

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1 NAME OF THE MEDICINAL PRODUCT**

Azithromycin 250mg Capsules

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each capsule contains 250mg azithromycin (as dihydrate).

#### Excipients with known effect

Azithromycin capsules contains sulfur dioxide (E220) which may rarely cause severe hypersensitivity reactions and bronchospasm

For the full list of excipients, see section 6.1.

### **3 PHARMACEUTICAL FORM**

Capsule, hard.

### **4 CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

Azithromycin is indicated for the treatment of the following infections when known or likely to be due to one or more susceptible microorganisms (see Section 5.1):

- bronchitis
- community-acquired pneumonia
- sinusitis
- pharyngitis/tonsillitis (see 4.4 regarding streptococcal infections)
- otitis media
- skin and soft tissue infections
- uncomplicated genital infections due to *Chlamydia trachomatis*

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

## 4.2 Posology and method of administration

### Posology

*Children over 45 kg body weight and adults, including elderly patients*

The total dosage of azithromycin is 1500 mg which should be given over three days (500 mg once daily).

In uncomplicated genital infections due to *Chlamydia trachomatis*, the dosage is 1000 mg as a single oral dose.

Azithromycin 250 mg capsules are suitable only for children of at least 45 kg body weight for whom the adult dose may be used.

### *Renal insufficiency:*

In patients whose renal function is slightly impaired (creatinine clearance >40 ml/min), dose adjustment is not necessary. No studies have been conducted in patients with a creatinine clearance of <40 ml/min and consequently caution must be exercised in the use of azithromycin for these patients.

### *Hepatic insufficiency:*

Since azithromycin is metabolised in the liver and excreted in the bile, the drug should not be given to patients suffering from severe liver diseases. No studies have been conducted regarding treatment of such patients with azithromycin.

### Method of Administration:

Azithromycin 250 mg capsules should be administered as a single daily dose and should be taken at least 1 hour before or 2 hours after food.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or erythromycin, any macrolide or ketolide antibiotic.

## 4.4 Special warnings and precautions for use

### Hypersensitivity

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

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

**Superinfections:** As with any antibacterial agent, there is a possibility that superinfections could occur (e.g. fungal infections).

Since the liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin (see Section 4.8). Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

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

In patients receiving ergot derivatives, ergotism has been precipitated by coadministration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergot and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be coadministered.

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

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

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarization (see Section 4.8) therefore caution is required when treating patients:

- With congenital or documented QT prolongation
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes IA and III, cisapride and terfenadine
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency

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).

The safety and efficacy of intravenous azithromycin for the treatment of infections in children has not been established.

Safety and efficacy for the prevention or treatment of MAC in children have not been established.

## **4.5 Interaction with other medicinal products and other forms of interaction**

*Antacids:* In a pharmacokinetic study investigating the effects of simultaneously administered antacids on the pharmacokinetics of azithromycin, no overall change has been observed in the bioavailability, although the peak concentrations of azithromycin measured in the plasma fell by 25 %. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously. Azithromycin should be taken at least 1 hour before or 2 hours after the antacid.

*Cetirizine:* In healthy volunteers, coadministration of a 5-day regimen of azithromycin with cetirizine 20 mg at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

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

*Digoxin and colchicine:* concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-glycoprotein substrates such as digoxin are administered concomitantly, the possibility of elevated serum digoxin concentrations should be considered. Clinical monitoring, and possibly serum digoxin levels, during treatment with azithromycin and after its discontinuation are necessary.

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

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

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

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

*Atorvastatin:* Coadministration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase inhibition assay).

*Carbamazepine:* In a pharmacokinetic interaction study conducted in healthy volunteers, azithromycin had no significant effect on the plasma levels of carbamazepine or its active metabolite.

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

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

*Cyclosporin:* In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of cyclosporin, the resulting cyclosporin  $C_{max}$  and  $AUC_{0-5}$  were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, cyclosporin levels should be carefully monitored, and the dose should be adjusted accordingly.

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

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

*Indinavir:* Coadministration of a single dose of 1200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

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

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

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

*Rifabutin:* Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either drug. Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established (see Section 4.8).

*Sildenafil:* In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500mg daily for 3 days) on the AUC and  $C_{\max}$ , of sildenafil or its major circulating metabolite.

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

*Theophylline:* Azithromycin did not affect the pharmacokinetics of theophylline when healthy volunteers received azithromycin and theophylline simultaneously. The combined use of theophylline and other macrolide antibiotics has sometimes led to an increased serum level of theophylline.

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

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

## **4.6 Fertility, Pregnancy and lactation**

### Pregnancy

Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. These studies demonstrated that azithromycin crosses the placenta, but have revealed no evidence of harm to the foetus. There are, however, no adequate and well controlled studies in pregnant women. Since animal studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed, and if adequate alternatives are not available.

### Breast-feeding

There are no data on secretion in breast milk. As many drugs are excreted in human milk, azithromycin should not be used in the treatment of a lactating woman unless the physician feels that the potential benefits justify the potential risks to the infant.

## **4.7 Effects on ability to drive and use machines**

Dizziness has been reported, which may affect the ability to drive or operate machinery.

## **4.8 Undesirable effects**

The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in *italics*. The frequency grouping is defined using the following convention: Very common ( $\geq 1/10$ ); Common ( $\geq 1/100$  to  $< 1/10$ ); Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); Very Rare ( $< 1/10,000$ ); and Not known (cannot be estimated).

from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

| <b>System Organ Class</b>                     | <b>Adverse reaction</b>                                                                                                    | <b>Frequency</b> |
|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|------------------|
| <b>Infections and Infestations</b>            | Candidiasis, oral candidiasis, vaginal infection                                                                           | Uncommon         |
|                                               | <i>Pseudomembranous colitis</i> (see Section 4.4)                                                                          | Not known        |
| <b>Blood and Lymphatic System Disorders</b>   | Leukopenia, neutropenia                                                                                                    | Uncommon         |
|                                               | <i>Thrombocytopenia, haemolytic anaemia</i>                                                                                | Not known        |
| <b>Immune System Disorders</b>                | Angioedema, hypersensitivity                                                                                               | Uncommon         |
|                                               | <i>Anaphylactic reaction</i> (see Section 4.4)                                                                             | Not known        |
| <b>Metabolism and Nutrition Disorders</b>     | Anorexia                                                                                                                   | Common           |
| <b>Psychiatric Disorders</b>                  | Nervousness                                                                                                                | Uncommon         |
|                                               | Agitation                                                                                                                  | Rare             |
|                                               | <i>Aggression, anxiety</i>                                                                                                 | Not known        |
| <b>Nervous System Disorders</b>               | Dizziness, headache, paraesthesia, dysgeusia                                                                               | Common           |
|                                               | Hypoaesthesia, somnolence, insomnia                                                                                        | Uncommon         |
|                                               | <i>Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia</i>                                          | Not known        |
|                                               | <i>Myasthenia gravis</i> (see Section 4.4)                                                                                 |                  |
| <b>Eye Disorders</b>                          | Visual impairment                                                                                                          | Common           |
| <b>Ear and Labyrinth Disorders</b>            | Deafness                                                                                                                   | Common           |
|                                               | Hearing impaired, tinnitus                                                                                                 | Uncommon         |
|                                               | Vertigo                                                                                                                    | Rare             |
| <b>Cardiac Disorders</b>                      | Palpitations                                                                                                               | Uncommon         |
|                                               | <i>Torsades de pointes</i> (see Section 4.4), <i>arrhythmia</i> (see Section 4.4) <i>including ventricular tachycardia</i> | Not known        |
| <b>Vascular Disorders</b>                     | <i>Hypotension</i>                                                                                                         | Not known        |
| <b>Gastrointestinal Disorders</b>             | Diarrhoea, abdominal pain, nausea, flatulence                                                                              | Very common      |
|                                               | Vomiting, dyspepsia                                                                                                        | Common           |
|                                               | Gastritis, constipation                                                                                                    | Uncommon         |
|                                               | <i>Pancreatitis, tongue discolouration</i>                                                                                 | Not known        |
| <b>Hepatobiliary Disorders</b>                | Hepatitis                                                                                                                  | Uncommon         |
|                                               | Hepatic function abnormal                                                                                                  | Rare             |
|                                               | <i>Hepatic failure</i> (see Section 4.4)*, <i>hepatitis fulminant, hepatic necrosis, jaundice cholestatic</i>              | Not known        |
| <b>Skin and Subcutaneous Tissue Disorders</b> | Rash, pruritus                                                                                                             | Common           |
|                                               | Stevens-Johnson syndrome, photosensitivity reaction, urticaria                                                             | Uncommon         |
|                                               | Acute generalised exanthematous pustulosis (AGEP)                                                                          | Rare             |
|                                               | <i>Toxic epidermal necrolysis, erythema multiforme, Drug reaction with eosinophilia and systemic symptoms</i>              | Not known        |

|                                                             |                                                                                                                                                                                 |           |
|-------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
|                                                             | (DRESS).                                                                                                                                                                        |           |
| <b>Musculoskeletal and Connective Tissue Disorders</b>      | Arthralgia                                                                                                                                                                      | Common    |
| <b>Renal and Urinary Disorders</b>                          | Renal failure acute, nephritis interstitial                                                                                                                                     | Not known |
| <b>General Disorders and Administration Site Conditions</b> | fatigue                                                                                                                                                                         | Common    |
|                                                             | Chest pain, oedema, malaise, asthenia                                                                                                                                           | Uncommon  |
| <b>Investigations</b>                                       | Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased                                                                                             | Common    |
|                                                             | Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal | Uncommon  |
|                                                             | <i>Electrocardiogram QT prolonged</i> (see Section 4.4)                                                                                                                         | Not known |

\*which has rarely resulted in death

#### 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 Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

The undesirable effects at doses in excess of those recommended were similar to those after normal doses. The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea. In cases of overdose, administration of medicinal charcoal and general symptomatic treatment as well as measures to support vital functions are indicated where necessary.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

ATC code: J01FA10

### Mechanism of action:

Azithromycin is a macrolide antibiotic belonging to the azalide group. The molecule is constructed by adding a nitrogen atom to the lactone ring of erythromycin A.

The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis by binding to the ribosomal 50S sub-unit and inhibition of peptide translocation.

### Mechanism of resistance:

Resistance of gram-positive organisms to the macrolides usually involves an alteration of the antimicrobial binding site. The MLSB type of resistance, which may be constitutive or induced by exposure to certain macrolides in staphylococci and which is inducible in streptococci, is mediated by a variety of acquired genes (*erm* family) encoding methylases targeted at the peptidyl transferase centre of 23S ribosomal RNA. Methylation impedes binding of antibacterials to the ribosome and gives rise to cross-resistance to macrolides (all macrolides when constitutive), lincosamides and type B streptogramins but not to type A streptogramins. Less frequent mechanisms of resistance include antimicrobial degradation by inactivating enzymes such as esterase and active efflux of the antimicrobial from the bacteria.

Gram negative organisms may be intrinsically resistant to the macrolides because of the inability of the macrolide to effectively penetrate the outer cell membrane; macrolides having a better penetration may have activity against some gram-negative organisms. Gram-negative organisms may also produce ribosomal methylase or macrolide inactivating enzymes.

### ***Breakpoints***

The CLSA susceptibility breakpoints for typical bacterial pathogens are:

- susceptible  $\leq 2$  mg/l; resistant  $\geq 8$  mg/l
- *Haemophilus* spp.: susceptible  $\leq 4$  mg/l
- *Streptococcus pneumoniae* and *Streptococcus pyogenes*:

susceptible  $\leq 0.5$  mg/l; resistant  $\geq 2$  mg/l

### ***Susceptibility***

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

| Commonly susceptible species                            |
|---------------------------------------------------------|
| Aerobic Gram-positive microorganisms                    |
| <b>Staphylococcus aureus</b><br>Methicillin-susceptible |

|                                                                                      |
|--------------------------------------------------------------------------------------|
| <i>Streptococcus pneumoniae</i><br>Penicillin-susceptible                            |
| <i>Streptococcus pyogenes</i>                                                        |
| <b>Aerobic Gram-negative microorganisms</b>                                          |
| <b>Haemophilus influenzae</b><br><i>Haemophilus parainfluenzae</i>                   |
| <i>Legionella pneumophila</i>                                                        |
| <i>Moraxella catarrhalis</i>                                                         |
| <i>Pasteurella multocida</i>                                                         |
| <b>Anaerobic microorganisms</b>                                                      |
| <b>Clostridium perfringens</b>                                                       |
| <b>Peptococcus and Peptostreptococcus spp.</b>                                       |
| <b>Other microorganisms</b>                                                          |
| <b>Chlamydia trachomatis</b>                                                         |
| <b>Species for which acquired resistance may be a problem</b>                        |
| <b>Aerobic Gram-positive microorganisms</b>                                          |
| <b>Streptococcus pneumoniae</b><br>Penicillin-intermediate*<br>Penicillin-resistant* |
| <i>Staphylococci MRSA, MRSE**</i>                                                    |
| <b>Inherently resistant organisms</b>                                                |
| <b>Aerobic Gram-positive microorganisms</b>                                          |
| <b>Enterococcus faecalis</b>                                                         |
| <b>Anaerobic microorganisms</b>                                                      |
| Bacteroides fragilis group                                                           |

\* Pneumococci that have some degree of reduced susceptibility to penicillin are more likely to be macrolide-resistant than penicillin-susceptible strains

\*\* Methicillin-resistant staphylococci have a very high prevalence of acquired resistance to macrolides and are rarely susceptible to azithromycin.

### Paediatric population

Following the assessment of studies conducted in children, the use of azithromycin is not recommended for the treatment of malaria, neither as monotherapy nor combined with chloroquine or artemisinin based drugs, as non-inferiority to anti-malarial drugs recommended in the treatment of uncomplicated malaria was not established.

## **5.2 Pharmacokinetic properties**

### Absorption

Bioavailability after oral administration is approximately 37%. Peak concentrations in the plasma are attained 2-3 hours after taking the medicinal product.

### Distribution

Orally administered azithromycin is widely distributed throughout the body.

In pharmacokinetic studies it has been demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (as much as 50 times) than those measured in plasma, which indicates that the agent strongly binds to tissues.

Binding to serum proteins varies according to concentration and ranges from 12% at 0.5 microgram/ml up to 52% at 0.05 microgram/ml. The mean volume of distribution at steady state ( $VV_{ss}$ ) has been calculated to be 31.1 l/kg.

### Elimination

Terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 2-4 days.

Approximately 12% of an intravenously administered dose of azithromycin is excreted unchanged in urine within the following three days. Particularly high concentrations of unchanged azithromycin have been found in human bile. In the same source, 10 metabolites were also detected, which were formed through N- and O-demethylation, hydroxylation of desosamine- and aglycone rings and degradation of cladinose conjugate. Comparison of the results of liquid chromatography and microbiological analyses has shown that the metabolites of azithromycin are not microbiologically active.

In animal tests, high concentrations of azithromycin have been found in phagocytes. It has also been established that during active phagocytosis higher concentrations of azithromycin are released than are released from inactive phagocytes. Consequently, in animal tests the azithromycin concentrations measured in inflammation foci were high.

## **5.3 Preclinical safety data**

In animal tests in which the dosages used amounted to 40 times the clinical therapeutic dosages, azithromycin was found to have caused reversible phospholipidosis, but as a rule, no true toxicological consequences were observed which were associated with this.

### *Carcinogenic potential:*

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

### *Mutagenic potential:*

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

*Reproductive toxicity:*

In animal studies of the embryotoxic effects of the substance, no teratogenic effect was observed in mice and rats. In rats, azithromycin dosages of 100 and 200 mg/kg bodyweight/day led to mild retardation of foetal ossification and maternal weight gain. In peri- and post-natal studies in rats, mild retardation was observed following treatment with 50 mg/kg/day azithromycin and above.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Capsule contents:

Cellulose microcrystalline,  
Sodium laurilsulfate,  
Magnesium stearate,

Capsule Shell:

Gelatin,  
Titanium dioxide (E-171),  
FD & C Blue 2 (E-132),  
Indigo carmine (E-132),  
Sulfur dioxide.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

**6.4 Special precautions for storage**

This medicine does not require any special storage conditions.

**6.5 Nature and contents of container**

Blisterpack PVC/PVDC/Aluminium.

Pack sizes 2, 4, 6 or 100 capsules. Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

None

**7 MARKETING AUTHORISATION HOLDER**

Teva UK Limited  
Brampton Road  
Hampden Park  
Eastbourne  
East Sussex  
BN22 9AG

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 00289/1570

**9      DATE OF FIRST AUTHORISATION/RENEWAL OF THE  
AUTHORISATION**

29/07/2008

**10     DATE OF REVISION OF THE TEXT**

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