SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Azitromycine ratiopharm 250 mg, filmomhulde tabletten
Azitromycine ratiopharm 500 mg, filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

250 mg tablets: Each film-coated tablet contains 250 mg azithromycin (as dihydrate).
500 mg tablets: 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.
250 mg tablets: White, oblong biconvex film-coated tablet 14.5 x 7.5 mm with imprint 'AI 250' on one side.
500 mg tablets: 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

For the treatment of the following infections when caused by micro-organisms sensitive to azithromycin (see sections 4.4 and 5.1):
- Acute bacterial sinusitis (adequately diagnosed)
- Acute bacterial otitis media (adequately diagnosed)
- Pharyngitis, tonsillitis
- Acute exacerbation of chronic bronchitis (adequately diagnosed)
- Mild to moderately severe community-acquired pneumonia
- Infections of the skin and soft tissues of mild to moderate severity e.g. folliculitis, cellulitis, erysipelas
- Uncomplicated *Chlamydia trachomatis* urethritis and cervicitis

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

4.2 Posology and method of administration

Posology

The duration of treatment in each of the infectious diseases is given below.

Paediatric population over 45 kg body weight, adults
The total dosage of azithromycin is 1,500 mg which is spread over three days (500 mg once daily). Alternatively, the dosage can be spread over five days (500 mg as a single dose on the first day and thereafter 250 mg once daily).

In uncomplicated *Chlamydia trachomatis* urethritis and cervicitis the dosage is 1,000 mg as a single oral dose.

For sinusitis, treatment is aimed at adults and adolescents over 16 years of age.

Paediatric population under 45 kg body weight
Tablets are not indicated for these patients. Other pharmaceutical forms of azithromycin, e.g. suspensions may be used.

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).

Renal impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min) (see section 4.4).

Hepatic impairment
A dose adjustment is not necessary for patients with mild to moderately impaired liver function (Child-Pugh class A or B) (see section 4.4).

Method of administration
{Product name} should be given as a single daily dose. The tablets can be taken with or without food.

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

Azithromycin is not the first choice for the empirical treatment of infections in areas where the prevalence of resistant isolates is 10% or more (see section 5.1).

Allergic reactions
As with erythromycin and other macrolides, serious allergic reactions, including angioneurotic oedema and anaphylaxis (rarely fatal), drug reaction with eosinophilia and systemic symptoms (DRESS) and severe dermatologic reactions such as acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson-syndrome and toxic epidermal necrolysis (TEN) 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.

Hepatic impairment
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 (see section 4.8). Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

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.

In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests/investigations should be performed immediately. Azithromycin administration should be stopped if liver dysfunction has emerged.

Ergot alkaloids and azithromycin
In patients receiving ergot derivatives, ergotism has been precipitated by coadministration 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 coadministered.

Renal impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min). Caution is advised in patients with severe renal impairment (GFR <10 ml/min) because in these patients a 33% increase in systemic exposure of azithromycin was observed (see section 5.2).

QT 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 torsades 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 such as antiarrhythmics of class IA (quinidine and procainamide) and class III (dofetilide, amiodarone and sotalol), hydroxychloroquine, cisapride and terfenadine; antipsychotic agents such as pimozide; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency

The following should be considered before prescribing azithromycin:

{Product name} is not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed.

In areas with a high incidence of erythromycin A resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other antibiotics.

Pneumonia
As for other macrolides, high resistance rates of *Streptococcus pneumoniae* (>30%) have been reported for azithromycin in some European countries (see section 5.1). This should be taken into account when treating infections caused by *Streptococcus pneumoniae*.

Soft tissue infection
The main causative agent of soft tissue infections, *Staphylococcus aureus*, is frequently resistant to azithromycin. Therefore, susceptibility testing is considered a precondition for treatment of soft tissue infections with azithromycin.

Pharyngitis/tonsillitis
Azithromycin is not the substance of first choice for the treatment of pharyngitis and tonsillitis caused by *Streptococcus pyogenes*. For this and for the prophylaxis of acute rheumatic fever penicillin is the treatment of first choice.

Sinusitis
Often, azithromycin is not the substance of first choice for the treatment of sinusitis.

Acute otitis media
Often, azithromycin is not the substance of first choice for the treatment of acute otitis media.

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

Sexually transmitted disease
In case of sexually transmitted diseases a concomitant infection by *T. pallidum* should be excluded.

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

Neurological or psychiatric diseases
Azithromycin should be administered with caution to patients suffering from neurological or psychiatric diseases.

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

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

C. difficile produces toxins A and B which 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. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. A careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Pseudomembranous colitis
Pseudomembranous colitis has been reported with the use of macrolide antibiotics. This diagnosis should therefore be considered in patients who develop diarrhea after starting treatment with azithromycin.

Long-term use
There is no experience regarding the safety and efficacy of long-term use of azithromycin for the mentioned indications. In case of rapid recurrent infections, treatment with another antibiotic should be considered.

Mycobacterium Avium Complex (MAC) infection in children
The safety and efficacy of azithromycin for the prevention or treatment of *Mycobacterium avium* complex (MAC) infection in children have not been established.

Excipient
Sodium
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

Antacids
In a pharmacokinetic study investigating the effects of simultaneous administration of antacid with azithromycin, no effect on overall bioavailability was seen although peak serum concentrations were reduced by approximately 25%. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously. Azithromycin should be taken at least 1 hour before or 2 hours after the antacid.
Coadministration of azithromycin prolonged-release granules for oral suspension with a single 20 ml dose of co-magaldrox (aluminium hydroxide and magnesium hydroxide) did not affect the rate and extent of azithromycin absorption.

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

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

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

Cytochrome P450
Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to undergo the pharmacokinetic interactions as seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.

Ergot
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 agents known to undergo significant cytochrome P450-mediated metabolism.

Atorvastatin
Coadministration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentration of atorvastatin (based on an 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 coadministration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of prothrombin time monitoring 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 C_{max} and AUC_{0-5} were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these agents. If combination treatment is necessary, the ciclosporin levels should be carefully monitored and the dosage adjusted accordingly.

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

Fluconazole
Coadministration of a single dose of 1,200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and half-life of azithromycin were unchanged by the coadministration of fluconazole, however, a clinically insignificant decrease in C_{max} (18%) of azithromycin was observed.

Indinavir
Coadministration of a single dose of 1,200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

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

Midazolam
In healthy volunteers, coadministration of azithromycin 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam.

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

Rifabutin
Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either agent.

Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established (see section 4.8).

Sildenafil
In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for three days) on the AUC and C_{max} of sildenafil or its major circulating metabolite.

Terfenadine
Pharmacokinetic studies have reported no evidence of an interaction between azithromycin and terfenadine.
There have been rare cases reported where the possibility of such an interaction could not be entirely excluded; however there was no specific evidence that such an interaction had occurred.

Azithromycin should be administered with caution in combination with terfenadine.

Theophylline
There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are coadministered to healthy volunteers.

Triazolam
In 14 healthy volunteers, coadministration of azithromycin 500 mg on day 1 and 250 mg on day 2 with 0.125 mg triazolam on day 2 had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

Trimethoprim/sulfamethoxazole
Coadministration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with azithromycin 1,200 mg on day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim or sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies.

Cisapride
Cisapride is metabolized in the liver by the enzyme CYP3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsades de pointes.

CYP3A4 substrates
Even though azithromycin does not appear to inhibit the enzyme CYP3A4, caution is advised when combining the medicinal product with quinidine, ciclosporine, cisapride, astemizole, terfenadine, ergot alkaloids, pimozide or other medicinal products with a narrow therapeutic index predominantly metabolised by CYP3A4.

Astemizole, alfentanil
No data are available on interactions with astemizole and alfentanil. Caution should be exercised with concomitant use of these agents and azithromycin in view of the described potentiation of its effect during concomitant use of the macrolide antibiotic erythromycin.

Substances that prolong the QT interval
Azithromycin should be used with caution in patients receiving medicines known to prolong the QT interval with potential to induce cardiac arrhythmia, e.g. hydroxychloroquine (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of azithromycin in pregnant women. In reproduction toxicity studies in animals azithromycin was shown to pass the placenta, but no teratogenic effects were observed. The safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Therefore azithromycin should only be used during pregnancy if the benefit outweighs the risk.

Breastfeeding
Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in nursing women that have characterized the pharmacokinetics of azithromycin excretion into human breast milk.
No serious adverse effects of azithromycin on the breast-fed infants were observed. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Among other things diarrhoea, fungus infection of the mucous membrane as well as sensitisation is possible in the nursed infant.

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 no or negligible influence on the ability to drive and use machines.
As dizziness and convulsions were reported with azithromycin, patients should be aware of how they react to this medicine before driving or operating machinery.

4.8 Undesirable effects

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

System organ class	**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)**
Infections and infestations			Candidiasis Vaginal infection Pneumonia Fungal infection Bacterial infection Pharyngitis Gastroenteritis Respiratory disorder Rhinitis Oral candidiasis			Pseudomembranous colitis (see section 4.4)
Blood and lymphatic system disorders			Leucopenia Neutropenia Eosinophilia			Thrombocytopenia Haemolytic anaemia
Immune system			Angioedema Hypersensitivity			Anaphylactic reaction (see section

System organ class	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)
disorders						4.4)
Metabolism and nutrition disorders			Anorexia			
Psychiatric disorders			Nervousness Insomnia	Agitation Depersonalisation		Aggression Anxiety Delirium Hallucination
Nervous system disorders		Headache	Dizziness Somnolence Dysgeusia Paraesthesia			Syncope Convulsions Hypoaesthesia Psychomotor hyperactivity Anosmia Ageusia Parosmia Myasthenia gravis (see section 4.4)
Eye disorders			Visual impairment			
Ear and labyrinth disorders			Ear disorder Vertigo			Hearing impairment including deafness and/or tinnitus
Cardiac disorders			Palpitations			Torsades de pointes (see section 4.4) Arrhythmia including ventricular tachycardia (see section 4.4) Electrocardiogram QT prolonged (see section 4.4)
Vascular disorders			Hot flush			Hypotension
Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis			
Gastrointestinal disorders	Diarrhoea	Vomiting Abdominal pain Nausea	Gastritis Constipation Flatulence Dyspepsia Dysphagia Abdominal distension Dry mouth Eructation Mouth ulceration Salivary	Discolouration of the teeth		Pancreatitis Tongue discolouration

System organ class	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)
			hypersecretion Loose stools			
Hepatobiliary disorders			Hepatitis	Hepatic function abnormal Jaundice cholestatic		Hepatic failure which has rarely resulted in death (see section 4.4) Hepatitis fulminant Hepatic necrosis
Skin and subcutaneous tissue disorders			Rash Pruritus Urticaria Dermatitis Dry skin Hyperhidrosis	Photosensitivity reaction, acute generalised exanthematous pustulosis (AGEP)	Drug reaction with eosinophilia and systemic symptoms (DRESS)	Stevens-Johnson syndrome Maculopapular rash Toxic epidermal necrolysis Erythema multiforme
Musculoskeletal and connective tissue disorders			Osteoarthritis Myalgia Back pain Neck pain			Arthralgia
Renal and urinary disorders			Dysuria Renal pain			Acute renal failure Interstitial nephritis
Reproductive system and breast disorders			Vaginitis Metrorrhagia Testicular disorder			
General disorders and administration site conditions			Oedema Asthenia Malaise Fatigue Face oedema Chest pain Pyrexia Pain Peripheral oedema			
Investigations		Lymphocyte count decreased Eosinophil count increased Blood bicarbonate decreased Basophils increased Monocytes	Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubin increased Blood urea increased Blood creatinine increased Blood potassium			

System organ class	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)
		increased Neutrophils increased	abnormal Blood alkaline phosphatase increased Chloride increased Glucose increased Platelets increased Hematocrit decreased Bicarbonate increased Abnormal sodium			
Injury, poisoning and procedural complications			Post procedural complication			

Adverse reactions possibly or probably related to Mycobacterium Avium Complex prophylaxis and treatment based on clinical trial experience and post-marketing surveillance. These adverse reactions differ from those reported with immediate release or the prolonged release formulations, either in kind or in frequency:

	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Metabolism and nutrition disorders		Anorexia	
Nervous system disorders		Dizziness Headache Paraesthesia Dysgeusia	Hypoaesthesia
Eye disorders		Visual impairment	
Ear and labyrinth disorders		Deafness	Hearing impaired Tinnitus
Cardiac disorders			Palpitations
Gastrointestinal disorders	Diarrhoea Abdominal pain Nausea Flatulence Abdominal discomfort Loose stools		
Hepatobiliary disorders			Hepatitis
Skin and subcutaneous tissue disorders		Rash Pruritus	Stevens-Johnson syndrome Photosensitivity reaction
Musculoskeletal and connective tissue disorders		Arthralgia	

General disorders and administration site conditions		Fatigue	Asthenia Malaise

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after 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

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses.

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

Treatment
In cases of overdose the administration of medicinal charcoal and general symptomatic treatment and measures to support vital functions are indicated as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use; macrolides
ATC code: J01FA10

Azithromycin is a macrolide antibiotic belonging to the azalide group.

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.

Mechanism of action
The action mechanism of azithromycin is based upon the suppression of bacterial protein synthesis, by binding to the 50 S subunit and thus inhibiting the translocation of peptides.

(Cross)-Resistance
Generally, the resistance of different bacterial species to macrolides has been reported to occur by three mechanisms associated with target site alteration, antibiotic modification, or altered antibiotic transport (efflux). The efflux in streptococci is conferred by the *mef* genes and results in a macrolide-restricted resistance (M phenotype). Target modification is controlled by *erm* encoded methylases.

A complete cross-resistance exists among erythromycin, azithromycin, other macrolides and lincosamides for *Streptococcus pneumoniae*, beta-haemolytic streptococci of group A, *Enterococcus* spp. and *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA).

Penicillin-sensitive *S. pneumoniae* are more likely to be susceptible to azithromycin than are penicillin-resistant strains of *S. pneumoniae.* Methicillin-resistant *S. aureus* (MRSA) is less likely to be susceptible to azithromycin than methicillin-sensitive *S. aureus* (MSSA).

The induction of significant resistance in both *in vitro* and *in vivo* models is ≤1 dilution rise in MICs for *S. pyogenes, H. influenzae* and *Enterobacterciae* after nine sub-lethal passages of active substance and three dilution increase for *S. aureus* and development of *in vitro* resistance due to mutation is rare.

Breakpoints
Azithromycin susceptibility breakpoints for typical bacterial pathogens:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) Breakpoints (2021, v. 11.0):

Pathogens	**susceptible [mg/l]**	**resistant [mg/l]**
Staphylococcus spp.[1]	≤ 1	>2
Streptococcus groups A, B, C and G[1]	≤0.25	>0.5
Streptococcus pneumoniae[1]	≤ 0.25	>0.5
Haemophilus influenzae	Note[2]	Note[2]
Moraxella catarrhalis[1]	≤ 0.25	>0.5
Neisseria gonorrhoeae	≤ Note[3]	>Note[3]

[1] Erythromycin can be used to determine susceptibility to azithromycin.
[2] Clinical evidence for the efficacy of macrolides in H. influenzae respiratory infections is conflicting due to high spontaneous cure rates. Should there be a need to test any macrolide against this species, the epidemiological cut-offs (ECOFFs) should be used to detect strains with acquired resistance. The ECOFF for azithromycin is 4 mg/L.
[3] Azithromycin is always used in conjunction with another effective agent. For testing purposes with the aim of detecting acquired resistance mechanisms, the ECOFF is 1 mg/L.

Susceptibility
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.

Species for which acquired resistance may be a problem: prevalence of resistance is equal to or greater than 10% in at least one country in the European Union.

Table 1: Antibacterial spectrum of azithromycin

Species
Commonly susceptible species
Aerobic Gram-positive
Corynebacterium diphteriae
Streptococcus pneumoniae Erythromycin-sensitive Penicillin-sensitive
Streptococcus pyogenes Erythromycin-sensitive
Aerobic Gram-negative
Bordetella pertussis
Escherichia coli-ETEC
Escherichia coli-EAEC
Haemophilus influenzae
Haemophilus ducreyi
Legionella spp.
Moraxella catarrhalis Erythromycin-sensitive Erythromycin-intermediate
Pasteurella multocida

Species
Anaerobic
Fusobacterium nucleatum
Fusobacterium necrophorum
Prevotella spp.
Porphyromonas spp.
Propionibacterium spp.
Other micro-organisms
Chlamydia pneumoniae
Chlamydia trachomatis
Listeria spp.
Mycobacterium avium Complex
Mycoplasma pneumoniae
Ureaplasma urealyticum
Species for which acquired resistance may be a problem
Aerobic Gram-positive
Staphylococcus aureus Methicillin-susceptible
Coagulase-neg. staphylococci Methicillin-susceptible[+]
Streptococcus pneumoniae Penicillin-intermediate Penicillin-resistant Erythromycin-intermediate
Streptococcus pyogenes Erythromycin-intermediate
Streptococci viridans group Penicillin-intermediate
Aerobic Gram-negative
Moraxella catarrhalis Erythromycin-resistant
Anaerobic
Peptostreptococcus spp.
Inherently resistant organisms
Aerobic Gram positive
Corynebacterium spp.
Enterococcus spp.
Staphylococci MRSA, MRSE
Streptococcus pneumoniae Erythromycin-resistant Penicillin & Erythromycin resistant
Streptococcus pyogenes Erythromycin-resistant
Streptococci viridans group Penicillin-resistant Erythromycin-resistant
Aerobic Gram-negative
Pseudomonas aeruginosa
Anaerobic
Bacteroides fragilis group

[+] Resistance is greater than 50%.

Paediatric population

Following the assessment of studies conducted in children, the use of azithromycin is not recommended

for the treatment of malaria, neither as monotherapy nor combined with chloroquine or artemisinin based drugs, as non-inferiority to anti-malarial drugs recommended in the treatment of uncomplicated malaria was not established.

5.2 Pharmacokinetic properties

Absorption
Following oral administration the bioavailability of azithromycin is approximately 37%. Peak plasma levels are reached after 2-3 hours.

Distribution
Orally administered azithromycin is widely distributed throughout the body. Pharmacokinetic studies have shown considerably higher azithromycin concentrations in the tissues (up to 50 times the maximum concentration observed in the plasma) than in the plasma. This indicates that the substance is extensively bound in the tissues (steady-state volume of distribution approximately 31 l/kg). The mean maximum concentration observed (C_{max}) after a single dose of 500 mg is approximately 0.4 µg/ml, 2-3 hours after administration. With the recommended dosage no accumulation in the serum/plasma occurs. Accumulation does occur in the tissues where the levels are much higher than in the serum/plasma. Three days after administration of 500 mg as a single dose or in divided doses concentrations of 1.3-4.8 µg/g, 0.6-2.3 µg/g, 2.0-2.8 µg/g and 0-0.3 µg/ml are found in lung, prostate, tonsil and serum respectively.

Mean peak concentrations measured in peripheral leukocytes are higher than the MIC_{90} of the most common pathogens.

In experimental *in vitro* and *in vivo* studies, azithromycin accumulates in phagocytes; release is promoted by active phagocytosis. In animal models this process appeared to contribute to the accumulation of azithromycin in the tissue.

The binding of azithromycin to plasma proteins is variable, and varies from 52% at 0.05 µg/ml to 18% at 0.5 µg/ml, depending on the serum concentration.

Biotransformation and elimination
The terminal plasma elimination half-life follows the tissue depletion half-life of 2 to 4 days. In elderly volunteers (> 65 years), higher (29%) AUC values were always observed after a 5-day course than in younger volunteers (< 45 years). However, these differences are not considered to be clinically relevant; no dose adjustment is therefore recommended. Approximately 12% of an intravenously administered dose is excreted in unchanged form with the urine over a period of 3 days; the major proportion in the first 24 hours. Concentrations of up to 237 µg/ml azithromycin, 2 days after a 5-day course of treatment, have been found in human bile, together with 10 metabolites (formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by splitting of the cladinose conjugate). A comparison of HPLC and microbiological determination suggests that the metabolites do not play a role in the microbiological activity of azithromycin.

Pharmacokinetics in special populations

Renal impairment
Following a single oral dose of azithromycin 1 g, mean C_{max} and AUC_{0-120} increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 10-80 ml/min) compared with normal renal function (GFR > 80 ml/min). In subjects with severe renal impairment (GFR <10 ml/min), the mean C_{max} and AUC_{0-120} increased 61% and 35% respectively compared to normal.

Hepatic impairment
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. There are no data on azithromycin use in cases of more severe hepatic impairment.

Elderly
The pharmacokinetics of azithromycin in elderly men was similar to that of young adults; however, in elderly women, although higher peak concentrations (increased by 30-50%) were observed, no significant accumulation occurred.

Paediatric population
Pharmacokinetics have been studied in children aged 4 months-15 years taking capsules, granules or suspension. At 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5, the C_{max} achieved is slightly lower than adults with 224 µg/l in children aged 0.6-5 years and after 3 days dosing and 383 µg/l in those aged 6-15 years. The $t_{1/2}$ of 36 h in the older children was within the expected range for adults.

5.3 Preclinical safety data

In animal studies using exposures 40 times those achieved at the clinical therapeutic dosages, azithromycin was found to have caused reversible phospholipidosis, but as a rule there were no associated toxicological consequences. The relevance of this finding to humans receiving azithromycin in accordance with the recommendations is unknown.

Electrophysiological investigations have shown that azithromycin prolongs the QT interval.

Carcinogenic potential
Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenic potential
There was no evidence of a potential for genetic and chromosome mutations in *in vivo* and *in vitro* test models.

Reproductive toxicity
No teratogenic effects were observed in embryotoxicity studies in rats after oral administration of azithromycin. In rats, azithromycin dosages of 100 and 200 mg/kg body weight/day led to mild retardations in foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardations following treatment with 50 mg/kg/day azithromycin and above were 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 gedeeltelijke wijziging betreft de rubrieken 4.4 en 4.5: 15 juli 2022.