SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AZIQUE I.V.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:

Azithromycin USP (as dihydrate) Equivalent to Azithromycin (anhydrous) USP.....500 mg For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile lyophilized powder for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AZIQUE I.V. is indicated in the treatment of community-acquired pneumonia caused by susceptible organisms, including Legionella pneumophila, in patients who require an initial therapy intravenously. AZIQUE I.V. is indicated in the treatment of pelvic inflammatory disease caused by susceptible organisms, in patients who require an initial therapy intravenously.

4.2 Posology and method of administration

In the treatment of community-acquired pneumonia, the recommended dosage for an adult is 500 mg of AZIQUE I.V. in a single daily dose intravenously for at least two days. Intravenous therapy must be followed by oral therapy with a dose of 500 mg once-daily dosing regimen for a total period of treatment of 7-10 days. The time it takes to make the transition to oral therapy must be decided by the physician depending on the clinical

response. In the treatment of pelvic inflammatory disease, the recommended

dosage for an adult is 500 mg of Azithromycin powder for solution for infusion in a single daily dose intravenously for one or two days. Intravenous therapy must be followed by oral therapy with a dose of 250 mg once-daily dosing regimen for a total period of treatment of 7 days. The time it takes to make the transition to oral therapy must be decided by the physician depending on the clinical response.

Elderly The same dosage regimen can be applied to elderly patients. Since elderly patients are more susceptible to developing cardiac arrhythmia, particular caution is recommended due to the risk of developing cardiac arrhythmia and torsade de pointes. Paediatric population The efficacy and tolerability of Azithromycin powder for solution for infusion in the treatment of infections in children and adolescents under the age of 16 years have not been established. In controlled clinical trials azithromycin by oral administration was administered to paediatric patients (aged from 6 months to 16 years). For information on the use of azithromycin in the treatment of paediatric patients, see the of the oral formulations of the azithromycin. Renal Impairment No dose adjustment is required for patients with a glomerular filtration rate

(GFR) of 10 - 80 mL/min; however, caution is necessary for patients with a

GFR of < 10 mL/min. Hepatic Impairment No dose adjustment is required for patients with mild to moderate hepatic impairment, but the medicinal product should be used with caution in patients with significant hepatic diseases Method of administration Azithromycin powder for solution for infusion after reconstitution and dilution should be administered by intravenous infusion. The concentration of the solution and the duration of the infusion must be equal to: 1 mg/mL in 3 hours or 2 mg/mL in 1 hour. Azithromycin powder for solution for infusion should not be administered as a bolus or intramuscularly. Preparation Of the Solution for Intravenous Administration Reconstitution The initial solution must be prepared by adding 4.8 mL of water for injections in the vial containing the powder. Shake the vial until the powder has completely dissolved. Using a standard 5-mL syringe is recommended to take the exact volume of 4.8 mL of sterile water for

injections. 1 mL of reconstituted solution contains 100 mg of

azithromycin. The drugs to be administered via parenteral route must be carefully controlled to exclude the presence of particulate in the solution. If suspended particles can be seen, the solution should be discarded. The reconstituted solution must be diluted prior to administration by following the instructions below. Dilution In order to obtain a concentration of azithromycin equal to 1.0-2.0 mg/mL, remove 5 mL of the reconstituted solution from the vial (concentration of 100 mg/mL),

adding it to the appropriate volume of one of the solvents Final concentration of the solution for infusion Solvent volume

1.0 mg/mL 500 mL

2.0 mg/mL 250 mL

The intravenous administration of a 500 mg dose of azithromycin, diluted according to the instructions must be performed within a period of not less than 60 minutes.

4.3 Contraindications

Hypersensitivity to the active ingredient, to erythromycin, any other macrolide or ketolide antibiotics, or any other excipients list Azithromycin should not be co-administered with ergot derivatives because of the theoretical possibility of ergotism.

4.4 Special Warning and Precautions for use:

Hypersensitivity As with erythromycin and other macrolides serious rare allergic reactions have been reported, including angioneurotic oedema and anaphylaxis (rarely fatal), dermatological reactions including acute generalized exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and rash with eosinophilia and systemic symptoms (DRESS). Some of these reactions associated with Azithromycin have caused recurring symptoms and have required an observation period and prolonged treatment. If there is an allergic reaction, the administration of the medicinal product must be discontinued and adequate therapy started. Physicians should be aware of the fact that when the symptomatic therapy is suspended allergic symptoms may occur. Hepatotoxicity Azithromycin must be used with caution in patients with serious liver disease since its primary route of elimination is the liver. With azithromycin, there have been reports of hepatic impairment, hepatitis, cholestatic jaundice, hepatic necrosis and fulminant hepatic failure, potentially caused by hepatic impairment, some of which had fatal

results. A few patients may have had previous hepatic diseases or may

have taken other hepatotoxic medicinal products. If signs and symptoms of hepatic dysfunction develop, such as rapid appearance of asthaenia associated with jaundice, dark urine, bleeding or hepatic encephalopathy, diagnostic

analysis/exams must be run on hepatic function immediately. Immediately suspend treatment with azithromycin if any signs of hepatic dysfunction develop. Infantile hypertrophic pyloric stenosis (IHPS) As a result of the use of azithromycin in infants (treatment up to 42nd day of life), infantile hypertrophic pyloric stenosis (IHPS) has been

reported. Parents and health operators must be told to contact their

physician if vomiting or irritability occurs after eating. Ergotamine Derivatives Co-administration of macrolide antibiotics in patients being treated with ergotamine derivatives has precipitated convulsive ergotism. There are no data currently available on the possibility of interaction between ergotamine and azithromycin. However, due to the theoretical possibility of ergotism, azithromycin and ergotamine must not be co-administered. As with all other antibiotic preparations, it is recommended to carefully monitor for any development of super infections with resistant microorganisms including fungi. Diarrhoea associated with Clostridium difficile As with almost all antibiotics, including azithromycin, there have been reports of diarrhoea associated with Clostridium difficile (CDAD), the severity of which can vary from mild diarrhoea to fatal colitis. Treatment with antibiotics alters the normal flora of the colon and results in excessive growth of C. difficile.

C. difficile produces toxins A and B, which contribute to the

development of diarrhoea. The strains of C. difficile that produce excess toxins cause an increase in morbidity and mortality rates as these infections are usually refractory to antibacterial therapy and often require a colectomy. The possibility of diarrhoea associated with

C. difficile must be considered in all patients who develop diarrhoea

after a treatment with antibiotics. A detailed patient history is also necessary because cases of diarrhoea associated with C. difficile have been reported over two months after the administration of antibiotics. Renal Impairment In patients with a GFR of < 10 mL/min a 33% increase in systemic exposure to azithromycin was observed. Prolonged QT interval In treatment with macrolides, including azithromycin, a prolonged cardiac repolarisation and QT interval were found using ECG, with the risk of developing cardiac arrhythmia and torsade de pointes.

Therefore, given that the following situations can cause an increase in the risk of ventricular arrhythmias (including torsade de pointes) that can lead to cardiac arrest, azithromycin should be administered with caution in patients who have concomitant proarrhythmic conditions (especially women and elderly patients). Prescribers must take into account the risk of the prolongation of the QT interval, which can be fatal, in assessing the risks and benefits of

azithromycin in groups of patients at risk, such as:

• Patients with congenital or documented prolonged QT interval.

• Patients under treatment with other active ingredients that prolong

the QT interval such as class IA (quinidine and procainamide) and class III anti-arrhythmics (dofetilide, amiodarone and sotalol), cisapride and terfenadine, antipsychotic drugs such as pimozide, antidepressants such as citalopram, fluoroquinolones such as moxifloxacin, levofloxacin and chloroquine.

• Patients with electrolyte changes, especially in cases of

hypopotassaemia and hypomagnesaemia.

• Patients with clinically significant bradycardia, cardiac arrhythmia

or severe heart failure.

• Women and elderly patients who may demonstrate greater

sensitivity to the (drug-related) effects of alteration of the QT interval. In patients being treated with azithromycin, there have been reports of exacerbation in symptoms of myasthenia gravis and initial development of myasthenic syndroms,. The safety and efficacy of azithromycin for intravenous administration in the treatment of paediatric infections have not been established. Azithromycin powder for solution for infusion has to be reconstituted and diluted by following the instructions and must be administered with infusions lasting at least 60 minutes. Not for bolus injection or intramuscularly. AZIQUE I.V. contains 114 mg of sodium per each vial, equivalent to 5,7% of the WHO recommended maximum daily intake of 2 g sodium for an adult. AZIQUE I.V. may be further prepared for administration with sodiumcontaining solutions and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

4.5 Interaction with other medicinal products and other forms of interactions:

Antacids In a pharmacokinetic study on the effects caused by co-administration of antacids and oral azithromycin, no effects were detected on the bioavailability of azithromycin, even though a decrease of approximately 25% was observed in maximum serum concentrations. Therefore, patients being treated with oral azithromycin and antacids containing magnesium and aluminium must not take the two drugs concomitantly. The administration of oral antacids should not alter the characteristics of azithromycin administered intravenously. Cetirizine In healthy volunteers, the concomitant administration of a 5-day regimen of azithromycin and 20 mg of steady state cetirizine did not show any pharmacokinetic interactions or significant alterations in the QT interval. Didanosine It was observed that co-administration of daily doses of azithromycin 1,200 mg/day and didanosine 400 mg/day in six HIV-positive patients did not have any effect on the steady state pharmacokinetics of didanosine compared to placebo. Digoxin and colchicine (P-glycoprotein substrates) There have been reports that the administration of macrolide antibiotics, including azithromycin with P-glycoprotein substrates such as digoxin, has caused an increase in the blood serum levels of P-glycoprotein substrates. Therefore, the possibility of an increase in digoxin blood serum levels must be carefully considered when co-administering azithromycin and P-glycoprotein substrates, such as digoxin. Clinical monitoring is required both during and after interruption of azithromycin treatment, as well as monitoring for possible increases in digoxin levels. Zidovudine The administration of individual 1,000 mg doses and multiple 1,200 mg or 600 mg doses of azithromycin did not substantially modify the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, the administration of azithromycin resulted in increased concentrations of phosphorylated zidovudine, its clinically active metabolite, in the peripheral blood mononuclear cells. The clinical importance of this data is not clear, but it may still render benefits to the patient. Azithromycin does not significantly interact with the cytochrome P450 hepatic system. It is not

deemed to be involved in pharmacokinetic interactions as found with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome metabolite complex does not occur with azithromycin. Ergotamine Due to the potential onset of convulsive ergotism, concomitant use of azithromycin and ergotamine derivatives is not recommended. Pharmacokinetic studies have been conducted between azithromycin and the following drugs, for which significant metabolic activity was noted and mediated by cytochrome P450. HMG-CoA Reductase Inhibitors (Statins) The concomitant administration of atorvastatin (10 mg/day) and azithromycin (500 mg/day) did not alter the plasma concentrations of atorvastatin (based on an HMG-CoA reductase inhibition assay) and thus did not cause alterations of HMG-CoA reductase activity. However, postmarketing cases of rhabdomyolysis have been reported in patients treated with azithromycin and statins. Carbamazepine During an interaction study conducted in healthy volunteers, no significant effects were observed on plasma levels of carbamazepine or its active metabolite in patients who were taking azithromycin concomitantly. Cimetidine During a pharmacokinetic study conducted to assess the effects of a single dose of cimetidine administered 2 hours after azithromycin, no alterations were noted in azithromycin pharmacokinetics. Cyclosporine In a pharmacokinetic study conducted in healthy volunteers administered an oral dose of 500 mg/day of azithromycin for 3 days and then a single oral dose of 10 mg/kg of cyclosporine, significant increases in the Cmax and AUC0-5 values for cyclosporine were observed. Therefore, any coadministration of these two drugs requires caution. If co-administration of these two drugs is absolutely necessary, cyclosporine levels must be closely monitored and the dose of cyclosporine must be adjusted as needed. Efavirenz Co-administration of a single daily dose of azithromycin (600 mg) and efavirenz (400 mg) for seven days did not cause any clinically significant pharmacokinetic interaction. Fluconazole Co-administration of a single dose of azithromycin (1,200 mg) did not alter the pharmacokinetics of a single dose of fluconazole (800 mg). The total exposure time and half-life of azithromycin were not influenced by co-administration of fluconazole, although there was a clinically insignificant decrease in Cmax (18%). Indinavir Concomitant administration of a single dose of azithromycin (1,200 mg) did not show a statistically significant effect on the pharmacokinetics of indinavir administered three times a day for 5 days at

doses of 800 mg. Methylprednisolone A pharmacokinetic study conducted on healthy volunteers showed that azithromycin does not significantly influence methylprednisolone pharmacokinetics. Midazolam In healthy volunteers, concomitant administration of azithromycin 500 mg/day for 3 days did not cause any clinically significant changes in the pharmacokinetics or pharmacodynamics of a single dose of midazolam 15 mg. Nelfinavir Co-administration of azithromycin (1,200 mg) and steady state nelfinavir (750 mg three times per day) caused an increase in the concentrations of

azithromycin. No clinically significant adverse reactions were observed

and no dose adjustment was necessary. Rifabutin Concomitant administration of azithromycin and rifabutin does not change the serum concentrations of the two drugs. Cases of neutropenia have been observed in some patients taking the two drugs concomitantly; although it is known that rifabutin can cause neutropenia, it is not possible to verify a causal relation between the aforementioned episodes of neutropenia and the association of rifabutin and azithromycin. Sildenafil In healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg/day for 3 days) on the AUC and Cmax of sildenafil or its major circulating metabolite. Theophylline Co-administration of azithromycin and theophylline to healthy volunteers did not show any clinically significant interaction between the two drugs. Terfenadine Pharmacokinetic studies did not show any interactions between azithromycin and terfenadine. Some rare cases were reported in which the possibility of this interaction could not be completely ruled out; however, there is no scientific evidence that the interaction occurred. Triazolam In 14 healthy volunteers, concomitant administration of 500 mg of azithromycin on Day 1 and 250 mg on Day 2 and 0.125 mg of triazolam on Day 2 did not have significant effects on the pharmacokinetic variables of triazolam compared to triazolam and placebo. Trimethoprim/Sulfamethoxazole After concomitant administration of trimethoprim/sulfamethoxazole (160 mg/800 mg) and azithromycin (1,200mg) for 7 days, no significant effect was found on peak concentrations, exposure time, or urinary excretion of both trimethoprim and sulfamethoxazole on Day 7. Azithromycin serum concentrations were similar to those found in other studies. Coumarin-type Oral Anticoagulants In a pharmacokinetic study conducted on

healthy volunteers, it was observed that azithromycin did not modify the anticoagulant effect of a single 15 mg dose of warfarin. During the post-marketing phase, cases of increased anticoagulant action were reported following co-administration of azithromycin and coumarintype oral anticoagulants. Even though a causal relationship has not been established, it is recommended to re-evaluate the frequency of monitoring prothrombin time when administering azithromycin to patients receiving coumarin-type anticoagulants.

4.4 Special warnings and precautions for use

Not provided in the source SmPC.

4.5 Interaction with other medicinal products and other forms of interaction

Not provided in the source SmPC.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Animal reproduction studies have been conducted using scaled doses to reach moderately toxic maternal concentrations. No evidence of foetal risk due to azithromycin has emerged from these studies. In animal reproductive toxicology studies, there is evidence that azithromycin crosses the placenta, but no teratogenic effects have been observed. There is a large amount of data from observational studies performed in several countries on exposure to azithromycin during pregnancy, compared to no antibiotic use or use of another antibiotic during the same period. While most studies do not suggest an association with adverse fetal effects such as major congenital malformations or cardiovascular malformations, there is limited epidemiological evidence of an increased risk of miscarriage following azithromycin exposure in early pregnancy. Should only be used during pregnancy if clinically needed and the benefit of treatment is expected to outweigh any small increased risks which may exist.

Breastfeeding:

The limited information available from the published literature, indicates that azithromycin is present in human milk in a highest median daily dose estimated to be between 0.1 and 0.7 mg/kg/day. No side effects have been observed in breast-fed

infants. It must be decided whether to discontinue breastfeeding or discontinue/refrain from therapy with azithromycin taking into consideration the benefits of breastfeeding for the child and that of therapy for the woman. Fertility In fertility studies conducted in rats, a reduction in the fertility rate following administration of azithromycin was observed. The significance of these results in humans is unknown.

4.7 Effects on ability to drive and use machine:

There is no evidence that azithromycin affects the ability of patients to drive vehicles or use machines.

4.7 Effects on ability to drive and use machines

Not provided in the source SmPC.

4.8 Undesirable effects

The table below lists the side effects identified during clinical studies and post-marketing surveillance, and they are subdivided based on system organ class and frequency. The possible adverse reactions identified during post-marketing surveillance are shown in italics. Frequency is defined using the following parameters: Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1,000, < 1/100); Rare (≥ 1/10,000, < 1/1,000); Very Rare (< 1/10,000); Not known (frequency cannot be defined based on available data). Possible side effects are listed in order of decreasing severity within each frequency classification. Adverse reactions with possible or probable correlation to azithromycin based on the results of clinical studies and postmarketing surveillance. System Organ Class Adverse Reaction Frequency Candidiasis, vaginal infection, pneumonia, fungal Uncomon infection, bacterial infection, pharyngitis, Infections gastroenteritis, respiratory disorders, rhinitis, oral and candidiasis infestations Pseudomembranous colitis Not Known Blood and lymphatic Leukopaenia, neutropaenia, eosinophilia Uncommon system disorders Thrombocytopaenia, haemolytic anaemia Not Known Immune system Angiooedema, hypersensitivity Uncommon Disorders Anaphylactic reaction Not known Metabolism and Anorexia Uncommon nutrition disorders Nervousness, insomnia Uncommon Psychiatric Disorders Agitation Rare Agitation Rare Aggression, anxiety, delirium, hallucinations Not known Nervous System

Disorders Common Nervous System Dizziness, somnolence, dysgeusia, paraesthesia Uncommon Disorders Syncope, convulsions,hypoaesthesia, psychomotor Not known hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis Eye Disorders Vision impairment Uncommon Ear disorders, vertigo Uncommon Ear and Labyrinth Disorders Hearing impairment including deafness and/or Not known tinnitus Palpitations Uncommon Cardiac disorders Torsade de pointes, arrhythmia including Not known ventricular tachycardia, prolonged QT interval on the electrocardiogram Hot flashes Uncommon Vascular disorders Hypotension Not known Respiratory, Thoracic Dyspnoea, epistaxis Uncommon and Mediastinal Disorders Diarrhoea Very common Vomiting, abdominal pain, nausea Common Gastrointestinal Constipation, flatulence, dyspepsia, Uncommon disorders gastritis, dysphagia, abdominal distension, dry mouth, eructation, mouth ulceration, salivary hypersecretion Pancreatitis, tongue discolouration Not known Impaired hepatic function, cholestatic jaundice Rare Hepatobiliary disorders Hepatic failure (rarely fatal), fulminant Not known hepatitis, hepatic necrosis Rash, pruritus, urticaria, dermatitis, dry skin, Uncommon hyperhidrosis Photosensitivity reaction, acute generalized Rare Skin and subcutaneous exanthematous pustulosis (AGEP)§, Drug rash tissue disorders with eosinophilia and systemic symptoms (DRESS) Stevens-Johnson syndrome, toxic epidermal Not Known necrolysis, erythema multiforme Musculoskeletal Osteoarthritis, myalgia, back pain, neck pain Uncommon and connective Arthralgia Not Known tissue Disorders Renal and urinary Dysuria, renal pain Uncommon disorders Acute renal insufficiency, interstitial nephritis Not known Reproductive System Metrorrhagia, testicular disorders Uncommon and Breast Disorders Oedema, asthaenia, malaise, fatigue, facial Uncommon oedema, chest pain, pyrexia, pain, peripheral General disorders and oedema administration site conditions Pain at injection site*, inflammation at injection Common site* Decrease in lymphocyte count, increase in Common eosinophil count, decrease in blood bicarbonate, increase in basophils, increase in monocytes, increase in neutrophils Increase in aspartate aminotransferase (AST), Uncommon Diagnostic tests increase in alanine aminotransferase (ALT), increase in blood bilirubin, increase in blood urea, increase in blood creatinine, abnormal blood potassium, increase in blood alkaline phosphatase, increase in chloride levels, increase in glucose, increase in platelets, decrease in haematocrit, increase in blood bicarbonate, abnormal sodium

levels Injury and Poisoning Post-procedural complications Uncommon Frequency ADR represented by the estimated upper limit of the 95% confidence interval calculated using the "Rule of 3" * only for the powder for solution for infusion Adverse reactions possibly or probably related to Mycobacterium Avium Complex prophylaxis and treatment based on clinical trial experience and post-marketing surveillance. These adverse reactions differ from those reported with immediate release or prolonged

release formulations, in kind or in frequency:

Very common Common Uncommon (≥ 1/10) (≥ 1/100, < 1/10) (≥ 1/1,000, < 1/100) Metabolism and nutrition Anorexia Disorders Dizziness Nervous system Headache Hypoesthesia disorders Paraesthesi a Dysgeusia Ear and Labyrinth Deafness Impaired hearing Disorders Tinnitus Cardiac disorders Palpitations Stevens- Skin and Johnson Rash subcutaneous tissue syndrome Pruritu disorders s Photosensitivity reaction Musculoskeletal and connective tissue Arthralgia disorders General disorders and administration Asthaenia Fatigue site Malaise Conditions Eye Disorders Vision impairment Diarrhoea Abdominal pain Nausea Gastrointestinal Flatulence disorders Abdominal discomfort Loose stools Hepatobiliary Hepatitis Disorders Reporting of suspected adverse reactions. Healthcare professionals are requested to report any suspected adverse reactions via the Pharmacy and Poisons Board pharmacovigilance

Electronic Reporting system (PvERS):

4.9 Overdose

Side effects reported with doses greater than those recommended were similar to those reported with normal doses. In case of overdose, the appropriate general symptomatic and support measures are indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antibacterials for systemic use, Macrolides ATC Code: J01FA10 Azithromycin is the first drug in a sub-class of macrolide antibiotics called azalides, and is chemically different from erythromycin. It is chemically derived from

the insertion of a nitrogen atom into the lactone ring of the erythromycin A. Its chemical name is: 9-deoxy-9a-aza-9a-methyl-9ahomoerithromycin A. The molecular weight is 749.0. Mechanism of action Azithromycin binds to the 23S rRNA of 50S ribosomal subunit. Azithromycin blocks protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit. Cardiac electrophysiology The prolongation of the QT interval was studied in a randomized, placebocontrolled study in parallel groups on 116 healthy subjects who either took chloroquine (1,000 mg) alone or in combination with azithromycin (500 mg, 1,000 mg, 1,500 mg once a day). The coadministration with azithromycin resulted in an increase in QTc interval in a dose- and concentration-dependent way. Maximum increases in the QTcF compared with chloroquine monotherapy (whose differences observed with respect to the placebo vary in the range of between18.4 and 35 ms) were on average (upper limit of the 95% confidence interval) 5 (10 ms), 7 (12 ms) and 9 (14) ms following the concomitant administration of 500 mg, 1,000 mg, 1,500 mg of azithromycin respectively. Mechanism of resistance The two most frequently encountered mechanisms of resistance to macrolides, including azithromycin, are target modification (very often due to methylation of 23S rRNA) and active efflux. The occurrence of these resistance mechanisms varies from species to species, and within each species the frequency of resistance varies depending on the geographical location. The most important ribosomal modification that determines reduced binding of macrolides is posttranscriptional (N)- 6 demethylation of adenine at nucleotide A2058 (E.coli numbering system) of the 23S rRNA by the methylases codified by erm (erithromycin ribosomal methylase) genes. Ribosomal modifications often determine cross resistance

(MLSBphenotype) to other classes of antibiotics whose ribosomal binding

sites overlap that of the macrolides: the lincosamides (including clindamycin), and the Type B streptogramins (which include, for example, the quinupristin component of quinupristin/dalfopristin). Different erm genes are present in different bacterial species, in particular streptococci and staphylococci. Susceptibility to macrolides can also be affected by less frequently encountered mutational changes in nucleotides A2058 and A2059, and at some other positions of 23S rRNA or in the

large subunit ribosomal proteins L4 and L22. Efflux pumps occur in a number of species, including Gram-negatives, such as Haemophilus influenzae (where they may determine intrinsically higher minimum inhibitory concentrations [MICs]) and staphylococci. In streptococci and in enterococci, an efflux pump that recognizes macrolides measuring 14 and 15 atoms (including, respectively, erythromycin and azithromycin) is codified by mef (A) genes. Method for Determining In Vitro Susceptibility of Bacteria to Azithromycin Susceptibility testing should be conducted using standardised laboratory methods such as those described by the Clinical and Laboratory Standards Institute (CLSI). These include dilution methods (MIC

determination) and disk susceptibility methods.

Both the CLSI and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) provide interpretative criteria for these

methods. Based on a number of studies, it is recommended that the in

vitro activity of azithromycin be tested in ambient air to ensure physiological pH of the growth medium. Elevated CO2 pressures, such as those used for streptococci and anaerobic bacteria, and occasionally for other species, results in a reduction in the pH of the medium. This has a greater adverse effect on the apparent potency of azithromycin than on that of other macrolides. EUCAST has also established the susceptibility breakpoints for azithromycin based on MIC determination. The EUCAST susceptibility criteria are listed in the following table. Susceptibility breakpoints for azithromycin MIC (mg/L) Susceptible Resistant Staphylococcus spp. □1 >2 Streptococcus pneumoniae □ 0.25 > 0.5 Haemolytic streptococcus * □ 0.25 > 0.5 Haemophilus influenzae □ 0.12 >4 Moraxella catarrhalis □ 0.25 > 0.5 Neisseria gonorrhoeae □ 0.25 > 0.5 * includes groups A, B, C, G. EUCAST = European Committee on Antimicrobial Susceptibility Testing; MIC = Minimum inhibitory concentration. Antibacterial spectrum The prevalence of acquired resistance may vary geographically and over time for selected species, and it is helpful to have local information on resistances, in particular when treating serious infections. If necessary, expert advice should be requested if the local prevalence of resistant strains is such that the usefulness of agents, at least in certain types of infections, is disputable. Azithromycin shows cross resistance with erythromycin resistant

grampositive germs. As described above, some ribosomal modifications determine cross resistance with other classes of antibiotics whose ribosomal binding sites overlap that of the macrolides: the lincosamides (including clindamycin), and the Type B streptogramins (which include, for example, the quinupristin component of quinupristin/dalfopristin). Over the course of time, a decrease has been noted in macrolide susceptibility, in particular in Streptococcus pneumoniae and in Staphylococcus aureus, and has also been observed in viridans group streptococci and in Streptococcus agalactiae.

Organisms that are commonly susceptible to azithromycin include:

Aerobic and facultative gram-positive bacteria (erithromycin-susceptible isolates): S. aureus, Streptococcus agalactiae*, S. pneumoniae*, Streptococcus pyogenes*, other haemolytic B streptococci (groups C, F, G), viridans group streptococci. Macrolide-resistant germs are found relatively frequently among aerobic and facultative gram-positive bacteria, in particular among methicillin-resistant S. aureus (MRSA) and penicillin resistant S. pneumoniae (PRSP). Aerobic and facultative gram-negative bacteria: Bordetella pertussis, Campylobacter jejuni, Haemophilus ducreyi*, Haemophilus influenzae*, Haemophilus parainfluenzae*, Legionella pneumophila, Moraxella catarrhalis*, and Neisseria gonorrhoeae*. Pseudomonas spp. and the majority of Enterobacteriaceae are inherently resistant to azithromycin, although azithromycin has been used to treat Salmonella enterica infections. Anaerobes: Clostridium perfringens, Peptostreptococcus spp. and Prevotella bivia. Other bacterial species: Borrelia burgdorferi, Chlamydia trachomatis, Chlamydophila pneumoniae*, Mycoplasma pneumoniae*, Treponema pallidum, and Ureaplasma urealyticum. Opportunistic pathogens associated with HIV infection. MAC*, and the eukaryote micro-organisms Pneumocystis jirovecii and Toxoplasma gondii. *The efficacy of azithromycin against the described species has been demonstrated in clinical studies CLINICAL PHARMACOLOGY Treatment of community-acquired pneumonia In a non-comparative, open-label study carried out on patients suffering from community-acquired pneumonia, subjects were administered azithromycin for intravenous infusion (for 2-5 days) followed by azithromycin orally (to complete a total treatment period of 7-10 days). Among evaluable patients, the clinical success rates (recovery and

improvement) were equal to 88% (74/84) after 10-14 days from the end of

the therapy and 86% (73/85) after 4 to 6 weeks. In a randomised, open-label, comparative study between azithromycin (intravenously followed by oral therapy) and cefuroxime (intravenously followed by oral therapy, in combination with erythromycin or not) in community-acquired pneumonia therapy, no statistically significant differences were observed between the two treatments. In these two studies an overall recovery percentage of 84% (16/19) was found in patients with positive serology for Legionella pneumophila. Furthermore, in an open-label, non-comparative study, patients with Legionella pneumophila (serogroup 1) with the diagnosis made by a specific urinary antigen test were treated with azithromycin intravenously followed by azithromycin orally positive. After 10-14 days of therapy, clinical recovery was achieved in 16 of 17 of the evaluable patients and after 4-6 weeks, 20 patients out of 20 had recovered. Treatment of pelvic inflammatory disease The results of an open-label study indicate that three therapeutic regimens of pelvic inflammatory disease (azithromycin vs. azithromycin/metronidazole and vs. doxycycline, metronidazole, cefoxitin and probenecid) are comparable both from the point of view of efficacy and safety. In another open-label, comparative study, patients suffering from pelvic inflammatory disease were treated with azithromycin IV/oral

vs. azithromycin IV in combination with metronidazole IV/oral and vs.

doxycycline in combination with amoxicillin -clavulanic acid IV/oral. These regimens were shown to be comparable in terms of efficacy and safety. The data reported from these studies show overall clinical success (recovery and improvement) ≥ 97% in all treatment groups, with a ≥ 96% percentage of pathogens eradicated at the end of the therapy. In the follow-up, the percentage of pathogens eradicated was ≥ 90%. Paediatric population Following the assessment of studies conducted on children, because noninferiority has not been established with respect to the antimalarial drugs recommended in the treatment of uncomplicated malaria, the use of azithromycin is not recommended for the treatment of malaria, either as monotherapy or in combination with chloroquine or artemisinin-based drugs.

5.2 Pharmacokinetic properties

Absorption/Distribution In humans after oral administration, azithromycin spreads quickly and extensively throughout the body with a bioavailability of about 37%. The time required to obtain peak plasma levels is 2-3 hours. In hospitalised patients with community-acquired pneumonia who received a once-daily dosing regimen of 500 mg of azithromycin for infusion (for 1 hour, concentration equal to 2 mg/mL) for 2-5 days, the average Cmax reached was 3.63 ± 1.60 g/mL, the threshold level reached after 24 hours was 0.20 ± 0.15 g/mL and the AUC24 was equal to 9.60 ±

4.80 g h/mL.

In healthy volunteers who received 500 mg of azithromycin for infusion (for 3 hours, concentration equal to 1 mg/mL), the average Cmax reached was 1.14 ± 0.14 g/mL, the threshold level reached after 24 hours was 0.18 ± 0.02 g/mL and the AUC24 was equal to

8.03 ± 0.86 g h/mL.

In animal studies, high concentrations of azithromycin were observed inside phagocyte cells. In experimental models, higher concentrations of azithromycin were released by activated phagocytes than by nonactivated phagocytes. In the animal model, this phenomena causes high concentrations of azithromycin at the infection site. Pharmacokinetic studies in humans have shown higher azithromycin tissue levels compared to plasma levels (up to 50 times the maximum concentrations observe in plasma) indicating, therefore, that the drug is highly bound to tissues. Concentrations in tissues such as lung, tonsil, and prostate, exceed MIC90 values for common pathogens after a single administration of 500 mg of azithromycin. High concentrations of azithromycin have been found in gynaecological tissues 96 hours after a single oral administration of 500 mg. Biotransformation/Elimination The terminal plasma half-life time closely reflects the tissue depletion half-life time (from 2 to 4 days). In a study with multiple doses conducted on 12 healthy volunteers with a dosage of 500 mg intravenously (1 mg/mL in an hour) for 5 days, the amount of unchanged azithromycin eliminated in the urine in 24 hours was equal to about 11% after the 1st dose and approximately 14% after the 5th

dose. These values are higher than the rate of 6% of unchanged drug

reported for azithromycin administered orally. Biliary elimination is the primary route of unchanged drug elimination after oral administration. Very elevated concentrations of unchanged drug were found in human bile along with 10 metabolites formed by the N- and O-demethylation processes, by hydroxylation of the desosamine and the glyconic ring and by cleavage of the cladinosium-

conjugates. Comparison of HPLC and microbiological assays in tissues

suggests that metabolites play no part in the microbiological activity of azithromycin powder for solution for infusion. Pharmacokinetics in Special Patient Populations Elderly A study conducted in healthy volunteers highlighted that after a treatment period of 5 days, AUC values were slightly higher in elderly patients (> 65 years) compared to younger patients (< 40 years); however, because this data is not clinically significant, no dose adjustment is required. Renal Impairment Following single oral administration of 1 gram of azithromycin, no pharmacokinetic effects were found in patients with a GFR of 10 - 80 mL/min. However, statistically significant differences were found in AUC values0-120 (8.8 □ g-h/mL vs. 11.7 □ g-h/mL), Cmax (1.0 □ g/mL

vs. 1.6 □ g/mL) and CLr (2.3 mL/min/kg vs. 0.2 mL/min/kg) among

the group with a GFR of < 10 mL/min and a GFR of > 80 ml/min. Hepatic Impairment In patients with mild (Class A) and moderate (Class B) hepatic impairment, there was no evidence of significant changes in the blood pharmacokinetics of the azithromycin compared to patients with normal hepatic function. In these patients, elimination of azithromycin through urine seemed to increase, probably as compensation for reduced hepatic clearance.

5.3 Preclinical safety data

In animal studies conducted with elevated doses that exceeded 40 times the maximum dose used in clinical practice, it was found that azithromycin caused reversible phospholipidosis, generally without true toxicological consequences. The effect proved to be reversible with discontinuation of the azithromycin treatment. The significance of these results for animals as well as for humans is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric Acid (Monohydrate) Sodium Hydroxide

6.2 Incompatibilities

The reconstituted solution of azithromycin powder for solution for infusion should be diluted according to the instructions and with the compatible infusion solution. This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6. Other intravenous substances, additives or other medications should not be added or infused simultaneously through the same intravenous line.

6.3 Shelf life

36 Months. The reconstituted solution is chemically and physically stable for 24 hours if stored at temperatures no higher than 30°C. However, from a microbiological point of view, the product should be used immediately. If the solution is not used immediately, the people who use it need to check the storage times and conditions. However, it is advisable not to exceed 24 hours at temperatures of between 2 and 8°C, unless the reconstitution/dilution has taken place under validated and controlled aseptic conditions.

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture. Keep out of reach of children.

6.5 Nature and contents of container

The finished product viz. Azithromycin for Injection 500 mg is packed in

10 ml clear glass vials USP Type-I stoppered with 20 mm dark grey

bromobutyl “RFS” rubber stopper and 20 mm aluminum flip-off tear off

seal. Such 1 labeled vial packed in printed carton along with pack insert.

6.6 Special precautions for disposal and other handling

Keep out of the sight and reach of children. Azithromycin powder for solution for infusion is contained in a disposable vial. The contents of the vial should be reconstituted with

4.8 mL of sterile water for injections (100 mg/mL of azithromycin). For

administration, the required volume of the reconstituted solution is added to the compatible solution for infusion in order to obtain a solution of azithromycin with a concentration equal to 1.0-2.0 mg/mL. The drugs to be administered via parenteral route must be carefully controlled to exclude the presence of particulate in the solution. If suspended particles can be seen, the solution should be discarded. The chemical and physical stability after reconstitution has been demonstrated for 24 hours at 30°C. Once diluted according to the instructions, the solution is stable from a chemical and physical point of view for 24 hours at temperatures equal to or lower than 30°C or for

7 days if stored in a refrigerator (5°C).

However, from a microbiological point of view, the product should be used immediately. If the suspension is not used immediately, the people who use it need to check the storage times and conditions that would normally not be longer than 24 hours at temperatures of between 2 and 8°C, unless the reconstitution/dilution has taken place under validated and controlled aseptic conditions. The reconstituted solution must be diluted with one of the following solutions for infusion: Physiological solution (0.9% sodium chloride) Physiological solution (0.45% sodium

chloride) Ringer's lactate

Glucose 5% in water Glucose 5% in physiological solution (0.45% sodium chloride) with 20 mEq KCl Glucose 5% in physiological solution (0.45% sodium chloride) Glucose 5% in physiological solution (0.30% sodium

chloride) Glucose 5% in Ringer's lactate

The intravenous administration of a 500 mg dose of azithromycin, diluted according to the instructions must take place within a period of not less than 60 minutes. Azithromycin powder for solution for infusion should not be administered as a bolus or intramuscularly. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE

ADDRESS

MAH:

Surgilinks Building Mombasa Road P.O. Box 14461 – 00800, Nairobi Kenya

Manufacturing site address:

Gufic Biosciences Ltd. National Highway No. 8, Near Grid, Kabilpore - 396424, City: Navsari,

Dist. Navsari, Gujarat

State, India.

8. MARKETING AUTHORISATION NUMBER(S)

12119/R1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2026 August 31

10. DATE OF REVISION OF THE TEXT

2026 August 31