SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCTS

Azithro-Denk 250 mg
Azithro-Denk 500 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Azithro-Denk 250 mg
One film-coated tablet contains azithromycin monohydrate, corresponding to 250 mg azithromycin.

Azithro-Denk 500 mg
One film-coated tablet contains azithromycin monohydrate, corresponding to 500 mg azithromycin.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Azithro-Denk 250 mg
White or off-white, oblong and biconvex film-coated tablet.

Azithro-Denk 500 mg
White or off-white, oblong and biconvex film-coated tablet with a breaking score on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Azithro-Denk is indicated for the treatment of the following bacterial infections, when caused by azithromycin-susceptible bacteria in patients with known hypersensitivity to ß-lactam antibiotics or when ß-lactam antibiotics would be inappropriate for other reasons (see sections 4.4 and 5.1).

- Acute bacterial sinusitis (adequately diagnosed)
- Acute bacterial otitis media (adequately diagnosed)
- Streptococcal pharyngitis, tonsillitis: Only in cases were first line therapy with ß-lactams is not possible or when susceptibility of *Streptococcus pyogenes* towards azithromycin has been shown.
- Acute bacterial exacerbation of chronic bronchitis (adequately diagnosed)
- Mild to moderately severe community acquired pneumonia
- Skin and soft tissue infections of mild to moderate severity as an alternative when ß-lactam antibiotics are not appropriate
- Uncomplicated *Chlamydia trachomatis* urethritis and cervicitis

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

4.2 Posology and method of administration

Method of administration
Azithromycin should be given as a single daily dose. The film-coated tablets can be taken with or without food. The duration of treatment in each of the infectious diseases is given below.

Adults, adolescents and children over 45 kg body weight
The total dosage of azithromycin is 1500 mg spread over three days (500 mg once daily). Alternatively, the dosage can be spread over five days (500 mg as a single dose on the first day and thereafter 250 mg once daily).

In uncomplicated *Chlamydia trachomatis* urethritis and cervicitis the dosage is 1000 mg as a single oral dose.

Adolescents and children less than 45 kg body weight
Azythromycin film-coated tablets are not indicated for these patients. Other pharmaceutical forms of azithromycin, e.g. suspensions may be used.

In the elderly
The same dosage as in adult patients is used in the elderly. Since elderly patients can be patients with ongoing pro arrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsade de pointes (see section 4.4).

In patients with renal impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min). Caution is advised in patients with severe renal impairment (GFR < 10 ml/min) as systemic exposure may be increased (see sections 4.4 and 5.2).

Hepatic insufficiency
A dose adjustment is not necessary for patients with mild (Child-Pough A) to moderately (Child-Pough B) impaired liver function (see section 4.4).

4.3 Contraindications

The use of this product is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any excipient listed in section 6.1 (list of excipients).

4.4 Special warnings and precautions for use

Allergy
As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

Hepatic failure
Since liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin (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.

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

Superinfections
As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms, including fungi is recommended. A superinfection may require an interruption of the azithromycin treatment and initiation of adequate measures.

Pseudomembranous colitis
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.

Use in 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).

QT prolongation
Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsade de pointes, have been seen in treatment with other macrolides including azithromycin (see section 4.8). Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients:
- with congenital or documented QT prolongation;
- currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of class IA (quinidine and procainamide) and class III (dofetilide, amiodarone and sotalol), cisapride and terfenadine; antipsychotic agents such as pimozide; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin;
- with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia;
- with clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Sinusitis
Often, azithromycin is not the substance of first choice for the treatment of sinusitis.

Acute otitis media
Often, Azithromycin is not the substance of first choice for the treatment of acute otitis media.

Pneumonia
Due to the emerging resistance of *Streptococcus pneumoniae* towards macrolides Azithromycin is not the drug of first choice in community acquired pneumonia. In hospital acquired pneumonia Azithromycin should only be used in combination with further appropriate antibiotics.

Skin and soft tissue infections
The main causative agent of soft tissue infections, *Staphylococcus aureus*, is frequently resistant to azithromycin. Therefore, susceptibility testing is considered a precondition for treatment of soft tissue infections with azithromycin.

Cross Resistance
Due to cross-resistance existing among macrolides, in areas with a high incidence of erythromycin resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other antibiotics (see section 5.1).

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).

Oral Anticoagulants
It is recommended that prothrombin time be monitored in patients receiving concomitant treatment with anticoagulants (see 4.5).

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

Pharmaceutical Form
Azithromycin film-coated tablets are not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed.

4.5 Interaction 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. Co-administration of Azithromycin prolonged-release granules for oral suspension with a single 20 ml dose of co-magaldrox (aluminium hydroxide and magnesium hydroxide) did not affect the rate and extent of azithromycin absorption.

Cetirizine
In healthy volunteers, co-administration 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)
Co-administration 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 (P-gp substrates)
Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if Azithromycin and P-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered.

Zidovudine
Single l000 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.

CYP3A4 substrates
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.

Even though Azithromycin does not appear to inhibit the enzyme CYP3A4, caution is advised when combining the medicinal product with quinidine, ciclosporine, cisapride, astemizole, terfenadine, ergot alkaloids, pimozide or other medicinal products with a narrow therapeutic index predominantly metabolised by CYP3A4.

Ergot
Due to the theoretical possibility of ergotism, the concurrent use of Azithromycin with ergot derivatives is not recommended (see section 4.4).

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

Atorvastatin
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.

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 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.

Ciclosporin
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 ciclosporin, the resulting ciclosporin 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 co-administration of these drugs is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

Cisapride
Cisapride is metabolized in the liver by the enzyme CYP 3A4. Because other macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsade de pointes.

Efavirenz
Co-administration 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
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 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 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
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.

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

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

Triazolam
In 14 healthy volunteers, co-administration 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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of azithromycinin pregnant women. In reproduction toxicity studies in animals azithromycin was shown to pass the placenta, but no teratogenic effects were observed (see section 5.3). The safety of Azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Therefore Azithromycin should only be used during pregnancy if the benefit outweighs the risk.

Breastfeeding

Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in nursing women that have characterized the pharmacokinetics of Azithromycin excretion into human breast milk. Because it is not known whether Azithromycin may have adverse effects on the breast-fed infant, nursing should be discontinued during treatment with azithromycin. Among other things diarrhoea, fungus infection of the mucous membrane as well as sensitisation is possible in the nursed infant.

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 a patient's ability to drive or operate machinery.

4.8 Undesirable effects

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

The frequency grouping is defined using the following convention: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very Rare (< 1/10,000); and Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to<1/1,000)	Frequency Not known
Infections and Infestations			Candidiasis, vaginal infection, pneumonia, fungal infection, bacterial infection, pharyngitis, gastroenteritis, respiratory disorder, rhinitis, oral		*Pseudomembranous colitis* (*Clostridium difficile associated diarrhoea*) (see section 4.4)

			candidiasis		
Blood and Lymphatic System Disorders			Leukopenia, neutropenia, eosinophilia		*Thrombocytopenia, haemolytic anaemia*
Immune System Disorders			Angioedema, hypersensitivity		*Anaphylactic reaction* (see section 4.4)
Metabolism and Nutrition Disorders			Anorexia		
Psychiatric Disorders			Nervousness, insomnia	Agitation, depersonalisation	*Aggression, anxiety,* delirium, hallucination
Nervous System Disorders		Headache	Dizziness, somnolence, dysgeusia, paraesthesia		*Syncope, convulsion,* hypoaesthesia *psychomotor hyperactivity, anosmia, ageusia, parosmia, myasthenia gravis* (see section 4.4)
Eye Disorders			Visual impairment		
Ear and Labyrinth Disorders			Ear disorder, vertigo		Hearing impairment including deafness and/or tinnitus
Cardiac Disorders			Palpitations		*Torsade de pointes and arrhythmia* (see section 4.4), *including ventricular tachycardia*, electrocardiogram QT prolonged (see section 4.4)
Vascular Disorders			Hot flush		*Hypotension*
Respiratory, thoracic and mediastinal disorders			Dyspnoea, epistaxis		

Gastrointestinal Disorders	Diarrhoea	Vomiting, abdominal pain, nausea	Constipation, flatulence, dyspepsia, gastritis, dysphagia, abdominal distension, dry mouth, eructation, mouth ulceration, salivary hypersecretion		*Pancreatitis, tongue discolouration*
Hepatobiliary Disorders			Hepatitis	Hepatic function abnormal, *jaundice cholestatic*	*Hepatic failure (which has rarely resulted in death)* (see section 4.4), *hepatitis fulminant, hepatic necrosis*
Skin and Subcutaneous Tissue Disorders			Rash, pruritus, urticaria, dermatitis, dry skin, hyperhidrosis	Photosensitivity reaction	Stevens-Johnson syndrome, *toxic epidermal necrolysis, erythema multiforme*
Musculoskeletal and Connective Tissue Disorders			Osteoarthritis, myalgia, back pain, neck pain		Arthralgia
Renal and Urinary Disorders			Dysuria, renal pain		*Renal failure acute, nephritis interstitial*
Reproductive System and Breast Disorders			Metrorrhagia, testicular disorder		
General Disorders and Administration Site Conditions			Oedema, asthenia, malaise, fatigue, face oedema, chest pain, pyrexia, pain, peripheral oedema		
Investigations		Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased, basophils increased, monocytes increased, neutrophils increased	Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal, blood alkaline		

			phosphatase increased, chloride increased, glucose increased, platelets increased, hematocrit decreased, bicarbonate increased, abnormal sodium		
Injury and Poisoning			Post procedural complication		

Reporting of suspected adverse reactions

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

4.9 Overdose

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. In the event of overdosage, general symptomatic and supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Azithromycin is the first macrolide antibiotic of the azalide-group. The molecule is built 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.

Mode of action

The mode of action of Azithromycin is based on the inhibition of the bacterial protein synthesis by binding to the ribosomal 50 S subunit and inhibiting translocation of the peptides. The effect is mostly bacteriostatic.

Pharmacokinetic/pharmacodynamic relation

The efficacy depends mainly on the ratio between AUC (area under the curve) and MIC of the causative organism.

Mechanisms of resistance

Resistance against Azithromycin can be based on the following mechanisms:

- Efflux: Resistance can be caused by an increase in the number of efflux pumps in the cytoplasmatic membrane. Only 14- and 15-ring-membered macrolides are concerned (so called M-phenotype).

- Change of target structure: Affinity to ribosomal binding sites is lowered by methylation of the 23S rRNA, causing a resistance against macrolides (M), lincosamides (L) and streptgramines of the B-group (S_B) (so called MLS_B-phenotype).
- Effluxpumps can actively transport Azithromycin out of the cell.
- Enzymatic inactivation of macrolides is only of minor clinical interest.

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

Breakpoints
The testing of Azithromycin was done by using the usual dilution series. The following minimal inhibitory concentrations for sensitive and resistant organisms were defined.

EUCAST (European Committee on Antimicrobial Susceptibility Testing) Breakpoints

pathogens	**susceptible**	**resistant**
Staphylococcus spp.	≤ 1 mg/l	> 2 mg/l
Streptococcus spp. (groups A, B, C, G)	≤ 0,25 mg/l	> 0,5 mg/l
Streptococcus pneumoniae	≤ 0,25 mg/l	> 0,5 mg/l
Haemophilus influenzae	≤ 0,12 mg/l	> 4 mg/l
Moraxella catarrhalis	≤ 0,5 mg/l	> 0,5 mg/l
Neisseria gonorrhoeae	≤ 0,25 mg/l	> 0,5 mg/l

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information provides only an approximate guidance on the probability of an organism being susceptible to azithromycin.

Commonly susceptible species
Aerobic Gram-positive micro-organisms
Mycobacterium avium°
Streptococcus pyogenes [1]
Aerobic Gram-negative micro-organisms
Haemophilus influenzae[$]
Moraxella catarrhalis°
Neisseria gonorrhoeae
Other micro-organisms
Chlamydophila trachomatis°
Chlamydophila pneumoniae°

Legionella pneumophila°
Mycoplasma pneumoniae°
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms
Staphylococcus aureus (Methicillin-susceptible)
Staphylococcus aureus (Methicillin-resistant)[+]
Streptococcus agalactiae
Streptococcus pneumoniae
Inherently resistant organisms
Aerobic Gram-negative micro-organisms
Escherichia coli
Klebsiella spp.
Pseudomonas aeruginosa

° No updated data were available at release of tables. Primary literature, scientific standard literature and therapeutic recommendations assume susceptibility.

[$] Inherent susceptibility of most of the isolates shows intermediate resistance.

[+] At least one region shows resistance rates higher than 50%.

[1] The resistance rates are in some studies ≥10%.

Other information
(Cross) resistance

A complete cross resistance exists among erythromycin, azithromycin, other macrolides and lincosamides for *Streptococcus pneumoniae*, beta-haemolytic streptococcus of group A, *Enterococcus* spp. and *Staphylococcus aureus*, including methicillin resistant *S. aureus* (MRSA).

The induction of significant resistance in both *in vitro* and *in vivo* models is $\leq$1 dilution rise in MICs for *S.pyogenes*, *H.influenzae*, and *Enterobacterciae* after nine sub lethal passages of active substance and three dilution increase for *S.aureus* and development of *in vitro* resistance due to mutation is rare.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, the bioavailability of Azithromycin is approximately 37 %. Peak plasma levels are reached after 2-3 hours.

Distribution
Orally administered Azithromycin is widely distributed over the whole body. Pharmacokinetic studies have shown considerably higher Azithromycin concentrations in the tissues (up to 50 times the maximum concentration observed in the plasma) than in the plasma. This indicates that the substance is extensively bound in the tissues (steady-state volume of distribution approximately 31 l/kg). The mean maximum concentration observed (C_{max}) after a single dose of 500 mg is approximately 0.4 µg/ml, 2-3 hours after administration. With the recommended dosage no accumulation in the serum/plasma occurs. Accumulation does occur in the tissues where the levels are much higher than in

the serum/plasma. Three days after administration of 500 mg as a single dose or in divided doses, concentrations of 1.3-4.8 µg/g, 0.6-2.3 µg/g, 2.0-2.8 µg/g and 0-0.3 µg/ml are found in lung, prostate, tonsil and serum, respectively. Mean peak concentration measured in peripheral leucocytes, are higher than the MIC90 of the most common pathogens.

In experimental in-vitro and in-vivo studies, Azithromycin accumulates in phagocytes; release is promoted by active phagocytosis. In animal models this process appeared to contribute to the accumulation of Azithromycin in tissue. The binding of Azithromycin to plasma proteins is variable, and varies from 52 % at 0.05 µg/ml to 18 % at 0.5 µg/ml, depending on the serum concentration.

Metabolism and Excretion
The terminal plasma elimination half-life follows the tissue depletion half-life of 2 to 4 days. In elderly volunteers (>65 years), higher (29 %) AUC values were always observed after a 5-day course than in younger volunteers (<45 years). However, these differences are not considered to be clinically relevant; no dose adjustment is therefore recommended. Approximately 12 % of an intravenously administered dose is excreted in unchanged form with the urine over a period of 3 days; the major proportion in the first 24 hours. Concentrations of up to 237 µg/ml azithromycin, 2 days after a 5-day course of treatment, have been found in human bile, together with 10 metabolites (formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by splitting of the cladinose conjugate). A comparison of HPLC and microbiological methods of determination suggests that the metabolites do not play a role in the microbiological activity of azithromycin.

Pharmacokinetics in Special populations
Renal Insufficiency
Following a single oral dose of Azithromycin 1g, mean C_{max} and AUC_{0-120} increased by 5.1 % and 4.2 % respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 10-80 ml/min) compared with normal renal function (GFR>80ml/min). In subjects with severe renal impairment, the mean C_{max} and AUC_{0-120} increased 61 % and 35 % respectively compared to normal.

Hepatic insufficiency
In patients with mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of Azithromycin compared to normal hepatic function. In these patients, urinary recovery of Azithromycin appears to increase perhaps to compensate for reduced hepatic clearance.

Elderly
The pharmacokinetics of Azithromycin in elderly men was similar to that of young adults; however, in elderly women, although higher peak concentrations (increased by 30-50 %) were observed, no significant accumulation occurred.

Infants, toddlers, children and adolescents
Pharmacokinetics have been studied in children aged 4 months – 15 years taking capsules, granules or suspension. At 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5, the C_{max} achieved is slightly lower than adults with 224µg/l in children aged 0.6-5 years and after 3 days dosing and 383 µg/l in those aged 6-15 years. The $t_{1/2}$ of 36h in the older children was within the expected range for adults.

5.3 Preclinical safety data

In animal tests in which the dosages used amounted to 40times 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. Azithromycin has not been found to cause toxic reactions in patients when administered in accordance with the recommendations.

Electrophysiological investigations have shown that Azithromycin prolongs the QT interval.

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

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

In embryotoxicity studies in mice and rats no teratogenic effects were observed. In rats, Azithromycin dosages of 100 and 200 mg/kg bodyweight/day led to slight retardations in fetal ossification and in maternal weight gain. In peri-/postnatal studies in rats, slight retardations in physical development and delay in reflex development were observed following treatment with 50 mg/kg/day Azithromycin and above.

Neonate rats and dogs exhibited no greater sensitivity to Azithromycin than adult animals of the same species.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Calcium hydrogen phosphate
Microcrystalline cellulose
Hyprolose
Sodium dodecyl sulphate
Sodium carboxymethyl starch (type A)
Sodium stearyl fumarate

Coating:
Hypromellose
Macrogol 6000
Talc
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

PVC/PVDC/Al blister.

Azithro-Denk 250 mg
Pack sizes: 6 film-coated tablets.

Azithro-Denk 500 mg
Pack sizes: 3 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

DENK PHARMA GmbH & Co. KG
Prinzregentenstr. 79
81675 Munich
Germany

8 MARKETING AUTHORIZATION NUMBER IN GERMANY

Azithro-Denk 250 mg: 63092.00.00

Azithro-Denk 500 mg: 63093. 00.00

9 DATE OF FIRST AUTHORIZATION

07.12.2005

10 DATE OF REVISION OF THE TEXT

June 2016

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription