SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AZITRO 500 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains
Active substance:
Azithromycin dihydrate……524.032 mg (equivalent to 500 mg azithromycin).
Excipient(s):
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.
White, oblong, homogenous looking, odorless film coated tablets with "AZITRO" engraved on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AZITRO is indicated for infections caused by susceptible organisms; in lower respiratory tract infections such as bronchitis, mild community-acquired pneumonia due to *Streptococcus pneumonia* or *Haemophilus influenza*; in skin and soft tissue infections; in acute otitis media and in upper respiratory tract infections including sinusitis.

It is indicated for treatment of pharyngitis/tonsillitis caused by *Streptococcus pyogenes*, in the presence of penicillin allergy.

AZITRO is indicated for treatment of sexually transmitted, uncomplicated genital infections in males and females due to *Chlamydia trachomatis.*

It is also indicated for treatment of soft tissue ulcers due to *Haemophilus ducreyi* and uncomplicated genital infections due to non-multi resistant *Neisseria gonorrhoeae*, however concurrent infection with *Treponema pallidum* should be excluded.

4.2 Posology and method of administration

Posology/frequency and duration of administration
AZITRO should be given as a single daily dose.
The duration of treatment in each of the infectious disease are given below.

Adults:
The dosage for treatment of sexually transmitted diseases due to *Chlamydia trachomatis*, *Haemophilus ducreyi* or susceptible *Neisseria gonorrhoeae* is 1000 mg as a single oral dose.

The dosage for treatment of tonsillitis/pharyngitis due to *S. pyogenes*, is 500 mg on day 1 and 250 mg daily on the following days (days 2, 3, 4 and 5) for 5 days.

For all other indications, total dosage is 1500 mg, taken as 500 mg daily for 3 days.

Local treatment guidelines should be followed when prescribing for patients allergic to penicillin and/or cephalosporins.

Method of administration
For oral use.
Azithromycin tablets can be taken with or without meals.
The film coated tablets should be swallowed with some liquid without chewing.

Additional information on special populations
Renal impairment
No dosage adjustment is recommended for subjects with mild to moderate renal impairment (GFR 10-80 mL/min). Caution should be exercised when azithromycin is administered to subjects with severe renal impairment (GFR<10 mL/min) (see section 4.4).

Hepatic impairment
Same doses may be administered to patients with mild to moderate hepatic impairment as the patients with normal hepatic functions. As azithromycin is metabolized in the liver and eliminated by the bile, it should not be used in patients with severe hepatic impairment. There are no available studies of azithromycin use in patients with hepatic impairment (see section 4.4).

Pediatric population
For pediatric patients weighing over 45 kg, adult doses are administered. The maximum recommended total dose for any treatment other than tonsillitis/pharyngitis in children is 1500 mg (500 mg once daily) administered for 3 days. The dosage for treatment of tonsillitis/pharyngitis due to *S. pyogenes*, is 500 mg on day 1 and 250 mg daily on the following days (days 2, 3, 4 and 5) for 5 days.
Oral suspension forms are available for pediatric patients weighing less than 45 kg.
Efficacy and safety of azithromycin have not been established for infants younger than 6 months of age, therefore its use is not recommended for infants younger than 6 months of age.

Geriatric population:
The same dosage as in adult patients is used in the elderly patients. As elderly patients may have persistent proarrhythmic conditions, special caution is advised for the risk of developing cardiac arrhythmias and *torsades de pointes*.

4.3 Contraindications

The use of this medicine is contraindicated in patients with hypersensitivity to azithromycin or any of the macrolide or ketolide antibiotics, erythromycin or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity
As with erythromycin and other macrolides, rare serious allergic reactions including angioedema, acute generalized exanthematous pustulosis (AGEP) and anaphylaxis (rarely fatal), Stevens-Johnson syndrome, 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 initiated. The physician should be aware of the possibility of recurrence of allergic symptoms after discontinuation

of therapy.

Hepatotoxicity
Because azithromycin is predominantly eliminated via the hepatobiliary pathway, AZITRO should be administered with caution to patients with severe hepatic disease.

Conditions such as abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis and hepatic failure (some resulting in death) have been reported with azithromycin therapy (see section 4.8). Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

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

Ergot derivatives
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 derivatives and azithromycin. Concomitant use of azithromycin with ergot derivatives is not recommended because of the theoretical possibility of ergotism.

Superinfection
As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms including fungi is recommended. In case of superinfection, it may be necessary to discontinue azithromycin therapy and initiate appropriate therapy.

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

C. difficile produces hypertoxin A and B. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. Therefore, CDAD must be considered in patients who present with diarrhea during antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents. Discontinuation of therapy with azithromycin and the administration of specific treatment for *C. difficile* should be considered.

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

Streptococcal infections
Penicillin is usually the first choice for treatment of pharyngitis/tonsillitis due to *Streptococcus pyogenes* and also for prophylaxis of acute rheumatic fever. Azithromycin is in general effective against streptococcus in the oropharynx, but no data are available that demonstrate the efficacy of azithromycin in preventing acute rheumatic fever.

Prolongation of the QT interval
Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and *torsades de pointes*, have been seen in treatment with macrolides including azithromycin (see section 4.8).

Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients).

When prescribing azithromycin to the following patient groups, a benefit-risk analysis should be performed due to the risk of QT prolongation that may lead to death. The following patient groups may be more susceptible to drug-related QT interval prolongation.

- **Patients with known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmias or uncompensated heart failure**
- **Patients on drugs known to prolong the QT interval**
- **Patients with uncorrected hypokalemia or hypomagnesemia, or receiving antiarrhythmic agents of class IA (quinidine, procainamide) or class III (dofetilide, aminodarone, sotalol), cisapride and terfenadine; antipsychotic agents such as pimozide; antidepressants such as citalopram; fluoroquinolones such as moxifloxacin and levofloxacin**
- **Patients with clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency**
- **Female and elderly patients with existing proarrhythmia**

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).

4.5 Interactions with other medicinal products and other forms of interaction

Antacids
In a pharmacokinetic study investigating the effects of simultaneous administration of antacid with azithromycin, no effect on overall bioavailability was seen, although peak serum concentrations were reduced by approximately 25%. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously.

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

Didanosine (Dideoxyinosine)
Co-administration of 1200 mg/day azithromycin with 400 mg/day didanosine in six HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared to 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 derivatives
Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended (see section 4.4).

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

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

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

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.

Ciclosporin
In a pharmacokinetic study with healthy volunteers who 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 ciclosporin, the resulting ciclosporin's maximum concentration C_{max} and AUC_{0-5} were found to be significantly elevated (by 24% and 21% respectively), however no significant changes were seen in $AUC_{0-\infty}$. Consequently, caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

Efavirenz
Co-administration of a single dose of 600mg azithromycin and 400 mg efavirenz daily for 7 days did

not result in any clinically significant pharmacokinetic interactions.

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

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

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

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

Nelfinavir
Co-administration of 1200 mg azithromycin 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 was required.

Rifabutin
Co-administration of azithromycin and rifabutin did not affect the serum concentrations of either drug.

Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established (see section 4.8.).

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

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

Terfenadine
Although pharmacokinetic studies have shown no interaction between azithromycin and terfenadine, some reported cases indicates that this possibility cannot be completely excluded. Careful monitoring is recommended when azithromycin and terfenadine are used together.

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

for triazolam compared to triazolam and placebo.

Trimethoprim/sulfamethoxazole
Co-administration of trimethoprim/sulfamethoxazole (160 mg/800 mg) for 7 days with 1200mg azithromycin 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.

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

Additional information on special populations:
There is no sufficient data regarding drug interactions on special populations.

Pediatric population:
There is no sufficient data regarding drug interactions on the pediatric population.

4.6 Fertility, pregnancy and lactation

General recommendation
Pregnancy category: B

Women of childbearing potential / Birth control (Contraception)
Animal studies performed at mild to moderate maternally toxic dose concentrations are insufficient with respect to direct or indirect harmful effects on pregnancy, embryonal / fetal development / parturition or postnatal development. Therefore, appropriate contraceptive methods should be used in women planning to get pregnant or being uncertain about pregnancy while using this drug.

Pregnancy
There is no sufficient clinical data regarding the use of azithromycin in pregnant women. Animal studies are insufficient regarding effects on pregnancy /and-or/ embryonal/fetal development / and-or/ parturition /and-or/postnatal development (see section 5.3). In these studies, it was observed that azithromycin crossed the placenta and reached the fetus, but no evidence was found regarding its harm to the fetus. The potential risk for humans is unknown. Since the safety of azithromycin during pregnancy is not yet clear, it should be used during pregnancy only when absolutely necessary.

Breastfeeding
Azithromycin has been reported to pass into in human milk; however, there are no adequate and controlled studies characterizing the pharmacokinetics of azithromycin excretion in human milk in breastfeeding mothers. Therefore, azithromycin should be used in breast-feeding women only if the potential benefits to the mother outweigh the potential risk to the baby.

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

4.7 Effects on ability to drive and use machines

There is no evidence to suggest that azithromycin may have an effect on patient's ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects are listed according to these categories:
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.

Infections and infestations
Uncommon: Candidiasis, oral candidiasis, vaginal infection
Not known: Pseudomembranous colitis (see section 4.4)

Blood and lymphatic system disorders
Uncommon: Leukopenia, neutropenia
Not known: Thrombocytopenia, hemolytic anemia

Immunity system disorders
Uncommon: Angioedema, hypersensitivity
Not known: Anaphylactic reactions (see section 4.4)

Metabolism and nutrition disorders
Common: Anorexia

Psychiatric disorders
Uncommon: Nervousness
Rare: Agitation
Not known: Aggressive reactions, anxiety

Nervous system disorders
Common: Headache, drowsiness, paresthesia, dysgeusia
Uncommon: Hypoesthesia, somnolence, insomnia
Not known: Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis (see section 4.4)

Eye disorders
Common: Visual impairment

Ear and labyrinth disorders
Common: Deafness
Uncommon: Hearing impaired, tinnitus
Rare: Vertigo

Cardiac disorders
Uncommon: Palpitation
Not known: *Torsades de pointes*, arrhythmias including ventricular tachycardia (see section 4.4)

Vascular disorders
Not known : Hypotension

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnea, epistaxis

Gastrointestinal disorders
Very common: Diarrhea, abdominal pain, nausea, flatulence
Common: Vomiting, dyspepsia
Uncommon: Constipation, gastritis
Not known: Pancreatitis, tongue discoloration

Hepatobiliary disorders
Uncommon: Hepatitis
Rare: Hepatic function abnormalities
Not known: Hepatic failure (which has rarely resulted in death) (see section 4.4), hepatitis fulminant, hepatic necrosis, cholestatic jaundice

Skin and subcutaneous tissue disorders
Common: Itching, rash
Uncommon: Stevens Johnson Syndrome, photosensitivity reactions, urticaria
Rare: Acute Generalized Exanthematous Pustulosis (AGEP)*[+], drug reaction with eosinophilia and systemic symptoms (DRESS)* [+]
Not known: Toxic epidermal necrolysis, erythema multiforme

Musculoskeletal, connective tissue disorders
Common: Arthralgia

Renal and urinary disorders
Not known: Acute renal failure, interstitial nephritis

General disorders and administration site disorders
Common: Fatigue
Uncommon: Chest pain, edema, malaise/weakness, asthenia

Investigations
Common: Decreased lymphocyte count, increased eosinophil count, decreased blood bicarbonate
Uncommon: Increased aspartate aminotransferase, increased alanine aminotransferase, increased blood bilirubin, increased blood urea, increased blood creatinine, abnormal blood potassium
Not known: Electrocardiogram QT prolonged (see section 4.4)

*ADR identified post-marketing
[+]ADR frequency represented by the estimated upper limit of the 95% confidence interval calculated using the “Rule of 3”.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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.

4.9 Overdose

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhea. In the event of overdose, the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, macrolides
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 chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A. The molecular weight is 749.0.

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

Mechanism of resistance
Resistance to azithromycin may be inherent or acquired. There are three main mechanisms of resistance in bacteria: target site alteration, alteration in antibiotic transport and modification of the antibiotic.

Azithromycin demonstrates cross resistance with erythromycin resistant gram positive isolates. A decrease in macrolide susceptibility over time has been noted particularly *in Streptococcus pneumoniae* and *Staphylococcus aureus*. Similarly, decreased susceptibility has been observed among *Streptococcus viridans* and *Streptococcus agalactiae* (Group B) streptococcus against other macrolides and lincosamides.

Breakpoints
Azithromycin breakpoints for typical bacterial pathogens published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST):

	Minimum inhibition concentration (MIC) breakpoints (mg/L)	
	Susceptible	**Resistant**
Staphylococcus spp.	≤1	>2
Streptococcus groups A, B, C and G	≤0.25	>0.5
Streptococcus pneumoniae	≤0.25	>0.5
Haemophilus influenzae	≤0.12	>4
Moraxella catarrhalis	≤0.25	>0.5
Neisseria gonorrhoeae	≤0.25	>0.5

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.

Table: Antibacterial spectrum of azithromycin

Commonly susceptible species
Aerobic Gram-positive microorganisms
Staphylococcus aureus Methycillin-susceptible
Streptococcus pneumoniae Penicillin-susceptible
Streptococcus pyogenes **(Group A)**
Aerobic Gram-negative microorganisms
Haemophilus influenzae *Haemophilus parainfluenzae*
Legionella pneumophila
Moraxella catarrhalis
Neisseria gonorrhoeae
Pasteurella multocida
Anaerobic microorganisms
Clostridium perfringens
Fusobacterium spp.
Prevotella spp.
Porphyromonas spp.
Other microorganisms
Chlamydia trachomatis
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Streptococcus pneumoniae Penicillin-intermediate Penicillin-resistant
Inherently resistant organisms
Aerobic Gram-positive microorganisms
Enterococcus faecalis
Staphylococci MRSA, MRSE*
Anaerobic microorganisms
Bacteroides fragilis group

* Methycillin-resistant staphylococci have a very high prevalence of acquired resistance to macrolides and have been placed here because they are rarely susceptible to azithromycin.

Pediatric 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

General properties

Absorption:
Bioavailability after oral administration is approximately 37%. Peak plasma concentrations are attained 2 to 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 plasma concentration and ranges from 12% at 0.5 microgram/mL up to 52% at 0.05 microgram azithromycin/mL serum. The mean volume of distribution at steady state has been calculated to be 31.1 L/kg.

Biotransformation:
Particularly high concentrations of unchanged azithromycin have been found in human bile. Also in bile, ten metabolites were detected, which were formed through N- and O- demethylation, hydroxylation of desosamine and aglycone rings and cleavage 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 from inactive phagocytes. In animal models this results in high concentrations of azithromycin being delivered to the site of infection.

Elimination
The terminal plasma elimination half-life closely reflects the elimination half-life from tissues (2 to 4 days).

Approximately 12% of an intravenously administered dose of azithromycin is excreted unchanged in urine within the following 3 days.

5.3 Preclinical safety data

Phospholipidosis (intracellular phospholipid accumulation) has been observed in several tissues (e.g. eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and/or pancreas) 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 the finding for animals and humans is unknown.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Calcium phosphate dibasic anhydrous
Sodium carboxymethyl cellulose 150
Microcrystalline cellulose PH 102
Sodium lauryl sulphate
Magnesium stearate

Film coating material (Opadry OY-D-7233 white):
Hypromellose
Titanium dioxide
Talc
Polyethylene glycol/Macrogol
Sodium lauryl sulphate

6.2 Incompatibilities

There is no known incompatibility.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Keep at room temperature below 25°C.

6.5 Nature and contents of packaging

Blister with transparent PVDC on one side and printed aluminum foil on the other side.
Each cardboard box contains 3 film coated tablets.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No: 1
34303 Küçükçekmece - Istanbul/TURKEY

8. MARKETING AUTHORIZATION NUMBER

178/41

9. DATE OF FIRST AUTHORIZATION /RENEWAL OF THE AUTHORIZATION

Date of first Authorization : 17.06.1996
Date of last renewal : 08.01.2013

10. DATE OF REVISION OF THE TEXT

15.10.2021