SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<Product name> 20 mg, orodispersible tablets
<Product name> 100 mg, orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<Product name> 20 mg: Each orodispersible tablet contains 20 mg azithromycin (*Azithromycinum*) as azithromycin dihydrate.
<Product name> 100 mg: Each orodispersible tablet contains 100 mg azithromycin *(Azithromycinum)* as azithromycin dihydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet.

<Product name> 20 mg: white or almost white to cream of, slightly marbled surface, round of 8 mm diameter, on one side convex, on the other side concave, with concave break-mark on concave side tablet
The tablet can be divided into equal doses.

<Product name> 100 mg: white or almost white to cream of slightly marbled surface, oblong of 18.9 mm length, biconvex tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Azithromycin is indicated for the following infections if caused by bacteria susceptible:

- Upper respiratory tract infections: sinusitis, pharyngitis, tonsillitis (see section 4.4)
- Lower respiratory tract infections: bronchitis, mild to moderately severe community-acquired pneumonia
- Acute otitis media
- Mild to moderately severe skin and soft tissue infections, e.g. folliculitis, cellulitis, erysipelas
- Uncomplicated urethritis and cervicitis caused by *Chlamydia trachomatis*

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

Azithromycin is not the drug-of-choice for empirical treatment in areas where the prevalence of resistant strains is 10% or higher (see section 5.1).

4.2 Posology and method of administration

Posology

Adults

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

For all other indications the dosage is 1,500 mg; to be administered as 500 mg per day for three consecutive days. Alternatively the same total dosage (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.

Paediatric population
In lower respiratory tract infections, otitis media, skin and soft tissue infections, a total dose is 30 mg/kg body weight, i.e. 10 mg/kg body weight, once daily for 3 days.

The dosage in children depends on the body weight, and its example is given in the table below:

Weight	**Azithromycin daily dose**
5 kg	50 mg (2.5 tablets a 20 mg)
6 kg	60 mg (3 tablets a 20 mg)
7 kg	70 mg (3.5 tablets a 20 mg)
8 kg	80 mg (4 tablets a 20 mg)
9 kg	90 mg (4.5 tablets a 20 mg)
10-14 kg	100 mg (1 tablet a 100 mg)
15-24 kg	200 mg (2 tablets a 100 mg)
25-34 kg	300 mg (3 tablets a 100mg)
35-44 kg	400 mg (4 tablets a 100 mg)
≥45 kg	500 mg (5 tablets a 100 mg)

Elderly patients
For elderly patients the same dose as for adults can be applied. Since elderly 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).

Patients with renal disorders
No dose adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance >40 ml/min). No data is available on the use of azithromycin in patients with CrCl < 40 ml/min, therefore caution should be exercised when treating these patients.

Patients with hepatic disorders
A dose adjustment is not necessary for patients with mild to moderately impaired liver function. However, azithromycin is metabolized in the liver and excreted with bile, therefore this medicinal product should not be used in patients with severe hepatic failure. Azithromycin has not been studied in this patient group.

Method of administration

Orodispersible tablet can be taken with or without food.

Orodispersible tablet should be placed in the mouth, on the tongue, where it will rapidly disperse in saliva. Alternatively, the orodispersible tablet may be dispersed in the spoon of water. In both cases, it should be swallowed immediately with a glass of water. Since the orodispersible tablet is fragile, it should be taken immediately after opening the blister.

4.3 Contraindications

The use of this product is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipient 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 <Product name> 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.

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

Patients with hepatic disorders
Since the 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.

Ergot derivatives 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 ergotamine derivatives and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered (see section 4.5).

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

Clostridium difficile associated diarrhoea (CDAD) has been reported with 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. Hyper-production of toxins by some 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. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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

- With congenital or documented acquired 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; 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.

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).

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

Serious infections
Azithromycin is not indicated for the treatment of serious infections where it is essential to achieve a high blood concentration rapidly.

Areas with high prevalence of resistance to erythromycin
In areas with a high prevalence of resistance to erythromycin it is especially important to consider resistance to azithromycin as well.

Resistance in Streptococcus pneumoniae
As with other macrolides a high rate of azithromycin resistance (> 30%) in *Streptococcus pneumoniae* has been reported in some European countries (see section 5.1). This must be considered when treating infections caused by *S. pneumoniae*.

Resistance in Staphylococcus aureus
The main bacterial pathogen in soft tissue infections, *Staphylococcus aureus*, is often resistant to azithromycin. Therefore, susceptibility testing is considered to be a prerequisite when treating such infections with azithromycin.

Pharyngitis/tonsillitis
Azithromycin is not the drug-of-choice for the treatment of pharyngitis/tonsillitis caused by *Streptococcus pyogenes*. In such cases and in the prophylaxis against rheumatic fever penicillin is the drug-of-choice.

Sinusitis
In general, azithromycin is not the drug-of-choice for the treatment of sinusitis.

Acute otitis media
In general, azithromycin is not the drug-of-choice for the treatment of acute otitis media.

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

Sexually transmitted infections

When treating sexually transmitted infections concomitant infection with *Treponema pallidum* should be excluded.

Neurological and psychiatric disorders
Azithromycin should be administered with caution to patients who suffers from neurological or psychiatric disorders.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids
In a pharmacokinetic study investigating the effects of simultaneous administration of antacids with azithromycin, no effect on overall bioavailability was seen, although peak serum levels were reduced by approximately 25%. In patients receiving both azithromycin and antiacids, the drugs should not be taken simultaneously. Azithromycin must be taken at least 1 hour before or 2 hours after antacids.

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-glycoprotein 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-glycoprotein substrates such as digoxin are administered concomitantly, the possibility of elevated serum digoxin concentrations should be considered. Clinical monitoring, and possibly serum digoxin levels, during treatment with azithromycin and after its discontinuation are necessary.

Zidovudine
Single 1000 mg doses and multiple doses of 600 mg or 1200 mg 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.

Ergotamine derivatives
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 drugs 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 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.

Lovastatin
Co-administration of azithromycin and lovastatin should be avoided because increased plasma concentration of lovastatin may occur, leading to rabdomyolysis.

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 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 Cmax and AUC0-5 were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose 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 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 coadministration of fluconazole, however, a clinically insignificant decrease in Cmax (18%) of azithromycin was observed.

Indinavir
Coadministration 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, 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 (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
Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either drug.

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 Cmax 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. As interactions of other macrolides with theophylline have been reported, alertness to signs that indicate a rise in theophylline levels is advised.

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 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.

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 (see section 5.3). 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.

Breast-feeding
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.

It is recommended to discard the milk during treatment and up until 2 days after discontinuation of treatment. Nursing may be resumed thereafter.

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 patient's ability to drive or operate machinery.

4.8 Undesirable effects

The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in italics. 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:

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);	Frequency not known
Infections and infestations			Candidiasis Vaginal infection Oral candidiasis		Pseudomembranous colitis (see section 4.4)
Blood and lymphatic system disorders			Leukopaenia Neutropaenia		Thrombocytopaenia Haemolytic anaemia
Immune system disorders			Angioedema Hypersensitivity		Anaphylactic reaction (see section 4.4)
Metabolism and nutrition disorders		Anorexia			
Psychiatric disorders			Nervousness	Agitation	Aggression Anxiety
Nervous system disorders		Dizziness Headache Paraesthesia Dysgeusia	Hypoaesthesia Somnolence Insomnia		Syncope Convulsion Psychomotor hyperactivity Anosmia Ageusia Parosmia Myasthenia gravis (see section 4.4)
Eye disorders		Visual impairment			

Ear and labyrinth disorders		Deafness	Hearing impaired tinnitus	Vertigo	
Cardiac disorders			Palpitations		Torsades de pointes (see section 4.4) Arrhythmia (see section 4.4) including ventricular tachycardia
Vascular disorders					Hypotension
Gastrointestinal disorders	Diarrhoea Abdominal pain Nausea Flatulence	Vomiting Dyspepsia	Gastritis Constipation		Pancreatitis Tongue discolouration
Hepatobiliary disorders			Hepatitis	Hepatic function abnormal	Hepatic failure (see section 4.4), which has rarely resulted in death) Hepatitis fulminant Hepatic necrosis Jaundice cholestatic
Skin and subcutaneous tissue disorder		Pruritus Rash	Stevens-Johnson syndrome Photosensitivity reaction Urticaria	Acute generalised exanthematous pustulosis (AGEP)	Toxic epidermal necrolysis Erythema multiforme
Musculoskeletal and connective tissue disorders		Arthralgia			
Renal and urinary disorders					Renal failure acute Nephritis interstitial
General disorders and administration site conditions		Fatigue	Chest pain Oedema Malaise Asthenia		
Investigations		Lymphocyte count decreased Eosinophil count increased Blood bicarbonate decreased	Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubine increased Blood urea increased Blood creatinine increased Blood potassium abnormal		Electrocardiogram QT prolonged (see section 4.4)

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. In the event of overdosage general symptomatic and general supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Azithromycin is an azalide, a sub-class of the macrolide antibiotics. It suppresses bacterial protein synthesis, by binding to the 50 S subunit and thus inhibiting the RNA-dependent protein-synthesis.

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

Mechanism of resistance
Resistance to azithromycin may be inherent or acquired. Three major mechanisms of bacterial resistance are: target site alteration, alteration of the antibiotic transport, and antibiotic modification.

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).

Breakpoints
Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Staphylococcus spp: susceptible ≤1 mg/l; resistant >2 mg/l
- *Streptococcus pneumoniae*: susceptible ≤0.25 mg/l; resistant >0.5 mg/l
- *Streptococcus* groups A, B, C and G: susceptible ≤0.25 mg/l; resistant >0.5 mg/l
- *Haemophilus influenzae*: susceptible ≤0.12 mg/l; resistant >4 mg/l
- *Moraxella catarrhalis*: susceptible ≤0.25 mg/l; resistant >0.5 mg/l
- *Neisseria gonorrhoeae*: susceptible ≤0.25 mg/l; resistant >0.5 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.

Commonly susceptible species:

-	Aerobic Gram-positive:	Methicillin-sensitive *Staphylococcus aureus,* penicillin-sensitive *Streptococcus pneumoniae, Streptococcus pyogenes* (beta haemolytic streptococci group A).
-	Aerobic Gram-negative:	*Haemophilus influenzae, Haemophilus parainfluenzae, Legionella pneumophila, Moraxella catarrhalis, Pasteurella multocida*

-	Anaerobic:	*Clostridium perfringens, Fusobacterium* spp., *Prevotella* spp., *Porphyromonas* spp.
-	Other micro-organisms:	*Borrelia burgdorferi, Chlamydia trachomatis, Chlamydia pneumoniae, Mycoplasma pneumoniae.*

Species in which acquired resistance may occur:

Aerobic Gram-positive:	Penicillin-intermediate and penicillin-resistant *Streptococcus pneumoniae*.

Inherently resistant organisms:

-	Aerobic Gram-positive:	*Enterococcus faecalis, Staphylococcus spp.* MRSA, MRSE (methicillin-resistant staphylococci generally demonstrate an inherited resistance to macrolides; however, they have been listed here, since they are rarely susceptible to azithromycin).
-	Gram-negative:	*Pseudomonas aeruginosa, Klebsiella* spp.
-	Anaerobic:	*Bacteroides fragilis* group

5.2 Pharmacokinetic properties

Absorption

Following oral administration azithromycin is rapidly absorbed from the gastrointestinal tract. Peak plasma levels are reached after 2-3 hours following oral administration (following oral administration of a single dose 500 mg C_{max} was approx. 0.4 µg/ml), and bioavailability following oral administration is 37%.

Distribution

Azithromycin reaches considerably higher (up to 50 times higher) concentrations in the tissues than in the plasma.

The binding of azithromycin to plasma proteins is variable and varies from 12% at 0.5 µg/ml to 52% at 0.05 µg/ml depending on the serum concentration. Steady-state (VV_{ss}) mean volume of distribution is 31.1 l/kg.

Biotransformation

Azithromycin is metabolized in the liver. A total of 10 azithromycin metabolites have been identified in the bile, 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 micro-biological activity of azithromycin. The terminal plasma elimination half-life follows the tissue depletion half-life of 2 to 4 days.

Elimination

Azithromycin is excreted mainly in bile (unchanged form and as metabolites). Approximately 12% of an intravenously administered dose is excreted in an unchanged form with urine over a period of 3 days.

Animal studies have demonstrated that azithromycin accumulates in the phagocytes and is released through active phagocytosis. In animal studies, azithromycin reached high concentration in inflammatory foci.

Pharmacokinetics in special populations

Renal impairment

Following a single oral dose of azithromycin 1 g, 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 AUC0-120 increased 61% and 33% 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.

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 of azithromycin have been studied in children aged 4 months – 15 years taking capsules, granules or suspension. at 10 mg/kg body weight on day 1, followed by 5 mg/kg on days 2-5. Maximum concentrations amounting to 224 µg/l in children aged 7.5 months to 5 years and 383 µg/l in children aged 6 to 15 years, were slightly lower than concentration in adults. The $t_{½}$ of 36 h in older children was within the expected range for adults.

5.3 Preclinical safety data

In animal studies, azithromycin administered in doses 40 -times exceeded the clinical therapeutic doses, caused reversible phospholipidosis (generally without associated toxicological consequences). Symptoms of toxicity were not observed when azithromycin was administered according to guidelines.

Carcinogenic potential
Long-term studies in animals have not been performed to evaluate carcinogenic potential as the drug is indicated for short-term treatment only, and there were no signs indicative of carcinogenic activity.

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 animal studies of the embryotoxic effects of the substance, no teratogenic effect was observed in mice and rats. In rats, azithromycin dosages of 100 and 200 mg/kg bodyweight/day led to mild retardations in foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, slight retardations in physical development and delay in reflex development following treatment with 50 mg/kg/day azithromycin were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline type 101
Silica, colloidal anhydrous (E551)
Basic butylated methacrylate copolymer
Sodium laurilsulfate
Dibutyl sebacate
Talc
Titanium dioxide (E171)
Cellulose microcrystalline type 200
Hydroxypropylcellulose low substituted
Apple flavour [containing as main components maltodextrin, arabic gum (E414), triacetin (E1518), natural flavouring substances]

Sucralose (E955)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PE/PVDC/Aluminium blisters

Pack sizes:
<Product name> 20 mg: 9, 12, 15 orodispersible tablets
<Product name> 100 mg: 3, 6 orodispersible tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

PharmaSwiss Česká republika s.r.o.
Jankovcova 1569/2c
170 00 Prague 7
Czech Republic

8. MARKETING AUTHORISATION NUMBER(S)

<To be completed nationally>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

{DD month YYYY}