2 Incompatibilities

After reconstitution Zithromax IV may be diluted according to the instructions in Section 4.2 using the listed diluents. Other intravenous substances, additives or other medications should neither be added to the solution for infusion nor infused simultaneously through the same intravenous line.

6.3 Shelf life

Do not use Zithromax IV after the expiry date which is stated on the Vial label after EXP:. The expiry date refers to the last day of that month.
For single use only. Residual amounts of solution must be discarded.

When diluted according to the instructions the concentrated azithromycin solution is chemically and physically stable for 24 hours below 30°C

6.4 Special precautions for storage

Do not store above 30 ° C.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Off-white lyophilisate in glass vials with rubber stoppers and aluminium cap.

Hospital packs of 1 vial

6.6 Special precautions for disposal

Keep out of the sight and reach of children.

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

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.

7. FURTHER INFORMATION

MARKETING AUTHORISATION HOLDER

Pfizer Corporation Austria Ges.m.b.H., Vienna

MANUFACUTRED AND PRIMARY PACKAGING BY
Pharmacia and Upjohn Company LLC
7000 Portage Rd.
Kalamazoo, Michigan
USA

SECONDARY PACKED & RELEASED BY
Fareva Amboise
Zone Industrielle
29 route des Industries
37530 Pocé-sur-Cisse
France

8. DATE OF REVISION OF THE TEXT

March 2024

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 and sight of children

Council of Arab Health Ministers
Union of Arabic Pharmacists