SUMMARY OF PRODUCTS CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
ZITHROTEL 500mg/vial powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 500 mg of azithromycin (as azithromycin dihydrate), which after reconstitution results in a 100 mg/ml azithromycin solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion: Glass vial type I (12 ml), sealed with rubber stopper and aluminium cap with plastic flip-off seal, containing white to off white lyophilized powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
It is indicated for the treatment of community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Legionella pneumophila, Moraxella catarrhalis, Mycoplasma pneumoniae* or *Streptococcus pneumoniae* in patients who require initial intravenous therapy.
It is also indicated for the treatment of pelvic inflammatory disease due to *Chlamydia trachomatis, Neisseria gonorrhoeae,* or *Mycoplasma hominis* in patients who require initial intravenous therapy.

4.2 Posology and method of administration
Adults
The recommended dose for the treatment of community-acquired pneumonia due to the indicated susceptible microorganisms is of 500 mg administered as a single intravenous daily dose for at least two consecutive days. The intravenous therapy should be followed by the oral administration of azithromycin in a single daily dose of 500 mg up to 7 to 10 days of treatment. Transition to oral therapy should be carried out when indicated by the doctor and according to the clinical response.

The recommended dose for the treatment of pelvic inflammatory disease (PID) due to the indicated susceptible microorganisms is of 500 mg administered as a single intravenous daily dose for one or two days. The intravenous therapy should be followed by the oral administration of azithromycin in a single daily dose of 250 mg up to 7 days of treatment. Transition to oral therapy should be carried out when indicated by the doctor and according to the clinical response. If anaerobic microorganisms are suspected of contributing to the infection, an antimicrobial anaerobic agent may be administered in combination with azithromycin.

Children
The efficacy and safety of IV azithromycin for the treatment of infections in children and adolescents has not been established.

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

Use in patients with renal impairment
No dose adjustment is recommended in patients with mild to moderate renal impairment (GFR 10 - 80 ml/min). Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR < 10 ml/min) (see section 4.4 and section 5.2).

Use in patients with hepatic impairment

Dose adjustment is not required for patients with mild to moderate hepatic dysfunction but the medicinal product should be used with caution in patients with significant hepatic diseases (see section 4.4 Special warnings and precautions for use).

Method of administration

Once the product is reconstituted and diluted, it is intended to be administered by intravenous infusion. It should not be administered as an intravenous bolus or an intramuscular injection (see section 4.4 and section 6.6).

The concentration of the solution for infusion and the infusion rate of azithromycin as powder for solution for infusion should be 1 mg/ml over 3 hours or 2 mg/ml over 1 hour. Concentrations >2mg/ml should be avoided.

Preparation of the solution for intravenous administration is as follows:

Reconstitution

The initial solution of azithromycin is prepared by adding 4.8 ml of sterile water for injections to the 500 mg vial and shaking the vial until all the drug is dissolved. It is recommended that a standard 5 ml (non-automated) syringe be used to ensure that the exact volume of 4.8 ml of sterile water for injections is dispensed. Each ml of reconstituted solution contains azithromycin dihydrate equivalent to 100 mg azithromycin (100 mg/ml).

Parenteral administration drugs should be inspected visually for particulate in suspension prior to administration. If particulate in suspension is evident in reconstituted solution, the drug solution should be discarded.

The reconstituted solution must be further diluted prior to administration as instructed below.

Dilution

To provide azithromycin over a concentration range of 1.0 - 2.0 mg/ml, transfer 5 ml of the 100 mg/ml azithromycin solution to the appropriate amount of any of the diluents listed in section 6.6.

Final infusion solution concentration (mg/ml)	Amount of diluent (ml)
1.0 mg/ml	500 ml
2.0 mg/ml	250 ml

It is recommended that a 500 mg dose of azithromycin as powder for solution for infusion, diluted according to the instructions above, be administered as an intravenous infusion over at least 60 minutes.

4.3 Contraindications

The use of the product is contraindicated in patients with a known hypersensitivity to azithromycin, erythromycin or any of the macrolide or ketolide antibiotics or to any excipients listed in section 6.1.

Co-administration of macrolides with cisapride is contraindicated.

4.4 Special warnings and precautions for use

Hypersensitivity

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

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

Hepatotoxicity
Since the liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease.
Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur.

Infantile hypertrophic pyloric stenosis (IHPS)
Cases of infantile hypertrophic pyloric stenosis (IHPS) have been reported following the administration of azithromycin in newborns (treatment during the first 42 days after birth). Parents and nursing staff should be asked to contact their doctor if vomiting or irritability with feeding occurs.

Ergot derivatives
In patients receiving ergot derivatives, ergotism has been precipitated by co-administration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergot and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administrated.

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

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

Strains of *C. difficile* producing hypertoxin A and B contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. Therefore, CDAD must be considered in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Discontinuation of therapy with azithromycin and the administration of specific treatment for *C. difficile* should be considered.

Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

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

Prolongation of the QT interval
Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides, including azithromycin. (see Section 4.8); Prescribers should consider the risk of QT prolongation, which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including patients:
• With congenital or documented QT prolongation
• Currently receiving treatment with other active substance known to prolong QT interval such as antiarrhythmics of classes IA and III, antipsychotic agents, antidepressants, and fluoroquinolone

• With electrolyte disturbance, particularly in case 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

QTc interval prolongation was studied in a randomized, placebo-controlled parallel trial in 116 healthy subjects who received either chloroquine (1000 mg) alone or in combination with azithromycin (500 mg, 1000 mg, and 1500 mg once daily). Co-administration of azithromycin increased 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, 1000 mg and 1500 mg azithromycin, respectively.

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

Children
The efficacy and safety of azithromycin as powder for solution for infusion for the treatment of infections in children and adolescents has not been established.

Intravenous use
Azithromycin powder for solution for infusion should be reconstituted and diluted according to the instructions and should be administered as an intravenous infusion over at least 60 minutes.
ZITHROTEL should not be administered as an intravenous bolus or an intramuscular injection (section 6.6).

4.5 Interaction with other medicinal products and other forms of interaction

Cetirizine: In healthy volunteers, co-administration of a 5-day regimen of azithromycin with cetirizine 20 mg at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

Didanosine *(Dideoxyinosine)***:** Co-administration of 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

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

Zidovudine: Single 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients.
Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to undergo the pharmacokinetic drug interactions as seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.

Ergot derivatives: Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended (See section 4.4).

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

Atorvastatin: Co-administration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase inhibition assay). However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin 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 co-administration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Ciclosporin: In a pharmacokinetic study with healthy volunteers 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 ciclosporin, the resulting ciclosporin Cmax and AUC0-5 were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

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

Fluconazole: Co-administration of a single dose of 1200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and half-life of azithromycin were unchanged by the co-administration of fluconazole, however, a clinically insignificant decrease in Cmax (18%) of azithromycin was observed.

Indinavir: Co-administration of a single dose of 1200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

Methylprednisolone: In a pharmacokinetic interaction study in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

Midazolam: In healthy volunteers, co-administration of 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: Co-administration of azithromycin (1200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment is required.

Rifabutin: Co-administration of azithromycin and rifabutin did not affect the serum concentrations of either drug. Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of

rifabutin, a causal relationship to combination with azithromycin has not been established (see section 4.8 Undesirable effects).

Sildenafil: In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC and Cmax, 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. The co-administration of theophylline and macrolides has been associated with increased theophylline serum levels. As a consequence, the measurement of theophylline levels is recommended when azithromycin and theophylline are co-administered.

Triazolam: In 14 healthy volunteers, co-administration 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-administration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with azithromycin 1200 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.

Cisapride: Cisapride is metabolised on liver by the enzyme CYP 3A4. Co-administration of cisapride with macrolides may increase the risk of developing cardiac arrhythmia (QT prolongation, Torsades de pointes) because macrolides inhibit the enzyme CYP 3A4. Therefore, Cisapride should not be co-administered with those drugs.

4.6 Pregnancy and lactation

Pregnancy

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

There is a large amount of data from observational studies performed in several countries on exposure to azithromycin during pregnancy, compared to no antibiotic use or use of another antibiotic during the same period. 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. Therefore, azithromycin should only be used during pregnancy if clinically needed and the benefit of treatment is expected to outweigh any small increased risks which may exist.

Lactation

Limited information available from the 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 treatment taking into account the benefit of breast-feeding for the child and the benefit of treatment for the woman.

Fertility

In fertility studies performed in rats, reduced pregnancy rates were observed after azithromycin administration. The causal relationship of this finding to humans is unknown.

4.7 Effects on ability to drive and use machines

There is no evidence to suggest that azithromycin as powder for solution for infusion may have an effect on a patient's ability to drive or operate machinery.

4.8 Undesirable effects

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

In clinical trials, the following undesirable effects have been reported:

Blood and Lymphatic System Disorders: Transient episodes of mild neutropenia have occasionally been observed in clinical trials, although a causal relationship to azithromycin has not been established.

Ear and Labyrinth Disorders: Hearing impairment (including hearing loss, deafness and/or tinnitus) has been reported in some patients receiving azithromycin. Many of these have been associated with prolonged use of high doses in investigational studies. In those cases where follow-up information was available, the majority of these events were reversible.

Gastrointestinal Disorders: Nausea, vomiting, diarrhea, loose stools, abdominal discomfort (pain/cramps), and flatulence.

Hepatobiliary Disorders: Abnormal liver function.

Skin and Subcutaneous Tissue Disorders: Allergic reactions including rash and angioedema.
General Disorders and Administration Site Conditions: Local pain and inflammation at the site of infusion.

In post-marketing experience, the following additional undesirable effects have been reported:

Infections and Infestations: Moniliasis and vaginitis.

Blood and Lymphatic System Disorders: Thrombocytopenia.

Immune System Disorders: Anaphylaxis (rarely fatal) (see **section 4.4**).

Metabolism and Nutrition Disorders: Anorexia.

Psychiatric Disorders: Aggressive reaction, nervousness, agitation, and anxiety.

Nervous System Disorders: Dizziness, convulsions, headache, hyperactivity, hypoesthesia, paresthesia, somnolence, and syncope. There have been rare reports of taste/smell perversion and/or loss.

Ear and Labyrinth Disorders: Deafness, tinnitus, hearing impaired, and vertigo.

Cardiac Disorders: Palpitations and arrhythmias including ventricular tachycardia have been reported. There have been rare reports of QT prolongations and torsades de pointes (see **section 4.4**).

Vascular Disorders: Hypotension.

Gastrointestinal Disorders: Vomiting/diarrhea (rarely resulting in dehydration), dyspepsia, constipation, pseudomembranous colitis, pancreatitis, and rare reports of tongue discoloration.

Hepatobiliary Disorders: Hepatitis and cholestatic jaundice have been reported, as well as rare cases of hepatic necrosis and hepatic failure, which have resulted in death (see **section 4.4**).

Skin and Subcutaneous Tissue Disorders: Allergic reactions including pruritus, rash, photosensitivity, edema, urticaria, and angioedema. Rarely, serious cutaneous adverse reactions including erythema multiforme, AGEP, SJS, TEN and DRESS have been reported.

Musculoskeletal and Connective Tissue Disorders: Arthralgia.

Renal and Urinary Disorders: Interstitial nephritis and acute renal failure.

General Disorders and Administration Site Conditions: Asthenia, fatigue, and malaise.

4.9 Overdose

Symptoms

The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea.

Treatment

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Macrolides, ATC code: J01FA10

Mechanism of action

Azithromycin is the first antibiotic of a subgroup of macrolides, known as azalides, which is chemically different from erythromycin. The molecule is constructed by adding a nitrogen atom to the lactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl-9a-homo-erythromycin A. The molecular weight is 749.0.

Azithromycin binds to the 23S rRNA of the bacterial 50S ribosomal subunit. It stops bacterial protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit.

Mechanism of resistance:

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

The most important ribosomal modification that determines reduced binding of macrolides is post-transcriptional (N6)-dimethylation of adenine at nucleotide A2058 (E. coli numbering system) of the 23S rRNA by methylases encoded by erm (erythromycin ribosome methylase) genes. Ribosomal modifications often determine cross resistance (MLSB phenotype) 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). 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 MICs) and staphylococci. In streptococci and enterococci, an efflux pump that recognizes 14- and 15-membered macrolides (which include, respectively, erythromycin and azithromycin) is encoded by mef(A) genes.

Methodology for determining the in vitro susceptibility of bacteria to azithromycin 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 CO2 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.

The CLSI susceptibility breakpoints, based on broth microdilution or agar dilution testing, with incubation in ambient air, are given in the table below.

CLSI Dilution Susceptibility Interpretive Criteria

	Broth microdilution MIC (mg/L)		
Organism	**Susceptible**	**Intermediate**	**Resistant**
Haemophilus species	≤4	-	-[b]
Moraxella catarrhalis	≤0,25	-	-
Neisseria meningitidis	≤2	-	-[b]
Staphylococcus aureus	≤2	4	≥8
Streptococci[a]	≤0,5	1	≥2

a Includes Streptococcus pneumoniae, b-hemolytic streptococci and viridans streptococci.
b The current absence of data on resistant strains precludes defining any category other than susceptible. If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.
Incubation in ambient air.
CLSI = Clinical and Laboratory Standards Institute; MIC = Minimal inhibitory concentration.
Source: CLSI, 2012; CLSI, 2010

Susceptibility can also be determined by the disk diffusion method, measuring inhibition zone diameters after incubation in ambient air. Susceptibility disks contain 15 micrograms of azithromycin. Interpretive criteria for inhibition zones, established by the CLSI on the basis of their correlation with MIC susceptibility categories, are listed in the table below:

CLSI Disk Zone Interpretive Criteria

	Disk inhibition zone diameter (mm)		
Organism	**Susceptible**	**Intermediate**	**Resistant**
Haemophilus species	≥ 12	-	-
Moraxella catarrhalis	≥ 26	-	-
Neisseria meningitidis	≥ 20	-	-
Staphylococcus aureus	≥ 18	14 - 17	≤ 13
Streptococci[a]	≥ 18	14 - 17	≤ 13

a Includes Streptococcus pneumoniae, b-hemolytic streptococci and viridans streptococci.
Incubation in ambient air
CLSI = Clinical and Laboratory Standards Institute; MIC = Minimal inhibitory concentration.
Source: CLSI, 2012; CLSI, 2010

The validity of both the dilution and disk diffusion test methods should be verified using quality control (QC) strains, as indicated by the CLSI. Acceptable limits when testing azithromycin against these organisms are listed in the table below.

Quality Control Ranges for Azithromycin Susceptibility Tests (CLSI)

Broth microdilution MIC	
Organism	Quality control range (mg/L azithromycin)
Haemophilus influenzae ATCC 49247	1 - 4
Staphylococcus aureus ATCC 29213	0.5 - 2
Streptococcus pneumoniae ATCC 49619	0.06 – 0.25
Disk inhibition zone diameter (15 microgram disk)	
Organism	Quality control range (mm)
Haemophilus influenzae ATCC 49247	13 - 21
Staphylococcus aureus ATCC 25923	21 - 26
Streptococcus pneumoniae ATCC 49619	19 - 25

Incubation in ambient air.
CLSI = Clinical and Laboratory Standards Institute; MIC = Minimal inhibitory concentration.
Source: CLSI, 2012.

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

EUCAST Susceptibility Breakpoints for Azithromycin

	MIC (mg/L)	
	Susceptible	Resistant
Staphylococcus spp	≤1	>2
Streptococcus spp (Group A,B,C,G)	≤0,25	>0,5
Streptococcus pneumoniae	≤0,25	>0,5
Haemophilus influenzae	≤0,12	>4
Moraxella catarrhalis	≤0,25	>0,5
Neisseria gonorrhoeae	≤0,25	>0,5

EUCAST = European Committee on Antimicrobial Susceptibility Testing; MIC = Minimal inhibitory concentration.
Source: EUCAST January 2017

Antibacterial Spectrum
The susceptibility of bacterial species to azithromycin is shown below.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

In-vitro susceptibility data do not always correlate with clinical results.

Commonly susceptible species

Aerobic gram-positive bacteria:
Streptococci (Groups C, F, G) and Viridans group streptococci.

Aerobic gram-negative bacteria:
Bordetella pertussis, Haemophilus ducreyi, Haemophilus influenzae[*$], Haemophilus parainfluenzae*[*], Legionella pneumophila, Moraxella catarrhalis* and Neisseria gonorrhoeae.*

Other:
Chlamydia pneumoniae[*], Chlamydia trachomatis, Mycoplasma pneumoniae*[*] and Ureaplasma urealyticum.*

Species for which acquired resistance may be a problem

Aerobic gram-positive bacteria:
Streptococcus pneumoniae[*]
Streptococcus pyogenes[*]
Staphylococcus aureus

Inherently resistant organisms:
Enterobacteriaceae
Pseudomonas spp.

Note: Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive strains and most strains of methicillin resistant-staphylococci.

[*]Species for which efficacy has been demonstrated in clinical trials.
[$]Species with natural intermediate susceptibility.

5.2 Pharmacokinetic properties

Distribution
In animal tests, high concentrations of azithromycin have been found in phagocytes. It has also been established that during active phagocytosis higher concentrations of azithromycin are released than from non-stimulated phagocytes. In animal models this results in high concentrations of azithromycin being delivered to the site of infection.

In pharmacokinetic studies it has been demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (as much as 50 times) than those measured in plasma, which indicates that the agent strongly binds to tissues.

Concentrations in target tissues such as lungs, tonsils and prostate exceed the MIC_{90} level for expected pathogens after a single dose of 500 mg.

Biotransformation/Elimination
Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. About 12% of an intravenously administered dose is excreted in the urine unchanged over a period of 3 days; the majority in the first 24 hours. Biliary excretion of azithromycin, is a major route of elimination after oral administration. Particularly high concentrations of unchanged azithromycin have been found in human bile. Also in bile, ten metabolites were detected, which were formed through N- and O-demethylation, hydroxylation of desosamine and aglycone rings and cleavage of cladinose conjugate. Comparison of the results of liquid chromatography and microbiological analyses carried has shown that the metabolites do not contribute to azithromycin microbiological activity.

Pharmacokinetics in special patient groups
Elderly
In elderly volunteers (>65 years), slightly higher AUC values were always observed after a 5-day course than in younger volunteers (<40 years). However, these differences are not considered to be clinically relevant; no dose adjustment is therefore recommended.

Renal insufficiency
In renally impaired patients with a glomerular filtration rate of 10 to 80 ml/min, the pharmacokinetics was unchanged after a single oral dose of 1 g azithromycin. Statistically significant differences were observed in $AUC_{0\text{-}120}$ (8.8 µg × h/ml vs. 11.7 µg × h/ml), Cmax (1.0 µg/ml vs. 1,6 µg/ml) and CLr (2.3 ml/min/kg vs. 0.2 ml/min/kg) between the group of patients with severe renal impairment (GFR <10 ml/min) and the group of patients with normal kidney function.

Hepatic insufficiency

In patients with mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to normal hepatic function. In these patients, urinary recovery of azithromycin appears to increase perhaps to compensate for reduced hepatic clearance.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid anhydrous and sodium hydroxide

6.2 Incompatibilities

Azithromycin reconstituted solution can be diluted according to the instructions and compatible solutions for infusion, indicated in Section 6.6. Other intravenous substances, additives or other medications should not be added or infused simultaneously through the same intravenous line.

6.3 Shelf life

3 years.

Concentrated solution after reconstitution, prepared according to the instructions is chemically and physically stable 24 hours, when stored below 25°C.
Diluted solutions, prepared according to the instructions, are chemically and physically stable for 24 hours at or below 25°C, or for 3 days if stored under refrigeration (2-8°C).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless the reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at temperatures below 30 ºC (see Section 6.3).

6.5 Nature and contents of container

Uncoloured type I glass vials with bromobutyl rubber stopper and aluminium cap.

Pack sizes of 1 vial with powder for solution for infusion.

6.6 Special precautions for disposal and other handling

Azithromycin as powder for solution for infusion is supplied in single dose vials.
The initial solution of azithromycin is prepared by adding 4.8 ml of sterile water for injections (azithromycin 100 mg/ml). For the administration, the required volume of reconstituted solution is added in a compatible solution for infusion to provide azithromycin over a concentration range of 1.0-2.0 mg/mL.
Concentrations >2mg/ml should be avoided.

Parenteral administration drugs should be inspected visually for particulate in suspension prior to administration. If particulate in suspension is evident in reconstituted solution, the drug solution should be discarded.

The reconstituted solution may be diluted with:

Normal Saline (0.9% sodium chloride)
½ Normal Saline (0.45% sodium chloride)
5% Dextrose in water
Lactated Ringer's Solution
5% Dextrose in ½ Normal Saline (0.45% sodium chloride) with 20 mEq KCl
5% Dextrose in Lactated Ringer's Solution
5% Dextrose in 1/3 Normal Saline (0.3% sodium chloride)
5% Dextrose in ½ Normal Saline (0.45% sodium chloride)
It is recommended that a 500 mg dose of azithromycin as powder for solution for infusion, diluted according to the instructions above, be administered as an intravenous infusion over at least 60 minutes.

Azithromycin should not be administered as an intravenous bolus or an intramuscular injection (See section 4.4 and section 6.6.

7. PRODUCT OWNER
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8. PRODUCT REGISTRATION NUMBER(S)

9. DATE OF REVISION OF THE TEXT
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