Zithromax IV®

500mg

Powder for solution for infusion

Azithromycin

Reference Market: Germany

Bahrain, Kuwait, Qatar, UAE

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zithromax® i.v.
500 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Excipient with known effect: azithromycin

One vial contains 500 mg azithromycin powder (as dihydrate) equivalent to 100 mg/ml following reconstitution of a concentrate for the preparation of a solution for infusion. The solution for infusion to be prepared should have a final concentration of 1 mg azithromycin per ml.

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 i.v. is indicated in patients who require initial intravenous therapy, for the treatment of the following infections caused by azithromycin-susceptible pathogens:
- community acquired pneumonia including legionellosis
- uncomplicated ascending adnexitis

Note
For severe/ICU care requiring pneumonia and/or in the presence of existing risk factors, combined therapy (e.g. with a beta-lactam antibiotic) is required. Azithromycin monotherapy is not indicated in complicated infections, in particular, infections in which azithromycin-resistant pathogens cannot be excluded.

Consideration should be given to official guidance on the appropriate use of antibiotics.

4.2 Posology and method of administration

Posology

Adults

Community-acquired pneumonia
The recommended dose of Zithromax i.v. for adults is 500 mg as a single daily infusion for at least 2 days. Intravenous therapy should be followed by azithromycin by the oral route as a single daily dose of 500 mg to complete a 7 to 10-day course of therapy.

Uncomplicated ascending adnexitis
The recommended dose of Zithromax i.v. for adults is 500 mg as a single daily infusion for 1 or 2 days. Intravenous therapy should be followed by azithromycin by the oral route as a single daily dose of 250 mg to complete a 7-day course of therapy.

The timing of the switch to oral therapy should be chosen in accordance with clinical response and at the discretion of the treating physician.

Elderly patients
The same dose as in adult patients is used in elderly patients. Since elderly patients can be patients with ongoing proarrhythmic conditions particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes (see section 4.4).

Paediatric population
For children and adolescents with a body weight up to 45 kg Zithromax powder for oral suspension is available.

Efficacy and safety of azithromycin i.v. for the treatment of infections in children and adolescents have not been established.

Renal impairment
No dose adjustment is required in patients with renal impairment and a glomerular filtration rate of 10 to 80 ml/min (see sections 4.4 and 5.2).

Hepatic impairment
Patients with impairment of hepatic function: see sections 4.4 and 5.2.

Method of administration
Following reconstitution and dilution, Zithromax i.v. is to be used exclusively for administration as intravenous infusion. Zithromax i.v. must not be given as an intravenous bolus or intramuscular injection (see section 4.4).

The concentration of azithromycin solution for infusion and the rate of infusion should be 1 mg/ml over 3 hours.

Instructions for the preparation of the solution for intravenous administration are as follows:

Reconstitution of the powder
Prepare the initial solution of azithromycin powder for solution for infusion by adding 4.8 ml water for injections to the 500 mg vial and shake the vial until all of the powder is dissolved. It is recommended that a standard 5 ml syringe be used to ensure that the exact amount of 4.8 ml water for injection is dispensed. Each ml of reconstituted solution (concentrate) contains 100 mg of azithromycin.
Parenteral products should be inspected visually for particulate matter prior to administration. If particulate matter is evident in reconstituted fluids, the product solution should be discarded.
Dilute this solution further prior to administration as instructed below.

Dilution and use of ready for use solution for infusion
Transfer 5 ml of the 100 mg/ml azithromycin solution into the appropriate amount (500 ml) of any of the diluents listed in the following:

Diluents
0.9% sodium chloride solution
0.45% sodium chloride solution
5% dextrose in water
Lactated Ringer's solution
5% dextrose in lactated Ringer's solution
5% dextrose in 0.3% sodium chloride solution
5% dextrose in 0.45% sodium chloride solution

Final infusion solution concentration (mg/ml)	Amount of diluent (ml)
1.0 mg/ml	500 ml

The final concentration should be 1.0 mg / ml.

Duration of administration

It is recommended that a 500 mg dose of azithromycin be infused over a period of at least 180 minutes.

4.3 Contraindications

Zithromax i.v. is contraindicated in patients with known hypersensitivity to the active substance azithromycin, erythromycin, any other macrolide or ketolide antibiotic, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hepatotoxicity
Zithromax i.v. should be used with caution in patients with severe hepatic disease, since azithromycin is mainly eliminated via the hepatobiliary route. Cases of abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis and hepatic failure, some of which have resulted in death, have been reported for the treatment with azithromycin (see section 4.8). Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

In case of signs and symptoms of impaired hepatic function, such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests/ examinations should be performed. Treatment with azithromycin should be stopped as soon as signs of impaired liver function occur.

Infantile hypertrophic pyloric stenosis
Cases of infantile hypertrophic pyloric stenosis (IHPS) have been reported following use of azithromycin on newborns (treatment during the first 42 days after birth). Parents and nursing staff are advised to contact their doctor if vomiting or irritations occur when feeding.

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

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* are associated with increased morbidity and mortality, because these infections may be refractory to antimicrobial therapy and may require colectomy. CDAD must therefore be considered in all patients experiencing diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur up to two months after the administration of antibacterial agents.

Pseudomembranous colitis
Cases of pseudomembranous colitis have been reported after administration of macrolide antibiotics. Therefore, this diagnosis should be borne in mind for patients experiencing diarrhoea after the start of or up to about 3 weeks after treatment with azithromycin. Antiperistaltic medicinal products are contraindicated in the presence of pseudomembranous colitis induced by Zithromax i.v..

Superinfection

Observation for signs of superinfection with non-susceptible pathogens including fungi is recommended. Development of superinfection may necessitate interruption of treatment with Zithromax i.v. and initiation of appropriate measures.

Cross-resistance
Because of an existing cross-resistance to erythromycin-resistant gram-positive strains and most strains of methicillin-resistant staphylococci Zithromax i.v. should not be used in such cases. Consideration should be given to regional resistance patterns with regard to azithromycin and other antibiotics.

Renal impairment
No information is available on the safety of the usual intravenous dose of azithromycin in patients with renal impairment and a glomerular filtration rate of <10 ml/min. It has only been ascertained that no dose reduction is required in patients with a glomerular filtration rate of 10 to 80 ml/min.

Long-term use
There is no experience regarding safety and efficacy of long-term use of azithromycin for the above-mentioned indications. For rapidly recurring infections treatment with a different antibiotic should be considered.

Pharyngitis/ tonsillitis
Azithromycin is not the medicinal product of first choice for the treatment of pharyngitis or tonsillitis caused by *Streptococcus pyogenes*. For the treatment of these conditions and for the prophylaxis of acute rheumatic fever penicillin is the medicinal product of first choice.

Sinusitis
Azithromycin is frequently not the medicinal product of first choice for the treatment of sinusitis.

Acute otitis media
Azithromycin is frequently not the medicinal product of first choice for the treatment of acute otitis media.

Infected burn lesions
Azithromycin is not indicated for the treatment of infected burn lesions.

Sexually transmitted diseases
For sexually transmitted diseases concomitant infection caused by *T. palladium* should be excluded.

Neurological and psychiatric disorders
Azithromycin should be administered with caution to patients with neurological or psychiatric disorders.

Hypersensitivity
As with erythromycin and other macrolides, rare serious allergic reactions, including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions, including acute generalized 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 IV have resulted in recurrent symptoms and required a longer period of observation and treatment.
If an allergic reaction occurs, the medicinal product should be discontinued and appropriate therapy should be initiated. Physicians should be aware that reappearance of the allergic symptoms may reoccur when symptomatic therapy is discontinued.

Ergot alkaloids (ergot alkaloids) and azithromycin
Concomitant use of ergot alkaloids and macrolide antibiotics has been described to accelerate development of ergotism. Interactions between ergot alkaloids and azithromycin have not been studied.

There is, however, the possibility of ergotism so that azithromycin and ergot alkaloid derivatives should not be used concomitantly (see section 4.5).

QT prolongation
Prolonged cardiac repolarisation and prolongation of the QT interval, imparting a risk of developing cardiac arrhythmia or torsades de pointes, have been seen in the treatment with macrolides, including azithromycin (see section 4.8). Providers should consider the risk of QT prolongation which can lead to cardiac arrest (sometimes fatal) when weighing the risks and benefits of azithromycin for at-risk groups including:

- Patients with congenital or documented acquired QT prolongation
- Patients who concomitantly take other active medicinal products that prolong the QT interval such as antiarrhythmics of class IA (quinidine and procainamide) and class III (dofetilide amiodarone and sotalol), cisapride and terfenadine (see section 4.5); antipsychotic active substances such as pimozide; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin.
- Patients with electrolyte disturbance, especially in cases of hypokalaemia and hypomagnesaemia
- Patients with clinically significant bradycardia, cardiac arrhythmia or severe cardiac failure.
- Women and elderly patients with existing proarrhythmia

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

Zithromax i.v. must be reconstituted and diluted as indicated and must be given by intravenous infusion over at least 180 minutes. It must not be given as bolus or intramuscular injection.

Each vial contains 4.96 mmol (114.02 mg) sodium. This is to be taken in consideration for patients on a controlled sodium diet (low sodium/low salt).

4.5 Interaction with other medicinal products and other forms of interaction

Antacids or gastric acid secretion inhibitors
Mineral antacids should not be given simultaneously with Zithromax i.v. since a study revealed peak serum levels of azithromycin to be reduced by up to 24%. Therefore, a time interval of 2 to 3 hours should be observed. However, the extent of absorption (parameter: AUC) was not reduced.

Cimetidine had no influence on the rate and extent of absorption of azithromycin. Therefore, it can be co-administered with Zithromax i.v.

Cetirizine
In healthy volunteers, co-administration of a 5-day regimen of azithromycin with cetirizine 20 mg in the steady-state neither resulted in pharmacokinetic interaction nor in significant changes in the QT interval.

Ergot alkaloids (ergot alkaloids)
Although no corresponding experience is available so far, vasoconstrictive effects with circulatory disorders in particular in fingers and toes cannot be excluded if Zithromax i.v. and dihydroergotamine or non-hydrated ergot alkaloids are administered concomitantly. Therefore, concomitant administration should be avoided for safety reasons (see section 4.4).

Virostatics
No sufficient data on interactions with antiviral medicinal products are available to recommend dose adjustments. The following substances were investigated:

- Zidovudine

Single 1,000 mg doses and multiple 1,200 mg or 600 mg doses of azithromycin had only little effect on the plasma pharmacokinetics or and urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral mononuclear erythrocytes. The clinical significance of this finding is unclear, but it may be of benefit to patients.

- Didanosine:
Co-administration of 1,200 mg/day azithromycin with didanosine (400 mg/day) to 6 HIV-positive patients did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

Rifabutin
Co-administration of azithromycin and rifabutin did not markedly change the mean serum concentrations of either medicinal product.
Neutropenia was observed in persons receiving concomitant treatment of azithromycin and rifabutin (see section 4.8).

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

Azithromycin does not interact significantly with the hepatic cytochrome P450 system. Therefore, azithromycin is not expected to show the pharmacokinetic interactions seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via a cytochrome-metabolite complex does not occur with azithromycin. The following medicinal products metabolised via cytochrome P450 did not show significant interactions with azithromycin in clinical studies: atorvastatin, carbamazepine, efavirenz, fluconazole, indinavir, methylprednisolone, midazolam, sildenafil, triazolam, trimethoprime/sulfamethoxazole. However, caution is indicated with the concomitant use of these agents together with azithromycin.

Atorvastatin
Co-administration of atorvastatin (10 mg/day) and azithromycin (500 mg/day) did not alter the plasma concentration 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.

Theophylline
Neither pharmacokinetic nor clinical studies with azithromycin revealed any evidence of interactions with theophylline. However since interactions between theophylline and some macrolides have been described, patients with concomitant use of azithromycin and theophylline derivatives should be observed for typical signs of increased theophylline levels.

Anticoagulants
A pharmacokinetic interaction study with healthy volunteers revealed no evidence of azithromycin exerting any influence on the anticoagulant effect of a single 15-mg dose of warfarin. However, there have been reports of potentiated anticoagulation subsequent to co-administration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of prothrombin time monitoring.

Ciclosporin

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

Terfenadine
Pharmacokinetic studies revealed no signs of any interaction between azithromycin and terfenadine. Rare cases were reported, in which the possibility of such an interaction could not be completely excluded, however, no specific evidence for such an interaction was found. Caution is indicated with the concomitant administration of azithromycin and terfenadine.

Other antibiotics
The potential of parallel resistance between azithromycin and macrolide antibiotics (e.g. erythromycin) as well as lincomycin, and clindamycin should be borne in mind. Therefore, co-administration of multiple medicinal products of this substance class is not recommended.

Substances prolonging the QT interval
Azithromycin should not be used together with other active substances prolonging the QT interval (see section 4.4).

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

4.6 Fertility, pregnancy and lactation

Fertility
In fertility studies conducted on rats, reduced pregnancy rates were noted following administration of azithromycin. The relevance of this finding to humans is unknown.

Pregnancy
There are no adequate data on the use of Zithromax i.v. in pregnant women. Animal studies with respect to reproductive toxicity have shown that azithromycin crosses the placenta reaching the foetus, but no teratogenic effects were observed (see section 5.3.). Zithromax 500 mg film-coated tablets can only be used during pregnancy if a clear indication exists, as currently no conclusive assessment of the safety of this therapy is possible.

Breastfeeding
Azithromycin is excreted in human milk. Adverse effects of azithromycin on newborns/infants have not been studied. Zithromax powder for oral suspension should not be used during breastfeeding. Among other things, breastfed infants may experience sensitisation, irritation of the intestinal bacteria flora and shoot fungal infection. It is recommended to pump off and discard the human milk during treatment and 2 days after the conclusion of the treatment. Breast-feeding may resume thereafter.

4.7 Effects on ability to drive and use machines

As yet, azithromycin has generally no influence on alertness and reactivity. However, occurrence of undesirable effects (see section 4.8), may possibly affect reactivity and impair the ability to drive and operate machines.

4.8 Undesirable effects

The assessment of undesirable effects is based on the following frequencies:

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)
Not known (cannot be estimated from the available data)

When azithromycin was given by the intravenous route and followed by oral administration for the treatment of community-acquired pneumonia, the most frequently reported side effects were diarrhoea/soft stool, nausea, abdominal pain and vomiting. Local inflammation and pain at the infusion site have been reported with intravenous administration of azithromycin.

When azithromycin was given by the intravenous route and followed by oral administration for the treatment of uncomplicated ascending adnexitis, the most frequently reported side effects were diarrhoea, nausea, abdominal pain, lack of appetite, rash, pruritus and vaginitis.

When azithromycin was coadministered with metronidazole in these studies, a relatively higher incidence of side effects such as nausea, abdominal pain, vomiting, infusion site reaction, stomatitis, dizziness, and dyspnoea was reported.

Table 1: Adverse reactions possibly or probably related to azithromycin based on clinical trial experience and post-marketing surveillance:

System Organ Class	**Very common (≥ 1/10)**	**Common (≥ 1/100 bis < 1/10)**	**Uncommon (≥ 1/1.000 bis < 1/100)**	**Rare (≥ 1/10.000 bis < 1/1.000)**	**Very rare (< 1/10.000)**	**Incidence not known** (cannot be estimated from the available data)
Infections and infestations			Candidiasis, vaginal infection, pneunomia, fungal infection, bacterial infection, pharyngitis, gastroenteritis, respiratory disorder, rhinitis, oral candidiasis			Pseudomembranous colitis (see section 4.4)
Blood and lymphatic system disorders			Leukopenia, neutropenia, eosinophilia			Thrombocytopenia, hemolytic anaemia
Immune system disorders			Angioedema, hypersensitivity reaction			Severe (partially life-threatening) anaphylactic reaction (e.g. anaphylactic shock) (see section 4.4)
Metabolism and nutrition disorders			Anorexia			
Psychiatric disorders			Nervousness, insomnia	Agitation		Aggression, anxiety, delirium, hallucinations
Nervous system disorders		Headache~~,~~	Dizziness, somnolence, dysgeusia, paraesthesia~~i~~			Syncope, convulsion, hypoesthesia, psychomotor, hyperactivity, anosmia/ ageusia, parosmia, myasthenia gravis (see section 4.4)
Eye disorders			Visual impairment			
Ear and labyrinth disorders			Ear disorder, vertigo			Hearing impairment including deafness and/or tinnitus

Cardiac disorders			Palpitations			Torsades de pointes (see section 4.4), arrhythmia (see section 4.4) including ventricular tachycardia, electrocardiogram QT prolonged (see section 4.4)
Vascular disorders			Hot flush			Hypotension
Respiratory, thoracic and mediastinal disorders			Dyspnoea, epistaxis			
Gastrointestinal disorders	Diarrhoea	Vomiting, abdominal pain, nausea	Constipation, flatulence, dyspepsia, gastritis, dysphagia, distended abdomen, dry mouth, eructation, ulceration of oral mucosa, excessive saliva excretion, soft stool			Pancreatitis, tongue discolouration
Hepatobiliary disorders				Liver function disorder, jaundice, cholestasis		Hepatic failure (which has rarely resulted in death), hepatitis, hepatic necrosis
Skin and subcutaneous tissue disorders			Rash, pruritus, urticaria, dermatitis, dry skin, hyperhidrosis	Photosensitivity reaction, Acute Generalized Exanthematous Pustulosis (AGEP), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome)[§]		Stevens-Johnson syndrome, toxic epidermal necrolysis,
Musculoskeletal and connective tissue disorders			Osteoarthritis, myalgia, back pain, neck pain			Arthralgia
Renal and			Dysuria,			Interstitial

urinary disorders			renal pain			Nephritis, acute renal failure
Reproductive system and breast disorders			Metrorrhagia, testicular disorder			
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, hematocrit decreased, bicarbonate increased; abnormal sodium			
Injury and poisoning			Post procedural complications			

[§] ADR frequency estimated using "The Rule of 3"

Table 2: Adverse reactions resulting possibly or very probably from prophylaxis or treatment of a *Mycobacterium avium* infection. The data are from clinical trials or post-marketing investigations. These

adverse reactions differ either in type or frequency from the adverse reactions reported for immediate release or prolonged release medicinal products:

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 bis < 1/10)	Rare (≥ 1/10.000 bis < 1/1.000)
Metabolism and nutrition disorders		Anorexia	
Nervous system disorders		Dizziness, headache, paraesthesia, dysgeusia	Hypoesthesia
Eye disorders		Deteriorating eyesight	
Ear and labyrinth disorders		Deafness	Hearing disorder, tinnitus
Cardiac disorders			Palpitations
Gastrointestinal disorders	Diarrhoea, abdominal pain, nausea, flatulence, abdominal discomfort, soft stool		
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	Asthenia, malaise

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 reactions experienced at higher than recommended doses were similar to those seen at normal doses.

Symptoms or signs
The typical symptoms of an overdose with macrolide antibiotics are reversible hearing loss, severe nausea, vomiting and diarrhoea.

Treatment
In the event of an overdose, general symptomatic treatment and support of vital functions are indicated, if required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: J01FA10

Mechanism of action
The mechanism of action of azithromycin is based on the inhibition of protein biosynthesis by binding to the 50S subunit of the bacterial ribosome, thus mostly causing a bacteriostatic effect.

Relation between pharmacokinetics and pharmacodynamics
Effectiveness mainly depends on the ratio of AUC (area under the curve area under the concentration-time curve) and minimal inhibitory concentration (MIC) of the pathogen.

Mechanisms 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 (S_B) (so-called MLS_B 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 MLS_B phenotype additionally implies cross-resistance to clindamycin and streptogramin B. Partial cross-resistance exists to the 16-membered macrolide spiramycin.

Breakpoints
Testing of azithromycin is carried out by means of the usual dilution series.
The following MIC breakpoints were determined for susceptible and resistant pathogens:

Table 3: EUCAST (European Committee on Antimicrobial Susceptibility Testing) Breakpoints

Pathogen	Susceptible	Resistant
Staphylococcus spp.[1)]	≤1 mg/l	>2 mg/l
Staphylococcus spp. (Groups A, B, C, G)[1)]	≤0.25 mg/l	>0.5 mg/l
Staphylococcus pneumoniae[1)]	≤0.25 mg/l	>0.5 mg/l
Moraxella catarrhalis[1)]	≤0.5 mg/l	>0.5 mg/l
Neisseria gonorrhoeae[2)]	≤0.25 mg/l	>0.5 mg/l

[1)] Erythromycin can be used as test substance to detect the sensitivity to Azithromycin.
[2)] Thresholds refer to single dose of 2 g in monotherapy.

Prevalence of acquired resistance in Germany
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 adequate treatment of severe infections. Expert advice on therapy should be sought if the local prevalence of resistance is such that the effectiveness of azithromycin seems questionable. Particularly with serious infections or therapeutic failure, a microbiological diagnosis with identification of the pathogen and determination of its susceptibility to azithromycin should be sought.

Table 4: Prevalence of acquired resistance in Germany based on data from national resistance surveillance projects and studies of the past 5 years (status: February 2018):

Commonly susceptible species
Aerobic gram-positive microorganisms
Mycobacterium avium°
Streptococcus pyogenes
Aerobic gram-negative microorganisms
Haemophilus influenzae[$]
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)[+]
Streptococcus agalactiae
Streptococcus pneumoniae
Inherently resistant species
Aerobic gram-negative microorganisms
Escherichia coli
Klebsiella spp.
Pseudomonas aeruginosa

° At the time of publication of these tables no up-to-date data were available. In primary and standard literature and therapy recommendations susceptibility is assumed.

[$] Natural susceptibility of most isolates is within the intermediate range.

+The resistance rate exceeds 50% in at least one region.

5.2 Pharmacokinetic properties

Absorption

The time taken to peak plasma levels is 2 to 3 hours following oral administration. Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. In elderly patients (>65 years), slightly higher AUC values were seen after a 5-day regimen than in persons under age 40, but these are not considered clinically significant, and hence no dose adjustment is recommended.

In animal studies, high azithromycin concentrations have been observed in phagocytes. In experimental models, higher concentrations of azithromycin are released during active phagocytosis than from non-stimulated phagocytes. In animal models this resulted in high concentrations of azithromycin being delivered to the site of infection.

Non-linearity

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

Distribution

Studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times) indicating that the medicinal product is heavily tissue bound. Concentrations in target tissues, such as lung, tonsils and prostate exceed the MIC_{90} for likely pathogens after a single dose of 500 mg.

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 distribution volume in the steady-state (V_{SS}) was calculated with 31.1 l/kg.

Elimination
In a multiple-dose study with 12 normal volunteers utilising a daily 500 mg one-hour azithromycin infusion (concentration 1 mg/ml) for five days, the amount of administered azithromycin dose excreted in urine in 24 hours was approximately 11% after the 1st dose and 14% after the 5th dose. These values are greater in each case than those reported after oral azithromycin dosing (6% excreted in urine in unchanged form). Approximately 12% of an intravenously administered dose is excreted unchanged over three days, the majority in the first 24 hours. Biliary excretion is the major route of elimination for unchanged drug following oral administration. Following oral administration azithromycin is primarily excreted unchanged via the bile. Very high concentrations of unchanged azithromycin have been found in human bile, together with 10 metabolites, formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by cleavage of the cladinose conjugate. Corresponding assays suggest that the metabolites play no part in the microbiological activity of azithromycin.

Pharmacokinetic / pharmacodynamic relationships
In patients with community-acquired pneumonia receiving a single daily one-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 and the AUC_{24} was 9.60 ± 4.80 µg x h/ml.

In volunteers receiving a three-hour intravenous infusion of 500 mg azithromycin at a concentration of 1 mg/ml, the mean C_{max} and AUC_{24} were 1.14 ± 0.14 µg/ml and 8.03 ± 0.86 µg x h/ml, respectively.

Renal impairment
Following a single dose of azithromycin 1 g orally, the pharmacokinetics in patients with renal impairment and a glomerular filtration rate of 10 to 80 ml/min were unchanged. Statistically significant differences in AUC_{0-120} (8.8 µg x h/ml vs. 11.7 µg x 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) were observed between the group with a glomerular filtration rate of <10 ml/min and the group with normal renal function.

Hepatic impairment
In patients with mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) hepatic impairment, there is no evidence of a change in serum pharmacokinetics of azithromycin compared to those with normal hepatic function. In these patients urinary clearance of azithromycin appears to increase, perhaps to compensate for reduced hepatic clearance.

Bioavailability
Following oral administration in humans, azithromycin is distributed throughout the body; mean bioavailability is approx. 37%.

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 high doses of azithromycin. Phospholipidosis of similar extent has been observed in the tissue of neonatal rats and dogs. This effect has been shown to be reversible after cessation of azithromycin treatment. The clinical significance of these findings is unknown.

Electrophysiological studies have shown that azithromycin prolongs the QT interval.

In vivo and *in vitro studies* to investigate gene and chromosomal mutations revealed no evidence of a mutagenic potential.

Carcinogenicity studies of azithromycin were not carried out since only short-term use is envisaged and no signs of mutagenic or cancerogenic properties have been reported.

No teratogenic effects were observed in animal studies of embryotoxicity in mice and rats. In rats, azithromycin doses of 100 and 200 mg/kg BW/day led to mild retardation in maternal weight gain and foetal ossification. In the peri-/postnatal study on rats, mild retardations were seen following treatment with doses of 50 mg/kg BW/day azithromycin and above (retardation of physical development and reflex behaviour).

Neonatal studies in rats and dogs did not show an increased sensitivity to azithromycin compared to adult animals of the same species.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, sodium hydroxide

6.2 Incompatibilities

Although no specific incompatibilities are known, no other intravenous substances, additives or medicinal products except for the compatible solutions for infusion described in section 4.2 should be added to Zithromax i.v. or 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.

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

Keep out of the sight and reach of children.

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.

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

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MANUFACUTRED AND PRIMARY PACKAGING BY
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USA

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

8. DATE OF REVISION OF THE TEXT

October 2018

9. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

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