SUMMARY OF PRODUCT CHARACTERISTICS

1. NAAM VAN HET GENEESMIDDEL

Azitromycine Sandoz 100 mg/5 ml, poeder voor orale suspensie

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml reconstituted suspension contains 102.4 mg of azithromycin monohydrate equivalent to 100 mg of azithromycin.
Each 1 ml reconstituted suspension contains 20.48 mg of azithromycin monohydrate equivalent to 20 mg of azithromycin.

Excipients with known effect
Each 5 ml reconstituted suspension contains 3.81 g of sucrose, 0.030 g of aspartame (E 951) and up to 130 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.

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

Patients with hepatic impairment:
A dose adjustment is not 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 (MLSB 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), 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 hypomagnesemia
- 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/ tonsilitis
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 and sulphites

Azithromycin 100mg/5 ml
Caution in diabetic patients: 5 ml of reconstituted suspension contain 3.81 g of sucrose.

Azithromycin 200mg/5 ml
Caution in diabetic patients: 5 ml of reconstituted suspension contain 3.70 g of sucrose.

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

Azithromycin 100mg/5 ml and Azithromycin 200mg/5 ml contain aspartame which 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 sulphites
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.

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).

4.6 Fertility, Pregnancy and lactation

Pregnancy
There are no adequate and well-controlled studies on 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 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..Visual impairment and vision blurred may have an effect on a patient's ability to drive or operate machinery (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 (≥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); 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 (≥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		Pseudomembranous colitis (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**
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	Aggression Anxiety Delirium Hallucination
Nervous System Disorders		Headache	Dizziness Somnolence Dysgeusia Paraesthesia		Syncope, convulsion Hypoestheia Psychomotor hyperactivity Anosmia Ageusia Parosmia Myasthenia gravis (see Section 4.4)
Eye Disorders					Visual impairment, blurred vision

	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**
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 (see section 4.4) including ventricular tachycardia Electrocardiogram QT prolonged (see section 4.4)
Vascular Disorders			Hot flush		Hypotension
Respiratory, thoracic and mediastinal			Dyspnoea, Epistaxis		
Gastrointestinal Disorders	Diarrhea	Vomiting Abdominal pain Nausea	Constipation Flatulence Dyspepsia, Gastritis dysphagia Abdominal distension Dry mouth Eructation Mouth ulceration Salivary hypersecretion		Pancreatitis Tongue discolouration

	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**
Hepatobiliary Disorders				Hepatic function abnormal Jaundice cholestatic	Hepatic failure (which has rarely resulted in death) (see section 4.4) Hepatitis
Skin and Subcutaneous Tissue Disorders			Rash Pruritus Urticaria, Dermatitis Dry skin Hyperhidrosis	Photosensitivity reaction Acute generalised exanthematous pustulosis (AGEP) DRESS (drug reaction with eosinophilia and systemic symptoms)	Stevens-Johnson syndrome Toxic epidermal necrolysis Erythema multiforme
Musculoskeletal and Connective			Osteoarthritis, Myalgia Back pain Neck pain		Arthralgia
Renal and Urinary Disorders			Dysuria Renal pain		Renal failure acute Nephritis
Reproductive system and			Metrorrhagia, Testicular disorder		
General Disorders and Administration Site Conditions		Injection site pain * Injection site inflammation	Oedema Asthenia Malaise Fatigue 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		
Injury and poisoning			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)**	**Rare (≥ 1/10,000 to <1/1,000)**
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.

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

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.

Mechanism of resistance:
Resistance to azithromycin may be inherent or acquired. There are three main mechanisms of resistance in bacteria: target site alteration, alteration in antibiotic transport and modification of the antibiotic.
Complete cross resistance exists among *Streptococcus pneumoniae*, betahaemolytic streptococcus of group A, *Enterococcus faecalis* and *Staphylococcus aureus*, including methicillin resistant *S. aureus* (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

Breakpoints

EUCAST (European Committee on Antimicrobial Susceptibility Testing)

Pathogens	**susceptible (mg/l)**	**resistant (mg/l)**
Staphylococcus spp.[1]	≤ 1	> 2
Streptococcus spp. (Group A, B, C, 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.
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 *Haemophilus influenzae** *Moraxella catarrhalis**
Other microorganisms *Chlamydophila pneumoniae* *Chlamydia trachomatis* *Legionella pneumophila* *Mycobacterium avium* *Mycoplasma pneumonia**
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms *Staphylococcus aureus** *Streptococcus agalactiae* *Streptococcus pneumoniae** *Streptococcus pyogenes**
Other microorganisms *Ureaplasma urealyticum*
Inherently resistant organisms
Aerobic Gram-positive microorganisms *Staphylococcus aureus* – methicillin resistant and erythromycin resistant strains *Streptococcus pneumoniae* – penicillin resistant strains
Aerobic Gram-negative microorganisms *Escherichia coli* *Pseudomonas aeruginosa* *Klebsiella* spp.
Anaerobic Gram-negative microorganisms *Bacteroides fragilis-group*

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

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
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.
Concentrations in the infected tissues, such as lungs, tonsil and prostate are higher than the MRC90 of the most frequently occurring pathogens after a single dose of 500 mg.
The protein binding of azithromycin in serum is variable and varies, depending on the serum concentration, from 52% at 0.05 mg/l to 12% 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.

<u>Pharmacokinetics in special populations</u>

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 (E415)
Hydroxypropylcellulose
Trisodium phosphate anhydrous

Silica, colloidal anhydrous (E551)
Aspartame (E951)
Cream caramel flavour (contains sulphites)
Titanium dioxide (E171)

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.
Veluwezoom 22
1327 AH Almere
Nederland

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

RVG 32016

9. DATUM VAN EERSTE VERLENING VAN DE 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, 4.5, 4.8, 5.1 en 9: 26 oktober 2020