Annex III

Amendments to relevant sections of the product information

Note:

These amendments to the relevant sections of the product information are the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

Amendments to relevant sections of the product information

The existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below.

SUMMARY OF PRODUCT CHARACTERISTICS

Solid oral formulations (film-coated tablets and hard capsules) (authorised strengths: 125 mg, 250 mg, 500 mg, 600 mg) and dispersible tablets (authorised strengths: 250 mg, 500 mg, 600 mg, 1000 mg)]

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

[This section should read as indicated below. Indications should only be implemented if the product was already approved for the condition.

Wording related to the following indications should be removed throughout:

- Gastro-duodenal infections caused by Helicobacter pylori

- Treatment of (moderate) acne vulgaris

- Prevention of exacerbations of eosinophilic and non-eosinophilic asthma]

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

- Acute streptococcal tonsillitis and pharyngitis
- Acute bacterial sinusitis
- Acute bacterial otitis media
- Community-acquired pneumonia (CAP)
- Acute bacterial skin and skin structure infections (ABSSSI)
- Erythema migrans (early localised Lyme disease)
- Periodontal abscesses and periodontitis
- Urethritis and cervicitis caused by *Chlamydia trachomatis*
- Urethritis and cervicitis caused by *Neisseria gonorrhoeae*, in combination with another appropriate antibacterial agent (e.g. ceftriaxone)
- Chronic prostatitis caused by *Chlamydia trachomatis*
- Chancroid
- Disseminated *Mycobacterium avium* complex (DMAC) infection in people living with advanced HIV infection, in combination with ethambutol

<Invented name> is also indicated for the prophylaxis of *Mycobacterium avium* complex (MAC) infection in people living with HIV with inadequate immune restoration.

<Invented name> is indicated for the treatment of adult patients with acute exacerbation of chronic bronchitis or with pelvic inflammatory disease, the latter always in combination with other appropriate antibacterial agent(s) (e.g. metronidazole).

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

4.2 Posology and method of administration

[This section should read as follows:]

Posology

Adults and adolescents weighing at least 45 kg

Azithromycin should be administered as a single daily dose.

[Dosing recommendations given in table 1 should be in line with section 3 and section 4.1: the table should only include posology information of approved indications; the 5-day regimen should only be included in the dosing table below if it can be administered with the product e.g. 250 mg tablets or 500 mg tablets with a score line to break the tablet into equal doses]

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

Indication	Azithromycin dosing regimen
Acute streptococcal tonsillitis and pharyngitis Acute bacterial sinusitis Acute bacterial otitis media Acute exacerbation of chronic bronchitis* Community-acquired pneumonia[#] Acute bacterial skin and skin structure infections Periodontal abscesses and periodontitis	500 mg/day for 3 days or 500 mg on day 1, followed by 250 mg/day on days 2-5
Erythema migrans (early localised Lyme disease)	1000 mg on day 1, followed by 500 mg/day on days 2-10
Urethritis and cervicitis caused by *Chlamydia trachomatis*	1000 mg as a single dose
Urethritis and cervicitis caused by *Neisseria gonorrhoeae*, in combination with another appropriate antibacterial agent (e.g. ceftriaxone)	1000 mg or 2000 mg* as a single dose
Pelvic inflammatory disease, in combination with other appropriate agent(s) (e.g. metronidazole)*[+]	Only as an oral switch after intravenous administration if clinically indicated: 250 mg once daily to complete a 7- day course of treatment
Chronic prostatitis caused by *Chlamydia trachomatis*	500 mg/day on 3 consecutive days per week for 3 weeks (total dose: 4500 mg)
Chancroid	1000 mg as a single dose
Treatment of disseminated *Mycobacterium avium* complex (DMAC) infection in people living with advanced HIV infection (in combination with ethambutol)	<500 mg> *or* <600 mg> once daily
Prophylaxis of *Mycobacterium*	<1200 mg> *or* <1250 mg> once a week

avium complex (MAC) infections in people living with HIV with inadequate immune restoration	
* for treatment of adults only # in adults, oral treatment may also follow intravenous treatment, if clinically indicated to complete a 7- to 10-day total course of treatment (for details refer to the Summary of Product Characteristics of azithromycin IV formulations). + oral azithromycin should not be used for the initial treatment of pelvic inflammatory disease (for details refer to the Summary of Product Characteristics of azithromycin IV formulations). Consideration should be given to the treatment regimens, doses and duration of treatment as recommended in updated treatment guidelines for each indication.	

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

Special populations

Renal impairment
No dose adjustment is required in patients with GFR ≥10 ml/min. In patients with GFR <10 ml/min azithromycin should be administered with caution (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B) (see section 5.2). No data are available in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, azithromycin should be administered with caution in these patients (see section 4.4).

Elderly
No dose adjustment is required in elderly patients (see section 5.2). Since the elderly are more likely to experience proarrhythmic conditions, particular caution is recommended due to the risk of developing cardiac arrhythmia and torsade de pointes (see section 4.4).

Paediatric population

[if the product is indicated for treatment of pelvic inflammatory disease in adult patients]
The safety and efficacy of <Invented name> for the treatment of adolescent girls with pelvic inflammatory disease has not been established.

[if the product is indicated for treatment of acute exacerbation of chronic bronchitis in adult patients]
There is no relevant use of <Invented name> for the treatment of acute exacerbations of chronic bronchitis in paediatric patients.

[if the product is indicated for treatment and/or prophylaxis of Mycobacterium avium complex infections]
The safety and efficacy of <Invented name> in prevention or treatment of *Mycobacterium avium* complex infections in paediatric patients < 12 years has not been established.

[Tablets/Capsules: all medicinal products with any of these pharmaceutical forms should include the following information]
Other pharmaceutical forms are available that may be more appropriate to treat patients unable to swallow <tablets/capsules> as well as paediatric patients weighing less than 45 kg.

[Dispersible Tablets: all medicinal products with this pharmaceutical form should include the following information]
Other medicinal products are available with strengths that are more appropriate to treat paediatric patients weighing less than 45 kg.

Method of administration

[The appropriate product-specific information should be chosen in line with the information given in section 3; if more than one strength and/or formulation are covered in the same SmPC, the information should state instead of the pharmaceutical form the invented name]

[Tablets (without any score line)]

For oral use.

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

[Tablets (with score line only for ease of swallowing)]

For oral use.

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

Tablets should be swallowed whole or can be divided for ease of swallowing and taken as a single daily dose.

[Tablets (with score line for dose adjustment)]

For oral use.

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

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

[Hard capsules]

For oral use.

Capsules should be swallowed whole, as a single daily dose, either at least one hour before or two hours after a meal.

[Dispersible tablets (with data on compatibility and volume)]

For oral use.

The tablet should be dispersed by stirring in a sufficient amount of liquid (at least 30 ml) such as water, apple or orange juice until a fine suspension is obtained which should be taken immediately. Any remaining residue of the suspension must be resuspended in a small volume of water and swallowed. The suspension can be taken with or without food. Administration immediately before a meal may enhance the gastrointestinal tolerability.

[Dispersible tablets (without any data on compatibility and volume)]

For oral use.

The intact tablet should be dispersed by stirring in a glass of water until a fine suspension is obtained which should be taken immediately. Any remaining residue of the suspension must be resuspended in a small volume of water and swallowed. The suspension can be taken with or without food. Administration immediately before a meal may enhance the gastrointestinal tolerability.

4.3 Contraindications

[This section should read as follows:]

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 precaution for use

[This section should read as follows:]

Potential for resistance
Azithromycin could favour the development of resistance due to the associated long-lasting and decreasing levels in plasma and tissues after the end of treatment (see section 5.2). Treatment with azithromycin should only be initiated after a careful assessment of the benefit and the risks, considering the local prevalence of resistance, and when preferred treatment regimens are not indicated.

Severe skin and hypersensitivity reactions
Rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with azithromycin treatment (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment. If an allergic reaction occurs, azithromycin should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

QT interval prolongation
Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides including azithromycin (see section 4.8). Therefore, as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients:
• With congenital or documented QT prolongation
• Currently receiving treatment with other active substances known to prolong QT interval (see section 4.5)
• With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
• With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency
• Elderly patients: Elderly patients may be more susceptible to drug-associated effects on the QT interval

Hepatotoxicity
Since liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin. Hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have also been reported with azithromycin, some of which have resulted in death (see section 4.8). Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products. Patients should be advised to stop azithromycin administration and to contact their physician if signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency

or hepatic encephalopathy develop. In such cases liver function tests/investigations should be performed immediately.

Clostridioides difficile associated diarrhoea (CDAD), pseudomembranous colitis
CDAD and pseudomembranous colitis have been reported with azithromycin and may range in severity from mild diarrhoea to fatal colitis (see section 4.8). CDAD and pseudomembranous colitis must be considered in patients who present with diarrhoea during or subsequent to the administration of azithromycin. Discontinuation of therapy with azithromycin and the use of supportive measures together with the administration of specific treatment for *C. difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Sexually transmitted infections
Neisseria gonorrhoeae is very likely to be resistant to macrolides, including the azalide azithromycin (see section 5.1). Therefore, azithromycin is not recommended for the treatment of uncomplicated gonorrhoea and pelvic inflammatory disease unless laboratory results have confirmed susceptibility of the organism to azithromycin. If left untreated or treated sub-optimally, this condition may lead to late onset complications such as infertility and ectopic pregnancy.

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

Furthermore, a concomitant infection caused by *Treponema pallidum* should be excluded as symptoms of incubating syphilis could be masked delaying diagnosis.

For all patients with sexually transmitted urogenital infections, appropriate antibacterial therapy and microbiological follow-up tests should be initiated.

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

Non-susceptible organisms
The use of azithromycin may result in the overgrowth of non-susceptible organisms. If superinfection occurs, interruption of treatment or other appropriate measures may be required.

Ergot derivatives
In patients receiving ergot derivatives, ergotism has been precipitated by co-administration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergot and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives may not be co-administered.

<Excipient(s) with known effect>

[A warning about any excipient that could result in unwanted undesirable effects e.g. in patients with specific metabolism disorders (e.g. phenylketonuria, fructose intolerance, glucose-galactose malabsorption, sucrase/isomaltase deficiency) or allergies should be added in this section as per the QRD template. Each MAH will need to mention any relevant excipient(s) and related warning(s) for their formulation(s).]

<For the full list of excipients, see section 6.1.>

4.5 Interaction with other medicinal products and other forms of interaction

[This section should read as follows:]

Although azithromycin is a weak CYP450 inhibitor and does not interact significantly with CYP450 substrates, CYP3A4 inhibition cannot be completely ruled out. Therefore, caution is recommended in case of co-administration with CYP3A4 substrates with narrow therapeutic index.
Azithromycin is an inhibitor of the transporter P-glycoprotein (P-gp). Co-administration of azithromycin with P-gp substrates, such as digoxin and colchicine, may increase their exposure. For narrow therapeutic index drugs, caution and clinical and/or therapeutic drug monitoring and dose adjustment as appropriate are advised. The relatively long half-life of azithromycin should be taken into account in this context (see section 5.2).

Medicinal products that are known to prolong the QT interval
Azithromycin should be used with caution in patients receiving medicinal products known to prolong the QT interval (see section 4.4), such as antiarrhythmics of Classes IA (e.g. quinidine and procainamide) and III (e.g. dofetilide, amiodarone and sotalol), antipsychotic agents (e.g. pimozide), antidepressants (e.g. citalopram), fluoroquinolones (e.g. moxifloxacin and levofloxacin), cisapride, chloroquine and hydroxychloroquine.

Drug interaction information for azithromycin with potential concomitant medicinal products is summarised in the table and text below. The drug interactions described are based on clinical drug-drug interaction studies conducted with azithromycin or, where indicated, are potential drug interactions that may occur with azithromycin.

Table 2: Clinically relevant drug interactions between azithromycin and other medicinal products

Medicinal product (therapeutic area)	**Interaction Effect on exposure**	**Mechanism**	**Recommendation concerning co-administration**
Atorvastatin (HMG CoA reductase inhibitor) Azithromycin 500 mg orally once daily for 3 days. Atorvastatin 10 mg orally once daily.	Azithromycin: ND Atorvastatin: ↔ AUC ↔ C_{max}	Atorvastatin is a CYP3A4 and P-gp substrate.	Caution should be exercised since post-marketing cases of rhabdomyolysis in patients receiving azithromycin concomitantly with statins have been reported.
Ciclosporin (immunosuppressant) Azithromycin 500 mg orally once daily for 3 days. Ciclosporin 10 mg/kg orally single dose.	Azithromycin: ND Ciclosporin: ↔ AUC ↑C_{max} 24 %	Ciclosporin is a CYP3A4 and P-gp substrate with narrow therapeutic index and/or competition for biliary excretion.	Clinical monitoring and therapeutic drug monitoring as appropriate should be performed during and after treatment with azithromycin. Ciclosporin dose should be adjusted if required.
Colchicine (gout)	Azithromycin: ND Colchicine: ↑ 57% AUC_{0-t} ↑ 22% C_{max}	Colchicine is a P-gp substrate with narrow therapeutic index.	Clinical monitoring is needed during and after treatment with azithromycin.
Dabigatran (oral	ND	Dabigatran is a P-gp	Caution should be

anticoagulant)	*Expected:* ↑ Dabigatran	substrate with narrow therapeutic index.	exercised since post-marketing data suggest an increased risk for haemorrhages in patients receiving azithromycin concomitantly with dabigatran.
Digoxin (cardiac glycosides)	ND *Expected:* ↑ Digoxin	Digoxin is a P-gp substrate with narrow therapeutic index.	Clinical monitoring, and possibly digoxin level monitoring, is needed during and after treatment with azithromycin.
Warfarin (oral anticoagulant) Azithromycin 500 mg orally once daily for 1 day and then 250 mg orally once daily for 4 days. Warfarin 15 mg orally single dose.	Azithromycin: ND Warfarin: ND No change in prothrombin time in clinical drug interaction study but post-marketing reports of potentiated anticoagulation of coumarin-type oral anticoagulants upon co-administration with azithromycin.	Not known.	A higher frequency of prothrombin time monitoring should be considered during and after treatment with azithromycin.
Note: statistically significant changes by more than 10% are indicated as "↑" or "↓", no change as "↔", not determined as "ND".			

No clinically relevant change in the exposure of azithromycin or the co-administered medicinal products was observed in clinical studies evaluating potential drug-drug interactions of azithromycin with oral antacids (aluminium hydroxide/magnesium hydroxide), carbamazepine, cetirizine, cimetidine, efavirenz, fluconazole, methylprednisolone, midazolam, rifabutin, sildenafil, theophylline, triazolam, trimethoprim/sulfamethoxazole and zidovudine.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

[This section should read as follows:]

Pregnancy
Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of teratogenic effects was found. There are, however, no adequate and well-controlled studies in pregnant women.

There is a large amount of data from observational studies on exposure to azithromycin during pregnancy (more than 7000 azithromycin exposed pregnancies). Most of these studies do not suggest an increased risk of adverse foetal effects such as major congenital malformations or cardiovascular malformations.

Epidemiological evidence related to the risk of miscarriage following azithromycin exposure in early pregnancy is inconclusive. Animal studies do not indicate reproductive toxicity (see section 5.3). Azithromycin should only be used during pregnancy if clinically needed.

Breast-feeding
Azithromycin is excreted in human milk to substantial extent. No serious adverse effects of azithromycin on the breast-fed infants were observed, while effects such as diarrhoea, mucosal fungal infection as well as hypersensitivity can occur in breast-fed newborns/infants even at sub-therapeutic doses. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
In fertility studies conducted in rat, reduced pregnancy rates were noted following administration of azithromycin. The relevance of this finding to humans is unknown.

4.7 Effects on ability to drive and use machines

[This section should read as follows:]

<Invented name> has a moderate influence on the ability to drive and use machines. Dizziness, drowsiness and convulsions have been reported in some patients taking azithromycin and some patients experienced visual and/or auditory impairment. This should be considered when assessing a patient's ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

[This section should read as follows:]

Summary of the safety profile
The most commonly reported adverse reactions during treatment include diarrhoea, headache, vomiting, abdominal pain, nausea and abnormal laboratory test values. Other important adverse reactions include anaphylactic reactions, torsade de pointes, arrhythmia including ventricular tachycardia, pseudomembranous colitis and hepatic failure (see section 4.4). Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP) have been reported in association with azithromycin treatment (see section 4.4).

Tabulated list of adverse reactions
Adverse reactions identified through clinical trial experience and post marketing surveillance are listed below, by system organ class and frequency.

[information on adverse reactions related to treatment and/or prophylaxis of MAC infections should only be included if the product is indicated for these treatments]

Frequencies of adverse reaction occurrence are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3: Tabulated list of adverse reactions

System organ class	Very common	Common	Uncommon	Rare	Not known

Infections and infestations			*Candida* infection Pneumonia Fungal infection Bacterial infection Vaginal infection Pharyngitis Gastroenteritis Rhinitis Oral candidiasis		
Blood and lymphatic system disorders		Lymphocyte count decreased Eosinophil count increased Basophil count increased Monocyte count increased Neutrophil count increased	Leukopenia Neutropenia Eosinophilia Platelet count increased Haematocrit decreased		Thrombocytopenia Haemolytic anaemia
Immune system disorders			Angioedema Hypersensitivity (see section 4.4)		Anaphylactic reaction
Metabolism and nutrition disorders			Decreased appetite[#2]		
Psychiatric disorders			Nervousness Insomnia	Agitation	Anxiety Delirium Hallucination Aggression
Nervous system disorders		Headache	Dizziness[#2] Dysgeusia[#2] Paraesthesia[#2] Somnolence		Myasthenia gravis (see section 4.4) Seizure Anosmia Ageusia Hypoaesthesia[#3] Psychomotor hyperactivity Parosmia Syncope
Eye disorders			Visual impairment[#2]		

Ear and labyrinth disorders			Ear disorder Vertigo		Deafness[#2] Hypoacusis[#3] Tinnitus[#3]
Cardiac disorders			Palpitations		Torsades de pointes (see section 4.4) Arrhythmia including ventricular tachycardia (see section 4.4) Electrocardiogram QT prolonged (see section 4.4)
Vascular disorders			Hot flush		Hypotension
Respiratory, thoracic and mediastinal disorders			Dyspnoea Respiratory disorder Epistaxis		
Gastrointestinal disorders	Diarrhoea Abdominal discomfort*	Vomiting Abdominal pain[#1] Nausea[#1]	Gastritis Constipation Dyspepsia Dysphagia Abdominal distension Dry mouth Mouth ulceration Salivary hypersecretion Eructation Flatulence[#1]		Pancreatitis Pseudomembranous colitis (see section 4.4) Tongue discolouration
Hepatobiliary disorders			Hepatitis* Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubin increased Blood alkaline phosphatase increased	Hepatic function abnormal Jaundice cholestatic	Hepatic failure (see section 4.4) Hepatitis fulminant Hepatic necrosis
Skin and subcutaneous tissue disorders			Rash[#2] Pruritus[#2] Urticaria	Acute generalised exanthematous	Toxic epidermal necrolysis

			Dermatitis Dry skin Hyperhidrosis	pustulosis (AGEP) Drug reaction with eosinophilia and systemic symptoms (DRESS) Photosensitivity reaction[#3]	Stevens-Johnson syndrome[#3] Erythema multiforme
Musculoskeletal and connective tissue disorders			Osteoarthritis Myalgia Back pain Neck pain		Arthralgia[#2]
Renal and urinary disorders			Dysuria Renal pain Blood urea increased Blood creatinine increased		Acute kidney injury Tubulointerstitial nephritis
Reproductive system and breast disorders			Intermenstrual bleeding Testicular disorder		
General disorders and administration site conditions			Oedema Asthenia Malaise Fatigue[#2] Face oedema Chest pain Pyrexia Pain Peripheral oedema		
Investigations		Blood bicarbonate decreased	Blood potassium abnormal Blood chloride increased Blood glucose increased Blood bicarbonate increased Blood sodium abnormal		
Injury, poisoning and procedural complications			Post procedural complication		

* These ADRs were only seen during azithromycin administration for MAC prophylaxis and/or therapy

#1 In MAC the frequency of these ADRs was Very Common (>1/10).
#2 In MAC the frequency of these ADRs was Common (>1/100 to <1/10).
#3 In MAC the frequency of these ADRs was Uncommon (>1/1 000 to <1/100).

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

[This section should read as follows:]

Symptoms
Adverse reactions experienced with higher than recommended doses were similar to those seen at normal doses (see section 4.8). The typical symptoms of an overdose with azithromycin include gastrointestinal symptoms, i.e. vomiting, diarrhoea, abdominal pain and nausea.

Treatment
In the event of an overdose, general symptomatic treatment and support of vital functions are indicated and, if required, administration of medicinal charcoal or gastric lavage.
There are no data on the effects of dialysis on the elimination of azithromycin. However, due to the elimination mechanism of azithromycin, dialysis is unlikely to result in significant removal of the active substance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

[This section should read as follows:]

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

Mechanism of action
The mechanism of action of azithromycin is based on the inhibition of the bacterial protein synthesis by binding to the ribosomal 50 S subunit and inhibiting translocation of the peptides.

Pharmacokinetic/pharmacodynamic relation
The efficacy depends mainly on the ratio between AUC (area under the curve) and MIC (minimum inhibitory concentration) of the causative organism.

Mechanisms of resistance
Resistance against azithromycin can be based on the following mechanisms:

- Efflux: Resistance can be caused by an increase in the number of efflux pumps in the cytoplasmic membrane. Only 14- and 15-ring-membered macrolides are concerned (so called M-phenotype).
- Change of target structure: Affinity to ribosomal binding sites is lowered by methylation of the 23S rRNA causing a resistance against macrolides (M), lincosamides (L) and streptogramins of the B-group (SB) (so called MLSB-phenotype). Resistance-conferring methylases are encoded by *erm* genes. Affinity to ribosomal binding sites is also lowered by mutations in the 23S rRNA target structure or by mutations in the large subunit ribosomal proteins.
- Enzymatic inactivation of macrolides is only of minor clinical interest.

With the M-phenotype a complete cross-resistance between azithromycin, clarithromycin, erythromycin and roxithromycin is observed. The MLS_B-phenotype shows an additional cross-resistance with clindamycin and streptogramin B. With the 16-ring-membered macrolide spiramycin a partial cross-resistance is exerted.

Due to low permeability of the outer membrane, most Gram-negative species are inherently resistant to macrolides.

Susceptibility testing interpretive criteria

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for azithromycin and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

Prevalence of acquired resistance

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. Particularly in the case of severe infections or therapeutic failure, a microbiological diagnosis with identification of the pathogen and determination of its susceptibility to azithromycin should be sought.

[Only species relevant to the approved indications should be listed in the following table, e.g. Borrelia burgdorferi should only be included, if the medicinal product is indicated for early Lyme disease]

Table 4: Prevalence of acquired resistance

Commonly susceptible species
Aerobic Gram-positive microorganisms
Mycobacterium avium complex°
Streptococcus pyogenes
Aerobic Gram-negative microorganisms
Haemophilus ducreyi
Haemophilus influenzae
Legionella pneumophila°
Moraxella catarrhalis
Anaerobic microorganisms
Peptostreptococcus spp.
Porphyromonas gingivalis
Tannerella forsythia
Treponema denticola
Other microorganisms
Aggregatibacter actinomycetemcomitans (formerly *Actinobacillus actinomycetemcomitans*)
Borrelia burgdorferi
Chlamydia trachomatis°
Chlamydophila pneumoniae°
Chlamydophila psittaci
Mycoplasma pneumoniae°

Prevotella intermedia
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Staphylococcus aureus[+]
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
Streptococcus agalactiae
Streptococcus pneumoniae[++]
Viridans streptococci
Aerobic Gram-negative microorganisms
Neisseria gonorrhoeae
Anaerobic microorganisms
Fusobacterium spp.
Prevotella spp.
Inherently resistant organisms
Aerobic Gram-negative microorganisms
Escherichia coli
Klebsiella spp.
Pseudomonas aeruginosa
Anaerobic microorganisms
Bacteroides spp.

[°]No updated data were available at release of tables. Primary literature, scientific standard literature and therapeutic recommendations assume susceptibility.
[+]At least one region shows resistance rates higher than 50% for methicillin-resistant *Staphylococcus aureus*.
[++]Penicillin susceptible strains of *Streptococcus pneumoniae* are more likely to be susceptible to azithromycin than are penicillin resistant strains of *Streptococcus pneumoniae*.

5.2 Pharmacokinetic properties

[This section should read as follows:]

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

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

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

Table 5: AUC_{0-24} and C_{max} of azithromycin for the 3-day and 5-day regimen at last day of dosing

Dose regimen, formulation	**AUC_{0-24} (µg•h/ml)**	**C_{max} (µg/ml)**
3-day regimen (500 mg daily), tablet	1.88 (0.96)	0.42 (0.21)
5-day regimen (500 mg D1, 250 mg D2 to D5), tablet	0.80 (0.42)	0.18 (0.10)
5-day regimen (500 mg D1, 250 mg D2 to D5), capsule	2.1 (0.6)	0.24 (0.08)

Distribution
Azithromycin is widely and rapidly distributed from plasma to the extravascular compartment, including tissues such as tonsil, lung and gynaecological tissues as well as the intracellular compartment, in particular to polymorphonuclear leukocytes, macrophages, and monocytes. Pharmacokinetic studies have shown considerably higher azithromycin concentrations in certain tissues (up to 50 times the maximum concentration observed in the plasma). This indicates an extensive binding to these tissues with a steady-state volume of distribution ranging from 23 to 31 L/kg. The redistribution phase from the intracellular to the extracellular compartment and to the plasma may result in prolonged low concentrations after treatment cessation.
Azithromycin shows low plasma protein binding, mainly to alpha 1-acid glycoprotein, and it decreases with increasing concentrations of antibiotic: 50%, 23% and 7% protein binding at concentrations of 0.05, 0.1 and 1 mg/L, respectively.

Biotransformation
Azithromycin is minimally metabolised in the liver. The primary route of biotransformation is N-demethylation of the desosamine sugar. Other pathways include O-demethylation, hydrolysis of cladinose (deconjugation of the cladinose sugar), and hydroxylation of desosamine sugar and macrolide ring.

There is no evidence of clinically relevant hepatic cytochrome CYP 3A4 induction or inhibition via the formation of a cytochrome-metabolite complex. Also, auto-induced metabolism of azithromycin by this pathway has not been detected.

Elimination
Azithromycin is mainly eliminated by (active) biliary excretion mostly as unchanged drug, but also as metabolites which are devoid of antibacterial activity. Urinary excretion represents a minor route of elimination with less than 6% of an oral dose and around 20% of the drug that reaches the systemic circulation excreted in urine. More than 50% of faecal, and 12% or urinary excretion is in the form of unchanged compound.

Following the administration of a single 500 mg azithromycin dose, a plasma clearance of 630 ml/min was estimated with a terminal half-life of approximately 68 hours. Renal clearance is generally in the range of 100-189 ml/min, substantially smaller than plasma clearance as expected due to the relatively poor contribution of the renal route to elimination.

Linearity/non-linearity
Following oral administration of an immediate release formulation, dose proportionality on AUC_{0-24} and C_{max} was shown in the range of 250 mg to 1000 mg.

Special populations

Renal Impairment
Azithromycin pharmacokinetics was investigated in 43 adults (21 to 85 years of age) following the oral administration of a single 1.0 g dose of azithromycin (4 x 250 mg capsules) to subjects with GFR >80 ml/min (n =12), subjects with GFR between 10 and 80 ml/min (n = 12) and subjects with GFR <10 ml/min (n = 19).

The pharmacokinetics of azithromycin in subjects with GFR between 10 and 80 ml/min were not affected (mean C_{max} and AUC_{0-120} increased by 5.1% and 4.2%, respectively compared to subjects with GFR >80 ml/min). The mean C_{max} and AUC_{0-120} increased 61% and 35%, respectively, in subjects with GFR <10 ml compared to subjects with GFR >80 ml/min.

No data are available for subjects undergoing dialysis, but due to the elimination mechanism of azithromycin, dialysis is unlikely to result in significant removal of the active substance.

Hepatic Impairment
Azithromycin pharmacokinetics was investigated in 22 adults following the oral administration of a single 500 mg dose of azithromycin (2 x 250 mg capsules) to subjects with normal hepatic function (n = 6), Child-Pugh A (n = 10) and Child-Pugh B (n = 6). The pharmacokinetics of azithromycin in subjects with Child-Pugh A and B were 3% and 19% lower on AUC_{0-inf} and 34% and 72% higher on C_{max}, respectively, compared to subjects with normal hepatic function.

Elderly
In elderly volunteers (> 65 years) given azithromycin 500 mg (2 x 250 mg capsules) on day 1 followed by 250 mg from days 2 to 5 in the fasted state the AUC_{0-24} on Days 1 and 5 were 3.0 and 2.7 µg•h/ml, respectively. A 29% higher AUC_{0-24}, a 8% higher C_{max} and a 37.5% higher T_{max} than in younger volunteers (<40 years) were observed at day 5. Since these differences are not considered clinically significant, no dose adjustment is required for elderly subjects with normal renal and hepatic function.

Paediatric population
The pharmacokinetics of azithromycin oral suspension have been characterised in 14 children aged 6 to15 years with pharyngitis and in 7 children aged 1 year to 5 years with otitis media. In these two studies, azithromycin oral suspension was dosed at 10 mg/kg on day 1, followed by 5 mg/kg on days 2 through 5. Following 5 days of treatment, mean AUC_{0-24} values were 3.1 µg•h/ml and 1.8 µg•h/ml, respectively. The mean C_{max} value was 0.38 µg/ml and the corresponding mean T_{max} value was 2.4 hours in children aged 6 to 15 years and 0.22 µg/ml and 1.9 hours for children 1 to 5 years of age. The mean C_{max} and AUC_{0-24} values are 1.7 times greater in children 6 to 15 years of age than in children 1 to 4 years of age.

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

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

5.3 Preclinical safety data

[This section should read as follows:]

Non-clinical data based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity did not indicate adverse reactions clearly relevant to humans not already considered in other sections of the SmPC.

However, phospholipidosis (intracellular phospholipid accumulation) has been observed in several tissues of mice, rats, and dogs given multiple doses of azithromycin. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs. The effect has been shown to be reversible after cessation of azithromycin treatment. The significance of this finding for humans is in general unknown.

In animal studies for embryotoxic effects performed up to moderately maternal toxic doses (2 to 3 times the maximum recommended adult daily dose of (500 mg based on body surface area), no teratogenic effect was observed in mice and rats. Azithromycin was shown to cross the placenta. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day (2 to 3 times the maximum recommended adult daily dose of 500 mg based on body surface area) led to mild retardation of foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardation following treatment with azithromycin doses of 200 mg/kg/day (3 times the maximum recommended adult daily dose of 500 mg based on body surface area) was observed.

PACKAGE LEAFLET

Solid oral formulations (film-coated tablets and hard capsules) (authorised strengths: 125 mg, 250 mg, 500 mg, 600 mg) and dispersible tablets (authorised strengths: 250 mg, 500 mg, 600 mg, 1000 mg)

1. What <invented name> is and what it is used for

[This section should read as follows:]

<Invented name> contains the active substance azithromycin. Azithromycin is an antibiotic that belongs to a group of antibiotics known as macrolides, which block the growth of susceptible bacteria.

<Invented name> is taken for the treatment of the following infections:

Adults and adolescents weighing 45 kg and over

- Infections of the tonsils (tonsillitis) or throat (pharyngitis) caused by streptococcal bacteria
- Bacterial sinus infections (sinusitis)
- Bacterial infections of the middle ear (otitis media)
- Pneumonia (community-acquired pneumonia, not contracted in a hospital)
- Bacterial infections of the skin and underlying tissues
- Early localised Lyme disease (erythema migrans, mainly caused by tick bites)
- Bacterial infections of the gums (periodontitis) or abscess in gums (periodontal abscess)
- Infections of urethra and cervix caused by *Chlamydia trachomatis* bacteria
- Infections of urethra and cervix caused by *Neisseria gonorrhoeae* bacteria. <Invented name> should be used in combination with another antibiotic that is selected by your doctor or pharmacist.
- Chronic inflammation of the prostate caused by *Chlamydia trachomatis* bacteria
- Bacterial infections of genitals with painful sores (chancroid)
- Infections caused by *Mycobacterium avium* complex (MAC) bacteria in people with advanced HIV infection. <Invented name> should be used in combination with another antibiotic called ethambutol.

<Invented name> is also taken for prevention of infections caused by *Mycobacterium avium* complex (MAC) bacteria in people living with HIV infection.

Adults:

- Bacterial infections in patients with long-term inflammation of the lungs (chronic bronchitis)
- Bacterial infection of the womb, fallopian tubes and ovaries (pelvic inflammatory disease) always in combination with another antibiotic(s) that is selected by your doctor or pharmacist.

2. What you need to know before you take <invented name>

[This section should read as follows:]

Do not take <Invented name>

- if you are allergic to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or, pharmacist before taking <Invented name> if you have or have had any of the following conditions:

- heart problems (e.g. problems with your heart rhythm or cardiac insufficiency) or low levels of potassium or magnesium in your blood: these conditions may contribute to serious cardiac side effects of azithromycin
- liver problems: your doctor may need to monitor your liver function or stop the treatment
- severe diarrhoea after administration of any other antibiotics

- localised muscle weakness (myasthenia gravis), as the symptoms of this disease may worsen during treatment
- or if you are taking any ergot derivatives such as ergotamine (used to treat migraine) as these medicines should not be taken together with <Invented name>.

Stop taking this medicine and contact your doctor immediately (see also "Serious side effects" in section 4):
- if you feel you are having an allergic reaction (e.g. difficulty in breathing, swelling of the face or throat, rash, blistering).
- if you notice any of the symptoms as described in section 4 related to serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP), which have been reported in association with azithromycin treatment.
- if you feel you have an abnormal heartbeat or palpitations, get dizzy or faint when taking <Invented name>.
- if you develop signs of liver problems (e.g. dark urine, loss of appetite or yellowing of the skin or whites of the eyes).
- if you develop severe diarrhoea during or after treatment. Do not take any medicine to treat your diarrhoea without first checking with your doctor. If your diarrhoea continues or reappears within the first weeks after treatment, please also inform your doctor.

Superinfection
Your doctor may observe you for signs of additional bacterial or fungal infections that cannot be treated with <invented name> (superinfection).

Sexually transmitted infections
Your doctor may test for and exclude a potential infection with syphilis, a sexually transmitted disease that may otherwise progress undetected and be diagnosed delayed. Furthermore, in any case of sexually transmitted bacterial infections your doctor will initiate laboratory follow-up tests to monitor the success of therapy.

Children and adolescents
This medicinal product is not recommended if:
- *[if the product is indicated for treatment of pelvic inflammatory disease in adults]* you are less than 18 years old and have been diagnosed with pelvic inflammatory disease
- *[if indicated for prevention or treatment of MAC infections]* you are less than 12 years old and you are infected or at risk of being infected with organisms that belong to the *Mycobacterium avium* complex which usually affect people living with HIV who have low defences as its efficacy and safety have not been studied in these cases.

If you weigh less than 45 kg, other medicinal products containing azithromycin exist that may be more convenient for you to take.

Other medicines and <Invented name>
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Taking <Invented name> at the same time as some other medicines may result in side effects. Therefore, it is particularly important that you tell your doctor if you are using any of the following medicines:
- Atorvastatin and other medicines from the statins group (to lower blood cholesterol and prevent heart disease, including heart attacks and strokes)
- Ciclosporin (to prevent rejection of organ transplants by the body)
- Colchicine (to treat gout and familial Mediterranean fever)
- Dabigatran (to prevent and treat blood clot formation (anticoagulant))
- Digoxin (to treat heart diseases)

- Warfarin or similar medicines used to thin the blood (anticoagulants)
- Medicines that may cause the heart muscle to take longer to contract and relax than usual (QT prolongation), such as the following:
  - Quinidine, procainamide, dofetilide, amiodarone and sotalol (to treat an irregular heartbeat, including a too fast or too slow heartbeat - cardiac arrhythmia)
  - Pimozide (to treat mental illness)
  - Citalopram (to treat depression)
  - Moxifloxacin and levofloxacin (antibiotics)
  - Cisapride (to treat disorders in the gastrointestinal tract)
  - Hydroxychloroquine or chloroquine (to treat autoimmune diseases including rheumatoid arthritis, or to treat or prevent malaria)

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
Your doctor will decide if you should take this medicine during pregnancy, only after making sure that the benefits outweigh the potential risks.

Breast-feeding
<Invented name> passes into breast milk. Your doctor will decide therefore whether you should stop breast-feeding or should avoid treatment with <Invented name> taking into account both the benefit of breast-feeding for your child and the benefit of therapy for you.

Driving and using machines

<Invented name> has a moderate influence on the ability to drive and use machines. <Invented name> has been reported to cause dizziness, drowsiness and seizures, as well as problems with seeing and hearing in some people. These possible side effects may have an influence on your ability to drive and use machines.

<<Invented name> contains {name the excipient(s)}>

[A warning about any excipient that could result in unwanted undesirable effects e.g. in patients with specific metabolism disorders (e.g. phenylketonuria, fructose intolerance, glucose-galactose malabsorption, sucrase/isomaltase deficiency) or allergies should be added in this section as per the QRD template. Each MAH will need to mention any relevant excipient(s) and related warning(s) for their formulation(s).]

3. How to take <invented name>

[This section should read as follows:]

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The amount of <Invented name> that you need to take each day depends on the bacterial infection that you are being treated for and the specific treatment course that your doctor or pharmacist has instructed you to follow.

[Dosing recommendations given in the table below should be in line with the indications in section 1; the 5-day regimen should only be included if it can be administered with the product e.g. 250 mg tablets or 500 mg tablets with a score line to break the tablet into equal doses]

Adults and adolescents weighing at least 45 kg

Infection	Treatment course with azithromycin
Infections of the tonsils (tonsillitis) or throat (pharyngitis) caused by streptococcal bacteria Bacterial sinus infections (sinusitis) Bacterial infections of the middle ear (otitis media) Bacterial infections in patients with long-term inflammation of the lungs (chronic bronchitis)* Pneumonia (community-acquired pneumonia, not contracted in a hospital)# Bacterial infections of the skin and underlying tissues Bacterial infections of the gums (periodontitis) or abscess in gums (periodontal abscess)	There is a 3-day or a 5-day treatment course for these infections, and the amount of <Invented name> to take each day is described for these treatment courses below. *3-day treatment course* 500 mg taken once daily for 3 days. *5-day treatment course* 500 mg taken on the first day of treatment and then 250 mg taken once daily for the following 4 days.
Early localised Lyme disease (erythema migrans, mainly caused by tick bites)	1000 mg taken on the first day of treatment and then 500 mg taken once daily for the following 9 days.
Infections of urethra and cervix caused by *Chlamydia trachomatis* bacteria	1000 mg taken as a single dose
Infections of urethra and cervix caused by *Neisseria gonorrhoeae* bacteria. <Invented name> should be used in combination with another antibiotic that is selected by your doctor or pharmacist.	1000 mg or 2000 mg* taken as a single dose
Bacterial infection of the womb, fallopian tubes and ovaries (pelvic inflammatory disease). <Invented name> should be used in combination with another antibiotic that is selected by your doctor or	Only if treatment has been started with intravenous azithromycin: 250 mg once daily to complete a 7day course of treatment

pharmacist*[#]	
Chronic inflammation of the prostate caused by *Chlamydia trachomatis* bacteria	500 mg/day taken on 3 consecutive days per week for a total of 3 weeks
Bacterial infections of genitals with painful sores (chancroid)	1000 mg taken as a single dose
Infections caused by *Mycobacterium avium* complex (MAC) bacteria in people with advanced HIV infection. <Invented name> should be used in combination with another antibiotic called ethambutol.	<500 mg> *or* <600 mg> once per day
Prevention of infections caused by *Mycobacterium avium* complex (MAC) bacteria in people living with HIV infection	<1200 mg> *or* <1250 mg> once per week
*only for adult patients [#] for adult patients oral treatment may follow an initial intravenous treatment	

Use in children and adolescents
If your weight is less than 45 kg <or you are not able to swallow this medicinal product>, ask your doctor or pharmacist as other medicinal products containing azithromycin are also available that may be more appropriate for you.

Method of administration
[the appropriate product-specific information should be chosen]

[Tablets (without any score line):]

For oral use.

<Invented name> should be taken by mouth as a single daily dose . Tablets should be swallowed whole with some water, with or without a meal. Taking this medicine just before a meal may help make it easier on your stomach.

[Tablets (with score line only for ease of swallowing)]

For oral use.

<Invented name> should be taken by mouth as a single daily dose. The score line on the tablets is only there to help you break the tablet if you have difficulty swallowing it whole. The halves should be taken one immediately after the other.

Tablets may be taken with or without a meal. Taking this medicine just before a meal may help make it easier on your stomach.

[Tablets (with score line for dose adjustment)]

For oral use.

<Invented name> should be taken by mouth as a single daily dose. Tablets may be taken with or without a meal. Taking this medicine just before a meal may help make it easier on your stomach.

Tablets can be split in two equal halves which can be used to adjust the dose as your doctor or pharmacist has told you.

[Hard capsules]

For oral use.
<Invented name> should be taken by mouth as a single daily dose. Capsules should be swallowed whole with some water. The capsules should be taken at least one hour before or two hours after a meal.

[Dispersible tablets (with data on compatibility and volume)]

For oral use after dispersion.
This medicinal product should be taken by mouth as a single daily dose. Reconstitute the intact tablet in a glass by the addition of an adequate amount (at least 30 ml) of clean potable water or orange or apple juice immediately before administration. Stir well until the tablet gets properly dispersed and then swallow it. If some of the suspension remains in the glass, add a small amount of water, swirl the glass and then swallow the remaining suspension.

The suspension can be taken with or without a meal. Taking this medicine just before a meal may help make it easier on your stomach.

[Dispersible tablets (without any data on compatibility and volume)]

For oral use after dispersion.
This medicinal product should be taken by mouth as a single daily dose. Reconstitute the intact tablet in a glass with clean potable water immediately before administration. Stir well until the tablet gets properly dispersed and then swallow it. If some of the suspension remains in the glass, add a small amount of water, swirl the glass and then swallow the remaining suspension. The suspension can be taken with or without a meal. Taking this medicine just before a meal may help make it easier on your stomach

If you take more <Invented name> than you should

If you take more <Invented name> than you should then you may feel unwell. Typical signs of an overdose are vomiting, diarrhoea, abdominal pain and nausea.Tell your doctor or contact your nearest hospital emergency department immediately.

If you forget to take <Invented name>

If you forget to take <Invented name> take it as soon as you can, as long as this is at least 12 hours before the next dose is due. If it is less than 12 hours left to your next dose, skip the missed dose and take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking <Invented name>

If you stop taking <Invented name> too soon, the infection may return. Take <Invented name> for the full time of treatment, even when you begin to feel better.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

[This section should read as follows:]

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Stop using <Invented name> and seek medical attention immediately if you notice any of the following symptoms:

- sudden wheeziness, difficulty in breathing, swelling of eyelids, face or lips, rash or itching especially affecting the whole body (*anaphylactic reaction*, frequency not known)
- rapid or irregular heartbeat (*cardiac arrhythmia or torsades de pointes tachycardia*, frequency not known)
- dark urine, loss of appetite or yellowing of the skin or whites of the eyes, which are signs of liver disorders (*hepatic failure* or *hepatic necrosis* (frequency not known), *hepatitis** (uncommon: may affect up to 1 in 100 people)).
- severe diarrhoea with abdominal cramps, bloody stools and/or fever may mean that you have an infection of the large intestine (*antibiotic-associated colitis*, frequency not known). Do not take medicines against diarrhoea that inhibit the bowel movements (*antiperistaltics*).
- reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (*Stevens-Johnson syndrome*[#] or *toxic epidermal necrolysis*, frequency not known).
- widespread rash, high body temperature and enlarged lymph nodes (*DRESS syndrome* or *drug hypersensitivity syndrome*, rare (may affect up to 1 in 1,000 people)).
- a red, scaly widespread rash with bumps under the skin and blisters accompanied by fever. The symptoms usually appear at the initiation of treatment (*acute generalised exanthematous pustulosis*, rare (may effect up to 1 in 1,000 people)).

Other side effects

Very common (may affect more than 1 in 10 people)
- diarrhoea
- abdominal discomfort[*]

Common (may affect up to 1 in 10 people)
- headache
- being sick (*vomiting*), stomach pain[#], feeling sick (*nausea*)[#]

- changes in blood test results (*lymphocyte count decreased, eosinophil count increased, basophil count increased, monocyte count increased, neutrophil count increased, blood bicarbonate decreased*)

Uncommon (may affect up to 1 in 100 people)
- thrush (*candidiasis*) - a fungal infection of the mouth and vagina, other fungal infections
- pneumonia, bacterial infection of the throat, inflammation of the gastrointestinal tract, respiratory disorder, inflammation of the mucous membrane inside the nose, vaginal infection
- changes in the number of white blood cells (*leukopenia, neutropenia, eosinophilia*)
- platelet count increased
- reduction in the proportion of all blood cells in the total blood volume (*hematocrit decreased*)
- allergic reactions, swelling of the hands, feet and face (*angiooedema*)
- lack of appetite[#]
- nervousness, difficulty sleeping (*insomnia*)
- feeling dizzy[#], feeling drowsy (*somnolence*), change in your sense of taste (*dysgeusia*)[#], sensation of pins and needles or numbness (*paraesthesia*)[#]
- impaired vision[#]
- ear disorder
- spinning sensation (*vertigo*)
- feeling your heartbeat (*palpitations*)
- hot flush
- sudden wheeziness, bleeding from the nose

- constipation, wind[#], impaired digestion (*dyspepsia*), inflammation of the lining of the stomach (*gastritis*), difficulty in swallowing (*dysphagia*), swollen belly, dry mouth, belching (*eructation*), mouth ulceration, increased salivation
- rash[#], itching[#], hives (*urticaria*), dermatitis, dry skin, abnormally increased sweating (*hyperhidrosis*)
- swelling and pain in the joints (*osteoarthritis*), muscle pain, back pain, neck pain
- painful urination (*dysuria*), kidney pain
- menstrual bleeding at irregular intervals (*metrorrhagia*), testicular disorder
- swelling due to fluid retention, especially of the face, ankles and feet (*oedema, face oedema, peripheral oedema*)
- weakness, tiredness[#], general feeling of being unwell, fever
- chest pain, pain
- abnormal laboratory test results (e.g. blood or liver tests)
- post procedural complication

Rare (may affect up to 1 in 1,000 people)
- feeling irritated
- liver problems, yellowing of the skin or eyes
- increased sensitivity to sunlight[#]

Not known (frequency cannot be estimated from the available data)
- reduced number of red blood cells due to increased cell breakdown which can cause tiredness and pale skin (*haemolytic anaemia*)
- reduction in number of platelets which can lead to bleeding and bruising (*thrombocytopenia*)
- feeling angry, aggressive, feeling of fear and concern (*anxiety*), acute confusional state (*delirium*),
- hallucination
- fainting (*syncope*)
- fits (*seizures*)
- reduced sensation to touch, pain and temperature (*hypoaesthesia*)[#]
- feeling hyperactive
- change in your sense of smell (*anosmia, parosmia*)
- total losstof your sense of taste (*ageusia*)
- muscle weakness (*myasthenia gravis*)
- abnormal electrocardiogramm (ECG) heart tracing (*QT prolongation*)
- deafness[#], reduced hearing[#] or ringing in your ears (*tinnitus*)[#]
- low blood pressure
- inflammation of the pancreas causing severe pain in the belly and back (*pancreatitis*)
- your tongue changes colour
- joint pain (*arthralgia*)[#]
- kidney inflammation (*interstitial nephritis)* and kidney failure

[information on adverse reactions related to treatment and/or prophylaxis of MAC infections should only be included if the product is indicated for these treatments]

* These side effects were only seen during azithromycin administration for the prophylaxis and/or therapy of *Mycobacterium avium* complex infections in people living with HIV with insufficient recovery of the immune system.
# These side effects were more common during azithromycin administration for the prophylaxis and/or therapy of *Mycobacterium avium* complex infections in people living with HIV with insufficient recovery of the immune system.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.
You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

SUMMARY OF PRODUCT CHARACTERISTICS

Liquid oral formulations (powder for oral suspension (in bottle) (authorised strengths: 20 mg/ml, 40 mg/ml) or (in sachet) (authorised strengths: 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 400 mg, 500 mg, 1000 mg) or (granules for oral suspension in bottle) authorised strength: 40 mg/ml)

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

[This section should read as indicated below. Indications should only be implemented if the product was already approved for the condition
Wording related to the following indications should be removed:

- Gastro-duodenal infections caused by Helicobacter pylori

- Treatment of (moderate) acne vulgaris

- Prevention of exacerbations of eosinophilic and non-eosinophilic asthma]

<Invented name> is indicated for the treatment of the following infections (see sections 4.4 and 5.1):

Paediatric patients aged 6 months and older and weighing less than 45 kg
- Acute streptococcal tonsillitis and pharyngitis
- Acute bacterial sinusitis
- Acute bacterial otitis media
- Community-acquired pneumonia (CAP)
- Acute bacterial skin and skin structure infections (ABSSSI)
- Erythema migrans (early localised Lyme disease)
- Periodontal abscesses and periodontitis

Adults and adolescents weighing at least 45 kg and unable to swallow solid pharmaceutical forms:
In addition to the indications listed above, this medicinal product is also indicated for the treatment of:
- Urethritis and cervicitis caused by *Chlamydia trachomatis*
- Urethritis and cervicitis caused by *Neisseria gonorrhoeae*, in combination with another appropriate antibacterial agent (e.g. ceftriaxone)
- Chronic prostatitis caused by *Chlamydia trachomatis*
- Chancroid
- Disseminated *Mycobacterium avium* complex (DMAC) infection in people living with advanced HIV infection, in combination with ethambutol
- Prophylaxis of *Mycobacterium avium* complex (MAC) infection in people living with HIV with inadequate immune restoration.
- Adult patients with acute exacerbation of chronic bronchitis or with pelvic inflammatory disease, the latter always in combination with other appropriate antibacterial agent(s) (e.g. metronidazole).

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

4.2 Posology and method of administration

[This section should read as follows:]

Posology

Paediatric patients aged 6 months and older weighing less than 45 kg

[Powder for oral suspension in bottles, 20 mg/ml and 40 mg/ml, and granules for oral suspension 40 mg/ml, the table below should only include posology information of authorised indications in line with section 4.1]

Azithromycin should be administered as a single daily dose
(see Table 1).

Table 1: Dosing recommendations for paediatric patients aged 6 months and older weighing less than 45 kg

Indication	Azithromycin dosing regimen
Acute bacterial sinusitis Community-acquired pneumonia Acute bacterial skin and skin structure infections Periodontal abscesses and periodontitis	10 mg/kg/day for 3 days or 10 mg/kg on day 1, followed by 5 mg/kg/day on days 2-5
Acute bacterial otitis media	single dose of 30 mg/kg or 10 mg/kg/day for 3 days or 10 mg/kg on day 1, followed by 5 mg/kg/day on days 2-5
Acute streptococcal tonsillitis and pharyngitis	20 mg/kg/day for 3 days or 12 mg/kg/day for 5 days
Erythema migrans (early localised Lyme disease)	20 mg/kg once daily the first day followed by a single dose of 10 mg/kg on days 2 to 10
Consideration should be given to the treatment regimens, doses and duration of treatment as recommended in updated treatment guidelines for each indication.	

The azithromycin daily dose should not exceed the adult daily dose of 500 mg, with exception of the 1-day treatment course (single dose) for acute bacterial otitis media for which the maximum total dose of 1500 mg should not be exceeded. The maximum recommended total dose for any treatment for paediatric patients weighing less than 45 kg is 1500 mg, except for the 5-day regimen for acute streptococcal tonsillitis and pharyngitis and for erythema migrans (early localised Lyme disease). See Table 2.

Table 2: Maximum recommended daily doses of azithromycin per dosing regimen

Body weigth (Kg)	**Azitromycin maximum dose per day**				
	5 mg/kg (5-day regimen, Days 2 to 5)	**10 mg/kg** (3-day regimen or 5-day regimen, Day 1; 10-day regimen, Days 2 to 10 erythema migrans)	**12 mg/kg** (5-day regimen streptococcal pharyngotonsillitis)	**20 mg/kg** (3-day regimen streptococcal pharyngotonsillitis; 10-day regimen, Day 1 erythema migrans)	**30 mg/kg** (single dose regimen acute otitis media)
7	35 mg	70 mg	84 mg	140 mg	210 mg
8	40 mg	80 mg	96 mg	160 mg	240 mg
9	45 mg	90 mg	108 mg	180 mg	270 mg

10	50 mg	100 mg	120 mg	200 mg	300 mg
11	55 mg	110 mg	132 mg	220 mg	330 mg
12	60 mg	120 mg	144 mg	240 mg	360 mg
13	65 mg	130 mg	156 mg	260 mg	390 mg
14	70 mg	140 mg	168 mg	280 mg	420 mg
15	75 mg	150 mg	180 mg	300 mg	450 mg
16 - 25	100 mg	200 mg	250 mg	400 mg	600 mg
26 - 35	150 mg	300 mg	350 mg	500 mg#	900 mg
36 - <45	200 mg	400 mg	450 mg	500 mg#	1200 mg

not to exceed the adult daily dose of 500 mg

The volume to be administered to obtain the above doses is shown in Table 3.

[Powder for oral suspension in bottles, 20 mg/ml; for a dosing device with 0.5 ml steps]

Table 3: Maximum daily dosing recommendations and related volumes of the oral suspension (20 mg/ml) for paediatric patients aged 6 months and older weighing less than 45 kg

Body weight (kg)	**Azithromycin maximum dose per day**				
	5 mg/kg	**10 mg/kg**	**12 mg/kg**	**20 mg/kg**	**30 mg/kg**
7	2.00 ml (40 mg)+	3.50 ml (70 mg)	4.50 ml (90 mg)++	7.00 ml (140 mg)*	10.50 ml (210 mg)*
8	2.00 ml (40 mg)	4.00 ml (80 mg)	5.00 ml (100 mg)++	8.00 ml (160 mg)*	12.00 ml (240 mg)*
9	2.50 ml (50 mg)+	4.50 ml (90 mg)	5.50 ml (110 mg)++*	9.00 ml (180 mg)*	13.50 ml (270 mg)*
10	2.50 ml (50 mg)	5.00 ml (100 mg)	6.00 ml (120 mg)*	10.00 ml (200 mg)*	15.0 ml (300 mg)*
11	3.00 ml (60 mg)+	5.50 ml (110 mg)*	6.50 ml (130 mg)++*	11.00 ml (220 mg)*	16.50 ml (330 mg)*
12	3.00 ml (60 mg)	6.00 ml (120 mg)*	7.50 ml (150 mg)++*	12.00 ml (240 mg)*	18.00 ml (360 mg)*
13	3.50 ml (70 mg)+	6.50 ml (130 mg)*	8.00 ml (160 mg)++*	13.00 ml (260 mg)*	19.50 ml (390 mg)*
14	3.50 ml (70 mg)	7.00 ml (140 mg)*	8.50 ml (170 mg)++*	14.00 ml (280 mg)*	21.00 ml (420 mg)*
15	4.00 ml (80 mg)+	7.50 ml (150 mg)*	9.00 ml (180 mg)*	15.00 ml (300 mg)*	22.50 ml (450 mg)*
16-25	5.00 ml (100 mg)	10.00 ml (200 mg)*	12.50 ml (250 mg)*	20.00 ml (400 mg)*	30.00 ml (600 mg)*
26-35	7.50 ml (150 mg)*	15.00 ml (300 mg)*	17.50 ml (350 mg)*	25.00 ml (500 mg) *#	45.00 ml (900 mg)*
36- < 45	10.00 ml (200 mg)*	20.00 ml (400 mg)*	22.50 ml (450 mg)*	25.00 ml (500 mg) *#	60.00 ml (1200 mg)*

[+] 5 mg/kg dose: the recommended doses are 1.75 ml (35 mg), 2.25 ml (45 mg), 2.75 ml (55 mg), 3.25 ml (65 mg), and 3.75 ml (75 mg) that can only be administered with an oral dosing syringe graduated in 0.25 ml divisions. These values have been rounded to obtain an appropriate dose to be administered in case of oral dosing syringe graduated in 0.50 ml divisions.

[++] 12 mg/kg dose: the recommended doses are 4.20 ml (84 mg), 4.8 ml (96 mg), 5.4 ml (108 mg), 6.6 ml (132 mg), 7.2 ml (144 mg), 7.8 ml (156 mg), and 8.4 ml (168 mg) that can only be administered with an oral syringe graduated in 0.20 ml divisions. These values have been rounded to obtain an appropriate dose to be administered in case of oral dosing syringe graduated in 0.50 ml divisions.

*azithromycin 40 mg/ml (200 mg/5 ml) powder for oral suspension is most appropriate to treat these patients.

[#] not to exceed the adult daily dose of 500 mg

[Powder for oral suspension in bottles, 40 mg/ml; for a dosing device with 0.25 ml steps]

Table 3: Maximum daily dosing recommendations and related volumes of the oral suspension (40 mg/ml) for paediatric patients aged 6 months and older weighing less than 45 kg

Body weight (kg)	**Azithromycin maximum dose per day**				
	5 mg/kg	**10 mg/kg**	**12 mg/kg**	**20 mg/kg**	**30 mg/kg**
7	1.00 ml (40 mg)+*	1.75 ml (70 mg)*	2.25 ml (90 mg)++	3.50 ml (140 mg)	5.25 ml (210 mg)
8	1.00 ml (40 mg)*	2.00 ml (80 mg)*	2.50 ml (100 mg)++	4.00 ml (160 mg)	6.00 ml (240 mg)
9	1.25 ml (50 mg)+*	2.25 ml (90 mg)	2.75 ml (110 mg)++	4.50 ml (180 mg)	6.75 ml (270 mg)
10	1.25 ml (50 mg)*	2.50 ml (100 mg)	3.00 ml (120 mg)	5.00 ml (200 mg)	7.50 ml (300 mg)
11	1.50 ml (60 mg)+*	2.75 ml (110 mg)	3.25 ml (130 mg)++	5.50 ml (220 mg)	8.25 ml (330 mg)
12	1.50 ml (60 mg)*	3.00 ml (120 mg)	3.75 ml (150 mg)++	6.00 ml (240 mg)	9.00 ml (360 mg)
13	1.75 ml (70 mg)+*	3.25 ml (130 mg)	4.00 ml (160 mg)++	6.50 ml (260 mg)	9.75 ml (390 mg)
14	1.75 ml (70 mg)*	3.50 ml (140 mg)	4.25 ml (170 mg)++	7.00 ml (280 mg)	10.50 ml (420 mg)
15	2.00 ml (80 mg)+*	3.75 ml (150 mg)	4.50 ml (180 mg)	7.50 ml (300 mg)	11.25 ml (450 mg)
16-25	2.50 ml (100 mg)	5.00 ml (200 mg)	6.25 ml (250 mg)	10.00 ml (400 mg)	15.00 ml (600 mg)
26-35	3.75 ml (150 mg)	7.50 ml (300 mg)	8.75 ml (350 mg)	12.50 ml (500 mg)#	22.50 ml (900 mg)
36-< 45	5.00 ml (200 mg)	10.00 ml (400 mg)	11.25 ml (450 mg)	12.50 ml (500 mg)#	30.00 ml (1200 mg)

[+] 5 mg/kg dose: the recommended doses are 0.875 ml (35 mg), 1.125 ml (45 mg), 1.375 ml (55 mg), 1.625 ml (65 mg), and 1.875 ml (75 mg). These values have been rounded to obtain an appropriate dose to be administered.

[++]12 mg/kg: the recommended doses are 2.10 ml (84 mg), 2.40 ml (96 mg), 2.70 ml (108 mg), 3.30 ml (132 mg), 3.60 ml (144 mg), 3.9 ml (156 mg), and 4.2 ml (168 mg). These values have been rounded to obtain an appropriate dose to be administered.

* azithromycin 20 mg/ml (100 mg/5 ml) powder for oral suspension is most appropriate to treat these patients.

[#] not to exceed the adult daily dose of 500 mg

[Powder for oral suspension in bottles, 20 mg/ml and 40 mg/ml, granules for oral suspension 40 mg/ml]

Adults and adolescents weighing at least 45 kg and unable to swallow solid pharmaceutical forms

Azithromycin should be administered as a single daily dose (see Table 4).

Table 4: Dosing recommendations for adults and adolescents weighing at least 45 kg and unable to swallow solid pharmaceutical forms

Indication	Azithromycin dosing regimen

Acute streptococcal tonsillitis and pharyngitis Acute bacterial sinusitis Acute bacterial otitis media Acute exacerbations of chronic bronchitis* Community-acquired pneumonia[#] Acute bacterial skin and skin structure infections Periodontal abscesses and periodontitis	500 mg/day for 3 days or 500 mg on day 1, followed by 250 mg/day on days 2-5
Erythema migrans (early localised Lyme disease)	1000 mg on day 1, followed by 500 mg/day on days 2-10
Urethritis and cervicitis caused by *Chlamydia trachomatis*	1000 mg as a single dose
Urethritis and cervicitis caused by *Neisseria gonorrhoeae*, in combination with another appropriate antibacterial agent (e.g. ceftriaxone)	1000 mg or 2000 mg* as a single dose
Chronic prostatitis caused by *Chlamydia trachomatis*	500 mg/day on 3 consecutive days per week for 3 weeks (total dose: 4500 mg)
Chancroid	1000 mg as a single dose
Treatment of disseminated *Mycobacterium avium* complex (DMAC) infection in people living with advanced HIV infection (in combination with ethambutol)	600 mg once daily
Prophylaxis of *Mycobacterium avium* complex (MAC) infections in people living with HIV with inadequate immune restoration	1200 mg once a week
Pelvic inflammatory disease in combination with other appropriate antibacterial agent(s) (e.g. metronidazole)*[+]	Only as an oral switch after intravenous administration if clinically indicated: 250 mg once daily to complete a 7- day course of treatment
* for treatment of adults only [#] in adults, oral treatment may also follow intravenous treatment, if clinically indicated to complete a 7- to 10-day total course of treatment (for details refer to the Summary of Product Characteristics of azithromycin IV formulations). [+] oral azithromycin should not be used for the initial treatment of pelvic inflammatory disease (for details refer to the Summary of Product Characteristics of azithromycin IV formulations). Consideration should be given to the treatment regimens, doses and duration of treatment as recommended in updated treatment guidelines for each indication.	

[Powder for oral suspension in sachets]
Paediatric patients aged 6 months and older weighing less than 45 kg

Azithromycin should be administered as a single daily dose (see Table 1).

Table 1: Dosing recommendations for paediatric patients aged 6 months and older weighing less than 45 kg

Indication	Azithromycin dosing regimen
Acute bacterial sinusitis Community-acquired pneumonia Acute bacterial skin and skin structure infections Periodontal abscesses and periodontitis	10 mg/kg/day for 3 days or 10 mg/kg on day 1, followed by 5 mg/kg/day on days 2-5
Acute bacterial otitis media	single dose of 30 mg/kg or 10 mg/kg/day for 3 days or 10 mg/kg on day 1, followed by 5 mg/kg/day on days 2-5
Acute streptococcal tonsillitis and pharyngitis	20 mg/kg/day for 3 days or 12 mg/kg/day for 5 days
Erythema migrans (early localised Lyme disease)	20 mg/kg once daily the first day followed by a single dose of 10 mg/kg on days 2 to 10
Consideration should be given to the treatment regimens, doses and duration of treatment as recommended in updated treatment guidelines for each indication.	

Azithromycin daily dose should not exceed the adult daily dose of 500 mg, with exception of the 1-day treatment course (single dose) for acute bacterial otitis media for which the maximum total dose of 1500 mg should not be exceeded. The maximum recommended total dose for any treatment for paediatric patients weighing less than 45 kg is 1500 mg, except for the 5-day regimen for acute streptococcal tonsillitis and pharyngitis and for erythema migrans (early localised Lyme disease). See Table 2.

The powder for oral suspension in sachet cannot be used to dose children weighing less than 16 kg due to the lack of appropriate strengths. For these children the powder for oral suspension in bottle or other suitable formulations should be used.

Table 2: Maximum recommended daily doses of azithromycin per dosing regimen

Body weigth (Kg)	**Azitromycin maximum dose per day**				
	5 mg/kg (5-day regimen, Days 2 to 5)	**10 mg/kg** (3-day regimen or 5-day regimen, Day 1; 10-day regimen, Days 2 to 10 erythema migrans)	**12 mg/kg** (5-day regimen streptococcal pharyngotonsillitis)	**20 mg/kg** (3-day regimen streptococcal pharyngotonsillitis; 10-day regimen, Day 1 erythema migrans)	**30 mg/kg** (single dose regimen acute otitis media)
16 - 25	100 mg	200 mg	250 mg	400 mg	600 mg

26 - 35	150 mg	300 mg	350 mg	500 mg#	900 mg
36 - <45	200 mg	400 mg	450 mg	500 mg#	1200 mg

not to exceed the adult daily dose of 500 mg

Adults and adolescents weighing at least 45 kg and unable to swallow solid pharmaceutical forms

Azithromycin should be administered as a single daily dose (see Table 3).

Table 3: Dosing recommendations for adults and adolescents weighing at least 45 kg and unable to swallow solid pharmaceutical forms

Indication	Azithromycin dosing regimen
Acute streptococcal tonsillitis and pharyngitis Acute bacterial sinusitis Acute bacterial otitis media Acute exacerbations of chronic bronchitis* Community-acquired pneumonia[#] Acute bacterial skin and skin structure infections Periodontal abscesses and periodontitis	500 mg/day for 3 days or 500 mg on day 1, followed by 250 mg/day on days 2-5
Erythema migrans (early localised Lyme disease)	1000 mg on day 1, followed by 500 mg/day on days 2-10
Urethritis and cervicitis caused by *Chlamydia trachomatis*	1000 mg as a single dose
Urethritis and cervicitis caused by *Neisseria gonorrhoeae*, in combination with another appropriate antibacterial agent (e.g. ceftriaxone)	1000 mg or 2000 mg* as a single dose
Chronic prostatitis caused by *Chlamydia trachomatis*	500 mg/day on 3 consecutive days per week for 3 weeks (total dose: 4500 mg)
Chancroid	1000 mg as a single dose
Treatment of disseminated *Mycobacterium avium* complex (DMAC) infection in people living with advanced HIV infection (in combination with ethambutol)	600 mg once daily
Prophylaxis of *Mycobacterium avium* complex (MAC) infections in people living with HIV with inadequate immune restoration	1200 mg once a week
Pelvic inflammatory disease in combination with other appropriate antibacterial agent(s) (e.g. metronidazole)*+	Only as an oral switch after intravenous administration if clinically indicated: 250 mg once daily to complete a 7-day course of treatment

* for treatment of adults only
# in adults, oral treatment may also follow intravenous treatment, if clinically indicated to complete a 7- to 10-day total course of treatment (for details refer to the Summary of Product Characteristics of azithromycin IV formulations).
+ oral azithromycin should not be used for the initial treatment of pelvic inflammatory disease (for details refer to the Summary of Product Characteristics of azithromycin IV formulations).

Consideration should be given to the treatment regimens, doses and duration of treatment as recommended in updated treatment guidelines for each indication.

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

Special populations

Renal impairment
No dose adjustment is required in patients with GFR ≥10 ml/min. In patients with GFR <10 ml/min azithromycin should be administered with caution (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B) (see section 5.2). No data are available in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, azithromycin should be administered with caution in these patients (see section 4.4).

Elderly
No dose adjustment is required in elderly patients (see section 5.2). Since the elderly are more likely to experience proarrhythmic conditions, particular caution is recommended due to the risk of developing cardiac arrhythmia and torsade de pointes (see section 4.4).

Paediatric population
The safety and efficacy of azithromycin have not been established in children under 6 months of age for any of the indications listed in section 4.1.

[if the product is indicated for treatment of pelvic inflammatory disease in adults and adolescents weighing at least 45 kg and unable to swallow solid pharmaceutical forms]

The safety and efficacy of <Invented name> for the treatment of adolescent girls with pelvic inflammatory disease have not been established.

[if the product is indicated for treatment of acute exacerbation of chronic bronchitis in adults and adolescents weighing at least 45 kg and unable to swallow solid pharmaceutical forms]

There is no relevant use of <Invented name> for the treatment of acute exacerbations of chronic bronchitis in paediatric patients.

[if the product is indicated for treatment and/or prophylaxis of Mycobacterium avium complex infections]

The safety and efficacy of <Invented name> in prevention or treatment of *Mycobacterium avium* complex infections in paediatric patients < 12 years has not been established.

Method of administration

[Powder for oral suspension in bottle]

For oral use after reconstitution.

Powder for oral suspension should be taken as a single daily dose with or without a meal. Administration immediately before a meal may enhance the gastrointestinal tolerability.

Patients should be advised to shake the bottle of the reconstituted oral suspension before each new dose.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

[Powder for oral suspension in sachet]

For oral use after reconstitution.

The entire content of the sachet should be mixed thoroughly with approximately 60 ml of water into a homogenous suspension. The reconstituted suspension should be taken immediately as a single daily dose with or without a meal. Any remaining residue of the suspension must be resuspended in a small volume of water and swallowed. Administration immediately before a meal may enhance the gastrointestinal tolerability.

[In case two sachets are needed to make the dose)]

For oral use after reconstitution.

The entire content of 2 sachets should be mixed thoroughly with approximately 60 ml of water into a homogenous suspension. The reconstituted suspension should be taken immediately as a single daily dose with or without a meal. Any remaining residue of the suspension must be resuspended in a small volume of water and swallowed. Administration immediately before a meal may enhance the gastrointestinal tolerability.

[Granules for oral suspension]

[The below instructions are specific for the granules for oral suspension authorised at time of this procedure and should be carefully checked for accuracy]

For oral use after reconstitution.

Granules for oral suspension should be taken as a single daily dose, with or without a meal. Administration immediately before a meal may enhance the gastrointestinal tolerability.

Patients should be advised to shake the bottle of the reconstituted oral suspension before each new dose.

Instructions for reconstitution

Each bottle contains an additional 5 ml of suspension to ensure complete dosing. For reconstitution, the appropriate volume of water should be added to the bottle with the granules using the oral syringe (supplied in the box) until a homogenous suspension is obtained.

- For 20 ml (X mg): 12 ml water should be added.
- For 30 ml (X mg): 16.5 ml water should be added.
- For 37.5 ml (X mg): 20 ml water should be added.

The dose of the medication should be measured using the oral syringe provided.

4.3 Contraindications

[This section should read as follows:]

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 precaution for use

[This section should read as follows:]

Potential for resistance
Azithromycin could favour the development of resistance due to the associated long-lasting and decreasing levels in plasma and tissues after the end of treatment (see section 5.2). Treatment with azithromycin should only be initiated after a careful assessment of the benefit and the risks, considering the local prevalence of resistance, and when preferred treatment regimens are not indicated.

Severe skin and hypersensitivity reactions
Rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), which can be life- threatening or fatal, have been reported in association with azithromycin treatment (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment. If an allergic reaction occurs, azithromycin should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

QT interval prolongation
Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides including azithromycin (see section 4.8). Therefore, as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients:
• With congenital or documented QT prolongation
• Currently receiving treatment with other active substances known to prolong QT interval (see section 4.5)
• With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
• With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency
• Elderly patients: Elderly patients may be more susceptible to drug-associated effects on the QT interval

Hepatotoxicity
Since liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin. Hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have also been reported with azithromycin, some of which have resulted in death (see section 4.8). Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products. Patients should be advised to stop azithromycin administration and to contact their physician if signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy develop. In such cases liver function tests/investigations should be performed immediately.

Clostridioides difficile associated diarrhoea (CDAD), pseudomembranous colitis

CDAD and pseudomembranous colitis have been reported with azithromycin and may range in severity from mild diarrhoea to fatal colitis (see section 4.8). CDAD and pseudomembranous colitis must be considered in patients who present with diarrhoea during or subsequent to the administration of azithromycin. Discontinuation of therapy with azithromycin and the use of supportive measures together with the administration of specific treatment for *C. difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Sexually transmitted infections
Neisseria gonorrhoeae is very likely to be resistant to macrolides, including the azalide azithromycin (see section 5.1). Therefore, azithromycin is not recommended for the treatment of uncomplicated gonorrhoea and pelvic inflammatory disease unless laboratory results have confirmed susceptibility of the organism to azithromycin. If left untreated or treated sub-optimally, this condition may lead to late onset complications such as infertility and ectopic pregnancy.

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

Furthermore, a concomitant infection caused by *Treponema pallidum* should be excluded as symptoms of incubating syphilis could be masked delaying diagnosis.

For all patients with sexually transmitted urogenital infections, appropriate antibacterial therapy and microbiological follow-up tests should be initiated.

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

Non-susceptible organisms
The use of azithromycin may result in the overgrowth of non-susceptible organisms. If superinfection occurs, interruption of treatment or other appropriate measures may be required.

Ergot derivatives
In patients receiving ergot derivatives, ergotism has been precipitated by co-administration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergot and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives may not be co-administered.

Paediatric population
Infantile hypertrophic pyloric stenosis (IHPS)
Cases of infantile hypertrophic pyloric stenosis have been reported following the administration of azithromycin for the first 42 days after birth. Parents and caregivers should be asked to contact their doctor if projectile vomiting or irritability with feeding occurs.

Excipients with known effect

[A warning about any excipient that could result in unwanted undesirable effects e.g. in patients with specific metabolism disorders (e.g. phenylketonuria, fructose intolerance, glucose-galactose malabsorption, sucrase/isomaltase deficiency) or allergies should be added in this section as per the QRD template. Each MAH will need to mention any relevant excipient(s) and related warning(s) for their formulation(s).]

<For the full list of excipients, see section 6.1.>

4.5 Interaction with other medicinal products and other forms of interaction

[This section should read as follows:]

Although azithromycin is a weak CYP450 inhibitor and does not interact significantly with CYP450 substrates, CYP3A4 inhibition cannot be completely ruled out. Therefore, caution is recommended in case of co-administration with CYP3A4 substrates with narrow therapeutic index.
Azithromycin is an inhibitor of the transporter P-glycoprotein (P-gp). Co-administration of azithromycin with P-gp substrates, such as digoxin and colchicine, may increase their exposure. For narrow therapeutic index drugs, caution and clinical and/or therapeutic drug monitoring and dose adjustment as appropriate are advised. The relatively long half-life of azithromycin should be taken into account in this context (see section 5.2).

Medicinal products that are known to prolong the QT interval
Azithromycin should be used with caution in patients receiving medicinal products known to prolong the QT interval (see section 4.4), such as antiarrhythmics of Classes IA (e.g. quinidine and procainamide) and III (e.g. dofetilide, amiodarone and sotalol), antipsychotic agents (e.g. pimozide), antidepressants (e.g. citalopram), fluoroquinolones (e.g. moxifloxacin and levofloxacin), cisapride, chloroquine and hydroxychloroquine.

Drug interaction information for azithromycin with potential concomitant medicinal products is summarised in the table and text below. The drug interactions described are based on clinical drug-drug interaction studies conducted with azithromycin or, where indicated, are potential drug interactions that may occur with azithromycin.

Table 4: Clinically relevant drug interactions between azithromycin and other medicinal products

Medicinal product (therapeutic area)	**Interaction Effect on exposure**	**Mechanism**	**Recommendation concerning co-administration**
Atorvastatin (HMG CoA reductase inhibitor) Azithromycin 500 mg orally once daily for 3 days. Atorvastatin 10 mg orally once daily.	Azithromycin: ND Atorvastatin: ↔ AUC ↔ C_{max}	Atorvastatin is a CYP3A4 and P-gp substrate.	Caution should be exercised since post-marketing cases of rhabdomyolysis in patients receiving azithromycin concomitantly with statins have been reported.
Ciclosporin (immunosuppressant) Azithromycin 500 mg orally once daily for 3 days. Ciclosporin 10 mg/kg orally single dose.	Azithromycin: ND Ciclosporin: ↔ AUC ↑C_{max} 24 %	Ciclosporin is a CYP3A4 and P-gp substrate with narrow therapeutic index and/or competition for biliary excretion.	Clinical monitoring and therapeutic drug monitoring as appropriate should be performed during and after treatment with azithromycin. Ciclosporin dose should be adjusted if required.
Colchicine (gout)	Azithromycin: ND Colchicine*:* ↑ 57% AUC_{0-t} ↑ 22% C_{max}	Colchicine is a P-gp substrate with narrow therapeutic index.	Clinical monitoring is needed during and after treatment with azithromycin.
Dabigatran (oral anticoagulant)	ND *Expected:* ↑ Dabigatran	Dabigatran is a P-gp substrate with narrow therapeutic index.	Caution should be exercised since post-marketing data suggest an increased risk for haemorrhages in patients receiving azithromycin concomitantly with dabigatran.
Digoxin (cardiac glycosides)	ND *Expected:* ↑ Digoxin	Digoxin is a P-gp substrate with narrow therapeutic index.	Clinical monitoring, and possibly digoxin level monitoring, is needed during and after treatment with azithromycin.
Warfarin (oral anticoagulant) Azithromycin 500 mg orally once daily for 1 day and then 250 mg orally once daily for 4 days. Warfarin 15 mg orally single dose.	Azithromycin: ND Warfarin: ND No change in prothrombin time in clinical drug interaction study but post-marketing reports of potentiated anticoagulation of	Not known.	A higher frequency of prothrombin time monitoring should be considered during and after treatment with azithromycin.

	coumarin-type oral anticoagulants upon co-administration with azithromycin.		
Note: statistically significant changes by more than 10% are indicated as "↑" or "↓", no change as "↔", not determined as "ND".			

No clinically relevant change in the exposure of azithromycin or the co-administered medicinal products was observed in clinical studies evaluating potential drug-drug interactions of azithromycin with oral antacids (aluminium hydroxide/magnesium hydroxide), carbamazepine, cetirizine, cimetidine, efavirenz, fluconazole, methylprednisolone, midazolam, rifabutin, sildenafil, theophylline, triazolam, trimethoprim/sulfamethoxazole and zidovudine.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

[This section should read as follows:]

Pregnancy
Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of teratogenic effects was found. There are, however, no adequate and well-controlled studies in pregnant women.

There is a large amount of data from observational studies on exposure to azithromycin during pregnancy (more than 7000 azithromycin exposed pregnancies). Most of these studies do not suggest an increased risk of adverse foetal effects such as major congenital malformations or cardiovascular malformations.

Epidemiological evidence related to the risk of miscarriage following azithromycin exposure in early pregnancy is inconclusive. Animal studies do not indicate reproductive toxicity (see section 5.3). Azithromycin should only be used during pregnancy if clinically needed.

Breast-feeding
Azithromycin is excreted in human milk to substantial extent. No serious adverse effects of azithromycin on the breast-fed infants were observed, while effects such as diarrhoea, mucosal fungal infection as well as hypersensitivity can occur in breast-fed newborns/infants even at sub-therapeutic doses. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
In fertility studies conducted in rat, reduced pregnancy rates were noted following administration of azithromycin. The relevance of this finding to humans is unknown.

4.7 Effects on ability to drive and use machines

[This section should read as follows:]

<Invented name> has a moderate influence on the ability to drive and use machines. Dizziness, drowsiness and convulsions have been reported in some patients taking azithromycin and some patients experienced visual and/or auditory impairment. This should be considered when assessing a patient's ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

[This section should read as follows:]

Summary of the safety profile

The most commonly reported adverse reactions during treatment include diarrhoea, headache, vomiting, abdominal pain, nausea and abnormal laboratory test values. Other important adverse reactions include anaphylactic reactions, torsade de pointes, arrhythmia including ventricular tachycardia, pseudomembranous colitis and hepatic failure (see section 4.4). Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP) have been reported in association with azithromycin treatment (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions identified through clinical trial experience and post marketing surveillance are listed below, by system organ class and frequency.

Frequencies of adverse reaction occurrence are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 5: Tabulated list of adverse reactions

System organ class	**Very common**	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations			*Candida* infection Pneumonia Fungal infection Bacterial infection Vaginal infection Pharyngitis Gastroenteritis Rhinitis Oral candidiasis		
Blood and lymphatic system disorders		Lymphocyte count decreased Eosinophil count increased Basophil count increased Monocyte count increased Neutrophil count increased	Leukopenia Neutropenia Eosinophilia Platelet count increased Haematocrit decreased		Thrombocytopenia Haemolytic anaemia

Immune system disorders			Angioedema Hypersensitivity (see section 4.4)		Anaphylactic reaction
Metabolism and nutrition disorders			Decreased appetite[#2]		
Psychiatric disorders			Nervousness Insomnia	Agitation	Anxiety Delirium Hallucination Aggression
Nervous system disorders		Headache	Dizziness[#2] Dysgeusia[#2] Paraesthesia[#2] Somnolence		Myasthenia gravis (see section 4.4) Seizure Anosmia Ageusia Hypoaesthesia[#3]Psychomotor hyperactivity Parosmia Syncope
Eye disorders			Visual impairment[#2]		
Ear and labyrinth disorders			Ear disorder Vertigo		Deafness[#2] Hypoacusis[#3] Tinnitus[#3]
Cardiac disorders			Palpitations		Torsades de pointes (see section 4.4) Arrhythmia including ventricular tachycardia (see section 4.4) Electrocardiogram QT prolonged (see section 4.4)
Vascular disorders			Hot flush		Hypotension
Respiratory, thoracic and mediastinal disorders			Dyspnoea Respiratory disorder Epistaxis		
Gastrointestinal disorders	Diarrhoea Abdominal Discomfort*	Vomiting Abdominal pain[#1] Nausea[#1]	Gastritis Constipation Dyspepsia Dysphagia Abdominal distension		Pancreatitis Pseudomembranous colitis (see section 4.4)

			Dry mouth Mouth ulceration Salivary hypersecretion Eructation Flatulence[#1]		Tongue discolouration
Hepatobiliary disorders			Hepatitis* Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubin increased Blood alkaline phosphatase increased	Hepatic function abnormal Jaundice cholestatic	Hepatic failure (see section 4.4) Hepatitis fulminant Hepatic necrosis
Skin and subcutaneous tissue disorders			Rash[#2] Pruritus[#2] Urticaria Dermatitis Dry skin Hyperhidrosis	Acute generalised exanthematous pustulosis (AGEP) Drug reaction with eosinophilia and systemic symptoms (DRESS) Photosensitivity reaction[#3]	Toxic epidermal necrolysis Stevens-Johnson syndrome[#3] Erythema multiforme
Musculoskeletal and connective tissue disorders			Osteoarthritis Myalgia Back pain Neck pain		Arthralgia[#2]
Renal and urinary disorders			Dysuria Renal pain Blood urea increased Blood creatinine increased		Acute kidney injury Tubulointerstitial nephritis
Reproductive system and breast disorders			Intermenstrual bleeding Testicular disorder		
General disorders and administration site conditions			Oedema Asthenia Malaise Fatigue[#2]		

			Face oedema Chest pain Pyrexia Pain Peripheral oedema		
Investigations		Blood bicarbonate decreased	Blood potassium abnormal Blood chloride increased Blood glucose increased Blood bicarbonate increased Blood sodium abnormal		
Injury, poisoning and procedural complications			Post procedural complication		

***** These ADRs were only seen during azithromycin administration for MAC prophylaxis and/or therapy
#1 In MAC the frequency of these ADRs was Very Common (>1/10).
#2 In MAC the frequency of these ADRs was Common (>1/100 to <1/10).
#3 In MAC the frequency of these ADRs was Uncommon (>1/1 000 to <1/100).

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

[This section should read as follows:]

Symptoms
Adverse reactions experienced with higher than recommended doses were similar to those seen at normal doses (see section 4.8). The typical symptoms of an overdose with azithromycin include gastrointestinal symptoms, i.e. vomiting, diarrhoea, abdominal pain and nausea.

Treatment
In the event of an overdose, general symptomatic treatment and support of vital functions are indicated and, if required, administration of medicinal charcoal or gastric lavage.
There are no data on the effects of dialysis on the elimination of azithromycin. However, due to the elimination mechanism of azithromycin, dialysis is unlikely to result in significant removal of the active substance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

[This section should read as follows:]

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

Mechanism of action
The mechanism of action of azithromycin is based on the inhibition of the bacterial protein synthesis by binding to the ribosomal 50 S subunit and inhibiting translocation of the peptides.

Pharmacokinetic/pharmacodynamic relation
The efficacy depends mainly on the ratio between AUC (area under the curve) and MIC (minimum inhibitory concentration) of the causative organism.

Mechanisms of resistance
Resistance against azithromycin can be based on the following mechanisms:

- Efflux: Resistance can be caused by an increase in the number of efflux pumps in the cytoplasmic membrane. Only 14- and 15-ring-membered macrolides are concerned (so called M-phenotype).
- Change of target structure: Affinity to ribosomal binding sites is lowered by methylation of the 23S rRNA causing a resistance against macrolides (M), lincosamides (L) and streptogramins of the B-group (SB) (so called MLSB-phenotype). Resistance-conferring methylases are encoded by *erm* genes. Affinity to ribosomal binding sites is also lowered by mutations in the 23S rRNA target structure or by mutations in the large subunit ribosomal proteins.
- Enzymatic inactivation of macrolides is only of minor clinical interest.

With the M-phenotype a complete cross-resistance between azithromycin, clarithromycin, erythromycin and roxithromycin is observed. The MLSB-phenotype shows an additional cross-resistance with clindamycin and streptogramin B. With the 16-ring-membered macrolide spiramycin a partial cross-resistance is exerted.

Due to low permeability of the outer membrane, most Gram-negative species are inherently resistant to macrolides.

Susceptibility testing interpretive criteria
MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for azithromycin and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

Prevalence of acquired resistance
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. Particularly in the case of severe infections or therapeutic failure, a microbiological diagnosis with identification of the pathogen and determination of its susceptibility to azithromycin should be sought.

[Only species relevant to the approved indications should be listed in the following table, e.g. Borrelia burgdorferi should only be included, if the medicinal product is indicated for early Lyme disease.]

Table 4: Prevalence of acquired resistance

Commonly susceptible species

Aerobic Gram-positive microorganisms
Mycobacterium avium complex°
Streptococcus pyogenes
Aerobic Gram-negative microorganisms
Haemophilus ducreyi
Haemophilus influenzae
Legionella pneumophila°
Moraxella catarrhalis
Anaerobic microorganisms
Peptostreptococcus spp.
Porphyromonas gingivalis
Tannerella forsythia
Treponema denticola
Other microorganisms
Aggregatibacter actinomycetemcomitans (formerly *Actinobacillus actinomycetemcomitans*)
Borrelia burgdorferi
Chlamydia trachomatis°
Chlamydophila pneumoniae°
Chlamydophila psittaci
Mycoplasma pneumoniae°
Prevotella intermedia
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Staphylococcus aureus+
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
Streptococcus agalactiae
Streptococcus pneumoniae++
Viridans streptococci
Aerobic Gram-negative microorganisms
Neisseria gonorrhoeae
Anaerobic microorganisms
Fusobacterium spp.
Prevotella spp.
Inherently resistant organisms
Aerobic Gram-negative microorganisms
Escherichia coli
Klebsiella spp.
Pseudomonas aeruginosa
Anaerobic microorganisms

Bacteroides spp.

°No updated data were available at release of tables. Primary literature, scientific standard literature and therapeutic recommendations assume susceptibility.
+At least one region shows resistance rates higher than 50% for methicillin-resistant *Staphylococcus aureus*.
++Penicillin susceptible strains of *Streptococcus pneumoniae* are more likely to be susceptible to azithromycin than are penicillin resistant strains of *Streptococcus pneumoniae*.

5.2 Pharmacokinetic properties

[This section should read as follows:]

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

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

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

Table 5: AUC_{0-24} and C_{max} of azithromycin for the 3-day and 5-day regimen at last day of dosing

Dose regimen, formulation	**AUC_{0-24} (µg•h/ml)**	**C_{max} (µg/ml)**
3-day regimen (500 mg daily), tablet	1.88 (0.96)	0.42 (0.21)
5-day regimen (500 mg D1, 250 mg D2 to D5), tablet	0.80 (0.42)	0.18 (0.10)
5-day regimen (500 mg D1, 250 mg D2 to D5, capsule	2.1 (0.6)	0.24 (0.08)

Distribution
Azithromycin is widely and rapidly distributed from plasma to the extravascular compartment, including tissues such as tonsil, lung and gynaecological tissues as well as the intracellular compartment, in particular to polymorphonuclear leukocytes, macrophages, and monocytes. Pharmacokinetic studies have shown considerably higher azithromycin concentrations in certain tissues (up to 50 times the maximum concentration observed in the plasma). This indicates an extensive binding to these tissues with a steady-state volume of distribution ranging from 23 to 31 L/kg. The redistribution phase from the intracellular to the extracellular compartment and to the plasma may result in prolonged low concentrations after treatment cessation.
Azithromycin shows low plasma protein binding, mainly to alpha 1-acid glycoprotein, and it decreases with increasing concentrations of antibiotic: 50%, 23% and 7% protein binding at concentrations of 0.05, 0.1 and 1 mg/L, respectively.

Biotransformation
Azithromycin is minimally metabolised in the liver. The primary route of biotransformation is N-demethylation of the desosamine sugar. Other pathways include O-demethylation, hydrolysis of cladinose (deconjugation of the cladinose sugar), and hydroxylation of desosamine sugar and macrolide ring.

There is no evidence of clinically relevant hepatic cytochrome CYP 3A4 induction or inhibition via the formation of a cytochrome-metabolite complex. Also, auto-induced metabolism of azithromycin by this pathway has not been detected.

Elimination
Azithromycin is mainly eliminated by (active) biliary excretion mostly as unchanged drug, but also as metabolites which are devoid of antibacterial activity. Urinary excretion represents a minor route of elimination with less than 6% of an oral dose and around 20% of the drug that reaches the systemic circulation excreted in urine. More than 50% of faecal, and 12% or urinary excretion is in the form of unchanged compound.

Following the administration of a single 500 mg azithromycin dose, a plasma clearance of 630 ml/min was estimated with a terminal half-life of approximately 68 hours. Renal clearance is generally in the range of 100-189 ml/min, substantially smaller than plasma clearance as expected due to the relatively poor contribution of the renal route to elimination.

Linearity/non-linearity
Following oral administration of an immediate release formulation, dose proportionality on AUC_{0-24} and C_{max} was shown in the range of 250 mg to 1000 mg.

Special populations

Renal Impairment
Azithromycin pharmacokinetics was investigated in 43 adults (21 to 85 years of age) following the oral administration of a single 1.0 g dose of azithromycin (4 x 250 mg capsules) to subjects with GFR >80 ml/min (n =12), subjects with GFR between 10 and 80 ml/min (n = 12) and subjects with GFR <10 ml/min (n = 19).

The pharmacokinetics of azithromycin in subjects with GFR between 10 and 80 ml/min were not affected (mean C_{max} and AUC_{0-120} increased by 5.1% and 4.2%, respectively compared to subjects with GFR >80 ml/min). The mean C_{max} and AUC_{0-120} increased 61% and 35%, respectively, in subjects with GFR <10 ml compared to subjects with GFR >80 ml/min.

No data are available for subjects undergoing dialysis, but due to the elimination mechanism of azithromycin, dialysis is unlikely to result in significant removal of the active substance.

Hepatic Impairment
Azithromycin pharmacokinetics was investigated in 22 adults following the oral administration of a single 500 mg dose of azithromycin (2 x 250 mg capsules) to subjects with normal hepatic function (n = 6), Child-Pugh A (n = 10) and Child-Pugh B (n = 6). The pharmacokinetics of azithromycin in subjects with Child-Pugh A and B were 3% and 19% lower on AUC_{0-inf} and 34% and 72% higher on C_{max}, respectively, compared to subjects with normal hepatic function.

Elderly
In elderly volunteers (> 65 years) given azithromycin 500 mg (2 x 250 mg capsules) on day 1 followed by 250 mg from days 2 to 5 in the fasted state the AUC_{0-24} on Days 1 and 5 were 3.0 and 2.7 µg•h/ml, respectively. A 29% higher AUC_{0-24}, a 8% higher C_{max} and a 37.5% higher T_{max} than in younger volunteers (<40 years) were observed at day 5. Since these differences are not considered clinically significant, no dose adjustment is required for elderly subjects with normal renal and hepatic function.

Paediatric population
The pharmacokinetics of azithromycin oral suspension have been characterised in 14 children aged 6 to15 years with pharyngitis and in 7 children aged 1 year to 5 years with otitis media. In these two studies, azithromycin oral suspension was dosed at 10 mg/kg on day 1, followed by 5 mg/kg on days 2 through 5. Following 5 days of treatment, mean AUC_{0-24} values were 3.1 µg•h/ml and 1.8 µg•h/ml, respectively. The mean C_{max} value was 0.38 µg/ml and the corresponding mean T_{max} value was 2.4 hours in children aged 6 to 15 years and 0.22 µg/ml and 1.9 hours for children 1 to 5 years of age. The mean C_{max} and AUC_{0-24} values are 1.7 times greater in children 6 to 15 years of age than in children 1 to 4 years of age.

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

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

5.3 Preclinical safety data

[This section should read as follows:]

Non-clinical data based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity did not indicate adverse reactions clearly relevant to humans not already considered in other sections of the SmPC.

However, phospholipidosis (intracellular phospholipid accumulation) has been observed in several tissues of mice, rats, and dogs given multiple doses of azithromycin. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs. The effect has been shown to be reversible after cessation of azithromycin treatment. The significance of this finding for humans is in general unknown.

In animal studies for embryotoxic effects performed up to moderately maternal toxic doses (2 to 3 times the maximum recommended adult daily dose of (500 mg based on body surface area), no teratogenic effect was observed in mice and rats. Azithromycin was shown to cross the placenta. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day (2 to 3 times the maximum recommended adult daily dose of 500 mg based on body surface area) led to mild retardation of foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardation following treatment with azithromycin doses of 200 mg/kg/day (3 times the maximum recommended adult daily dose of 500 mg based on body surface area) was observed.

PACKAGE LEAFLET

Liquid oral formulations (powder for oral suspension (in bottles) (authorised strengths: 20 mg/ml, 40 mg/ml) or (in sachets) (authorised strengths: 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 400 mg, 500 mg, 1000 mg)

1. What <invented name> is and what it is used for

[This section should read as follows:]

<Invented name> contains the active substance azithromycin. Azithromycin is an antibiotic that belongs to a group of antibiotics known as macrolides, which blocks the growth of susceptible bacteria.

<Invented name> is taken for the treatment of the following infections:

Children aged 6 month and older weighing less than 45 kg

- Infections of the tonsils (tonsillitis) or throat (pharyngitis) caused by streptococcal bacteria
- Bacterial sinus infections (sinusitis)
- Bacterial infections of the middle ear (otitis media)
- Pneumonia (community-acquired pneumonia, not contracted in a hospital)
- Bacterial infections of the skin and underlying tissues
- Early localised Lyme disease (erythema migrans, mainly caused by tick bites)
- Bacterial infections of the gums (periodontitis) or abscess in gums (periodontal abscess)

Adults and adolescents weighing at least 45 kg who have difficulty in swallowing:
In addition to the infections listed above, <Invented name> can also be taken for the treatment of the following infections:

- Infections of urethra and cervix caused by *Chlamydia trachomatis* bacteria
- Infections of urethra and cervix caused by *Neisseria gonorrhoeae* bacteria. <Invented name> should be used in combination with another antibiotic that is selected by your doctor or pharmacist.
- Chronic inflammation of the prostate caused by *Chlamydia trachomatis* bacteria
- Bacterial infections of genitals with painful sores (chancroid)
- Infections caused by *Mycobacterium avium* complex (MAC) bacteria in people with advanced HIV infection. <Invented name> should be used in combination with another antibiotic called ethambutol.
- Adults with long-term inflammation of the lungs (chronic bronchitis) or with bacterial infection of the womb, fallopian tubes and ovaries (pelvic inflammatory disease), the latter always in combination with another antibiotic(s) that is selected by your doctor.

<Invented name> is also taken for prevention of infections caused by *Mycobacterium avium* complex (MAC) bacteria in people living with HIV infection.

2. What you need to know before you take <invented name>

[This section should read as follows:]

Do not take <Invented name>

- if you are allergic to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking <Invented name> if you have or have had any of the following conditions:

- heart problems (e.g. problems with your heart rhythm or cardiac insufficiency) or low levels of potassium or magnesium in your blood: these conditions may contribute to serious cardiac side effects of azithromycin
- liver problems: your doctor may need to monitor your liver function or stop the treatment
- severe diarrhoea after administration of any other antibiotics
- localised muscle weakness (myasthenia gravis), as the symptoms of this disease may worsen during treatment

- or if you are taking any ergot derivatives such as ergotamine (used to treat migraine) as these medicines should not be taken together with <Invented name>.

Stop taking this medicine and contact your doctor immediately (see also "Serious side effects" in section 4):
- if you feel you are having an allergic reaction (e.g. difficulty in breathing, swelling of the face or throat, rash, blistering).
- if you notice any of the symptoms as described in section 4 related to serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP), which have been reported in association with azithromycin treatment.
- if you feel you have an abnormal heartbeat or palpitations, get dizzy or faint when taking <Invented name>.
- if you develop signs of liver problems (e.g. dark urine, loss of appetite or yellowing of the skin or whites of the eyes).
- if you develop severe diarrhoea during or after treatment. Do not take any medicine to treat your diarrhoea without first checking with your doctor. If your diarrhoea continues or reappears within the first weeks after treatment, please also inform your doctor.

Superinfection
Your doctor may observe you for signs of additional bacterial or fungal infections that cannot be treated with <invented name> (superinfection).

Sexually transmitted infections
Your doctor may test for and exclude a potential infection with syphilis, a sexually transmitted disease that may otherwise progress undetected and be diagnosed delayed. Furthermore, in any case of sexually transmitted bacterial infections your doctor will initiate laboratory follow-up tests to monitor the success of therapy.

Children and adolescents

[powder for oral suspension in bottles, granules for oral suspension]
Ask your doctor or pharmacist if your child is under 6 months of age, as the efficacy and safety of this medicinal porduct have not demonstrated in these children.

This medicinal product is not recommended if:
- *[if the product is indicated for treatment of pelvic inflammatory disease in adults and adolescents weighing at least 45 kg and unable to swallow solid pharmaceutical forms]* you are less than 18 years old and have been diagnosed with pelvic inflammatory disease
- *[if indicated for prevention or treatment of MAC infections]* you are less than 12 years old and you are infected or at risk of being infected with organisms that belong to the *Mycobacterium avium* complex which usually affect people living with HIV who have low defences as its efficacy and safety have not been studied in these cases.

[powder for oral suspension in sachets]

Ask your doctor or pharmacist if your child is under 6 months of age, as the efficacy and safety of this medicinal product have not been demonstrated in these children or weighs less than 16 kg as other medicinal products exist that are more appopriate to treat him or her.

This medicinal product is not recommended if:
- *[if the product is indicated for treatment of pelvic inflammatory disease in adults and adolescents weighing at least 45 kg and unable to swallow solid pharmaceutical forms]* you are less than 18 years old and have been diagnosed with pelvic inflammatory disease
- *[if indicated for prevention or treatment of MAC infections]* you are less than 12 years old and you are infected or at risk of being infected with organisms that belong to the *Mycobacterium avium* complex

which usually affect people living with HIV who have low defences as its efficacy and safety have not been studied in these cases.

Infantile hypertrophic pyloric stenosis (IHPS)
If your child is less than 6 months of age and your doctor recommended treatment with azithromycin, stop administering this medicine to him or her and contact your doctor immediately if she or he presents with projectile vomiting or becomes irritable when fed or shortly after it.

Other medicines and <Invented name>
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Taking <Invented name> at the same time as some other medicines may result in side effects. Therefore, it is particularly important that you tell your doctor if you are using any of the following medicines:
- Atorvastatin and other medicines from the statins group (to lower blood cholesterol and prevent heart disease, including heart attacks and strokes)
- Ciclosporin (to prevent rejection of organ transplants by the body)
- Colchicine (to treat gout and familial Mediterranean fever)
- Dabigatran (to prevent and treat blood clot formation (anticoagulant))
- Digoxin (to treat heart diseases)
- Warfarin or similar medicines used to thin the blood (anticoagulants)
- Medicines that may cause the heart muscle to take longer to contract and relax than usual (QT prolongation), such as the following:
  - Quinidine, procainamide, dofetilide, amiodarone and sotalol (to treat an irregular heartbeat, including a too fast or too slow heartbeat - cardiac arrhythmia)
  - Pimozide (to treat mental illness)
  - Citalopram (to treat depression)
  - Moxifloxacin and levofloxacin (antibiotics)
  - Cisapride (to treat disorders in the gastrointestinal tract)
  - Hydroxychloroquine or chloroquine (to treat autoimmune diseases including rheumatoid arthritis, or to treat or prevent malaria)

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
Your doctor will decide if you should take this medicine during pregnancy, only after making sure that the benefits outweigh the potential risks.

Breast-feeding
<Invented name> passes into breast milk. Your doctor will decide therefore whether you should stop breast-feeding or should avoid treatment with <Invented name> taking into account both the benefit of breast-feeding for your child and the benefit of therapy for you.

Driving and using machines
<Invented name> has a moderate influence on the ability to drive and use machines. <Invented name> has been reported to cause dizziness, drowsiness and seizures, as well as problems with seeing and hearing in some people. These possible side effects may have an influence on your ability to drive and use machines.

<<Invented name> contains {name the excipient(s)}>

[A warning about any excipient that could result in unwanted undesirable effects e.g. in patients with specific metabolism disorders (e.g. phenylketonuria, fructose intolerance, glucose-galactose malabsorption, sucrase/isomaltase deficiency) or allergies should be added in this section as per the QRD template. Each MAH will need to mention any relevant excipient(s) and related warning(s) for their formulation(s).]

3. How to take <invented name>

[This section should read as follows:]

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended doses and duration of treatment are as follows.

Children aged 6 month and older weighing less than 45 kg

Infection	Treatment course with azithromycin
Bacterial sinus infections (sinusitis) Pneumonia (community-acquired pneumonia, not contracted in a hospital) Bacterial infections of the skin and underlying tissues Bacterial infections of the gums (periodontitis) or abscess in gums (periodontal abscess)	There is a 3-day or a 5-day treatment course for these infections *3-day treatment course* 10 mg/kg/day for 3 days *5-day treatment course* 10 mg/kg taken on the first day of treatment and then 5 mg/kg taken once daily for the following 4 days
Bacterial infections of the middle ear (otitis media)	There is a 1-day, a 3-day or a 5-day treatment course for this infection *1-day treatment course* single dose of 30 mg/kg *3-day treatment course* 10 mg/kg/day for 3 days *5-day treatment course* 10 mg/kg taken on the first day of treatment and then 5 mg/kg taken once daily for the following 4 days
Infections of the tonsils (tonsillitis) or throat (pharyngitis) caused by streptococcal bacteria	There is a 3-day or a 5-day treatment course for these infections *3-day treatment course* 20 mg/kg/day for 3 days *5-day treatment course* 12 mg/kg/day for 5 days
Early localised Lyme disease (erythema migrans, mainly caused by tick bites)	20 mg/kg taken on the first day of treatment and then 10 mg/kg taken once daily for the following 9 days

It is important to make sure that you use the amount of <Invented name> indicated in the table below according to the body weight of the patient, the infection being treated and the specific treatment course (1-day, 3-day 5-day, 10-day) that your doctor or pharmacist has instructed you to follow.

[Powder for oral suspension in bottles, 20 mg/ml;for a dosing device with 0.5 ml steps]

Body weight (kg)	**Azithromycin maximum dose per day 20 mg/ml oral suspension in bottle after reconstitution (X ml)^**				
	5 mg/kg+	**10 mg/kg**	**12 mg/kg++**	**20 mg/kg**	**30 mg/kg**
7	2.00 ml (40 mg)	3.50 ml (70 mg)	4.50 ml (90 mg)	7.00 ml (140 mg)*	10.50 ml (210 mg)*
8	2.00 ml (40 mg)	4.00 ml (80 mg)	5.00 ml (100 mg)	8.00 ml (160 mg)*	12.00 ml (240 mg)*
9	2.50 ml (50 mg)	4.50 ml (90 mg)	5.50 ml (110 mg)*	9.00 ml (180 mg)*	13.50 ml (270 mg)*
10	2.50 ml (50 mg)	5.00 ml (100 mg)	6.00 ml (120 mg)*	10.00 ml (200 mg)*	15.0 ml (300 mg)*
11	3.00 ml (60 mg)	5.50 ml (110 mg)*	6.50 ml (130 mg)*	11.00 ml (220 mg)*	16.50 ml (330 mg)*
12	3.00 ml (60 mg)	6.00 ml (120 mg)*	7.50 ml (150 mg)*	12.00 ml (240 mg)*	18.00 ml (360 mg)*
13	3.50 ml (70 mg)	6.50 ml (130 mg)*	8.00 ml (160 mg)*	13.00 ml (260 mg)*	19.50 ml (390 mg)*
14	3.50 ml (70 mg)	7.00 ml (140 mg)*	8.50 ml (170 mg)*	14.00 ml (280 mg)*	21.00 ml (420 mg)*
15	4.00 ml (80 mg)	7.50 ml (150 mg)*	9.00 ml (180 mg)*	15.00 ml (300 mg)*	22.50 ml (450 mg)*
16-25	5.00 ml (100 mg)	10.00 ml (200 mg)*	12.50 ml (250 mg)*	20.00 ml (400 mg)*	30.00 ml (600 mg)*
26-35	7.50 ml (150 mg)*	15.00 ml (300 mg)*	17.50 ml (350 mg)*	25.00 ml (500 mg) *#	45.00 ml (900 mg)*
36- < 45	10.00 ml (200 mg)*	20.00 ml (400 mg)*	22.50 ml (450 mg)*	25.00 ml (500 mg) *#	60.00 ml (1200 mg)*

^after reconstitution, the concentration of the oral suspension is 20 mg/ml and the total volume of suspension in the bottle is X ml (Y <mg, gr>), *as appropriate*)

+ Doses have been rounded to obtain an appropriate dose to be administered in case of oral dosing syringe graduated in 0.50 ml divisions. Exact doses can be administered with an oral syringe graduated in 0.25 ml divisions.

++ Doses have been rounded to obtain an appropriate dose to be administered in case of oral dosing syringe graduated in 0.50 ml divisions. Exact doses can be administered with an oral syringe graduated in 0.20 ml divisions.

* azithromycin 40 mg/ml (200 mg/5 ml) powder for oral suspension is most appropriate to administer these patients.

not to exceed the adult daily dose of 500 mg

[Powder for oral suspension in bottles, 40 mg/ml-for a dosing device with 0.25 ml steps]

Body weight (kg)	**Azithromycin maximum dose per day 40 mg/ml oral suspension in bottle after reconstitution (X ml)^**				
	5 mg/kg+	**10 mg/kg**	**12 mg/kg++**	**20 mg/kg**	**30 mg/kg**
7	1.00 ml (40 mg) *	1.75 ml (70 mg)*	2.25 ml (90 mg)	3.50 ml (140 mg)	5.25 ml (210 mg)

8	1.00 ml (40 mg)*	2.00 ml (80 mg)*	2.50 ml (100 mg)	4.00 ml (160 mg)	6.00 ml (240 mg)
9	1.25 ml (50 mg)*	2.25 ml (90 mg)	2.75 ml (110 mg)	4.50 ml (180 mg)	6.75 ml (270 mg)
10	1.25 ml (50 mg)*	2.50 ml (100 mg)	3.00 ml (120 mg)	5.00 ml (200 mg)	7.50 ml (300 mg)
11	1.50 ml (60 mg)*	2.75 ml (110 mg)	3.25 ml (130 mg)	5.50 ml (220 mg)	8.25 ml (330 mg)
12	1.50 ml (60 mg)*	3.00 ml (120 mg)	3.75 ml (150 mg)	6.00 ml (240 mg)	9.00 ml (360 mg)
13	1.75 ml (70 mg)*	3.25 ml (130 mg)	4.00 ml (160 mg)	6.50 ml (260 mg)	9.75 ml (390 mg)
14	1.75 ml (70 mg)*	3.50 ml (140 mg)	4.25 ml (170 mg)	7.00 ml (280 mg)	10.50 ml (420 mg)
15	2.00 ml (80 mg)*	3.75 ml (150 mg)	4.50 ml (180 mg)	7.50 ml (300 mg)	11.25 ml (450 mg)
16-25	2.50 ml (100 mg)	5.00 ml (200 mg)	6.25 ml (250 mg)	10.00 ml (400 mg)	15.00 ml (600 mg)
26-35	3.75 ml (150 mg)	7.50 ml (300 mg)	8.75 ml (350 mg)	12.50 ml (500 mg)#	22.50 ml (900 mg)
36-<45	5.00 ml (200 mg)	10.00 ml (400 mg)	11.25 ml (450 mg)	12.50 ml (500 mg)#	30.00 ml (1200 mg)

^after reconstitution, the concentration of the oral suspension is 40 mg/ml and the total volume of suspension in the bottle is X ml (Y <mg, gr>), *as appropriate*)

+ Doses have been rounded to obtain an appropriate dose to be administered.

++ Doses have been rounded to obtain an appropriate dose to be administered

* azithromycin 20 mg/ml (100 mg/5 ml) powder for oral suspension is most appropriate to administer these patients.

not to exceed the adult daily dose of 500 mg

[Powder for oral suspension in bottle, 20 mg/ml]

Adult and adolescent patients weighing at least 45 kg who have difficulty in swallowing

Infection	Treatment course with azithromycin
Infections of the tonsils (tonsillitis) or throat (pharyngitis) caused by streptococcal bacteria Bacterial sinus infections (sinusitis) Bacterial infections of the middle ear (otitis media) Bacterial infections in patients with long-term inflammation of the lungs (*chronic bronchitis*)* Pneumonia (community-acquired pneumonia, not contracted in a hospital)# Bacterial infections of the skin and underlying tissues Bacterial infections of the gums (periodontitis) or abscess in gums (periodontal abscess)	There is a 3-day or a 5-day treatment course for these infections, and the amount of <Invented name> to take each day is described for these treatment courses below. *3-day treatment course* 25 ml (500 mg) taken once daily for 3 days. *5-day treatment course* 25 ml (500 mg) taken on the first day of treatment and then 12.5 ml (250 mg) taken once daily for the following 4 days

Early localised Lyme disease (erythema migrans, mainly caused by tick bites)	50 ml (1000 mg) taken on the first day of treatment and then 25 ml (500 mg) taken once daily for the following 9 days
Infections of urethra and cervix caused by *Chlamydia trachomatis* bacteria	50 ml (1000 mg) taken as a single dose
Infections of urethra and cervix caused by *Neisseria gonorrhoeae* bacteria. <Invented name> should be used in combination with another antibiotic that is selected by your doctor or pharmacist.	50 ml (1000 mg) or 100 ml* (2000 mg) taken as a single dose
Chronic inflammation of the prostate caused by *Chlamydia trachomatis* bacteria	25 ml/day (500 mg) on 3 consecutive days per week for 3 weeks
Bacterial infections of genitals with painful sores (chancroid)	50 ml (1000 mg) taken as a single dose
Infections caused by *Mycobacterium avium* complex (MAC) bacteria in people with advanced HIV infection. <Invented name> should be used in combination with another antibiotic called ethambutol.	30 ml (600 mg) once per day
Prevention of infections caused by *Mycobacterium avium* complex (MAC) bacteria in people living with HIV infection	60 ml (1200 mg) once per week
Bacterial infection of the womb, fallopian tubes and ovaries (pelvic inflammatory disease) in combination with another antibiotic(s) that is selected by your doctor or pharmacist*	Only if treatment has been started with intravenous azithromycin: 12.5 ml (250 mg) once daily to complete a 7-day course of treatment

* only for adult patients

for adult patients oral treatment may follow an initial intravenous treatment

[Powder for oral suspension in bottle, 40 mg/ml, granules for oral suspension, 40 mg/ml]

Adult and adolescent patients weighing at least 45 kg who have difficulty in swallowing

Infection	Treatment course with azithromycin
Infections of the tonsils (tonsillitis) or throat (pharyngitis) caused by streptococcal bacteria Bacterial sinus infections (sinusitis) Bacterial infections of the middle ear (otitis media) Bacterial infections in patients with long-term inflammation of the lungs (*chronic bronchitis*)* Pneumonia (community-acquired pneumonia, not contracted in a hospital)# Bacterial infections of the skin and underlying tissues Bacterial infections of the gums (periodontitis) or abscess in gums (periodontal abscess)	There is a 3-day or a 5-day treatment course for these infections, and the amount of <Invented name> to take each day is described for these treatment courses below. *3-day treatment course* 12.5 ml (500 mg) taken once daily for 3 days *5-day treatment course* 12.5 ml (500 mg) taken on the first day of treatment and then 6.25 ml (250 mg) taken once daily for the following 4 days
Early localised Lyme disease (erythema migrans, mainly caused by tick bites)	25 ml (1000 mg) taken on the first day of treatment and then 12.5 ml (500 mg) taken once daily for the following 9 days
Infections of urethra and cervix caused by *Chlamydia trachomatis* bacteria	25 ml (1000 mg) taken as a single dose
Infections of urethra and cervix caused by *Neisseria gonorrhoeae* bacteria. <Invented name> should be used in combination with another antibiotic that is selected by your doctor or pharmacist.	25 ml (1000 mg) or 50 ml* (2000 mg) taken as a single dose
Chronic inflammation of the prostate caused by *Chlamydia trachomatis* bacteria	12.5 ml/day (500 mg) on 3 consecutive days per week for 3 weeks
Bacterial infections of genitals with painful sores (chancroid)	25 ml (1000 mg) taken as a single dose
Infections caused by *Mycobacterium avium* complex (MAC) bacteria in people with advanced HIV infection. <Invented name> should be used in combination with another antibiotic called ethambutol.	15 ml (600 mg) once per day
Prevention of infections caused by *Mycobacterium avium* complex (MAC) bacteria in people living with HIV infection	30 ml (1200 mg) once per week
Bacterial infection of the womb, fallopian tubes and ovaries (*pelvic inflammatory disease*) in combination with another antibiotic(s) that is selected by your doctor or pharmacist*	Only if treatment has been started with intravenous azithromycin: 6.25 ml (250 mg) once daily to complete a 7-day course of treatment

* only for adult patients

for adult patients oral treatment may follow an initial intravenous treatment

[Powder for oral suspension in sachets]

Children aged 6 months and older and adolescents weighing between 16 kg and 45 kg

Infection	Treatment course with azithromycin
Bacterial sinus infections (sinusitis) Pneumonia (community-acquired pneumonia, not contracted in a hospital) Bacterial infections of the skin and underlying tissues Bacterial infections of the gums (periodontitis) or abscess in gums (periodontal abscess)	There is a 3-day or a 5-day treatment course for these infections *3-day treatment course* 10 mg/kg/day for 3 days *5-day treatment course* 10 mg/kg taken on the first day of treatment and then 5 mg/kg taken once daily for the following 4 days
Bacterial infections of the middle ear (otitis media)	There is a 1-day, a 3-day or a 5-day treatment course for this infection *1-day treatment course* single dose of 30 mg/kg *3-day treatment course* 10 mg/kg/day for 3 days *5-day treatment course* 10 mg/kg taken on the first day of treatment and then 5 mg/kg taken once daily for the following 4 days
Infections of the tonsils (tonsillitis) or throat (pharyngitis) caused by streptococcal bacteria	There is a 3-day or a 5-day treatment course for these infections *3-day treatment course* 20 mg/kg/day for 3 days *5-day treatment course* 12 mg/kg/day for 5 days
Early localised Lyme disease (erythema migrans, mainly caused by tick bites)	20 mg/kg taken on the first day of treatment and then 10 mg/kg taken once daily for the following 9 days

It is important to make sure that you use the amount of <Invented name> indicated in the table below according to the body weight of the patient, the infection being treated and the specific treatment course (1-day, 3-day,5-day, 10-day) that your doctor or pharmacist has instructed you to follow.

Body weight (kg)	**Azitromycin maximum dose per day Powder for oral suspension in sachet**				
	5 mg/kg	**10 mg/kg**	**12 mg/kg**	**20 mg/kg**	**30 mg/kg**
16-25	100 mg	200 mg	250 mg	400 mg	600 mg
26-35	150 mg	300 mg	350 mg	500 mg#	900 mg

36- < 45	200 mg	400 mg	450 mg	500 mg#	1200 mg

not to exceed the adult daily dose of 500 mg

If your child weighs less than 16 kg, the powder for oral suspension in bottle of this medicine is more suitable; ask your doctor or pharmacist.

Adult and adolescent patients weighing at least 45 kg who have difficulty in swallowing

The recommended doses and duration of treatment are as follows.

Infection	Treatment course with azithromycin
Infections of the tonsils (tonsillitis) or throat (pharyngitis) caused by streptococcal bacteria Bacterial sinus infections (sinusitis) Bacterial infections of the middle ear (otitis media) Bacterial infections in patients with long-term inflammation of the lungs (*chronic bronchitis*)* Pneumonia (community-acquired pneumonia, not contracted in a hospital)# Bacterial infections of the skin and underlying tissues Bacterial infections of the gums (periodontitis) or abscess in gums (periodontal abscess)	There is a 3-day or a 5-day treatment course for these infections, and the amount of <Invented name> to take each day is described for these treatment courses below. *3-day treatment course* 500 mg taken once daily for 3 days *5-day treatment course* 500 mg taken on the first day of treatment and then 250 mg taken once daily for the following 4 days
Early localised Lyme disease (erythema migrans, mainly caused by tick bites)	1000 mg taken on the first day of treatment and then 500 mg taken once daily for the following 9 days.
Infections of urethra and cervix caused by *Chlamydia trachomatis* bacteria	1000 mg taken as a single dose
Infections of urethra and cervix caused by *Neisseria gonorrhoeae* bacteria. <Invented name> should be used in combination with another antibiotic that is selected by your doctor or pharmacist.	1000 mg or 2000 mg* taken as a single dose
Chronic inflammation of the prostate caused by *Chlamydia trachomatis* bacteria	500 mg/day on 3 consecutive days per week for 3 weeks
Bacterial infections of genitals with painful sores (chancroid)	1000 mg taken as a single dose
Infections caused by *Mycobacterium avium* complex (MAC) bacteria in people with advanced HIV infection. <Invented name> should be used in combination with another antibiotic called ethambutol.	600 mg once per day

Prevention of infections caused by *Mycobacterium avium* complex (MAC) bacteria in people living with HIV infection	1200 mg once per week
Bacterial infection of the womb, fallopian tubes and ovaries (pelvic inflammatory disease) in combination with another antibiotic(s) that is selected by your doctor or pharmacist*	Only if treatment has been started with intravenous azithromycin: 250 mg once daily to complete a 7-day course of treatment

* only for adult patients

for adult patients oral treatment may follow an initial intravenous treatment

Use in children and adolescents

[All liquid formulations]

The safety and efficacy of azithromycin have not been established in children under 6 months of age for any of the indications listed in section 1.

Method of administration

For oral use after reconstitution.

[Powder for oral suspension 20 mg/ml, 40 mg/ml]

<Invented name> should be taken by mouth as a single daily dose. The oral suspension may be taken with or without food. Taking this medicine just before a meal may help make it easier on your stomach.

[Add further details in accordance with local practice with regards to instructions for reconstitution and how to handle dosing devices by healthcare professions and/or patients, if applicable. Pictures should be proposed to further clarify these instructions]

If the bottle of <Invented name> you received from your doctor or pharmacist contains only powder and no liquid then you need to add a specific volume of water to the bottle before it is ready for use. If the powder was already dissolved for you by your doctor or pharmacist then you can proceed directly to the "Instructions for taking each daily dose of <Invented name> oral suspension" section below.

If you take more <Invented name> than you should

If you take more <Invented name> than you should then you may feel unwell. Typical signs of an overdose are vomiting, diarrhoea, abdominal pain and nausea.Tell your doctor or contact your nearest hospital emergency department immediately.

If you forget to take <Invented name>

If you forget to take <Invented name> take it as soon as you can, as long as this is at least 12 hours before the next dose is due. If it is less than 12 hours left to your next dose, skip the missed dose and take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking <Invented name>

If you stop taking <Invented name> too soon, the infection may return. Take <Invented name> for the full time of treatment, even when you begin to feel better.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

[This section should read as follows:]

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Stop using <Invented name> and seek medical attention immediately if you notice any of the following symptoms:

- sudden wheeziness, difficulty in breathing, swelling of eyelids, face or lips, rash or itching especially affecting the whole body (*anaphylactic reaction*, frequency not known)
- rapid or irregular heartbeat (*cardiac arrhythmia* or *torsades de pointes tachycardia*, frequency not known)
- dark urine, loss of appetite or yellowing of the skin or whites of the eyes, which are signs of liver disorders (*hepatic failure* or *hepatic necrosis* (frequency not known), *hepatitis** (uncommon: may affect up to 1 in 100 people)).
- severe diarrhoea with abdominal cramps, bloody stools and/or fever may mean that you have an infection of the large intestine (*antibiotic-associated colitis*, frequency not known). Do not take medicines against diarrhoea that inhibit the bowel movements (*antiperistaltics*).
- reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (*Stevens-Johnson syndrome*[#] or *toxic epidermal necrolysis*, frequency not known).
- widespread rash, high body temperature and enlarged lymph nodes (*DRESS syndrome* or *drug hypersensitivity syndrome*, rare (may affect up to 1 in 1,000 people)).
- a red, scaly widespread rash with bumps under the skin and blisters accompanied by fever. The symptoms usually appear at the initiation of treatment (*acute generalised exanthematous pustulosis*, rare (may effect up to 1 in 1,000 people)).

Other side effects

Very common (may affect more than 1 in 10 people)

- diarrhoea
- abdominal discomfort*

Common (may affect up to 1 in 10 people)

- headache
- being sick (*vomiting*), stomach pain[#], feeling sick (*nausea*)[#]
-
- changes in blood test results (*lymphocyte count decreased, eosinophil count increased, basophil count increased, monocyte count increased, neutrophil count increased, blood bicarbonate decreased*)

Uncommon (may affect up to 1 in 100 people)

- thrush (*candidiasis*) - a fungal infection of the mouth and vagina, other fungal infections
- pneumonia, bacterial infection of the throat, inflammation of the gastrointestinal tract, respiratory disorder, inflammation of the mucous membrane inside the nose, vaginal infection
- changes in the number of white blood cells (*leukopenia, neutropenia, eosinophilia)*
- platelet count increased
- reduction in the proportion of all blood cells in the total blood volume (*hematocrit decreased*)
- allergic reactions, swelling of the hands, feet and face (*angiooedema*)
- lack of appetite[#]
- nervousness, difficulty sleeping (*insomnia*)
- feeling dizzy[#], feeling drowsy (*somnolence*), change in your sense of taste (*dysgeusia*)#, sensation of pins and needles or numbness (*paraesthesia*)
- impaired vision[#]
- ear disorder
- spinning sensation (*vertigo*)

- feeling your heartbeat (*palpitations*)
- hot flush
- sudden wheeziness, bleeding from the nose
- constipation, wind#, impaired digestion (*dyspepsia*), inflammation of the lining of the stomach (*gastritis*), difficulty in swallowing (*dysphagia*), swollen belly, dry mouth, belching (*eructation*), mouth ulceration, increased salivation
- rash#, itching#, hives (*urticaria*)#, dermatitis, dry skin, abnormally increased sweating (*hyperhidrosis*)
- swelling and pain in the joints (*osteoarthritis*), muscle pain, back pain, neck pain
- painful urination (*dysuria*), kidney pain
- menstrual bleeding at irregular intervals (*metrorrhagia*), testicular disorder
- swelling due to fluid retention, especially of the face, ankles and feet (*oedema, face oedema, peripheral oedema*)
- weakness, tiredness#, general feeling of being unwell, fever
- chest pain, pain
- abnormal laboratory test results (e.g. blood or liver tests)
- post procedural complication

Rare (may affect up to 1 in 1,000 people)
- feeling irritated
- liver problems, yellowing of the skin or eyes
- increased sensitivity to sunlight#

Not known (frequency cannot be estimated from the available data)
- reduced number of red blood cells due to increased cell breakdown which can cause tiredness and pale skin (*haemolytic anaemia*)
- reduction in number of blood platelets which can lead to bleeding and bruising (*thrombocytopenia*)
- feeling angry, aggressive, feeling of fear and concern (*anxiety*), acute confusional state (*delirium*),
- hallucination
- fainting (*syncope*)
- fits (*seizures*)
- reduced sensation to touch, pain and temperature (*hypoaesthesia*)#
- feeling hyperactive
- change in your sense of smell (*anosmia, parosmia*)
- total loss of your sense of taste (*ageusia*)
- muscle weakness (*myasthenia gravis*)
- abnormal electrocardiogramm (ECG) heart tracing (*QT prolongation*)
- deafness#, reduced hearing# or ringing in your ears (*tinnitus)*#
- low blood pressure
- inflammation of the pancreas causing severe pain in the belly and back (*pancreatitis*)
- change intongue colour
- joint pain (*arthralgia*)#
- kidney inflammation (*interstitial nephritis*) and kidney failure

[information on adverse reactions related to treatment and/or prophylaxis of MAC infections should only be included if the product is indicated for these treatments]

* These side effects were only seen during azithromycin administration for the prophylaxis and/or therapy of *Mycobacterium avium* complex infections in people living with HIV with insufficient recovery of the immune system.
# These side effects were more common during azithromycin administration for the prophylaxis and/or therapy of *Mycobacterium avium* complex infections in people living with HIV with insufficient recovery of the immune system.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.
You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

SUMMARY OF PRODUCT CHARACTERISTICS

Formulations for intravenous use (500 mg powder for concentrate for solution for infusion)

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

[This section should read as follows:]

<Invented name> is indicated for the treatment of the following infections in adults (see sections 4.4 and 5.1):

- Community-acquired pneumonia (CAP)

- Pelvic inflammatory disease (PID), always in combination with other appropriate antibacterial agent(s) (e.g. metronidazole).

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

4.2 Posology and method of administration

[This section should read as follows:]

Posology

Azithromycin should be administered as a single daily dose. Dosing recommendations for adult patients are shown in Table 1.

Table 1: Dosing recommendations for intravenous azithromycin

Indication	Azithromycin dosing regimen
Community-acquired pneumonia	500 mg once daily for at least 2 days, followed by oral dose of 500 mg daily to complete a 7- to 10-day total course of treatment.
Pelvic inflammatory disease, in combination with other appropriate antibacterial agent(s) (e.g metronidazole)	500 mg once daily for 1 to 2 days, followed by oral dose of 250 mg once daily to complete a 7-day course of treatment.
Consideration should be given to the treatment regimens, doses and duration of treatment as recommended in updated treatment guidelines for each indication. The timing of the switch to oral therapy should be determined at the discretion of the physician and in accordance with clinical response.	

Special populations

Renal impairment

No dose adjustment is required in patients with GFR ≥10 ml/min. In patients with GFR <10 ml/min azithromycin should be administered with caution (see section 5.2).

Hepatic impairment

No dose adjustment is required in patients with mild (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B) (see section 5.2). No data are available in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, azithromycin should be administered with caution in these patients (see section 4.4).

Elderly
No dose adjustment is required in elderly patients (see section 5.2). Since the elderly are more likely to experience proarrhythmic conditions, particular caution is recommended due to the risk of developing cardiac arrhythmia and torsade de pointes (see section 4.4).

Paediatric population
The safety and efficacy of <Invented name> for the intravenous treatment of community acquired pneumonia in the paediatric population have not been established.

There is no relevant use of <Invented name> for the treatment of pelvic inflammatory disease in children under 12 years of age while the safety and efficacy in adolescent girls have not been established.

Method of administration

For intravenous use after reconstitution and dilution.

The recommended route of administration is by intravenous infusion only. Do not administer as an intravenous bolus or an intramuscular injection. The solution concentration and rate of infusion should be either 1 mg/ml over 3 hours or 2 mg/ml over 1 hour. A dose of 500 mg azithromycin should be infused for a minimum duration of 1 hour.

For instructions on reconstitution and dilution of this medicinal product before administration, see section 6.6.

4.3 Contraindications

[This section should read as follows:]

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 precaution for use

[This section should read as follows:]

Potential for resistance
Azithromycin could favour the development of resistance due to the associated long-lasting and decreasing levels in plasma and tissues after the end of treatment (see section 5.2). Treatment with azithromycin should only be initiated after a careful assessment of the benefit and the risks, considering the local prevalence of resistance, and when preferred treatment regimens are not indicated.

Severe skin and hypersensitivity reactions
Rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), which can be life- threatening or fatal, have been reported in association with azithromycin treatment (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment. If an allergic reaction occurs, azithromycin should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

QT interval prolongation
Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides including azithromycin (see section 4.8). Therefore, as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients:
• With congenital or documented QT prolongation
• Currently receiving treatment with other active substances known to prolong QT interval (see section 4.5)
• With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
• With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency
• Elderly patients: Elderly patients may be more susceptible to drug-associated effects on the QT interval

Hepatotoxicity
Since liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin. Hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have also been reported with azithromycin, some of which have resulted in death (see section 4.8). Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products. Patients should be advised to stop azithromycin administration and to contact their physician if signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy develop. In such cases liver function tests/investigations should be performed immediately.

Clostridioides difficile associated diarrhoea (CDAD), pseudomembranous colitis
CDAD and pseudomembranous colitis have been reported with azithromycin, and may range in severity from mild diarrhoea to fatal colitis (see section 4.8). CDAD and pseudomembranous colitis must be considered in patients who present with diarrhoea during or subsequent to the administration of azithromycin. Discontinuation of therapy with azithromycin and the use of supportive measures together with the administration of specific treatment for *C. difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Sexually transmitted infections

Neisseria gonorrhoeae is very likely to be resistant to macrolides, including the azalide azithromycin (see section 5.1). Therefore, azithromycin is not recommended for the treatment of uncomplicated gonorrhoea and pelvic inflammatory disease unless laboratory results have confirmed susceptibility of the organism to azithromycin. If left untreated or treated sub-optimally, this condition may lead to late onset complications such as infertility and ectopic pregnancy.

Furthermore, a concomitant infection caused by *Treponema pallidum* should be excluded as symptoms of incubating syphilis could be masked delaying diagnosis.

For all patients with sexually transmitted urogenital infections, appropriate antibacterial therapy and microbiological follow-up tests should be initiated.

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

Non-susceptible organisms
The use of azithromycin may result in the overgrowth of non-susceptible organisms. If superinfection occurs, interruption of treatment or other appropriate measures may be required.

Ergot derivatives
In patients receiving ergot derivatives, ergotism has been precipitated by co-administration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergot and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives may not be co-administered.

<Excipients with known effect>
[A warning about any excipient that could result in unwanted undesirable effects e.g. in patients with specific metabolism disorders (e.g. phenylketonuria, fructose intolerance, glucose-galactose malabsorption, sucrase/isomaltase deficiency) or allergies should be added in this section as per the QRD template. Each MAH will need to mention any relevant excipient(s) and related warning(s) for their formulation(s).]

<For the full list of excipients, see section 6.1.>

4.5 Interaction with other medicinal products and other forms of interaction

[This section should read as follows:]

Although azithromycin is a weak CYP450 inhibitor and does not interact significantly with CYP450 substrates, CYP3A4 inhibition cannot be completely ruled out. Therefore, caution is recommended in case of co-administration with CYP3A4 substrates with narrow therapeutic index.
Azithromycin is an inhibitor of the transporter P-glycoprotein (P-gp). Co-administration of azithromycin with P-gp substrates, such as digoxin and colchicine, may increase their exposure. For narrow therapeutic index drugs, caution and clinical and/or therapeutic drug monitoring and dose adjustment as appropriate are advised. The relatively long half-life of azithromycin should be taken into account in this context (see section 5.2).

Medicinal products that are known to prolong the QT interval
Azithromycin should be used with caution in patients receiving medicinal products known to prolong the QT interval (see section 4.4), such as antiarrhythmics of Classes IA (e.g.quinidine and procainamide) and III (e.g. dofetilide, amiodarone and sotalol), antipsychotic agents (e.g. pimozide), antidepressants (e.g. citalopram), fluoroquinolones (e.g. moxifloxacin and levofloxacin), cisapride, chloroquine and hydroxychloroquine.

Drug interaction information for azithromycin with potential concomitant medicinal products is summarised in the table and text below. The drug interactions described are based on clinical drug-drug interaction studies conducted with azithromycin or, where indicated, are potential drug interactions that may occur with azithromycin.

Table 2 Clinically relevant drug interactions between azithromycin and other medicinal products

Medicinal product (therapeutic area)	**Interaction Effect on exposure**	**Mechanism**	**Recommendation concerning co-administration**
Atorvastatin (HMG CoA reductase inhibitor) Azithromycin 500 mg orally once daily for 3 days. Atorvastatin 10 mg orally once daily.	Azithromycin: ND Atorvastatin: ↔ AUC ↔ C_{max}	Atorvastatin is a CYP3A4 and P-gp substrate.	Caution should be exercised since post-marketing cases of rhabdomyolysis in patients receiving azithromycin concomitantly with statins have been reported.

Ciclosporin (immunosuppressant) Azithromycin 500 mg orally once daily for 3 days. Ciclosporin 10 mg/kg orally single dose.	Azithromycin: ND Ciclosporin: ↔ AUC ↑C_{max} 24 %	Ciclosporin is a CYP3A4 and P-gp substrate with narrow therapeutic index and/or competition for biliary excretion.	Clinical monitoring and therapeutic drug monitoring as appropriate should be performed during and after treatment with azithromycin. Ciclosporin dose should be adjusted if required.
Colchicine (gout)	Azithromycin: ND Colchicine*:* ↑ 57% AUC_{0-t} ↑ 22% C_{max}	Colchicine is a P-gp substrate with narrow therapeutic index.	Clinical monitoring is needed during and after treatment with azithromycin.
Dabigatran (oral anticoagulant)	ND *Expected:* ↑ Dabigatran	Dabigatran is a P-gp substrate with narrow therapeutic index.	Caution should be exercised since post-marketing data suggest an increased risk for haemorrhages in patients receiving azithromycin concomitantly with dabigatran.
Digoxin (cardiac glycosides)	ND *Expected:* ↑ Digoxin	Digoxin is a P-gp substrate with narrow therapeutic index.	Clinical monitoring, and possibly digoxin level monitoring, is needed during and after treatment with azithromycin.
Warfarin (oral anticoagulant) Azithromycin 500 mg orally once daily for 1 day and then 250 mg orally once daily for 4 days. Warfarin 15 mg orally single dose.	Azithromycin: ND Warfarin: ND No change in prothrombin time in clinical drug interaction study but post-marketing reports of potentiated anticoagulation of coumarin-type oral anticoagulants upon co-administration with azithromycin.	Not known.	A higher frequency of prothrombin time monitoring should be considered during and after treatment with azithromycin.
Note: statistically significant changes by more than 10% are indicated as "↑" or "↓", no change as "↔", not determined as "ND".			

No clinically relevant change in the exposure of azithromycin or the co-administered medicinal products was observed in clinical studies evaluating potential drug-drug interactions of azithromycin with carbamazepine, cetirizine, efavirenz, fluconazole, methylprednisolone, midazolam, rifabutin, sildenafil, theophylline, triazolam, trimethoprim/sulfamethoxazole and zidovudine.

4.6 Fertility, pregnancy and lactation

[This section should read as follows:]

Pregnancy
Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of teratogenic effects was found. There are, however, no adequate and well-controlled studies in pregnant women.

There is a large amount of data from observational studies on exposure to azithromycin during pregnancy (more than 7000 azithromycin exposed pregnancies). Most of these studies do not suggest an increased risk of adverse foetal effects such as major congenital malformations or cardiovascular malformations.

Epidemiological evidence related to the risk of miscarriage following azithromycin exposure in early pregnancy is inconclusive. Animal studies do not indicate reproductive toxicity (see section 5.3). Azithromycin should only be used during pregnancy if clinically needed.

Breast-feeding
Azithromycin is excreted in human milk to substantial extent. No serious adverse effects of azithromycin on the breast-fed infants were observed, while effects such as diarrhoea, mucosal fungal infection as well as hypersensitivity can occur in breast-fed newborns/infants even at sub-therapeutic doses. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
In fertility studies conducted in rat, reduced pregnancy rates were noted following administration of azithromycin. The relevance of this finding to humans is unknown.

4.7 Effects on ability to drive and use machines

[This section should read as follows:]

<Invented name> has a moderate influence on the ability to drive and use machines. Dizziness, drowsiness and convulsions have been reported in some patients taking azithromycin and some patients experienced visual and/or auditory impairment. This should be considered when assessing a patient's ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

[This section should read as follows:]

Summary of the safety profile
The most commonly reported adverse reactions during treatment include diarrhoea, headache, vomiting, abdominal pain, nausea and abnormal laboratory test values. Other important adverse reactions include anaphylactic reactions, torsade de pointes, arrhythmia including ventricular tachycardia, pseudomembranous colitis and hepatic failure (see section 4.4). Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP) have been reported in association with azithromycin treatment (see section 4.4).

Tabulated list of adverse reactions
Adverse reactions identified through clinical trial experience and post marketing surveillance are listed below, by system organ class and frequency.

Frequencies of adverse reaction occurrence are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3: Tabulated list of adverse reactions

System organ class	Very common	Common	Uncommon	Rare	Not known
Infections and infestations			Candida infection Pneumonia Fungal infection Bacterial infection Vaginal infection Pharyngitis Gastroenteritis Rhinitis Oral candidiasis		
Blood and lymphatic system disorders		Lymphocyte count decreased Eosinophil count increased Basophil count increased Monocyte count increased Neutrophil count increased	Leukopenia Neutropenia Eosinophilia Platelet count increased Haematocrit decreased		Thrombocytopenia Haemolytic anaemia
Immune system disorders			Angioedema Hypersensitivity (see section 4.4)		Anaphylactic reaction
Metabolism and nutrition disorders			Decreased appetite		
Psychiatric disorders			Nervousness Insomnia	Agitation	Anxiety Delirium Hallucination Aggression
Nervous system disorders		Headache	Dizziness Dysgeusia Paraesthesia Somnolence		Myasthenia gravis (see section 4.4) Seizure Anosmia Ageusia

					Hypoaesthesia Psychomotor hyperactivity Parosmia Syncope
Eye disorders			Visual impairment		
Ear and labyrinth disorders			Ear disorder Vertigo		Deafness Hypoacusis Tinnitus
Cardiac disorders			Palpitations		Torsades de pointes (see section 4.4) Arrhythmia including ventricular tachycardia (see section 4.4) Electrocardiogram QT prolonged (see section 4.4)
Vascular disorders			Hot flush		Hypotension
Respiratory, thoracic and mediastinal disorders			Dyspnoea Respiratory disorder Epistaxis		
Gastrointestinal disorders	Diarrhoea Abdominal discomfort	Vomiting Abdominal pain Nausea	Gastritis Constipation Dyspepsia Dysphagia Abdominal distension Dry mouth Mouth ulceration Salivary hypersecretion Eructation Flatulence		Pancreatitis Pseudomembranous colitis (see section 4.4) Tongue discolouration
Hepatobiliary disorders			Hepatitis Aspartate aminotransferase increased Alanine aminotransferase increased	Hepatic function abnormal Jaundice cholestatic	Hepatic failure (see section 4.4) Hepatitis fulminant Hepatic necrosis

			Blood bilirubin increased Blood alkaline phosphatase increased		
Skin and subcutaneous tissue disorders			Rash Pruritus Urticaria Dermatitis Dry skin Hyperhidrosis	Acute generalised exanthematous pustulosis (AGEP) Drug reaction with eosinophilia and systemic symptoms (DRESS) Photosensitivity reaction	Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme
Musculoskeletal and connective tissue disorders			Osteoarthritis Myalgia Back pain Neck pain		Arthralgia
Renal and urinary disorders			Dysuria Renal pain Blood urea increased Blood creatinine increased		Acute kidney injury Tubulointerstitial nephritis
Reproductive system and breast disorders			Intermenstrual bleeding Testicular disorder		
General disorders and administration site conditions		Injection site pain Injection site inflammation	Oedema Asthenia Malaise Fatigue Face oedema Chest pain Pyrexia Pain Peripheral oedema		
Investigations		Blood bicarbonate decreased	Blood potassium abnormal Blood chloride increased Blood glucose increased		

			Blood bicarbonate increased Blood sodium abnormal		
Injury, poisoning and procedural complications			Post procedural complication		

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

[This section should read as follows:]

Symptoms
Adverse reactions experienced with higher than recommended doses were similar to those seen at normal doses (see section 4.8). The typical symptoms of an overdose with azithromycin include gastrointestinal symptoms, i.e. vomiting, diarrhoea, abdominal pain and nausea.

Treatment
In the event of an overdose, general symptomatic treatment and support of vital functions are indicated. There are no data on the effects of dialysis on the elimination of azithromycin. However, due to the elimination mechanism of azithromycin, dialysis is unlikely to result in significant removal of the active substance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

[This section should read as follows:]

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

Mechanism of action
The mechanism of action of azithromycin is based on the inhibition of the bacterial protein synthesis by binding to the ribosomal 50 S subunit and inhibiting translocation of the peptides.

Pharmacokinetic/pharmacodynamic relation
The efficacy depends mainly on the ratio between AUC (area under the curve) and MIC (minimum inhibitory concentration) of the causative organism.

Mechanisms of resistance
Resistance against azithromycin can be based on the following mechanisms:

- Efflux: Resistance can be caused by an increase in the number of efflux pumps in the cytoplasmic membrane. Only 14- and 15-ring-membered macrolides are concerned (so called M-phenotype).
- Change of target structure: Affinity to ribosomal binding sites is lowered by methylation of the 23S rRNA causing a resistance against macrolides (M), lincosamides (L) and streptogramins of the B-group (SB) (so called MLSB-phenotype). Resistance-conferring methylases are encoded by *erm* genes. Affinity to ribosomal binding sites is also lowered by mutations in the 23S rRNA target structure or by mutations in the large subunit ribosomal proteins.
- Enzymatic inactivation of macrolides is only of minor clinical interest.

With the M-phenotype a complete cross-resistance between azithromycin, clarithromycin, erythromycin and roxithromycin is observed. The MLSB-phenotype shows an additional cross- resistance with clindamycin and streptogramin B. With the 16-ring-membered macrolide spiramycin a partial cross-resistance is exerted.

Due to low permeability of the outer membrane, most Gram-negative species are inherently resistant to macrolides.

Susceptibility testing interpretive criteria
MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for azithromycin and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

Prevalence of acquired resistance
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. Particularly in the case of severe infections or therapeutic failure, a microbiological diagnosis with identification of the pathogen and determination of its susceptibility to azithromycin should be sought.

Table 4: Prevalence of acquired resistance

Commonly susceptible species
Aerobic Gram-negative microorganisms
Haemophilus influenzae
Legionella pneumophila°
Moraxella catarrhalis
Other microorganisms
Chlamydia trachomatis°
Chlamydophila pneumoniae°
Chlamydophila psittaci
Mycoplasma pneumoniae°
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Streptococcus pneumoniae+
Aerobic Gram-negative microorganisms
Neisseria gonorrhoeae
Inherently resistant organisms
Aerobic Gram-negative microorganisms
Escherichia coli
Klebsiella spp.
Pseudomonas aeruginosa
Anaerobic microorganisms
Bacteroides spp.

°No updated data were available at release of tables. Primary literature, scientific standard literature and therapeutic recommendations assume susceptibility.
+Penicillin susceptible strains of *Streptococcus pneumoniae* are more likely to be susceptible to azithromycin than are penicillin resistant strains of *Streptococcus pneumoniae*.

5.2 Pharmacokinetic properties

[This section should read as follows:]

In patients hospitalised with community-acquired pneumonia receiving single daily one-hour intravenous infusions for 2 to 5 days of 500 mg azithromycin at a concentration of 2 mg/ml, the mean C_{max} ± S.D. achieved was 3.63 ± 1.60 µg/ml, the mean C_{trough} (C_{24}) after the start of the final infusion dose was 0.2 µg/ml and the mean AUC_{0-24} was 9.6 ± 4.8 µg.h/ml.

The mean C_{max}, C_{trough} (C_{24}) and AUC_{0-24} values were 1.14 ± 0.14 µg/ml, 0.18 ± 0.02 µg/ml, and 8.03 ±0.86 µg·hr/ml, respectively, in normal volunteers receiving a 3-hour intravenous infusion of 500 mg azithromycin at a concentration of 1 mg/ml.
Comparison of the plasma pharmacokinetic parameters following the first and fifth daily doses of 500 mg intravenous azithromycin in healthy volunteers showed almost no change in C_{max}, but there was a 40-61% increase in AUC_{0-24} reflecting a 2.2- to 3-fold increase in C_{trough} (C_{24}) levels.

Distribution
Azithromycin is widely and rapidly distributed from plasma to the extravascular compartment, including tissues such as tonsil, lung and gynaecological tissues as well as the intracellular compartment, in particular to polymorphonuclear leukocytes, macrophages, and monocytes. Pharmacokinetic studies have shown considerably higher azithromycin concentrations certain tissues (up to 50 times the maximum concentration observed in the plasma). This indicates an extensive binding to these tissues with a steady-state volume of distribution ranging from 23 to 31 L/kg. The redistribution phase from the intracellular to the extracellular compartment and to the plasma may result in prolonged low concentrations after treatment cessation.
Azithromycin shows low plasma protein binding, mainly to alpha 1-acid glycoprotein, and it decreases with increasing concentrations of antibiotic: 50%, 23% and 7% protein binding at concentrations of 0.05, 0.1 and 1 mg/L, respectively.

Biotransformation
Azithromycin is minimally metabolised in the liver. The primary route of biotransformation is N-demethylation of the desosamine sugar. Other pathways include O-demethylation, hydrolysis of cladinose (deconjugation of the cladinose sugar), and hydroxylation of desosamine sugar and macrolide ring.

There is no evidence of clinically relevant hepatic cytochrome CYP 3A4 induction or inhibition via the formation of a cytochrome-metabolite complex. Also, auto-induced metabolism of azithromycin by this pathway has not been detected.

Elimination
Azithromycin is mainly eliminated by (active) biliary excretion mostly as unchanged drug, but also as metabolites which are devoid of antibacterial activity. Urinary excretion represents a minor route of elimination with less than 6% of an oral dose and around 20% of the drug that reaches the systemic circulation excreted in urine. More than 50% of faecal, and 12% or urinary excretion is in the form of unchanged compound.

Following the administration of a single 500 mg azithromycin dose, a plasma clearance of 630 ml/min was estimated with a terminal half-life of approximately 68 hours. Renal clearance is generally in the range of 100-189 ml/min, substantially smaller than plasma clearance as expected due to the relatively poor contribution of the renal route to elimination.

Linearity/non-linearity
Following oral administration of an immediate release formulation, dose proportionality on AUC_{0-24} and C_{max} was shown in the range of 250 mg to 1000 mg.

Special populations

Renal Impairment
Azithromycin pharmacokinetics was investigated in 43 adults (21 to 85 years of age) following the oral administration of a single 1.0 g dose of azithromycin (4 x 250 mg capsules) to subjects with GFR >80 ml/min (n =12), subjects with GFR between 10 and 80 ml/min (n = 12) and subjects with GFR <10 ml/min (n = 19).

The pharmacokinetics of azithromycin in subjects with GFR between 10 and 80 ml/min were not affected (mean C_{max} and AUC_{0-120} increased by 5.1% and 4.2%, respectively compared to subjects with GFR >80 ml/min). The mean C_{max} and AUC_{0-120} increased 61% and 35%, respectively, in subjects with GFR <10 ml compared to subjects with GFR >80 ml/min.

No data are available for subjects undergoing dialysis, but due to the elimination mechanism of azithromycin, dialysis is unlikely to result in significant removal of the active substance.

Hepatic Impairment
Azithromycin pharmacokinetics was investigated in 22 adults following the oral administration of a single 500 mg dose of azithromycin (2 x 250 mg capsules) to subjects with normal hepatic function (n = 6), Child-Pugh A (n = 10) and Child-Pugh B (n = 6). The pharmacokinetics of azithromycin in subjects with Child-Pugh A and B were 3% and 19% lower on AUC_{0-inf} and 34% and 72% higher on C_{max}, respectively, compared to subjects with normal hepatic function.

Elderly
In elderly volunteers (> 65 years) given azithromycin 500 mg (2 x 250 mg capsules) on day 1 followed by 250 mg from days 2 to 5 in the fasted state the AUC_{0-24} on Days 1 and 5 were 3.0 and 2.7 μg•h/ml, respectively. A 29% higher AUC_{0-24}, a 8% higher C_{max} and a 37.5% higher T_{max} than in younger volunteers (<40 years) were observed at day 5. Since these differences are not considered clinically significant, no dose adjustment is required for elderly subjects with normal renal and hepatic function.

5.3 Preclinical safety data

[This section should read as follows:]

Non-clinical data based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity did not indicate adverse reactions clearly relevant to humans not already considered in other sections of the SmPC.

However, phospholipidosis (intracellular phospholipid accumulation) has been observed in several tissues of mice, rats, and dogs given multiple doses of azithromycin. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs. The effect has been shown to be reversible after cessation of azithromycin treatment. The significance of this finding for humans is in general unknown.

In animal studies for embryotoxic effects performed up to moderately maternal toxic doses (2 to 3 times the maximum recommended adult daily dose of (500 mg based on body surface area), no teratogenic effect was observed in mice and rats. Azithromycin was shown to cross the placenta. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day (2 to 3 times the maximum recommended adult daily dose of 500 mg based on body surface area) led to mild retardation of foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardation following treatment with azithromycin doses of 200 mg/kg/day (3 times the maximum recommended adult daily dose of 500 mg based on body surface area) was observed.

PACKAGE LEAFLET

Formulations for intravenous use (500 mg powder for concentrate for solution for infusion)

1. What <invented name> is and what it is used for

[This section should read as follows:]

<Invented name> contains the active substance azithromycin. Azithromycin is an antibiotic that belongs to a group of antibiotics known as macrolides, which block the growth of susceptible bacteria.

<Invented name> is used for the treatment of the following infections in adults:
- Pneumonia (community-acquired pneumonia, not contracted in a hospital)
- Bacterial infection of the womb, fallopian tubes and ovaries (pelvic inflammatory disease) always in combination with another antibiotic(s) that is selected by your doctor or pharmacist.

2. What you need to know before <invented name> is given

[This section should read as follows:]

Do not use <Invented name>
- if you are allergic to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or, pharmacist before using <Invented name> if you have or have had any of the following conditions:
- heart problems (e.g. problems with your heart rhythm or cardiac insufficiency) or low levels of potassium or magnesium in your blood: these conditions may contribute to serious cardiac side effects of azithromycin
- liver problems: your doctor may need to monitor your liver function or stop the treatment
- severe diarrhoea after administration of any other antibiotics
- localised muscle weakness (myasthenia gravis), as the symptoms of this disease may worsen during treatment
- or if you are taking any ergot derivatives such as ergotamine (used to treat migraine) as these medicines should not be used together with <Invented name>.

Stop using this medicine and contact your doctor immediately (see also "Serious side effects" in section 4):
- if you feel you are having an allergic reaction (e.g. difficulty in breathing, swelling of the face or throat, rash, blistering).
- if you notice any of the symptoms as described in section 4 related to serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP), which have been reported in association with azithromycin treatment.
- if you feel you have an abnormal heartbeat or palpitations, get dizzy or faint when receiving <Invented name>.
- if you develop signs of liver problems (e.g. dark urine, loss of appetite or yellowing of the skin or whites of the eyes).
- if you develop severe diarrhoea during or after treatment. Do not take any medicine to treat your diarrhoea without first checking with your doctor. If your diarrhoea continues or reappears within the first weeks after treatment, please also inform your doctor.

<u>Superinfection</u>
Your doctor may observe you for signs of additional bacterial or fungal infections that cannot be treated with <invented name> (superinfection).

Sexually transmitted infections
Your doctor may test for and exclude a potential infection with syphilis, a sexually transmitted disease that may otherwise progress undetected and be diagnosed delayed. Furthermore, in any case of sexually transmitted bacterial infections your doctor will initiate laboratory follow-up tests to monitor the success of therapy.

Children and adolescents
If your child is under 12 years of age or if you are an adolescent (aged 12 to less than 18 years) do not use this medicinal product as its efficacy and safety have not been studied.

Other medicines and <Invented name>
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Using <Invented name> at the same time as some other medicines may result in side effects. Therefore, it is particularly important that you tell your doctor if you are using any of the following medicines:
- Atorvastatin and other medicines from the statins group (to lower blood cholesterol and prevent heart disease, including heart attacks and strokes)
- Ciclosporin (to prevent rejection of organ transplants by the body)
- Colchicine (to treat gout and familial Mediterranean fever)
- Dabigatran (to prevent and treat blood clot formation (anticoagulant))
- Digoxin (to treat heart diseases)
- Warfarin or similar medicines used to thin the blood (anticoagulants)
- Medicines that may cause the heart muscle to take longer to contract and relax than usual (QT prolongation), such as the following:
  - Quinidine, procainamide, dofetilide, amiodarone and sotalol (to treat an irregular heartbeat, including a too fast or too slow heartbeat - cardiac arrhythmia)
  - Pimozide (to treat mental illness)
  - Citalopram (to treat depression)
  - Moxifloxacin and levofloxacin (antibiotics)
  - Cisapride (to treat disorders in the gastrointestinal tract)
  - Hydroxychloroquine or chloroquine (to treat autoimmune diseases including rheumatoid arthritis, or to treat or prevent malaria)

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before receiving this medicine.

Pregnancy
Your doctor will decide if you should take this medicine during pregnancy, only after making sure that the benefits outweigh the potential risks.

Breast-feeding
<Invented name> passes into breast milk. Your doctor will decide therefore whether you should stop breast-feeding or should avoid treatment with <Invented name> taking into account both the benefit of breast-feeding for your child and the benefit of therapy for you.

Driving and using machines
<Invented name> has a moderate influence on the ability to drive and use machines. <Invented name> has been reported to cause dizziness, drowsiness and seizures, as well as problems with seeing and hearing in some people. These possible side effects may have an influence on your ability to drive and use machines.

<<Invented name> contains {name the excipient(s)}>

[A warning about any excipient that could result in unwanted undesirable effects e.g. in patients with specific metabolism disorders (e.g. phenylketonuria, fructose intolerance, glucose-galactose malabsorption, sucrase/isomaltase deficiency) or allergies should be added in this section as per the QRD template. Each MAH will need to mention any relevant excipient(s) and related warning(s) for their formulation(s).]

3. How to use <invented name>

[This section should read as follows:]

This medicine is administered once daily. It will be administered by a healthcare professional as an infusion into a vein over 3 hours or 1 hour. If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

The recommended dosing regimens for adult patients are shown in the table below.

Infection	**Treatment course**
Pneumonia (community-acquired pneumonia, not contracted in a hospital)	500 mg once daily for at least 2 days, followed by oral dose of 500 mg once daily to complete a 7-day to 10-day course of treatment.
Bacterial infection of the womb, fallopian tubes and ovaries (pelvic inflammatory disease) <Invented name> should be used in combination with another antibiotic that is selected by your doctor or pharmacist.	500 mg once daily for 1 to 2 days, followed by oral dose of 250 mg once daily to complete a 7-day course of treatment

Method of administration

[Information about method of administration including the EDQM standard term should be provided here according to section 4.2 of SmPC]

If you are given more <invented name> than you should

Your doctor will decide how to treat you, including stopping the treatment and monitoring for signs of ill effects. The most common side effects of having been given more <Invented name> than you should are vomiting, diarrhoea, stomach pain and nausea.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

[This section should read as follows:]

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Stop using <Invented name> and seek medical attention immediately if you notice any of the following symptoms:

- sudden wheeziness, difficulty in breathing, swelling of eyelids, face or lips, rash or itching especially affecting the whole body (*anaphylactic reaction*, frequency not known)
- rapid or irregular heartbeat (*cardiac arrhythmia* or *torsades de pointes tachycardia*, frequency not known)

- dark urine, loss of appetite or yellowing of the skin or whites of the eyes, which are signs of liver disorders (*hepatic failure* or *hepatic necrosis* (frequency not known), *hepatitis* (uncommon: may affect up to 1 in 100 people)).
- severe diarrhoea with abdominal cramps, bloody stools and/or fever may mean that you have an infection of the large intestine (*antibiotic-associated colitis*, frequency not known). Do not take medicines against diarrhoea that inhibit the bowel movements (*antiperistaltics*).
- reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (*Stevens-Johnson syndrome* or *toxic epidermal necrolysis*, frequency not known).
- widespread rash, high body temperature and enlarged lymph nodes (*DRESS syndrome* or *drug hypersensitivity syndrome*, rare (may affect up to 1 in 1,000 people)).
- a red, scaly widespread rash with bumps under the skin and blisters accompanied by fever. The symptoms usually appear at the initiation of treatment (*acute generalised exanthematous pustulosis*, rare (may effect up to 1 in 1,000 people)).

Other side effects

Very common (may affect more than 1 in 10 people)
- diarrhoea
- abdominal discomfort

Common (may affect up to 1 in 10 people)
- headache
- being sick (*vomiting*), stomach pain, feeling sick (*nausea*)
- changes in blood test results (*lymphocyte count decreased, eosinophil count increased, basophil count increased, monocyte count increased, neutrophil count increased, blood bicarbonate decreased*)
- pain at the injection site
- inflammation at the injection site

Uncommon (may affect up to 1 in 100 people)
- thrush (*candidiasis*) - a fungal infection of the mouth and vagina, other fungal infections
- pneumonia, bacterial infection of the throat, inflammation of the gastrointestinal tract, respiratory disorder, inflammation of the mucous membrane inside the nose, vaginal infection
- changes in the number of white blood cells (*leukopenia, neutropenia, eosinophilia)*
- platelet count increased
- reduction in the proportion of all blood cells in the total blood volume *(hematocrit decreased*)
- allergic reactions, swelling of the hands, feet and face (*angiooedema*)
- lack of appetite
- nervousness, difficulty sleeping (*insomnia*)
- feeling dizzy, feeling drowsy (*somnolence*), change in your sense of taste (*dysgeusia*), sensation of pins and needles or numbness (*paraesthesia*)
- impaired vision
- ear disorder
- spinning sensation (*vertigo*)
- feeling your heartbeat (*palpitations*)
- hot flush
- sudden wheeziness, bleeding from the nose
- constipation, wind, impaired digestion (*dyspepsia*), inflammation of the lining of the stomach (*gastritis*), difficulty in swallowing (*dysphagia*), swollen belly, dry mouth, belching (*eructation*), mouth ulceration, increased salivation
- rash, itching, hives (*urticaria*) , dermatitis, dry skin, abnormally increased sweating (*hyperhidrosis*)
- swelling and pain in the joints (osteoarthritis), muscle pain, back pain, neck pain

- painful urination (*dysuria*), kidney pain
- menstrual bleeding at irregular intervals (*metrorrhagia*), testicular disorder
- swelling due to fluid retention, especially of the face, ankles and feet (*oedema, face oedema, peripheral oedema*)
- weakness, tiredness, general feeling of being unwell, fever
- chest pain, pain
- abnormal laboratory test results (e.g. blood or liver tests)
- post procedural complication

Rare (may affect up to 1 in 1,000 people)
- feeling irritated
- liver problems, yellowing of the skin or eyes
- increased sensitivity to sunlight

Not known (frequency cannot be estimated from the available data)
- reduced number of red blood cells due to increased cell breakdown which can cause tiredness and pale skin (*haemolytic anaemia*)
- reduction in number of blood platelets which can lead to bleeding and bruising (*thrombocytopenia*)
- feeling angry, aggressive, feeling of fear and concern (*anxiety*), acute confusional state (*delirium*),
- hallucination
- fainting (*syncope*)
- fits (*seizures*)
- reduced sensation to touch, pain and temperature (*hypoaesthesia*)
- feeling hyperactive
- change in your sense of smell (*anosmia, parosmia*)
- total loss of your sense of taste (*ageusia*)
- muscle weakness (*myasthenia gravis*)
- abnormal electrocardiogram (ECG) heart tracing (*QT prolongation*)
- deafness, reduced hearing or ringing in your ears (*tinnitus)*
- low blood pressure
- inflammation of the pancreas causing severe pain in the belly and back (*pancreatitis*)
- change in tongue colour
- joint pain (*arthralgia*)
- kidney inflammation (*interstitial nephritis*) and kidney failure

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.
You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.