

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Azithromycine ratiopharm 250 mg, filmomhulde tabletten  
Azithromycine ratiopharm 500 mg, filmomhulde tabletten

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

{Product name} 250 mg

Each film-coated tablet contains 250 mg azithromycin (as dihydrate).

{Product name} 500 mg

Each film-coated tablet contains 500 mg azithromycin (as dihydrate).

For the full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Film-coated tablet.

{Product name} 250 mg

White, oblong biconvex film-coated tablet 14.5 x 7.5 mm with imprint 'AI 250' on one side.

{Product name} 500 mg

Pale blue, oblong, biconvex film-coated tablet 19.0 x 8.0 mm with imprint 'AI 500' and score line on one side.

The tablet can be divided into equal doses.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

{Product name} is indicated for the treatment of the following infections in adults and adolescents weighing at least 45 kg (see sections 4.4 and 5.1):

- Acute streptococcal tonsillitis and pharyngitis
- Acute bacterial sinusitis
- Acute bacterial otitis media
- Community-acquired pneumonia (CAP)
- Acute bacterial skin and skin structure infections (ABSSSI)
- Urethritis and cervicitis caused by *Chlamydia trachomatis*

{Product name} is indicated for the treatment of adult patients with acute exacerbation of chronic bronchitis.

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

#### 4.2 Posology and method of administration

Posology

*Adults and adolescents weighing at least 45 kg*  
Azithromycin should be administered as a single daily dose.

Table 1: Dosing recommendations for adults and adolescents weighing at least 45 kg

Indication	Azithromycin dosing regimen
Acute streptococcal tonsillitis and pharyngitis	500 mg/day for 3 days or 500 mg on day 1, followed by 250 mg/day on days 2-5
Acute bacterial sinusitis	
Acute bacterial otitis media	
Acute exacerbation of chronic bronchitis*	
Community-acquired pneumonia <sup>#</sup>	
Acute bacterial skin and skin structure infections	
Urethritis and cervicitis caused by <i>Chlamydia trachomatis</i>	1000 mg as a single dose
<p>* for treatment of adults only  <sup>#</sup> in adults, oral treatment may also follow intravenous treatment, if clinically indicated to complete a 7- to 10-day total course of treatment (for details refer to the Summary of Product Characteristics of azithromycin IV formulations).</p> <p>Consideration should be given to the treatment regimens, doses and duration of treatment as recommended in updated treatment guidelines for each indication.</p>	

#### *Missed dose*

If 12 hours or less have passed since the missed dose, the patient should be advised to take it as soon as possible and then take the next dose at the regularly scheduled time. If more than 12 hours have passed since the time the dose is usually taken, the patient should be advised to wait until the next scheduled dose.

#### Special populations

##### *Renal impairment*

No dose adjustment is required in patients with GFR  $\geq 10$  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

There is no relevant use of {Product name} for the treatment of acute exacerbations of chronic bronchitis in paediatric patients.

Other pharmaceutical forms are available that may be more appropriate to treat patients unable to swallow tablets as well as paediatric patients weighing less than 45 kg.

#### Method of administration

For oral use.

##### *{Product name} 250 mg*

Tablets should be swallowed whole as a single daily dose and may be taken with or without a meal. Administration immediately before a meal may enhance the gastrointestinal tolerability.

##### *{Product name} 500 mg*

Tablets may be taken with or without a meal. Administration immediately before a meal may enhance the gastrointestinal tolerability.

Tablets can be split in two equal halves which can be used to adjust the dose. The entire tablet or half a tablet should be taken as a single daily dose according to the dosing recommendations.

### **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.

In addition, if single dose azithromycin is considered for the treatment of urethritis and cervicitis due to *N. gonorrhoeae* or *C. trachomatis* (see section 4.2), concomitant urogenital infection by *Mycoplasma genitalium* should be excluded due to the high risk of emergence of resistance in this organism.

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.

Excipient with known effectSodium

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

**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 <sub>max</sub>	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 <sub>max</sub> 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 <sub>0-t</sub> ↑ 22% C <sub>max</sub>	Colchicine is a P-gp substrate with narrow therapeutic index.	Clinical monitoring is needed during and after treatment with azithromycin.
Dabigatran (oral anticoagulant)	ND  <i>Expected:</i> ↑ 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 <i>Expected:</i> ↑ 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 oral antacids (aluminium hydroxide/magnesium hydroxide), carbamazepine, cetirizine, cimetidine, efavirenz, fluconazole, methylprednisolone, midazolam, rifabutin, sildenafil, theophylline, triazolam, trimethoprim/sulfamethoxazole and zidovudine.

#### Paediatric population

Interaction studies have only been performed in adults.

#### **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

{Product name} 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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1\ 000$  to  $< 1/100$ ), rare ( $\geq 1/10\ 000$  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
<b>Infections and infestations</b>			<i>Candida</i> infection Pneumonia Fungal infection Bacterial infection Vaginal infection Pharyngitis Gastroenteritis Rhinitis Oral candidiasis		
<b>Blood and lymphatic system disorders</b>		Lymphocyte count decreased Eosinophil count increased Basophil count increased Monocyte count increased Neutrophil count increased	Leukopenia Neutropenia Eosinophilia Platelet count increased Haematocrit decreased		Thrombocytopenia Haemolytic anaemia
<b>Immune system disorders</b>			Angioedema Hypersensitivity (see section 4.4)		Anaphylactic reaction
<b>Metabolism and nutrition disorders</b>			Decreased appetite		
<b>Psychiatric disorders</b>			Nervousness Insomnia	Agitation	Anxiety Delirium Hallucination

					Aggression
<b>Nervous system disorders</b>		Headache	Dizziness Dysgeusia Paraesthesia Somnolence		Myasthenia gravis (see section 4.4) Seizure Anosmia Ageusia Hypoesthesia Psychomotor hyperactivity Parosmia Syncope
<b>Eye disorders</b>			Visual impairment		
<b>Ear and labyrinth disorders</b>			Ear disorder Vertigo		Deafness Hypoacusis Tinnitus
<b>Cardiac disorders</b>			Palpitations		Torsades de pointes (see section 4.4) Arrhythmia including ventricular tachycardia (see section 4.4) Electrocardiogram QT prolonged (see section 4.4)
<b>Vascular disorders</b>			Hot flush		Hypotension
<b>Respiratory, thoracic and mediastinal disorders</b>			Dyspnoea Respiratory disorder Epistaxis		
<b>Gastrointestinal disorders</b>	Diarrhoea	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
<b>Hepatobiliary disorders</b>			Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubin increased Blood alkaline phosphatase increased	Hepatic function abnormal Jaundice cholestatic	Hepatic failure (see section 4.4) Hepatitis fulminant Hepatic necrosis
<b>Skin and subcutaneous tissue disorders</b>			Rash Pruritus Urticaria Dermatitis Dry skin Hyperhidrosis	Acute generalised exanthematous pustulosis (AGEP) Drug reaction with eosinophilia and systemic symptoms (DRESS)	Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme

				Photosensitivity reaction	
<b>Musculoskeletal and connective tissue disorders</b>			Osteoarthritis Myalgia Back pain Neck pain		Arthralgia
<b>Renal and urinary disorders</b>			Dysuria Renal pain Blood urea increased Blood creatinine increased		Acute kidney injury Tubulointerstitial nephritis
<b>Reproductive system and breast disorders</b>			Intermenstrual bleeding Testicular disorder		
<b>General disorders and administration site conditions</b>			Oedema Asthenia Malaise Fatigue Face oedema Chest pain Pyrexia Pain Peripheral oedema		
<b>Investigations</b>		Blood bicarbonate decreased	Blood potassium abnormal Blood chloride increased Blood glucose increased Blood bicarbonate increased Blood sodium abnormal		
<b>Injury, poisoning and procedural complications</b>			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 national reporting system listed in Appendix V.

## 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 and, if required, administration of medicinal charcoal or gastric lavage.

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](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

<b>Commonly susceptible species</b>
<b><i>Aerobic Gram-positive microorganisms</i></b>
<i>Streptococcus pyogenes</i>
<b><i>Aerobic Gram-negative microorganisms</i></b>

<i>Haemophilus influenzae</i>
<i>Legionella pneumophila</i> <sup>o</sup>
<i>Moraxella catarrhalis</i>
<b>Anaerobic microorganisms</b>
<i>Peptostreptococcus</i> spp.
<b>Other microorganisms</b>
<i>Chlamydia trachomatis</i> <sup>o</sup>
<i>Chlamydophila pneumoniae</i> <sup>o</sup>
<i>Chlamydophila psittaci</i>
<i>Mycoplasma pneumoniae</i> <sup>o</sup>
<b>Species for which acquired resistance may be a problem</b>
<b>Aerobic Gram-positive microorganisms</b>
<i>Staphylococcus aureus</i> <sup>+</sup>
<i>Staphylococcus epidermidis</i>
<i>Staphylococcus haemolyticus</i>
<i>Streptococcus agalactiae</i>
<i>Streptococcus pneumoniae</i> <sup>++</sup>
Viridans streptococci
<b>Anaerobic microorganisms</b>
<i>Fusobacterium</i> spp.
<i>Prevotella</i> spp.
<b>Inherently resistant organisms</b>
<b>Aerobic Gram-negative microorganisms</b>
<i>Escherichia coli</i>
<i>Klebsiella</i> spp.
<i>Pseudomonas aeruginosa</i>
<b>Anaerobic microorganisms</b>
<i>Bacteroides</i> spp.

<sup>o</sup>No updated data were available at release of tables. Primary literature, scientific standard literature and therapeutic recommendations assume susceptibility.

<sup>+</sup>At least one region shows resistance rates higher than 50% for methicillin-resistant *Staphylococcus aureus*.

<sup>++</sup>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

### Absorption

The peak serum concentrations ( $C_{max}$ ) of azithromycin after 500 mg oral suspension (40 mg/ml), 1000 mg powder for oral suspension, 500 mg (2 x 250 mg) tablets and 1000 mg (4 x 250 mg) capsules in healthy volunteers under fasted conditions were 0.29, 0.75, 0.34, and 1.07 mg/L respectively. The time-to-peak plasma ( $T_{max}$ ) concentrations of azithromycin after oral administration ranges from 2 to 3 hours. The mean absolute bioavailability in healthy volunteers after 500 mg oral suspension and 1000 mg powder for oral suspension in sachet was 37% and 44% in fasted conditions, respectively.

The effect of food on the relative oral bioavailability of azithromycin is formulation dependent. After the administration of 500 mg of an oral suspension (40 mg/ml), 1000 mg as powder for oral suspension and 500 mg oral dose of azithromycin tablets (2 x 250 mg), similar exposure was obtained with high-fat meal vs fasted conditions. Following the administration of a single dose of 500 mg (2 x 250 mg) capsule formulation with a high-fat meal vs fasted conditions, the mean ratio of  $C_{max}$  and  $AUC_{0-24}$  was 52% and 43% lower.

Table 5 shows mean (SD) pharmacokinetic parameters in adult healthy volunteers after standard dosing regimens with tablets and capsules.

Table 5: AUC<sub>0-24</sub> and C<sub>max</sub> of azithromycin for the 3-day and 5-day regimen at last day of dosing

Dose regimen, formulation	AUC <sub>0-24</sub> (µg•h/ml)	C <sub>max</sub> (µg/ml)
3-day regimen (500 mg daily), tablet	1.88 (0.96)	0.42 (0.21)
5-day regimen (500 mg D1, 250 mg D2 to D5), tablet	0.80 (0.42)	0.18 (0.10)
5-day regimen (500 mg D1, 250 mg D2 to D5), capsule	2.1 (0.6)	0.24 (0.08)

### 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 in 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<sub>0-24</sub> and C<sub>max</sub> 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  $AUC_{0-\infty}$  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  $AUC_{0-24}$  on Days 1 and 5 were 3.0 and 2.7  $\mu\text{g}\cdot\text{h}/\text{ml}$ , respectively. A 29% higher  $AUC_{0-24}$ , 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.

#### Paediatric population

The pharmacokinetics of azithromycin oral suspension have been characterised in 14 children aged 6 to 15 years with pharyngitis and in 7 children aged 1 year to 5 years with otitis media. In these two studies, azithromycin oral suspension was dosed at 10 mg/kg on day 1, followed by 5 mg/kg on days 2 through 5. Following 5 days of treatment, mean  $AUC_{0-24}$  values were 3.1  $\mu\text{g}\cdot\text{h}/\text{ml}$  and 1.8  $\mu\text{g}\cdot\text{h}/\text{ml}$ , respectively. The mean  $C_{\max}$  value was 0.38  $\mu\text{g}/\text{ml}$  and the corresponding mean  $T_{\max}$  value was 2.4 hours in children aged 6 to 15 years and 0.22  $\mu\text{g}/\text{ml}$  and 1.9 hours for children 1 to 5 years of age. The mean  $C_{\max}$  and  $AUC_{0-24}$  values are 1.7 times greater in children 6 to 15 years of age than in children 1 to 4 years of age.

The PK of a 3-day course of azithromycin oral suspension at a dose of 10 mg/kg daily was also assessed in 16 children 6 months to 10 years with bacterial infections. The mean  $AUC_{0-24}$  for 7 children aged 2 to 4 years was 2.90  $\mu\text{g}\cdot\text{h}/\text{ml}$  while for the 8 children aged 5 to 10 years the value was 2.08  $\mu\text{g}\cdot\text{h}/\text{ml}$ . A low  $AUC_{0-24}$  value of 0.74  $\mu\text{g}\cdot\text{h}/\text{ml}$  was recorded for a single child in the 6 months to 2-year-old group.

Single dose pharmacokinetics of azithromycin in paediatric patients with given doses of 30 mg/kg have not been studied.

### **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**

#### Core

Calcium hydrogen phosphate  
Hypromellose  
Maize starch  
Starch, pregelatinised  
Cellulose, microcrystalline  
Magnesium stearate  
Sodium lauryl sulfate

#### Coating

Hypromellose  
Colour indigotin lake (E132) (500 mg tablets only)  
Titanium dioxide (E171)  
Polysorbate 80  
Talc

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

{Product name} 250 mg film-coated tablets are packed in clear, transparent PVC/Aluminium blisters.

Pack sizes: 2, 4, 6, 10 tablets

{Product name} 500 mg film-coated tablets are packed in clear, transparent PVC/Aluminium blisters.

Pack sizes: 1, 2, 3, 6, 30 tablets

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal**

No special requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Ratiopharm GmbH  
Graf-Arco-Strasse 3  
89079 Ulm  
Duitsland

## **8. MARKETING AUTHORISATION NUMBERS**

RVG 110859 – filmomhulde tabletten 250 mg  
RVG 110860 – filmomhulde tabletten 500 mg

## **9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION**

Datum van eerste verlening van de vergunning: 19 juni 2013  
Datum van laatste verlenging: 12 maart 2015

## **10. DATE OF REVISION OF THE TEXT**

Laatste volledige herziening: 5 februari 2026, wijzigingen in rubrieken 2, 3 en 4,1 t/m 5.3