SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AzitroFort 500 mg capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains the active substance azithromycin dihydrate, equivalent to 500 mg azithromycin.

Excipients with known effect: lactose monohydrate/maize starch (85:15).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules, hard.

Appearance of the capsules: hard gelatin capsules, body – white, cap - pink.

Appearance of the contents: white to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AzitroFort is indicated in adults and children weighing more than 45 kg for the treatment of infections known or suspected to have been caused by one or more azithromycin-susceptible microorganisms:

- Upper respiratory tract infections - pharyngitis/tonsillitis, sinusitis and otitis media;
- Lower respiratory tract infections - bacterial bronchitis and community acquired pneumonia;
- Skin and subcutaneous tissues – moderate acne vulgaris, erythema chronicum migrans (first stage of Lyme disease), erysipelas, impetigo and secondary pyoderma;
- Sexually transmitted diseases - uncomplicated urethritis and cervicitis caused by *Chlamydia trachomatis*.

The use of the product should be in line with national and local guidelines and recommendations for conducting antibacterial therapy.

4.2 Posology and method of administration

Adults, including the elderly and children weighing more than 45 kg

- Upper and lower respiratory tract infections

Total course dose of 1500 mg, which should be taken for 3 days (500 mg once daily).

- Moderate acne vulgaris

Total course dose of 6 g, which should be taken under the following recommended dosage regime: 500 mg once daily for 3 consecutive days, 500 mg once weekly for the next 9 weeks.
The dose for the second week should be taken 7 days after the administration of the first dose and the dose for the third to eighth weeks should be taken over 7-day intervals.

- Uncomplicated sexually transmitted diseases caused by *Chlamidia trachomatis*

The therapeutic dose is 1,000 mg, taken as a single dose.

- Erythema chronicum migrans (first stage of Lyme disease)

Total course dose of 3 g azithromycin, which should be taken under the following dosage regime: a single daily dose of 1 g on Day 1, single daily doses of 500 mg on Days 2-5.

Children weighing less than 45 kg

AzitroFort 500 mg capsules are not recommended in children weighing less than 45 kg, due to the lack of accurate dosing.

Renal impairment

No dose adjustment is required in patients with mild to moderate renal impairment (creatinine clearance >40 ml/min).
Caution should be exercised in patients with severe renal impairment (creatinine clearance <40 ml/min) (see section 4.4).

Hepatic impairment

Since azithromycin is metabolised in the liver and excreted in the bile, the product in contraindicated in patients suffering from severe liver diseases. No studies have been conducted in relation to the use of azithromycin in this patient group.

Method of administration

AzitroFort capsules should be swallowed whole, as a single daily dose. Like the other antibiotics, the product should be taken at least one hour before or two hours after meal.

4.3 Contraindications

- known hypersensitivity to azithromycin or to any of the excipients listed in section 6.1.
- known hypersensitivity to erythromycin, macrolide or ketolide antibiotics.
- due to existing theoretical possibility of developing ergotism, the product should not be administered concomitantly with medicines containing ergot derivatives (see section 4.4).

4.4 Special warnings and precautions for use

Allergic reactions

During the treatment with azithromycin, as with erythromycin and other macrolide antibiotics, serious allergic reactions may develop in rare cases, such as angioneurotic oedema and anaphylaxis (rarely fatal). In some of these reactions, recurrence of clinical symptoms may be observed, whereby a longer period of observation and treatment is necessary.
In case of hypersensitivity reactions occuarance, the product should be discontinued and symptomatic treatment should be administered. Due to the long tissue half-life of azithromycin, the clinical symptoms of hypersensitivity reactions may persist even after cessation of the anti-allergic treatment.

Heart disorders

Prolonged cardiac repolarisation and QT-interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been observed in treatment with other macrolides.
A similar effect with azithromycin cannot be completely ruled out in patients at an increased risk of prolonged cardiac repolarisation (see section 4.8). Therefore, azithromycin should be used with particular caution in patients with:

- congenital or acquired, clinically documented and confirmed prolongation of the QT-interval;
- cardiomyopathy, especially in case of existing heart failure;
- sinus bradycardia;
- existing symptomatic arrhythmia;

- current co-administration of other medicinal products known to prolong the QT-interval, such as anti-arrhytmics of classes IA and III, cisapride and terfenadine;
- electrolyte disturbances, particularly hypokalaemia, hypomagnesaemia and hypocalcaemia.

Superinfections

During the treatment with azithromycin, there is a possibility of developing superinfections, including fungal infections.
As with other antibacterial products, monitoring for symptoms of superinfections caused by non-susceptible microorganisms, including fungi, is recommended while conducting treatment with azithromycin.

Pseudomembranous colitis of varying severity may develop. Mild clinical forms usually do not occur after product discontinuation; moderate and severe forms require treatment with electrolyte solutions, amino acid solutions and those for parenteral nutrition, antibacterial agents with high antibacterial activity against *Clostridium difficile*.
Cases of diarrhoea caused by *Clostridium difficile* (CDAD) have been reported with the use of almost all antibacterial agents, including. azithromycin, as its severity may range from mild diarrhoea to fatal colitis leading to colectomy.
CDAD must always be taken into consideration in patients in whom the antibiotic therapy is accompanied by the development of diarrhoea. Careful monitoring by a specialist is required, since CDAD may occur over two months after cessation of the antibiotic use.

Streptococcal infections

Penicillin is the first choice for the treatment of pharyngitis/tonsillitis caused by *Streptococcus pyogenes*, as well as for the prevention of acute rheumatic fever.
Azithromycin is usually effective against streptococci in the oropharynx, but there are no data to demonstrate its efficacy in the prevention of acute rheumatism.

Renal impairment

In patients with severe renal impairment (creatinine clearance <40 ml/min), increases by 33% in the systemic exposure to azithromycin have been observed.
There are no clinical data on the safe use of azithromycin in patients with severe renal impairment and therefore, the product should be used with particular caution in such cases.
No dose adjustment is required in moderate and mild renal impairment (creatinine clearance >40 ml/min).

Hepatic impairment

Patients with marked hepatic dysfunction and cholestasis require attention and limiting the treatment with azithromycin, having in mind that the elimination is carried out mainly by the liver.

Treatment with azithromycin in patients with a severe liver disease requires caution, as there have been reports of fulminant hepatitis, potentially leading to life-threatening hepatic failure. The risk is higher in patients with pre-existing liver diseases or taking potentially hepatotoxic medicinal products.

In case of clinical symptoms and/or clinical laboratory evidence of liver dysfunction, such as rapidly developing asthenia, accompanied by jaundice, dark urine, bleeding tendency or symptoms of hepatic encephalopathy, significant elevations of liver enzymes, prompt liver function tests/investigations should be performed and the administration of the product should be discontinued, if needed.

Treatment with ergot derivatives
In patients taking ergot derivative-containing medicines, the concomitant use of macrolide antibiotics accelerates the development of ergotism.

There is no known evidence of such an interaction with azithromycin, but due to the existence of even a theoretical risk of such interaction, concomitant administration of azithromycin and ergotamine is unadvisable (see section 4.2).

Myasthenia gravis

Cases of exacerbations of the disease or onset of myasthenia have been reported in patients treated with azithromycin.

Other

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product because it contains lactose monohydrate as an excipient.

The gelatin capsule contains the colourant azorubine, carmoisine (E122), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicines on azithromycin

Antiacids

Co-administration with aluminum or magnesium-containing antacids has not led to changes in the bioavailability of azithromycin, although has resulted in reduction of the peak plasma concentrations by approximately 25%.
In view of these data, azithromycin should not be co-administered with antacids. Azithromycin intake should be at least 2 hours before or after the administration of antacids.

Cimetidine

Cimetidine, administered two hours before azithromycin, does not adversely affect pharmacokinetic behaviour of azithromycin.

Nelfinavir
In a study of 12 healthy volunteers receiving concomitant azithromycin (1,200 mg) and nelfinavir at the steady state (750 mg three times daily), 100% increase in azithromycin absorption and bioavailability has been found. No significant effect on the clearance has been reported. The clinical significance of this interaction is unknown, but caution is required in case of azithromycin administration in patients receiving nelfinavir.

Terfenadine

Due to the risk of serious arrhythmias, leading secondarily to prolongation of the QT- interval in patients receiving other antibacterial agents concurrently with terfenadine, clinical trials were conducted to study the possible pharmacokinetic interactions.
In the course of the studies, no evidence of interaction between azithromycin and terfenadine has been found. In some cases, it was not possible to exclude the possibility of such interactions, but no concrete evidence of their occurrence has been established.
As with other macrolides, azithromycin should be used with particular caution in combination with terfenadine.

Fluconazole

In an open-label, randomised, cross-over study in 18 healthy volunteers, the effects of oral 1,200 mg dose of azithromycin were investigated on the pharmacokinetics of fluconazole, administered at 800 mg and vice versa.
No significant pharmacokinetic interactions between fluconazole and azithromycin have been found.

Rifabutin

During co-administration of azithromycin and rifabutin, the serum concentrations of both medicines were not affected.
Neutropenia was found in individuals concomitantly treated with azithromycin and rifabutin. Neutropenia was rather associated with the use of rifabutin, as no causal relationship to the combination with azithromycin has been established (see section 4.8).

Effects of azithromycin on other medicines

Carbamazepine

In a clinical study in healthy volunteers for determining the potential pharmacokinetic interactions upon co-administration of azithromycin and carbamazepine, no significant effect on plasma concentrations of carbamazepine or its active metabolites has been observed.

Cisapride

Cisapride is metabolised in the liver by the CYP 3A4. Because macrolide antibiotics inhibit these enzymes, co-administration of cisapride may cause prolongation of the QT-interval, ventricular arrhythmias and such of the torsades de pointes type.

Cyclosporine

In a pharmacokinetic clinical trial in healthy volunteers receiving 500 mg azithromycin for three days, followed by a single oral dose of 10 mg/kg cyclosporine, significant increases in C_{max} and AUC_{0-5} by 24% and 21%, respectively, have been found for cyclosporine. Significant changes in $AUC_{0-\infty}$ have not been established.
These data require careful consideration on the appropriateness of co-administration of both products. If co-administration is required, cyclosporine levels should be monitored and the dose adjusted accordingly.

Digoxin

Some macrolide antibiotics have been reported to affect the microbial metabolism of digoxin in the intestines of some patients. The possibility of increased digoxin plasma concentrations in patients receiving concomitant azithromycin and digoxin should be taken into account. Monitoring of digoxin plasma levels should be considered.

Ergot derivatives

Due to an existing theoretical possibility of developing ergotism, azithromycin should not be co-administered with ergot derivative-containing products (see section 4.4).

Methylprednisolone

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

Theophylline

Upon co-administration, there was no evidence of untoward pharmacokinetic drug interactions.

Coumarin-type oral anticoagulants

In a clinical 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 from the post-marketing studies 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.

Zidovudine

Single 1,000 mg doses and multiple 1,200 mg or 600 mg doses of azithromycin had no effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolites. 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.

Didanosine

Co-administration of 1,200 mg/day azithromycin with didanosine in 6 patients did not appear to affect the pharmacokinetics of didanosine, compared with placebo.

Atorvastatin

Co-administration of azithromycin (500 mg daily) and atorvastatin (10 mg daily) did not alter the plasma concentrations of atorvastatin.

Cetirizine

Co-administration of a 5-day regimen of azithromycin with cetirizine (20 mg) at the steady-state resulted in no pharmacokinetic interaction and no significant prolongation of the QT-interval.

Efavirenz

Co-administration of a 600 mg single dose of azithromycin and 400 mg single dose of efavirenz for 7 days did not result in any clinically significant pharmacokinetic interactions.

Indinavir

Co-administration of a single dose of 1,200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered at 800 mg three times daily for 5 days.

Midazolam

Azithromycin, administered at the usual course dose (500 mg once daily for 3 consecutive days) did not result in untoward changes in the pharmacodynamics and pharmacokinetics of midazolam administered at a 15 mg dose.

Sildenafil

Administered at a single daily dose of 500 mg for 3 days, azithromycin did not affect the main pharmacokinetic parameters (AUC and C_{max}) of sildenafil or its major metabolite.

Triazolam

When co-administered with azithromycin (azithromycin of 500 mg on Day 1, 250 mg on Day 2 and 125 mg triazolam), there was no evidence of untoward drug pharmacokinetic interactions.

Trimotoprim/sulfamethoxazole

When co-administered with azithromycin (trimethoprim/sulfamethoxazole of 160 mg/800 mg, respectively, plus azithromycin of 1,200 mg for 7 days), there was no evidence of untoward drug pharmacokinetic interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

Studies on reproduction in animals are insufficient with respect to evaluation of effects on pregnancy, embryonal/foetal development, parturition or postnatal development.
The potential risk for humans is unknown. There are no data from controlled clinical trials in humans. Azithromycin should not to be used during pregnancy unless clearly needed.

Breast-feeding

There are insufficient, limited data on the excretion of azithromycin in human and mammalian milk. The risk to the infant cannot be ruled out. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the mother.

4.7 Effects on ability to drive and use machines

There is no evidence of effects on the ability to drive or use machines.

4.8 Undesirable effects

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 (the frequency cannot be estimated from the available data).

Blood and lymphatic system disorders	
Uncommon	Leukopenia, neutropenia
Not known	Thrombocytopenia, haemolytic anaemia
Cardiac disorders	
Uncommon	Palpitations
Not known	Arrhythmia, including ventricular rhythm disorders, prolongation of the QT-interval, severe rhythm disorders of the torsade de pointes type
Ear and labyrinth disorders	
Common	Deafness
Uncommon	Hearing impaired, tinnitus
Rare	Vertigo
Gastro-intestinal disorders	
Very common	Diarrhoea, abdominal discomfort (pains/spasms), nausea, flatulence
Common	Vomiting, dyspepsia

Uncommon	Gastritis, constipation
Not known	Pancreatitis, tongue discolouration
General disorders and administration site conditions	
Common	Fatigue
Uncommon	Chest pain, oedema, malaise, asthenia
Hepatobiliary disorders	
Uncommon	Hepatitis
Rare	Impaired hepatic function
Not known	Hepatitis fulminant, cholestatic jaundice, hepatic necrosis, hepatic failure
Immune system disorders	
Uncommon	Angioedema, hypersensitivity reactions
Not known	Anaphylactic reactions, including allergic shock (fatal in rare cases)
Infections and infestations	
Uncommon	Vaginitis, candidiasis (fungal infection)
Not known	Pseudomembranous colitis
Musculoskeletal and connective tissue disorders	
Common	Arthralgia
Nervous system disorders	
Common	Headache, dizziness, paraesthesia, dysgeusia
Uncommon	Hypoaesthesia, somnolence, insomnia
Not known	Syncope, convulsions, psychomotor hyperactivity, anosmia, ageusia, parosmia, myasthenia gravis
Eye disorders	
Common	Vision impaired
Psychiatric disorders	
Uncommon	Nervousness
Rare	Agitation
Not known	Aggression, anxiety
Renal and urinary disorders	
Not known	Interstitial nephritis, acute renal failure
Skin and subcutaneous tissue disorders	
Common	Pruritus, rash
Uncommon	Stevens-Johnson syndrome, photosensitivity, urticaria
Not known	Toxic epidermal necrolysis, erythema multiforme
Metabolism and nutrition disorders	
Common	Anorexia
Vascular disorders	
Not known	Hypotension

Investigations	
Common	Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased
Uncommon	ASAT increased, ALAT increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal
Not known	Prolonged QT-interval

4.9 Overdose

Adverse events experienced in higher than recommended doses were similar to those seen at normal therapeutic doses. The typical symptoms of an overdose with macrolide antibiotics include loss of hearing, severe vomiting, nausea and diarrhoea.
In the event of overdose, the administration of medicinal charcoal and general symptomatic treatment is required. Additional supportive measures should be considered with regard to vital functions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-infectious agents for systemic use, macrolides.
ATC code: J01FA10

Mechanism of action
Azithromycin is a macrolide antibiotic belonging to the azalide group. The molecule is constructed by adding a nitrogen atom to the lactone ring of erythromycin A. The mechanism of action of azithromycin is based mainly upon the suppression of bacterial protein synthesis by means of binding to the ribosomal 50s sub-unit and inhibition of peptide translocation.

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

Complete cross resistance exists among *Streptococcus pneumoniae*, β-haemolytic streptococcus of group A, *Enterococcus faecalis* and *Staphylococcus aureus*, including methicillin resistant species of S. *aureus* (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

The prevalence of acquired resistance may vary geographically and with time for selected species and local or regional information on resistance is desirable, particularly when treating severe infections. If needed, expert advice should be sought when the local prevalence of resistance is such that the effectiveness of utility of azithromycin is questionable.

Susceptibility breakpoints
Azithromycin susceptibility breakpoints for typical bacterial pathogens are:
NCCLS:
- Susceptible ≤ 2 mg/l; resistant ≥ 8 mg/l
- *Haemophilus spp.*: susceptible ≤ 4 mg/l
- *Streptococcus pneumoniae* and *Streptococcus pyogenes:*

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

Antibacterial spectrum of azithromycin

Susceptible species

Aerobic Gram+ microorganisms
Staphylococcus aureus
Methycillin-susceptible
Streptococcus pneumoniae
Penicillin-susceptible
Streptococcus pyogenes (Group A)

Aerobic Gram- microorganisms
Haemophilus influenzae
Haemophilus parainfluenzae
Legionella pneumophila
Moraxella catarrhalis
Pasteurella multocida

Anaerobic microorganisms
Clostridium perfringens
Fusobacterium spp.
Prevotella spp.
Porphyromonas spp.

Other microorganisms
Chlamydia trachomatis

Species for which acquired resistance may be a problem

Aerobic Gram+ microorganisms
Streptococcus pneumoniae
Penicillin-intermediate
Penicillin-resistant
Inherently resistant microorganisms
Aerobic Gram+ microorganisms - *Enterococcus faecalis,* Staphylococci **MRSA, MRSE***
Anaerobic microorganisms – Bacteroides fragilis group

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

5.2 Pharmacokinetic properties

Absorption
Bioavailability after oral administration is approximately 37%. Peak plasma concentrations are attained 2-3 hours after administration.

Distribution
Orally administered azithromycin is intensively and widely distributed throughout the body. In pharmacokinetic studies it has been demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (as much as 50 times) than those measured in plasma, which indicates that the active substance strongly binds to tissues.

Binding to plasma proteins varies according to plasma concentration and ranges from 12% at 0.5 mcg/ml up to 52% at 0.05 mcg azithromycin/ml serum.

The mean volume of distribution at steady state (VVss) has been calculated to be 31.1 l/kg.

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

Approximately 12% of an intravenously administered dose of azithromycin is excreted unchanged in urine within the following 3 days. Particularly high concentrations of unchanged azithromycin have been found in human bile. Also in bile, ten metabolites were detected, which were formed through N- and O- demethylation, hydroxylation of desosamine – and aglycone rings and cleavage of cladinose conjugate.
Comparison of the results of liquid chromatography and microbiological analyses has shown that the metabolites of azithromycin are not microbiologically active.

In animal studies, high concentrations of azithromycin have been found in phagocytes. It has also been established that during active phagocytosis, higher concentrations of azithromycin are released, compared to those from inactive phagocytes. In animal models this results in high concentrations of azithromycin being delivered to the site of infection.

5.3 Preclinical safety data

Azithromycin is characterised by low toxicity (LD_{50}, oral administration to mice and rats: >2000 mg/kg b.w.).
Clinical picture of intoxication - clonic convulsions and dyspnoea, followed by lethal outcome.

The administration of multiple doses in chronic experiments on rats and dogs treated with daily doses of about 200 mg/kg b.w. has resulted in detectable transient lipid infiltration of the liver and dose-and time-dependent increases in the plasma levels of liver enzymes.

Azithromycin may induce detectable damage (decrease) of fertility, when administered for a long period at daily doses of 20 and 30 mg/kg b.w., as the effect is dose-dependent. Doses of about 10 mg/kg b.w. have no effect on the reproductive function of experimental animals.

Azithromycin administered to mice and rats at daily doses of 10-200 mg/kg b.w. during organogenesis has shown no fetotoxic and teratogenic effects. No negative effects have been found in female animals and their off-spring related with the exposure to azithromycin. Newborns have not shown higher sensitivity to the effects of azithromycin, compared to adult animals.

Azithromycin has shown no genotoxic activity in *in vitro* and experiments on mammals. Mutagenic and carcinogenic effects have not been confirmed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium lauryl sulphate
Lactose monohydrate/Maize starch (85:15)
Magnesium stearate

Composition of the hard gelatin capsule:
Titanium dioxide (E171)
Gelatin
Azorubine, carmoisine (E122)

6.2 Incompatibilities

None known.

6.3 Shelf life

2 (two) years from the date of manufacture.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

3 (three) or 6 (six) hard gelatin capsules in a PVC/Al foil blister.
1 (one) blister with a leaflet/information for the user per carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Antibiotic-Razgrad AD
Office 201, 68 “Aprilsko vastanie” Blvd.
7200 Razgrad
Bulgaria

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

June 2012