

1. NAAM VAN HET GENEESMIDDEL

Azitromycine Sandoz 200 mg/5 ml, poeder voor orale suspensie

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml reconstituted suspension contains 104.80 mg of azithromycin dihydrate equivalent to 100 mg of azithromycin.

Each 1 ml reconstituted suspension contains 20.96 mg of azithromycin dihydrate equivalent to 20 mg of azithromycin.

Excipients with known effect

Each 5 ml reconstituted suspension contains 3.82 g of sucrose, 0.030 g of aspartame (E 951), up to 410 nanograms of benzyl alcohol, and up to 85 nanograms of sulphites.

Each 5 ml reconstituted suspension contains 209.6 mg of azithromycin dihydrate equivalent to 200 mg of azithromycin.

Each 1 ml reconstituted suspension contains 41.92 mg of azithromycin dihydrate equivalent to 40 mg of azithromycin.

Excipients with known effect

Each 5 ml reconstituted suspension contains 3.71 g of sucrose, 0.030 g of aspartame (E 951), up to 410 nanograms of benzyl alcohol and up to 85 nanograms of sulphites.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension.

White to off-white crystalline powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Azithromycin powder for oral suspension is indicated for the treatment of the following infections, when caused by micro-organisms sensitive to azithromycin (see section 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
- skin and soft tissue infections
- uncomplicated *Chlamydia trachomatis* urethritis and cervicitis

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

4.2 Posology and method of administration

Adults

In uncomplicated *Chlamydia trachomatis* urethritis and cervicitis, the dose is 1,000 mg in one single oral dose.

For all other indications the dose is 1,500 mg, to be administered as 500 mg per day for three consecutive days. Alternatively the same total dose (1,500 mg) can also be given over a period of 5 days with 500 mg on the first day and then 250 mg on days 2 to 5.

To treat these patients other pharmaceutical forms are also available.

Elderly people

The same dose as in adult patients is used in the older people. Since older patients 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).

Children and adolescents (< 18 years)

The total dose in children aged 1 year and older is 30 mg/kg administered as 10 mg/kg once daily for three days, or over a period of five days starting with a single dose of 10 mg/kg on the first day, followed by doses of 5 mg/kg per day for the following 4 days, according to the tables shown below. There are limited data on use in children younger than 1 year.

Azithromycin 100 mg/5 ml

Weight (kg)	3-day therapy	5-day therapy		Contents of the bottle
	Day 1-3 10 mg/kg/day	Day 1 10 mg/kg/day	Day 2-5 5 mg/kg/day	
10 kg	5 ml	5 ml	2.5 ml	20 ml
12 kg	6 ml	6 ml	3 ml	20 ml

Azithromycin 200 mg/5 ml

Weight (kg)	3-day therapy	5-day therapy		Contents of the bottle
	Day 1-3 10 mg/kg/day	Day 1 10 mg/kg/day	Day 2-5 5 mg/kg/day	
10 kg	2.5 ml	2.5 ml	1.25 ml	15 ml
12 kg	3 ml	3 ml	1.5 ml	15 ml
14 kg	3.5 ml	3.5 ml	1.75 ml	15 ml
16 kg	4 ml	4 ml	2 ml	15 ml
17 – 25 kg	5 ml	5 ml	2.5 ml	15 ml

26 – 35 kg	7.5 ml	7.5 ml	3.75 ml	22.5 ml
36 – 45 kg	10 ml	10 ml	5 ml	30 ml
> 45 kg	12.5 ml	12.5 ml	6.25 ml	22.5 ml + 15 ml

The dose for the treatment of pharyngitis caused by *Streptococcus pyogenes* is an exception: in the treatment of pharyngitis caused by *Streptococcus pyogenes* Azithromycin has proved to be effective when it is administered to children as a single dose of 10 mg/kg or 20 mg/kg for 3 days with a maximum daily dose of 500 mg. At these two doses a comparable clinical effect was observed, even if the eradication of the bacteria was more significant at a daily dose of 20 mg/kg.

Penicillin is however the drug of first choice in the treatment of pharyngitis caused by *Streptococcus pyogenes* and the prevention of subsequent rheumatic fever.

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:

No dose adjustment is necessary for patients with mild to moderately impaired liver function (see section 4.4).

Method of administration

Before use the powder should be reconstituted with water into a white to off white, homogenous suspension, see section 6.6. After reconstitution the drug can be administered using a PE/PP syringe for oral use.

After taking the suspension a bitter after-taste can be avoided by drinking fruit juice directly after swallowing. Azithromycin powder for oral suspension should be given in a single daily dose. The suspension may be taken together with 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

Hypersensitivity

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

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

Hepatotoxicity

Since 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.

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.

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur.

Infantile hypertrophic pyloric stenosis (IHPS)

Following the use of azithromycin in neonates (treatment up to 42 days of life), infantile hypertrophic pyloric stenosis (IHPS) has been reported. Parents and caregivers should be informed to contact their physician if vomiting or irritability with feeding occurs.

Pseudomembranous colitis

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

Ergot derivatives

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 (see section 4.5.).

Superinfection

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

Cross resistance

Cross-resistance exists between azithromycin and other macrolides (erythromycin, clarithromycin, roxithromycin), lincosamides and streptogramin B (MLS_B phenotype). Concomitant use of several medicinal products from the same or related group of antibacterial agents is not recommended.

Clostridoides difficile associated diarrhea

Clostridoides difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the 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 diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Renal impairment

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

Cardiovascular Events

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides including azithromycin (see section 4.8). 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 such as antiarrhythmics of class IA (quinidine and procainamide) and class III (dofetilide, amiodarone and sotalol), hydroxychloroquine, cisapride and terfenadine (see section 4.5); 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 hypomagnesaemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including azithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing azithromycin.

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).

Pediatric population

Safety and efficacy for the prevention or treatment of *Mycobacterium Avium* Complex in children have not been established.

The following should be considered before prescribing azithromycin:

Serious infections

Azithromycin powder for oral suspension is not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed.

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

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.

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*.

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.

Skin and soft tissue infections

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.

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.

Neurological or psychiatric diseases

Azithromycin should be used with caution in patients with neurological or psychiatric disorders.

[Nationally completed name] contains sucrose, sodium, aspartame, benzyl alcohol and sulphites

Azithromycin 100mg/5 ml

Caution in diabetic patients: 5 ml of reconstituted suspension contain 3.82 g of sucrose.

Azithromycin 200mg/5 ml

Caution in diabetic patients: 5 ml of reconstituted suspension contain 3.71 g of sucrose.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

Azithromycin 100mg/5 ml and Azithromycin 200mg/5 ml contains 0.030g of aspartame per 5 ml suspension

Aspartame is a source of phenylalanine. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

Azithromycin 100mg/5 ml and Azithromycin 200mg/5 ml contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Azithromycin 100mg/5 ml and Azithromycin 200mg/5 ml contains up to 410 nanograms of benzyl alcohol per 5 ml suspension

Benzyl alcohol may cause allergic reactions.

Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gasping syndrome") in neonates, therefore it should not be used in a new born baby (up to 4 weeks old).

Because of the increased risk of accumulation, it should not be used for more than a week in young children (less than 3 years old).

High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment or pregnant or breast-feeding because of the risk of accumulation and toxicity (metabolic acidosis).

Azithromycin 100mg/5 ml and Azithromycin 200mg/5 ml contains up to 85 nanograms of sulphites per 5 ml suspension

May rarely cause severe hypersensitivity reactions and bronchospasm.

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 24%. In patients receiving both azithromycin and antacids, the medicinal products should not be taken simultaneously, but with an interval of about 2 hours.

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 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

Digoxin and colchicine (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.

Ergot derivatives

Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended (see Section 4.4).

Zidovudine

Single 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients.

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

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

Astemizole, alfentanil

There are no known data on interactions with astemizole or alfentanil. Caution is advised in the co-administration of these medicines with Azithromycin because of the known enhancing effect of these medicines when used concurrently with the macrolid antibiotic erythromycin.

Atorvastatin

Co-administration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase inhibition assay). However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.

Carbamazepine

In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

Cisapride

Cisapride is metabolized in the liver by the enzyme CYP 3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsades de pointes.

Cimetidine

In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.

Coumarin-Type Oral Anticoagulants

In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15 mg dose of warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to co-administration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Cyclosporin

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 cyclosporin, the resulting cyclosporin C_{max} and AUC_{0-5} were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Efavirenz

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

Fluconazole

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

Indinavir

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

Methylprednisolone

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

Midazolam

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

Nelfinavir

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

Rifabutin

Co-administration of azithromycin and rifabutin did not affect the serum concentrations of either medicinal product.

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 3 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.

Theophylline

There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are co-administered to healthy volunteers.

Triazolam

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

Trimethoprim/sulfamethoxazole

Co-administration of trimethoprim/sulfamethoxazole (160 mg/800 mg) for 7 days with azithromycin 1200 mg on Day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim or sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies.

Hydroxychloroquine

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.

Medicinal products known to prolong the QT interval

Azithromycin should not be co-administered with other medicinal products, known to prolong the QT interval (see section 4.4).

Protease inhibitors

No data are available yet on possible interaction with protease inhibitors.

4.6 Fertility, Pregnancy and lactation

Pregnancy

In reproduction toxicity studies in animals azithromycin was shown to pass the placenta, but no teratogenic effects were observed (see section 5.3). There is a large amount of data from observational studies performed in several countries on exposure to azithromycin during pregnancy, compared to no antibiotic use or use of another antibiotic during the same period. While most studies do not suggest an association with adverse fetal effects such as major congenital malformations or cardiovascular

malformations, there is limited epidemiological evidence of an increased risk of miscarriage following azithromycin exposure in early pregnancy.

Azithromycin should only be used during pregnancy if clinically needed and the benefit of treatment is expected to outweigh any small increased risks which may exist.”

Breastfeeding

Azithromycin is excreted in breast milk. Because of the long half-life, accumulation in the milk is possible. Information available from published literature indicates that, in short-term use, this does not lead to clinically relevant quantities in the milk. No serious side effects have been observed by azithromycin in breast-fed children.

A decision should be taken whether breastfeeding is discontinued or that treatment with azithromycin is discontinued/initiated or not, taking into account the benefit of breastfeeding for the child and the benefit of treatment 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

There is no evidence to suggest that azithromycin may have an effect on a patient's ability to drive or operate machinery. When performing these functions, the occurrence of the adverse reaction of dizziness, visual impairment and vision blurred should be taken into account (section 4.8).

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.

The frequency grouping is defined using the following convention:

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 ($< 1/10,000$); and Not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

	Very Common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $< 1/1,000$)	Frequency Not Known
--	---------------------------------------	---	---	---	----------------------------

	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥ 1/10,000 to <1/1,000)	Frequency Not Known
Infections and Infestations			Candidiasis Vaginal infection Pneumonia Fungal infection Bacterial infection Pharyngitis Gastroenteritis Respiratory disorder Rhinitis		Pseudomembranous colitis (see section 4.4)
Blood and Lymphatic System Disorders			Leukopenia Neutropenia Eosinophilia		Thrombocytopenia Haemolytic anaemia
Immune System Disorders			Angioedema Hypersensitivity		severe (partly fatal) anaphylactic reaction e.g. anaphylactic shock (see section 4.4)
Metabolism and Nutrition Disorders			Anorexia		
Psychiatric Disorders			Nervousness Insomnia	Agitation Irritability	Aggression Anxiety Delirium Hallucination
Nervous System Disorders		Dizziness Headache Somnolence Dysgeusia Paraesthesia	Hypoaesthesia		Syncope Convulsion Psychomotor hyperactivity Anosmia Ageusia Parosmia Myasthenia gravis (see Section 4.4)

	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥ 1/10,000 to <1/1,000)	Frequency Not Known
Eye Disorders		Visual impairment			Blurred vision
Ear and Labyrinth Disorders		Deafness	Ear disorder Vertigo Hearing impairment including deafness and/or tinnitus		
Cardiac Disorders			Palpitations		Torsades de pointes (see section 4.4) Arrhythmia (see section 4.4) including ventricular tachycardia Electrocardiogram QT prolonged (see section 4.4)
Vascular Disorders			Hot flush		Hypotension
Respiratory, thoracic and mediastinal disorders			Dyspnoea, Epistaxis		
Gastrointestinal Disorders	Diarrhea Abdominal pain Nausea Flatulence	Vomiting Dyspepsia	Constipation Gastritis dysphagia Abdominal distension Dry mouth Eructation Mouth ulceration Salivary hypersecretion		Pancreatitis Tongue discolouration Discolouration of the teeth
Hepatobilia			Hepatic	Jaundice	Hepatic failure

	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥ 1/10,000 to <1/1,000)	Frequency Not Known
ry Disorders			function abnormal Hepatitis	cholestatic	(which has rarely resulted in death) (see section 4.4) Hepatitis fulminant Hepatic necrosis
Skin and Subcutaneous Tissue Disorders		Skin rash Pruritus	Urticaria, Dermatitis Dry skin Hyperhidrosis Stevens-Johnson syndrome Photosensitivity reaction	Acute generalised exanthematous pustulosis (AGEP) DRESS syndrome (drug reaction with eosinophilia and systemic symptoms)	Toxic epidermal necrolysis Erythema multiforme
Musculoskeletal and Connective		Arthralgia	Osteoarthritis Myalgia Back pain Neck pain		
Renal and Urinary Disorders			Dysuria Renal pain		Renal failure acute Nephritis
Reproductive system and breast disorders			Metrorrhagia, Testicular disorder		
General Disorders and Administration Site Conditions		Fatigue	Oedema Asthenia Malaise Face edema Chest pain Pyrexia Pain Peripheral edema		

	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥ 1/10,000 to <1/1,000)	Frequency Not Known
Investigations		Lymphocyte count decreased Eosinophil count increased Blood bicarbonate decreased Basophils increased Monocytes increased Neutrophils increased	Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubin increased Blood urea increased Blood creatinine increased Blood potassium abnormal Blood alkaline phosphatase increased Chloride increased Glucose increased platelets increased Hematocrit decreased Bicarbonate increased abnormal sodium		
Injury, 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 (≥1/1000 to < 1/100)

Metabolism and Nutrition Disorders		Anorexia	
Nervous System Disorders		Dizziness Headache Paraesthesia Dysgeusia	Hypoesthesia
Eye Disorders		Visual impairment	
Ear and Labyrinth Disorders		Deafness	Hearing impaired Tinnitus
Cardiac Disorders			Palpitations
Gastrointestinal Disorders	Diarrhea 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 the event of overdose, the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

General properties

Pharmacotherapeutic group: antibacterials for systemic use; macrolids; azithromycin, ATC code: J01FA10

Mode of action

Azithromycin is an azalide, a sub-class of the macrolid antibiotics. By binding to the 50S-ribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented.

Cardiac electrophysiology:

Extension of the QTc interval was studied in a randomised, placebo-controlled parallel trial in 116 healthy subjects who received chloroquine (1 000 mg), alone or in combination with azithromycin (500 mg, 1 000 mg, and 1 500 mg once a day). Concomitant administration of azithromycin increased the QTc interval in a dose and concentration-dependent manner. Compared to chloroquine alone, the maximum average (95% upper confidence limit) increases in the QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with the concomitant administration of 500 mg, 1 000 mg and 1 500 mg of azithromycin, respectively.

PK/PD relationship

For azithromycin the AUC/ MIC is the major PK/ PD parameter correlating best with the efficacy of azithromycin.

Mechanism of resistance:

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

The main ribosomal modification that determines the reduced binding of macrolides is posttranscriptional (N₆)-dimethylation of adenine in nucleotide A2058 (*E. coli* numbering system) of the 23S rRNA encoded by methylases by *erm* (*erythromycin ribosome methylase*) genes. Ribosomal modifications often determine cross-resistance (MLSB phenotype) against other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin) and streptogramins B (including, for example, the quinupristin component of quinupristin/dalfopristin). Different *erm* genes are present in different bacterial species, in particular streptococci and staphylococci. Sensitivity to macrolides may also be affected by less frequently occurring mutational changes in the nucleotides A2058 and A2059 and in several other loci of 23S rRNA, or in the large subunit

ribosomal proteins L4 and L22.

Efflux pumps occur in several types, including gram negatives, such as *Haemophilus influenzae* (where they can determine intrinsically higher MICs) and staphylococci. In streptococci and enterococci, an efflux pump that recognizes 14- and 15-pronged macrolides (including erythromycin and azithromycin respectively) is encoded by *mef* (A) genes.

Breakpoints

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for [Nationally completed name] and are listed here:

https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

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.

Pathogens for which 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 of susceptibility

Commonly susceptible species
Aerobic Gram-negative microorganisms <i>Haemophilus influenzae</i> * <i>Moraxella catarrhalis</i> * Other microorganisms <i>Chlamydophila pneumoniae</i> <i>Chlamydia trachomatis</i> <i>Legionella pneumophila</i> <i>Mycobacterium avium</i> <i>Mycoplasma pneumonia</i> *
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms <i>Staphylococcus aureus</i> * <i>Streptococcus agalactiae</i> <i>Streptococcus pneumoniae</i> * <i>Streptococcus pyogenes</i> * Other microorganisms <i>Ureaplasma urealyticum</i>
Inherently resistant organisms
Aerobic Gram-positive microorganisms <i>Staphylococcus aureus</i> – methicillin resistant and erythromycin resistant strains <i>Streptococcus pneumoniae</i> – penicillin resistant strains Aerobic Gram-negative microorganisms

<p><i>Escherichia coli</i> <i>Pseudomonas aeruginosa</i> <i>Klebsiella</i> spp. Anaerobic Gram-negative microorganisms <i>Bacteroides fragilis</i>-group</p>
--

* Clinical effectiveness is demonstrated by sensitive isolated organisms for approved clinical indications.

Antibacterial spectrum:

Azithromycin exhibits cross resistance with erythromycin-resistant Gram-positive isolates. As discussed above, several ribosomal modifications determine cross-resistance with other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin) and streptogramins B (including, for example, the quinupristin component of quinupristin/dalfopristin). A decrease in macrolide sensitivity over time has been noted in *Streptococcus pneumoniae* and *Staphylococcus aureus* and has also been observed in viridans streptococci and *Streptococcus agalactiae*.

Mycobacterium avium complex sensitivity:

The sensitivity methods and diagnostic procedures currently available *in vitro* to determine the MRC of *Mycobacterium avium* complex (MAC) organisms have not been generally accepted and validated.

Breaking points to show that clinically isolated strains of *M. avium* or *M. intracellulare* are sensitive to azithromycin have not yet been established.

Clinical trial data:

Patients receiving azithromycin in a placebo-controlled study had a one-year cumulative incidence of disseminated MAC disease of 8.24% compared to 20.22% in patients receiving placebo.

In a group of patients with a CD4 count $<10/\text{mm}^3$ combination therapy with another suitable medicine can be considered, as the benefits of the combination outweigh potential disadvantages.

In a comparative study, a lower risk of developing MAC bacteraemia was seen in patients treated with azithromycin than in patients treated with rifabutin. Patients treated with a combination of azithromycin and rifabutin were one-third less likely to develop a MAC bacteraemia than those treated with one of these medicines.

The one-year cumulative incidence of disseminated MAC disease was 7.62% with azithromycin, 15.25% with rifabutin and 2.75% with combination therapy of azithromycin and rifabutin. However, discontinuation in patients receiving combination therapy was greater due to poorer tolerance.

Studies on prophylaxis against MAC infections indicated that due to treatment with azithromycin, the occurrence of other bacterial infections were also reduced.

In clinical trials comparing the two doses of *Streptococcal pharyngitis* in children (a single

dose of 10 mg/kg or 20 mg/kg for 3 days), the efficacy was similar, but bacterial eradication was higher at the 20 mg/kg/day dose.

Paediatric population

After the assessment of studies carried out in children, the use of azithromycin is not recommended for the treatment of malaria, neither as monotherapy nor combined with chloroquine or artemisinin-based medicines, as the non-inferiority towards antimalarial medicines recommended in the treatment of uncomplicated malaria was not established.

5.2 Pharmacokinetic properties

Absorption

The biological availability of azithromycin after oral administration is approximately 37%. Peak plasma levels are achieved 2-3 hours after taking the medicinal product.

Distribution

Azithromycin penetrates throughout the body. After oral administration, azithromycin is distributed throughout the entire body. Pharmacokinetic studies have shown clearly higher azithromycin levels in the tissues than in the plasma (up to 50 times the maximum observed concentration in plasma). This indicates that the substance is bound in the tissues in considerable quantities. The average maximum observed serum level (C_{max}) after a single dose of 500 mg is approximately 0.4 mg/mL, 2-3 hours after administration. No accumulation occurs in the serum at the recommended dosage. Accumulation occurs in the tissues where the levels are much higher than in the serum. Three days after administration of 500 mg as a single dose, or in divided doses, concentrations of 1.3-4.8 mg/g, 0.6-2.3 mg/g, 2.0-2.8 mg/g and 0-0.3 mg/mL are found in the lung, prostate, tonsil and serum respectively.

Average peak concentrations measured in peripheral leukocytes, where the MAC infection was active, were 140 µg/mL. The concentration remained above 32 µg/mL for approximately 60 hours after a single oral administration of 1,200 mg.

These concentrations are higher than the mrc_{90} of the most common pathogens.

The protein binding of azithromycin in serum is variable and varies, depending on the serum concentration, from 52% at 0.05 mg/l to 18% at 0.5 mg/l. The steady state distribution volume is 31.1 l/kg.

Elimination

The terminal plasma-elimination half-life closely follows the tissue depletion half-life from 2 to 4 days.

Approximately 12% of an intravenously administered dose of azithromycin is, over a period of 3 days, excreted unchanged in the urine. High concentrations of unchanged azithromycin were found in human bile. In this, ten metabolites were also detected (formed by N- and O- desmethylation, by hydroxylation of the desosamin and aglycon rings and by splitting the cladinose conjugate). A comparison of fluid chromatography and microbiological assessment methods shows that the metabolites are microbiologically inactive.

In animal models high concentrations of azithromycin were found in phagocytes. Also it has been shown that during active phagocytosis higher concentrations of azithromycin are released than during

inactive phagocytosis. In animal models this process was shown to contribute to the accumulation of azithromycin in infectious tissue.

Pharmacokinetics in special populations

Renal insufficiency

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, the mean C_{max} and AUC_{0-120} increased 61% and 33% respectively compared to normal.

Hepatic insufficiency

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

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.

Infants, toddlers, children and adolescents

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 ug/l in children aged 0.6-5 years and after 3 days dosing and 383 ug/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 tests in which the doses used amounted to 40 times the clinical therapeutic doses, azithromycin was found to have caused reversible phospholipidosis, but as a rule no true toxicological consequences were observed which were associated with this. 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.

Mutagenic potential:

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

Reproductive toxicity:

In embryotoxicity studies in mice and rats no teratogenic effects were observed. In rats, azithromycin dosages of 100 and 200 mg/kg bodyweight/day led to slight retardations in fetal ossification and in maternal weight gain. In peri-/postnatal studies in rats, slight retardations in physical development and delay in reflex development were observed following treatment with 50 mg/kg/day azithromycin and above.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Xanthan gum (E 415)
Hydroxypropylcellulose
Trisodium phosphate anhydrous
Silica, colloidal anhydrous (E 551)
Aspartame (E 951)
Banana flavor (contains sulphites)
Vanilla Creme flavor (contains benzyl alcohol)
Cherry flavor (contains sulphites)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened bottle with dry powder: 3 years.
[For NL/H/0953-0954/002 only]

Reconstituted suspension: 5 days.

[For NL/H/0886/001-002 only]
Reconstituted suspension: 10 days.

Stability of the reconstituted suspension: Do not store above 25°C.

6.4 Special precautions for storage

Unopened bottle: Do not store above 30°C.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

HDPE bottles with a PP/ PE- closure with retaining ring.
PE/PP-dosage syringe (10 ml), graduated in 0.25 ml divisions.

100 mg/5 ml powder for oral suspension:

Packs of powder equivalent to 400 mg azithromycin. Content of the bottle after reconstitution: 20 ml.

200 mg/5 ml powder for oral suspension:

Packs of powder equivalent to 600 mg azithromycin. Content of the bottle after reconstitution: 15 ml.

Packs of powder equivalent to 800 mg azithromycin. Content of the bottle after reconstitution: 20 ml.

Packs of powder equivalent to 900 mg azithromycin. Content of the bottle after reconstitution:
22.5 ml.

Packs of powder equivalent to 1200 mg azithromycin. Content of the bottle after reconstitution: 30 ml.

Packs of powder equivalent to 1500 mg azithromycin. Content of the bottle after reconstitution 37.5
ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

100 mg/5 ml powder for oral suspension:

Preparation of the suspension:

Shake the dry powder loose. For 20 ml (400 mg) reconstituted suspension add 10.5 ml of purified water to the powder.

Shake well until a white to off white coloured, homogenous suspension is achieved. For administration the syringe adapter should be placed in the neck of the bottle and the stopper should be opened.

200 mg/5 ml powder for oral suspension:

Preparation of the suspension:

Shake the dry powder loose. Add the amount of water described below to the powder.

For 15 ml (600 mg) reconstituted suspension: add 8.0 ml water.

For 20 ml (800 mg) reconstituted suspension: add 10.5 ml water.

For 22.5 ml (900 mg) reconstituted suspension: add 11.0 ml water.

For 30 ml (1,200 mg) reconstituted suspension: add 15.0 ml water.

For 37.5 ml (1,500 mg) reconstituted suspension: add 18.5 ml water.

Shake well until a white to off white coloured, homogenous suspension is achieved. For administration the syringe adapter should be placed in the neck of the bottle and the stopper should be opened.

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

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Sandoz B.V.
Hospitaaldreef 29
1315 RC Almere
Nederland

8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 34292

9. DATUM VAN EERSTE VERGUNNING/ VERLENGING VAN DE VERGUNNING

Datum van eerste verlenging van de vergunning: 19 juni 2006

Datum van laatste verlenging: 28 februari 2012

10. DATUM VAN HERZIENING VAN DE TEKST

Laatste gedeeltelijke wijziging betreft de rubrieken 4.4 t/m 4.8, 5.1 en 5.2: 28 december 2024