SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zedbac 500 mg powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg of azithromycin (equivalent to 524.1 mg of azithromycin dihydrate), which after reconstitution results in a 100 mg/ml azithromycin solution. The concentrate should be further diluted to 1 mg/ml or 2 mg/ml.

Excipient(s) with known effect:
This medicinal product contains 114 mg (4.96 mmol) sodium per vial.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.
Free white powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Azithromycin is indicated for the treatment of the following infections in adults (see sections 4.4 and 5.1):
- Community-acquired pneumonia (CAP)
- Pelvic inflammatory disease (PID), always in combination with other appropriate antibacterial agent(s) (e.g. metronidazole).
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology
Azithromycin should be administered as a single daily dose. Dosing recommendations for adult patients are shown in Table 1.
Table 1: Dosing recommendations for intravenous azithromycin.

Indication	Azithromycin dosing regimen
Community-acquired pneumonia	500 mg once daily for at least 2 days, followed by oral dose of 500 mg daily to complete a 7- to 10-day total course of

	treatment
Pelvic inflammatory disease, in combination with other appropriate antibacterial agent(s) (e.g. metronidazole)	500 mg once daily for 1 to 2 days, followed by oral dose of 250 mg once daily to complete a 7-day course of treatment.
Consideration should be given to the treatment regimens, doses and duration of treatment as recommended in updated treatment guidelines for each indication. The timing of the switch to oral therapy should be determined at the discretion of the physician and in accordance with clinical response.	

Special populations

Renal impairment

No dose adjustment is required in patients with GFR ≥10 ml/min. In patients with GFR <10 ml/min azithromycin should be administered with caution (see section 5.2).

Hepatic impairment

No dose adjustment is required in patients with mild (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B) (see section 5.2). No data are available in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, azithromycin should be administered with caution in these patients (see section 4.4).

Elderly

No dose adjustment is required in elderly patients (see section 5.2). Since the elderly are more likely to experience proarrhythmic conditions, particular caution is recommended due to the risk of developing cardiac arrhythmia and torsade de pointes (see section 4.4).

Paediatric population

The safety and efficacy of Azithromycin for the intravenous treatment of community acquired pneumonia in the paediatric population have not been established.

There is no relevant use of Azithromycin for the treatment of pelvic inflammatory disease in children under 12 years of age while the safety and efficacy in adolescent girls have not been established.

Method of administration

For intravenous use after reconstitution and dilution.

The recommended route of administration is by intravenous infusion only. Do not administer as an intravenous bolus or an intramuscular injection. The solution concentration and rate of infusion should be either 1mg/1ml over 3 hours or 2mg/2ml over 1 hour. A dose of 500mg azithromycin should be infused for a minimum duration of 1 hour.

For instructions on reconstitution and dilution of this medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Potential for resistance

Azithromycin could favour the development of resistance due to the associated long-lasting and decreasing levels in plasma and tissues after the end of treatment (see section 5.2). Treatment with azithromycin should only be initiated after a careful assessment of the benefit and the risks, considering the local prevalence of resistance, and when preferred treatment regimens are not indicated.

Severe skin and hypersensitivity reactions

Rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), which can be life- threatening or fatal, have been reported in association with azithromycin treatment (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. 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, azithromycin 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.

QT interval prolongation

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides including azithromycin (see section 4.8). Therefore, as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients:

• With congenital or documented QT prolongation
• Currently receiving treatment with other active substances known to prolong QT interval (see section 4.5)
• With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
• 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

Hepatotoxicity
Since liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin. Hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have also been reported with azithromycin, some of which have resulted in death (see section 4.8). Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products. Patients should be advised to stop azithromycin administration and to contact their physician if signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy develop. In such cases liver function tests/investigations should be performed immediately.

Clostridioides difficile associated diarrhoea (CDAD), pseudomembranous colitis
CDAD and pseudomembranous colitis have been reported with azithromycin, and may range in severity from mild diarrhoea to fatal colitis (see section 4.8). CDAD and pseudomembranous colitis must be considered in patients who present with diarrhoea during or subsequent to the administration of azithromycin. Discontinuation of therapy with azithromycin and the use of supportive measures together with the administration of specific treatment for *C. difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Sexually transmitted infections

Neisseria gonorrhoeae is very likely to be resistant to macrolides, including the azalide azithromycin (see section 5.1). Therefore, azithromycin is not recommended for the treatment of uncomplicated gonorrhoea and pelvic inflammatory disease unless laboratory results have confirmed susceptibility of the organism to azithromycin. If left untreated or treated sub-optimally, this condition may lead to late onset complications such as infertility and ectopic pregnancy.

Furthermore, a concomitant infection caused by *Treponema pallidum* should be excluded as symptoms of incubating syphilis could be masked delaying diagnosis.

For all patients with sexually transmitted urogenital infections, appropriate antibacterial therapy and microbiological follow-up tests should be initiated.

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).

Non-susceptible organisms
The use of azithromycin may result in the overgrowth of non-susceptible organisms. If superinfection occurs, interruption of treatment or other appropriate measures may be required.

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 may not be co-administered.

This medicinal product contains 114 mg (4.96 mmol) sodium per vial, equivalent to approximately 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

Although azithromycin is a weak CYP450 inhibitor and does not interact significantly with CYP450 substrates, CYP3A4 inhibition cannot be completely ruled out. Therefore, caution is recommended in case of co-administration with CYP3A4 substrates with narrow therapeutic index.

Azithromycin is an inhibitor of the transporter P-glycoprotein (P-gp). Co-administration of azithromycin with P-gp substrates, such as digoxin and colchicine, may increase their exposure. For narrow therapeutic index drugs, caution and clinical and/or therapeutic drug monitoring and dose adjustment as appropriate are advised. The relatively long half-life of azithromycin should be taken into account in this context (see section 5.2).

Medicinal products that are known to prolong the QT interval
Azithromycin should be used with caution in patients receiving medicinal products known to prolong the QT interval (see section 4.4), such as antiarrhythmics of Classes IA (e.g.quinidine and procainamide) and III (e.g. dofetilide, amiodarone and sotalol), antipsychotic agents (e.g. pimozide), antidepressants (e.g. citalopram), fluoroquinolones (e.g. moxifloxacin and levofloxacin), cisapride, chloroquine and hydroxychloroquine.

Drug interaction information for azithromycin with potential concomitant medicinal products is summarised in the table and text below. The drug interactions described are based on clinical drug-drug interaction studies conducted with azithromycin or, where indicated, are potential drug interactions that may occur with azithromycin.

Table 2 Clinically relevant drug interactions between azithromycin and other medicinal products

Medicinal product (therapeutic area)	**Interaction Effect on exposure**	**Mechanism**	**Recommendation concerning co-administration**
Atorvastatin (HMG CoA reductase inhibitor) Azithromycin 500 mg orally once daily for 3 days. Atorvastatin 10 mg orally once daily.	Azithromycin: ND Atorvastatin: ↔ AUC ↔ C_{max}	Atorvastatin is a CYP3A4 and P-gp substrate.	Caution should be exercised since post-marketing cases of rhabdomyolysis in patients receiving azithromycin concomitantly with statins have been reported.

Ciclosporin (immunosuppressant) Azithromycin 500 mg orally once daily for 3 days. Ciclosporin 10 mg/kg orally single dose.	Azithromycin: ND Ciclosporin: ↔ AUC ↑C_{max} 24 %	Ciclosporin is a CYP3A4 and P-gp substrate with narrow therapeutic index and/or competition for biliary excretion.	Clinical monitoring and therapeutic drug monitoring as appropriate should be performed during and after treatment with azithromycin. Ciclosporin dose should be adjusted if required.
Colchicine (gout)	Azithromycin: ND Colchicine: ↑ 57% AUC_{0-t} ↑ 22% C_{max}	Colchicine is a P-gp substrate with narrow therapeutic index.	Clinical monitoring is needed during and after treatment with azithromycin.
Dabigatran (oral anticoagulant)	ND *Expected:* ↑ Dabigatran	Dabigatran is a P-gp substrate with narrow therapeutic index.	Caution should be exercised since post-marketing data suggest an increased risk for haemorrhages in patients receiving azithromycin concomitantly with dabigatran.
Digoxin (cardiac glycosides)	ND *Expected:* ↑ Digoxin	Digoxin is a P-gp substrate with narrow therapeutic index.	Clinical monitoring, and possibly digoxin level monitoring, is needed during and after treatment with azithromycin.

Warfarin (oral anticoagulant) Azithromycin 500 mg orally once daily for 1 day and then 250 mg orally once daily for 4 days. Warfarin 15 mg orally single dose.	Azithromycin: ND Warfarin: ND No change in prothrombin time in clinical drug interaction study but post-marketing reports of potentiated anticoagulation of coumarin-type oral anticoagulants upon co-administration with azithromycin.	Not known.	A higher frequency of prothrombin time monitoring should be considered during and after treatment with azithromycin.
Note: statistically significant changes by more than 10% are indicated as "↑" or "↓", no change as "↔", not determined as "ND".			

No clinically relevant change in the exposure of azithromycin or the co-administered medicinal products was observed in clinical studies evaluating potential drug-drug interactions of azithromycin with carbamazepine, cetirizine, efavirenz, fluconazole, methylprednisolone, midazolam, rifabutin, sildenafil, theophylline, triazolam, trimethoprim/sulfamethoxazole and zidovudine.

4.6 Fertility, 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 teratogenic effects was found. There are, however, no adequate and well-controlled studies in pregnant women.

There is a large amount of data from observational studies on exposure to azithromycin during pregnancy (more than 7000 azithromycin exposed pregnancies). Most of these studies do not suggest an increased risk of adverse foetal effects such as major congenital malformations or cardiovascular malformations.

Epidemiological evidence related to the risk of miscarriage following azithromycin exposure in early pregnancy is inconclusive. Animal studies do not indicate reproductive toxicity (see section 5.3).

Azithromycin should only be used during pregnancy if clinically needed.

Breast-feeding
Azithromycin is excreted in human milk to substantial extent. No serious adverse effects of azithromycin on the breast-fed infants were observed, while effects such as diarrhoea, mucosal fungal infection as well as hypersensitivity can occur in breast-fed newborns/infants even at sub-therapeutic doses. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

4.7 Effects on ability to drive and use machines

Azithromycin has a moderate influence on the ability to drive and use machines. Dizziness, drowsiness and convulsions have been reported in some patients taking azithromycin and some patients experienced visual and/or auditory impairment. This should be considered when assessing a patient's ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions during treatment include diarrhoea, headache, vomiting, abdominal pain, nausea and abnormal laboratory test values. Other important adverse reactions include anaphylactic reactions, torsade de pointes, arrhythmia including ventricular tachycardia, pseudomembranous colitis and hepatic failure (see section 4.4). Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP) have been reported in association with azithromycin treatment (see section 4.4).

Tabulated list of adverse reactions
Adverse reactions identified through clinical trial experience and post marketing surveillance are listed below, by system organ class and frequency.

Frequencies of adverse reaction occurrence are defined as 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3: Tabulated list of adverse reactions

System organ class	Very common	Common	Uncommon	Rare	Not known
Infections and infestations			Candida infection Pneumonia Fungal infection Bacterial infection Vaginal infection Pharyngitis Gastroenterit is Rhinitis Oral candidiasis		
Blood and lymphatic system disorders		Lymphocy te count decreased Eosinophil count increased Basophil count increased Monocyte count increased Neutrophil count increased	Leukopenia Neutropenia Eosinophilia Platelet count increased Haematocrit decreased		Thrombocyto penia Haemolytic anaemia
Immune system disorders			Angioedema Hypersensiti vity (see section 4.4)		Anaphylactic reaction
Metabolis m and nutrition disorders			Decreased appetite		
Psychiatric disorders			Nervousness Insomnia	Agitation	Anxiety Delirium Hallucination Aggression
Nervous system disorders		Headache	Dizziness Dysgeusia Paraesthesia Somnolence		Myasthenia gravis (see section 4.4) Seizure Anosmia Ageusia

					Hypoaesthesia Psychomotor hyperactivity Parosmia Syncope
Eye disorders			Visual impairment		
Ear and labyrinth disorders			Ear disorder Vertigo		Deafness Hypoacusis Tinnitus
Cardiac disorders			Palpitations		Torsades de pointes (see section 4.4) Arrhythmia including ventricular tachycardia (see section 4.4) Electrocardio gram QT prolonged (see section 4.4)
Vascular disorders			Hot flush		Hypotension
Respiratory, thoracic and mediastinal disorders			Dyspnoea Respiratory disorder Epistaxis		
Gastrointestinal disorders	Diarrhoea Abdominal discomfort	Vomiting Abdominal pain Nausea	Gastritis Constipation Dyspepsia Dysphagia Abdominal distension Dry mouth Mouth ulceration Salivary hypersecretion Eructation Flatulence		Pancreatitis Pseudomembranous colitis (see section 4.4) Tongue discolouration
Hepatobiliary disorders			Hepatitis Aspartate aminotransferase increased Alanine aminotransferase increased	Hepatic function abnormal Jaundice cholestatic	Hepatic failure (see section 4.4) Hepatitis fulminant Hepatic necrosis

			Blood bilirubin increased Blood alkaline phosphatase increased		
Skin and subcutaneous tissue disorders			Rash Pruritus Urticaria Dermatitis Dry skin Hyperhidrosis	Acute generalised exanthematous pustulosis (AGEP) Drug reaction with eosinophilia and systemic symptoms (DRESS) Photosensitivity reaction	Toxic epidermal necrolysis Stevens- Johnson syndrome Erythema multiforme
Musculoskeletal and connective tissue disorders			Osteoarthritis Myalgia Back pain Neck pain		Arthralgia
Renal and urinary disorders			Dysuria Renal pain Blood urea increased Blood creatinine increased		Acute kidney injury Tubulointerst itial nephritis
Reproductive system and breast disorders			Intermenstrual bleeding Testicular disorder		
General disorders and administration site conditions		Injection site pain Injection site inflammation	Oedema Asthenia Malaise Fatigue Face oedema Chest pain Pyrexia Pain Peripheral oedema		
Investigations		Blood bicarbonate decreased	Blood potassium abnormal Blood chloride increased Blood glucose increased		

			Blood bicarbonate increased Blood sodium abnormal		
Injury, poisoning and procedural complications			Post procedural complication		

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme (website: www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms
Adverse reactions experienced with higher than recommended doses were similar to those seen at normal doses (see section 4.8). The typical symptoms of an overdose with azithromycin include gastrointestinal symptoms, i.e. vomiting, diarrhoea, abdominal pain and nausea.

Treatment
In the event of an overdose, general symptomatic treatment and support of vital functions are indicated. There are no data on the effects of dialysis on the elimination of azithromycin. However, due to the elimination mechanism of azithromycin, dialysis is unlikely to result in significant removal of the active substance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, macrolides
ATC-code: J01FA10
Mechanism of action
The mechanism of action of azithromycin is based on the inhibition of the bacterial protein synthesis by binding to the ribosomal 50 S subunit and inhibiting translocation of the peptides.

Pharmacokinetic/pharmacodynamic relation
The efficacy depends mainly on the ratio between AUC (area under the curve) and MIC (minimum inhibitory concentration) of the causative organism.
Mechanisms of resistance
Resistance against azithromycin can be based on the following mechanisms:

- Efflux: Resistance can be caused by an increase in the number of efflux pumps in the cytoplasmic membrane. Only 14- and 15-ring-membered macrolides are concerned (so called M-phenotype).
- Change of target structure: Affinity to ribosomal binding sites is lowered by methylation of the 23S rRNA causing a resistance against macrolides (M), lincosamides (L) and streptogramins of the B-group (SB) (so called MLSB-phenotype). Resistance-conferring methylases are encoded by erm genes. Affinity to ribosomal binding sites is also lowered by mutations in the 23S rRNA target structure or by mutations in the large subunit ribosomal proteins.

- Enzymatic inactivation of macrolides is only of minor clinical interest.

With the M-phenotype a complete cross-resistance between azithromycin, clarithromycin, erythromycin and roxithromycin is observed. The MLSB-phenotype shows an additional cross- resistance with clindamycin and streptogramin B. With the 16-ring-membered macrolide spiramycin a partial cross- resistance is exerted.
Due to low permeability of the outer membrane, most Gram-negative species are inherently resistant to macrolides.

Susceptibility testing interpretive criteria
MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for azithromycin and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

Prevalence of acquired resistance
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. Particularly in the case of severe 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

Commonly susceptible species
Aerobic Gram-negative microorganisms
Haemophilus influenzae
Legionella pneumophila°
Moraxella catarrhalis
Other microorganisms
Chlamydia trachomatis°
Chlamydophila pneumoniae°
Chlamydophila psittaci
Mycoplasma pneumoniae°
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Streptococcus pneumoniae+
Aerobic Gram-negative microorganisms
Neisseria gonorrhoeae
Inherently resistant organisms
Aerobic Gram-negative microorganisms

Escherichia coli
Klebsiella spp.
Pseudomonas aeruginosa
Anaerobic microorganisms
Bacteroides spp.

°No updated data were available at release of tables. Primary literature, scientific standard literature and therapeutic recommendations assume susceptibility.
+Penicillin susceptible strains of *Streptococcus pneumoniae* are more likely to be susceptible to azithromycin than are penicillin resistant strains of *Streptococcus pneumoniae*.

5.2 Pharmacokinetic properties

In patients hospitalised with community-acquired pneumonia receiving single daily one-hour intravenous infusions for 2 to 5 days of 500 mg azithromycin at a concentration of 2 mg/ml, the mean C_{max} ± S.D. achieved was 3.63 ± 1.60 µg/ml, the mean C_{trough} (C_{24}) after the start of the final infusion dose was 0.2 µg/ml and the mean AUC_{0-24} was 9.6 ± 4.8 µg.h/ml.

The mean C_{max}, C_{trough} (C_{24}) and AUC_{0-24} values were 1.14 ± 0.14 µg/ml, 0.18 ± 0.02 µg/ml, and 8.03 ±0.86 µg·hr/ml, respectively, in normal volunteers receiving a 3-hour intravenous infusion of 500 mg azithromycin at a concentration of 1 mg/ml.

Comparison of the plasma pharmacokinetic parameters following the first and fifth daily doses of 500 mg intravenous azithromycin in healthy volunteers showed almost no change in C_{max}, but there was a 40-61% increase in AUC_{0-24} reflecting a 2.2- to 3-fold increase in C_{trough} (C_{24}) levels.

Distribution
Azithromycin is widely and rapidly distributed from plasma to the extravascular compartment, including tissues such as tonsil, lung and gynaecological tissues as well as the intracellular compartment, in particular to polymorphonuclear leukocytes, macrophages, and monocytes.
Pharmacokinetic studies have shown considerably higher azithromycin concentrations certain tissues (up to 50 times the maximum concentration observed in the plasma). This indicates an extensive binding to these tissues with a steady- state volume of distribution ranging from 23 to 31 L/kg. The redistribution phase from the intracellular to the extracellular compartment and to the plasma may result in prolonged low concentrations after treatment cessation.

Azithromycin shows low plasma protein binding, mainly to alpha 1-acid glycoprotein, and it decreases with increasing concentrations of antibiotic: 50%, 23% and 7% protein binding at concentrations of 0.05, 0.1 and 1 mg/L, respectively.

Biotransformation
Azithromycin is minimally metabolised in the liver. The primary route of biotransformation is N- demethylation of the desosamine sugar. Other pathways include O-demethylation, hydrolysis of cladinose (deconjugation of the cladinose sugar), and hydroxylation of desosamine sugar and macrolide ring.

There is no evidence of clinically relevant hepatic cytochrome CYP 3A4 induction or inhibition via the formation of a cytochrome-metabolite complex. Also, auto-induced metabolism of azithromycin by this pathway has not been detected.

Elimination
Azithromycin is mainly eliminated by (active) biliary excretion mostly as unchanged drug, but also as metabolites which are devoid of antibacterial activity. Urinary excretion represents a minor route of elimination with less than 6% of an oral dose and around 20% of the drug that reaches the systemic circulation excreted in urine. More than 50% of faecal, and 12% or urinary excretion is in the form of unchanged compound.

Following the administration of a single 500 mg azithromycin dose, a plasma clearance of 630 ml/min was estimated with a terminal half-life of approximately 68 hours. Renal clearance is generally in the range of 100-189 ml/min, substantially smaller than plasma clearance as expected due to the relatively poor contribution of the renal route to elimination.

Linearity/non-linearity
Following oral administration of an immediate release formulation, dose proportionality on AUC_{0-24} and C_{max} was shown in the range of 250 mg to 1000 mg.

Special populations

Renal Impairment
Azithromycin pharmacokinetics was investigated in 43 adults (21 to 85 years of age) following the oral administration of a single 1.0 g dose of azithromycin (4 x 250 mg capsules) to subjects with GFR >80 ml/min (n =12), subjects with GFR between 10 and 80 ml/min (n = 12) and subjects with GFR <10 ml/min (n = 19).

The pharmacokinetics of azithromycin in subjects with GFR between 10 and 80 ml/min were not affected (mean C_{max} and AUC_{0-120} increased by 5.1% and 4.2%, respectively compared to subjects with GFR >80 ml/min). The mean C_{max} and AUC_{0-120} increased 61% and 35%, respectively, in subjects with GFR <10 ml compared to subjects with GFR >80 ml/min.

No data are available for subjects undergoing dialysis, but due to the elimination mechanism of azithromycin, dialysis is unlikely to result in significant removal of the active substance.

Hepatic Impairment
Azithromycin pharmacokinetics was investigated in 22 adults following the oral administration of a single 500 mg dose of azithromycin (2 x 250 mg capsules) to subjects with normal hepatic function (n = 6), Child-Pugh A (n = 10) and Child-Pugh B (n = 6). The pharmacokinetics of azithromycin in subjects with Child-Pugh A and B were 3% and 19% lower on $AUC_{0\text{-}inf}$ and 34% and 72% higher on C_{max}, respectively, compared to subjects with normal hepatic function.

Elderly
In elderly volunteers (> 65 years) given azithromycin 500 mg (2 x 250 mg capsules) on day 1 followed by 250 mg from days 2 to 5 in the fasted state the $AUC_{0\text{-}24}$ on Days 1 and 5 were 3.0 and 2.7 μg•h/ml, respectively. A 29% higher $AUC_{0\text{-}24}$, a 8% higher C_{max} and a 37.5% higher T_{max} than in younger volunteers (<40 years) were observed at day 5. Since these differences are not considered clinically significant, no dose adjustment is required for elderly subjects with normal renal and hepatic function.

5.3 Preclinical safety data

Non-clinical data based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity did not indicate adverse reactions clearly relevant to humans not already considered in other sections of the SmPC.

However, phospholipidosis (intracellular phospholipid accumulation) has been observed in several tissues 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 this finding for humans is in general unknown.

In animal studies for embryotoxic effects performed up to moderately maternal toxic doses (2 to 3 times the maximum recommended adult daily dose of (500 mg based on body surface area), no teratogenic effect was observed in mice and rats. Azithromycin was shown to cross the placenta. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day (2 to 3 times the maximum recommended adult daily dose of 500 mg based on body surface area) led to mild retardation of foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardation following treatment with azithromycin doses of 200 mg/kg/day (3 times the maximum recommended adult daily dose of 500 mg based on body surface area) was observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous citric acid
Sodium hydroxide 31% (for pH adjustment)

6.2 Incompatibilities

Azithromycin reconstituted solution can be diluted according the instructions and compatible solutions for infusion, indicated in section 6.6 Special precautions for disposal and other handling.

This medicinal product must not be mixed with other medicinal products except those mentioned 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 (according to the instructions): azithromycin as powder for solution for infusion is chemically and physically stable during 24 hours, when stored below 25 ºC.

- Diluted solutions, prepared according to the instructions, are chemically and physically stable for 24 hours at or below 25°C, or for 72 hours if stored at 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 8ºC, unless the reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions prior to reconstitution.

For storage conditions after reconstitution and dilution of the medicinal product, see Section 6.3.

6.5 Nature and contents of container

Azithromycin is packed in 12 ml glass (type I) vials with bromobutyl rubber stopper and sealed with aluminium/plastic flip-off cap.

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

6.6 Special precautions for disposal

Azithromycin as powder for solution for infusion is supplied in single dose vials.

Preparation of reconstituted solution

The initial reconstituted solution is prepared by adding 4.8 ml of sterile water for injections to the 12 ml vial initial content using a standard 5 ml syringe (non-automated) and shaking the vial until all the drug is dissolved. Each ml reconstituted solution contains azithromycin dihydrate equivalent to 100 mg azithromycin (100 mg/ml).

The reconstituted medicinal product is chemically and physically stable during 24 hours, when stored below 25 ºC. Diluted solutions, prepared according to the instructions, are chemically and physically stable for 24 hours at or below 25°C, or for 72 hours if stored at 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 8ºC, unless the reconstitution/dilution has taken place in controlled and validated aseptic conditions.

The reconstituted solution must be further diluted prior to administration.

Dilution of reconstituted solution

To provide azithromycin at a concentration of 1.0 or 2.0 mg/ml, transfer 5 ml of the 100 mg/ml azithromycin solution to the appropriate amount of any of the diluents listed below.

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

The reconstituted solution can be diluted with:

0.9 % sodium chloride
0.45 % sodium chloride
5% dextrose in water
Lactated Ringer’s solution

5% dextrose in 0.3% sodium chloride
5% dextrose in 0.45% sodium chloride

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

It is recommended that the 500 mg dose of azithromycin as powder for solution for infusion, diluted as described 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.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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