SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AZITRO 200 mg/5 ml Powder for Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:
Each 5 ml of reconstituted oral suspension contains azithromycin dihydrate equivalent to 200 mg azithromycin.

Excipient(s):
Sodium phosphate, tribasic ..... 58.3 mg
Sodium benzoate ..... 10 mg
Sodium saccharin ..... 13.3 mg
Sucrose ..... 2655.3 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dry Powder for Oral Suspension
White to off white granular powder, a creamy-white, homogeneous suspension when reconstituted with a characteristic odor.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AZITRO is indicated for the treatment of the following infections, when caused by microorganisms sensitive to azithromycin:

- Lower respiratory tract infections such as bronchitis
- Mild to moderate community-acquired pneumonia due to *S. pneumonia* or *H. influenza*
- Skin and soft tissue infections
- Acute otitis media
- Upper respiratory tract infections including sinusitis

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

AZITRO is indicated in sexually transmitted, uncomplicated genital infections in males and females due to *Chlamydia trachomatis.* It is also indicated in 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.

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 days 2 through 5, the duration of therapy is 5 days.

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

Method of administration
For oral use.
The duration of treatment in each of the infectious disease are given below. AZITRO suspension can be taken with food.

Reconstitution
Shake the dry powder in bottle. Afterwards, pour boiled and then cooled water up to the mark on the supplied measuring device, add into the contents of bottle and shake well. 5 ml of the reconstituted suspension contains 200 mg of azithromycin. Shake the bottle before each use.

Using the measuring spoon:
Suspension is administered with double sided (2.5-5 ml) measuring spoon.

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. For indications except tonsillitis/pharyngitis, the recommended total dosage is 1500 mg which is spread over 3 days (500 mg once daily).

Except for the treatment of Streptococcal pharyngitis, in children total dose of 30 mg/kg given as 10 mg/kg once daily for 3 days or 10 mg/kg as a single dose on the first day followed by 5 mg/kg/day on days 2-5.

As alternative to the above dosing, for the treatment of acute otitis media, 30 mg/kg may be given as a single dose.

Weight (kg)	3 day therapy Administered once a day		5 day therapy Administered once a day		Total Dosage
	Day 1	Day 2 - 3	Day 1	Day 2 - 5	
< 15 kg	2,5 ml (100 mg)	2,5 ml (100 mg)	2,5 ml (100 mg)	1,25 ml (50 mg)	30 mg/kg
15-25 kg	5 ml (200 mg)	5 ml (200 mg)	5 ml (200 mg)	2,5 ml (100 mg)	600 mg
26-35 kg	7,5 ml (300 mg)	7,5 ml (300 mg)	7,5 ml (300 mg)	3,75 ml (150 mg)	900 mg
36-45 kg	10 ml (400 mg)	10 ml (400 mg)	10 ml (400 mg)	5 ml (200 mg)	1200 mg
Over 45 kg	Adult dosage				

Efficacy and safety of azithromycin have not been established for infants younger than 6 months of age, therefore it is not recommended.

For pediatric streptococcal pharyngitis, azithromycin given as a single dose of 10 mg/kg or 20 mg/kg for 3 days has been shown to be effective; however, a daily dose of 500 mg must not be exceeded. Comparing these 2 dosage regimens, similar clinical efficacy was observed but greater bacteriologic eradication was evident at the 20 mg/kg per day dose. However, penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including prophylaxis of rheumatic fever.

Geriatric population:
The same dosage as in adult patients is used in the elderly patients.

4.3 Contraindications
The use of this drug is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotics or any of the excipients listed in section 6.1.
Azithromycin and ergot derivatives should not be co-administered because of the possibility of ergotism.

4.4 Special warnings and precautions for use
As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic edema, anaphylaxis, Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported. Although rare, fatalities have been reported. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients should receive appropriate treatment and be monitored for some time. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is unknown at present.

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

As with other antibiotics, patients should be monitored for signs of superinfection with non-susceptible organisms including fungi.

***Clostridium difficile* related diarrhea (CDAD)**
Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all

antibacterial agents, including azithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

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

QT interval prolongation
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. Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving azithromycin.
Physicians should consider the risk of QT prolongation which can be fatal when weighing the risks and benefits of azithromycin for the following patient groups:

- **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 ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, aminodarone, sotalol) antiarrhythmic agents.**
- **Elderly patients may be more susceptible to drug-associated effects on the QT interval**.

Gastrointestinal disturbances
When azithromycin was administered to a limited number of subjects with GFR <10 ml/min, a higher incidence of gastrointestinal adverse events was observed (8 of 19 subjects).

Development of drug resistant bacteria
Prescribing AZITRO in the absence of a proven or strongly suspected bacterial infection increases the risk of the development of drug-resistant bacteria.

Sucrose content
This product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Sodium content
This medicine contains sodium less than 1 mmol (23 mg); sodium-related side effect is not expected at this dose.

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.

Didanosine (Dideoxynosine)
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
Some of the macrolide antibiotics have been reported to impair the microbial metabolism of digoxin in the gastrointestinal tract in some patients. In patients receiving concomitant azithromycin and digoxin the possibility of raised digoxin levels should be borne in mind.

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.

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.

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/day) and azithromycin (500 mg/day) did not alter the plasma concentrations of atorvastatin (based on HMG CoA-reductase inhibition assay).

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.

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.

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.

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

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

Nelfinavir
Co-administration of azithromycin (1200 mg) and nelfinavir at a steady state (750 mg 3 times daily) resulted in a 100% increase in azithromycin absorption and bioavailability. There was no significant effect upon the rate of absorption or the rate of clearance. No clinically significant adverse effects were observed and no dose adjustment is required. The clinical consequences of this interaction are unknown, caution should be exercised when prescribing azithromycin to patients taking nelfinavir.

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).

Cyclosporine
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 (by 24 and 21% respectively), however no significant changes were seen in $AUC_{0-\infty}$. Consequently, caution should be exercised before considering coadministration of these two drugs. If coadministration is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

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.

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.

Theophylline
There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are co-administered to healthy volunteers. Theophylline levels may be increased in patients taking AZITRO.

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 (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

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

Pediatric population:
There is no sufficient data.

4.6 Fertility, pregnancy and lactation

General principles
Pregnancy category is B

Women of child-bearing potential/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 available clinic data on use of azithromycin in pregnant women. Animal studies have been performed at mild to moderate maternally toxic dose concentrations. In these studies, no evidence of harm to the fetus due to azithromycin was found. Potential risks for humans are not known. Azithromycin should be used during pregnancy only if clearly needed.

Breast-feeding
It is not known whether azithromycin is excreted in human milk.
A decision on whether to continue/discontinue breast-feeding or to continue/ discontinue therapy with AZITRO should be made taking into account the benefit of breast-feeding to the child and the benefit of AZITRO therapy to the woman.

Fertility
There is no sufficient data.

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
AZITRO is well tolerated with a low incidence of side 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); unknown: cannot be estimated from the available data.

Infections and infestations
Uncommon : Candidiasis, oral candidiasis, vaginal infection
Unknown : Pseudomembranous colitis

Blood and lymphatic system disorders
Uncommon : Leukopenia, neutropenia
Unknown : Thrombocytopenia, hemolytic anemia

Immunity system disorders
Uncommon : Angioedema, hypersensitivity
Unknown : Anaphylactic reactions

Metabolism and nutrition disorders
Common : Anorexia

Psychiatric disorders
Uncommon : Nervousness
Rare : Agitation
Unknown : Aggression and anxiety

Nervous system disorders
Common : Drowsiness, headache, paresthesia, dysgeusia
Uncommon : Hypoesthesia, somnolence, insomnia
Unknown : Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia,

Myasthenia gravis

Eye disorders
Common : Visual impairment

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

Cardiac disorders
Uncommon : Palpitation
Unknown : *Torsades de pointes*, arrhythmias including ventricular tachycardia

Vascular disorders
Unknown : Hypotension

Gastrointestinal disorders
Very common : Diarrhea, abdominal pain, nausea, flatulence
Common : Vomiting, dyspepsia
Uncommon : Gastritis, constipation
Unknown : Tongue discoloration, pancreatitis

Hepatobiliary disorders
Uncommon : Hepatitis
Rare : Hepatic function abnormalities
Unknown : Hepatic failure**, hepatitis fulminant, hepatic necrosis, cholestatic jaundice
** which has rarely resulted in death

Skin and subcutaneous tissue disorders
Common : Pruritus, rash
Uncommon : Stevens Johnson Syndrome, photosensitivity reactions, urticaria
Unknown : Toxic epidermal necrolysis, erythema multiforme

Musculoskeletal, connective tissue disorders
Common : Arthralgia

Renal and urinary disorders
Unknown : Interstitial nephritis and acute renal failure

General disorders and administration site disorders
Common : Fatigue
Uncommon : Edema, chest pain, malaise, 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

Unknown : Electrocardiogram QT prolonged

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 to Turkey Pharmacovigilance Center (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone number: +90 800 314 00 08; fax: +90 312 218 35 99)

4.9 Overdose
Adverse events experienced in higher doses 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 medical charcoal and general symptomatic and supportive treatment is 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 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.

Cardiac Electrophysiology
QTc interval prolongation was studied in a randomized, placebo-controlled parallel trial in 116 healthy subjects who received either chloroquine (1000 mg) alone or in combination with azithromycin (500 mg, 1000 mg, and 1500 mg once daily). Co-administration of azithromycin increased the QTc interval in a dose-and concentration-dependent manner. In comparison to chloroquine alone, the maximum mean (95% upper confidence bound) increases in QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with the co-administration of 500 mg, 1000 mg and 1500 mg azithromycin, respectively.

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

Breakpoints
Azithromycin susceptibility breakpoints for typical bacterial pathogens are as follows:
National Committee of Clinic Laboratory Standards (NCCLS):

- Susceptible ≤2 mg/ml; resistant ≥8 mg/ml
- *Haemophilus* species: susceptible ≤4 mg/ml
- *Streptococcus pneumoniae* and *Streptococcus pyogenes:*

Susceptible ≤0.5 mg/l; resistant ≥2 mg/ml

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* *Pasteurella multocida*
Anaerobic microorganisms *Clostridium perfringens* *Fusobacterium species* *Prevotella species* *Porphyromonas species*
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 high prevalence of acquired resistance to macrolides and have been placed here because they are rarely susceptible to azithromycin.

5.2 Pharmacokinetic properties

General properties
Absorption:
Bioavailability of azithromycin after oral administration is approximately 37%. Administration of

medicinal product following substantial meal reduced bioavailability by at least 50%. Peak plasma levels are reached in 2-3 hours.

Distribution:
Pharmacokinetic studies have shown considerably higher azithromycin concentrations in the tissues (up to 50 times the maximum concentration observed in plasma). This indicates that the substance is extensively bound in the tissues. Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC_{90} values for likely pathogens after a single dose of 500 mg.

Binding to serum proteins varies according to plasma concentration and ranges from 12% at 0.5 µg/ml up to 52% at 0.05 µg azithromycin/ml serum. The mean volume of distribution at steady state (VVss) has been calculated to be 31.1 L/kg.

Following oral administration of daily doses of 600 mg azithromycin, mean maximum plasma concentration (C_{max}) was 0.33 µg/ml and 0.55 µg/ml at day 1 and day 2 respectively.

Biotransformation:
There is no sufficient data.

Elimination:
The terminal plasma elimination half life reflects the elimination half life of azithromycin from tissues (2-4 days).
Approximately 12% of an intravenously administered dose is excreted in the urine over 3 days as the parent drug, the majority in the first 24 hours. Very high concentrations of unchanged drug have been found in human bile, together with 10 metabolites. Comparison of HPLC and microbiological assays in tissues suggests that metabolites play no part in the microbiological activity of azithromycin.

Linearity/Non-linearity:
There is no sufficient data.

Characteristics in patients
Elderly:
In elderly volunteers (>65 years), slightly higher AUC values were seen after a 5-day regimen than in young volunteers (<40 years), but these are not considered clinically significant, and hence no dose adjustment is recommended.

Renal impairment:
The pharmacokinetics of azithromycin in subjects with mild to moderate renal impairment [GFR (glomular filtration rate) 10-80 ml/min] were not affected following a single dose (1 g) of immediate release azithromycin. Statistically significant differences in AUC_{0-120} (8.8 µg.hr/ml vs. 11.7 µg.hr/ml), C_{max} (1.0 µg/ml vs. 1.6 µg/ml) and renal clearance (CLr) (2.3 ml/min/kg vs. 0.2 ml/min/kg) were observed between the group with severe renal impairment (GFR <10 ml/min) and the group with normal renal function.

Hepatic Impairment:
In patients with mild (Class A) to moderate (Class B) hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to those with normal hepatic function. In these patients urinary clearance of azithromycin appears to increase, perhaps to compensate for reduced hepatic clearance.

5.3 Preclinical safety data

In animal studies using exposures 40 times those achieved at the clinical therapeutic dosages, azithromycin was found to have caused reversible phospholipidosis, but as a rule there were no associated toxicological consequences. The relevance of this finding to humans receiving azithromycin in accordance with the recommendations is unknown.
Electrophysiological investigations have shown that it has potential to prolong the QT interval.

Carcinogenetic 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 or chromosome mutations in *in-vivo* and *in vitro* test models.

Reproduction 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

Sodium phosphate, tribasic
Sodium benzoate
Sodium saccharin
Colloidal silicon dioxyde
Hydroxypropyl methylcellulose
Xanthan gum
Banana flavor
Sucrose

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Keep at room temperature below 25°C before reconstitution.
After reconstitution, it is stable at room temperature (below 25°C) for 5 days.

6.5 Nature and contents of container

Nature of packaging material:
White HDPE heat seal cap with Pilfer-proof safety ring and semi-opaque HDPE bottle.
Presented as 15 ml and 30 ml dry powder for suspension.

15 ml packaging:
Each cardboard box contains 1 bottle, a double sided measuring spoon of 5 and 2.5 ml, and a measuring device marked at 12 ml.
30 ml packaging:
Each cardboard box contains 1 bottle, a double sided measuring spoon of 5 and 2.5 ml, and a measuring device marked at 23 ml.

6.6 Special precautions for disposal and other handling
Any unused material should be disposed according to 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(S)

175/44

9. DATE OF FIRST AUTHORIZATION /RENEWAL OF THE AUTHORIZATION

Date of first authorization : 05.10.1995
Date of last renewal : 22.06.2011

10. DATE OF REVISION OF THE TEXT

10.10.2016