Bezanin®

AZITHROMYCIN 500mg

Film Coated Tablets

PATIENT INFORMATION LEAFLET

1. DETERMINATION OF THE MEDICINAL PRODUCT

1.1 Name: Bezanin

1.2 Composition: Active ingredient: Azithromycin dihydrate.

Excipients: Starch maize pregelatinized, Calcium phosphate dibasic, Croscarmellose sodium, Magnesium stearate, Sodium lauryl sulfate,

Coating: OPADRY II WHITE Y-30-18037 which consists of: Lactose monohydrate, Hypromellose 15cps, Titanium dioxide (E171, CI77891), Triacetin (glycerol triacetate).

1.3 Pharmaceutical form: Film coated tablets.

1.4 Content: Each tablet contains 500 mg of Azithromycin.

1.5 Description-Packaging: Carton box containing three 500 mg tablets in a PVC/PVDC/PE-Aluminum blister and a patient instruction leaflet.

1.6 Therapeutical category: Antibiotic.

1.7 Marketing Authorisation Holder-Manufacturer: IASIS PHARMA,
137, Filis Ave., 134 51 Athens, Greece. Tel: +30 210 2311031

2. THINGS THAT YOU SHOULD KNOW ABOUT THE MEDICINE PRESCRIBED BY YOUR DOCTOR

2.1 General information: Bezanin contains azithromycin, which is an antibiotic medication. Antibiotics are used for treating microorganism infections.

2.2 Indications: Bezanin is indicated for the treatment of mild to moderate infections of the respiratory tract, caused by susceptible strains of microorganisms, such as:

- Infections of the lower respiratory tract (when isolated or suspected pathogen, susceptible to azithromycin in vitro):

- Acute bacterial exacerbations of chronic bronchitis caused by Haemophilus influenzae, Moraxella catarrhalis, Haemophilus parainfluenzae, or Streptococcus pneumoniae.

- Community-acquired pneumoniae caused by Chlamydophila pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Mycoplasma pneumoniae or Streptococcus pneumoniae (regarding pneumonia, see note at the end of the paragraph).

- Upper respiratory tract infections:

- Acute bacterial sinusitis caused by Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae.

- Pharyngitis/tonsillitis due to Streptococcus pyogenes.

Especially, In Streptococcal tonsillitis, azithromycin should be used as an alternative therapy in patients where first choice therapy cannot be administered. Penicillin is usually the first choice for treatment of pharyngitis/tonsillitis due to Streptococcus pyogenes and also for prophylaxis of acute rheumatic fever. Azithromycin is in general effective against streptococci in the oropharynx, but no data are currently available to demonstrate the efficacy of azithromycin in preventing acute rheumatic fever.

- Bezanin is also indicated for treatment of skin and soft tissue infections and acute otitis media.

- In sexually transmitted diseases in men and women, Bezanin is indicated for the treatment of uncomplicated infections of the genital system due to Chlamydia trachomatis. Bezanin is also indicated for chancroid treatment in men due to Haemophilus ducreyi. Given the small number of women participating in the clinical studies, azithromycin efficacy in the treatment of chancroid in women has not been sufficiently established.

- Bezanin is also indicated for the treatment of uncomplicated infections of the genital system caused by non-multiresistant strains of Neisseria gonorrhoeae. In these cases coexisting infection caused by Treponema pallidum should be ruled out.

NOTE: Azithromycin should not be used orally in patients with pneumonia who are inappropriate for outpatient oral treatment, because of the moderate or heavy degree of their infection or because of any of the following risk factors:

- Patients infected by inpatient pathogens
- Patients with known or suspected bacteraemia.
- Patients demanding hospitalization
- Elderly or weak patients or
- Patients with existing serious health problems which may affect their ability to react against the disease (including immunodepression or functional asplenia)

For the treatment of community-acquired pneumonia, combinations of antibiotics are commonly used (mainly beta-lactam together with macrolide). In each case, national guidelines should be taken into account for the treatment of community-acquired pneumonia.

2.3 Contraindications: Bezanin is contra-indicated in patients with hypersensitivity to azithromycin, erythromycin or any of the macrolide or ketolide antibiotics or any of the excipients listed in Section 1.2 (Excipients). Co-administration of macrolides and cisapride is contraindicated.

2.4 Special warnings and precautions for use

2.4.1 General: As with erythromycin and other macrolides, rare serious allergic reactions, including angioneurotic oedema and anaphylaxis (rarely fatal), have been reported. Some of these reactions which occurred after the administration of azithromycin resulted in recurrent symptoms and required a longer period of observation and treatment.

Since the liver is the principal route of elimination for azithromycin, azithromycin should be used with caution in patients with severe hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin (see section 2.8). 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.

In patients receiving ergot derivatives (Ergot), ergotism has been presented when coadministered with certain 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-administrated.

As with any antibiotic, observation for signs of superinfection with non-susceptible organisms, including fungi is recommended.

Clostridium difficile associated diarrhea (CDAD) has been reported following the use of almost all antibacterial agents, including azithromycin, and may range in severity form mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.

C. difficile produces toxins A and B which contribute to the development of CDAD.

Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy.

Therefore, CDAD must be considered in patients who present with diarrhoea during or subsequent to the administration of any antibiotics.

Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

After the final diagnosis of pseudomembranous colitis, remedial measures should be implemented. Mild cases of pseudomembranous colitis usually respond to discontinuation of therapy.

In moderate or severe cases the need for administration of fluids and should be considered electrolytes, as well as protein supplementation and treatment with antimicrobial drugs that are clinically effective in colitis due to Clostridium difficile.

In patients with severe renal impairment (GFR <10 ml/min) a 33% increase in systemic exposure to azithromycin was observed,

Prolongation of cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been reported in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarisation, (see section 2.8. Undesirable effects). Therefore, caution should be exercised when treating patients:

- With congenital or documented acquired prolongation of theQT interval.
- Who are currently receiving treatment with other active substances, which are known to prolong QT, as antiarrhythmics Class IA and III, cisapride and terfenadine.
- With electrolyte imbalance, especially in cases of hypokalemia and hypomagnesemia.
- With clinically relevant bradycardia, cardiac arrhythmia or severe heart failure.

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy (see section 2.8).

Regarding the treatment of pneumonia, azithromycin has been shown to be safe and effective only for the treatment of low severity community-acquired pneumonia due to Streptococcus pneumoniae or Haemophilus influenzae, in patients who are appropriate for oral outpatient treatment. Azithromycin should not be used in patients with pneumonia who are inappropriate for outpatient oral therapy because of moderate or serious infection or due to the existence of any of the following risk factors:

- Patients infected by inpatient pathogens
- Patients with known or suspected bacteraemia.
- Patients demanding hospitalization
- Elderly or weak patients or
- Patients with existing serious health problems which may affect their ability to react against the disease (including immunodepression or functional asplenia).

For the treatment of community-acquired pneumonia, combinations of antibiotics are commonly used (mainly beta-lactam together with macrolide). In each case, national guidelines should be taken into account for the treatment of community-acquired pneumonia.

2.4.2 Elderly patients: No dosage adjustment is necessary in elderly patients who are required to receive azithromycin treatment.

2.4.3 Pregnancy: Azithromycin should not be used during pregnancy unless clearly necessary.

2.4.4 Lactation: As many drugs are excreted in human milk, azithromycin should not be used for the treatment of lactating women unless the physician decides that the potential benefits justify the potential risks to the infant.

2.4.5 Children: Azithromycin tablets should be used only in children who weigh more than 45 kilograms.

2.4.6 Effects on ability to drive and use machines: There is no evidence to suggest that Bezanin may have an effect on a patient's ability to drive or operate machinery.

2.5 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.

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 to placebo.

Digoxin: Some of the macrolide antibiotics have been reported to impair the microbial metabolism of digoxin in the intestine in some patients. In patients receiving concomitant azithromycin, a related azalide antibiotic, and digoxin the possibility of raised digoxin levels should be borne in mind.

Zidovudine: Single 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients.

Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to undergo the pharmacokinetic drug interactions as seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.

Ergot derivatives: Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended. (See Section 2.4 Special warnings and precautions for use).

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).

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 observed.

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.

Cyclosporin: In a pharmacokinetic study with healthy volunteers who were administered a 500 mg/day oral dose of azithromycin for 3 days and subsequently were administered a single 10 mg/kg oral dose of ciclosporin, the resulting ciclosporin Cmax 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.
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. It is not necessary to adjust the dose of azithromycin when administered with efavirenz.
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 Cmax (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. It is not necessary to adjust the dose of azithromycin when administered with indinavir.
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 2.8. Undesirable effects).
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 Cmax, 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. However, the combination of theophylline and macrolides has been associated with elevated serum levels of theophylline. Therefore, it is recommended to measure the levels of theophylline on concomitant azithromycin.
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 (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.
Cisapride: Cisapride is metabolized in the liver by the enzyme CYP 3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride with these substances can increase the risk of irregular heart rhythm (QT interval QT, ventricular arrhythmias, TORSADE DE POINTES). Therefore, cisapride should not be concomitantly administered with these drugs.

2.6 Posology and method of administration: Bezanin should be given as a single daily dose. Bezanin tablets may be administered with or without food and each tablet should be swallowed intact. **Adults:** For sexually transmitted infections the dose is 1000 mg as a single oral dose.
For all other indications, the total dose is 1500 mg, given in single daily 500 mg doses for three days. Alternatively, the same total 1500 mg dose can be administered in 5 days as follows: a single 500mg dose on the first day and single 250 mg doses on days 2 to 5.

2.7 Overdose - Treatment: In the event of overdose general symptomatic treatment and supportive measures are indicated as required.

2.8 Undesirable effects: The table below lists the adverse reactions identified through clinical trial experience and postmarketing 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 ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ 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	Undesirable effect	Frequency
Infections and Infestations	Candidiasis, oral candidiasis, vaginal infection	Uncommon
	Pseudomembranous colitis (See Section 2.4)	Not known
Blood and Lymphatic System Disorders	Leukopenia, neutropenia	Uncommon
	Thrombocytopenia, haemolytic anaemia	Not known
Immune System Disorders	Angioedema, hypersensitivity	Uncommon
	Anaphylactic reaction (See Section 2.4)	Not known
Metabolism and Nutrition Disorders	Anorexia	Common
Psychiatric Disorders	Nervousness	Uncommon
	Agitation	Rare
	Aggression, anxiety	Not known
Nervous System Disorders	Dizziness, headache, paraesthesia, dysgeusia	Common
	Hypoaesthesia, somnolence, insomnia	Uncommon
Nervous System Disorders	Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis (See Section 2.4).	Not known
Eye Disorders	Visual impairment	Common
Ear and Labyrinth Disorders	Deafness	Common
	Hearing impaired, tinnitus	Uncommon
	Vertigo	Rare
Cardiac Disorders	Palpitations	Uncommon
	Torsades de pointes (See Section 2.4), arrhythmia (See Section 2.4) including ventricular tachycardia	Not known
Vascular Disorders	Hypotension	Not known
Gastrointestinal Disorders	Diarrhoea, abdominal pain, nausea, flatulence	Very common
	Vomiting, dyspepsia	Common
	Gastritis, constipation	Uncommon
	Pancreatitis, tongue discolouration	Not known
Hepatobiliary Disorders	Hepatitis	Uncommon
	Hepatic function abnormal	Rare
	Hepatic failure (See Section 2.4)*, hepatitis fulminant, hepatic necrosis, jaundice cholestatic	Not known
Skin and Subcutaneous Tissue Disorders	Pruritus and rash	Common
	Stevens-Johnson syndrome, photosensitivity reaction, urticaria	Uncommon
	Toxic epidermal necrolysis, erythema multiforme	Not known
Musculoskeletal, Connective Tissue Disorders	Arthralgia	Common
Renal and Urinary Disorders	Renal failure acute, nephritis interstitial	Not known
General disorders and Administration Site Conditions	Fatigue	Common
	Chest pain, oedema, malaise, asthenia	Not known
Investigations	Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased	Common
	Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal	Uncommon
	Electrocardiogram QT prolonged (See Section 2.4)	Not known

* which has rarely resulted in death

2.9 If you miss a dose
Should the medicine be administered uninterruptedly and you have missed a dose, you should take the missed dose as soon as possible. If the appropriate time for the next dose administration is close, do not take the dose you have missed, but continue normal treatment instead.

2.10 Expiration of the product
It is indicated on the outer and inner packaging. Do not use this drug after the expiration date.

2.11 Special precautions for storage
Bezanin must be stored at temperature not exceeding 25°C

2.12 Date of last product information leaflet revision
12-11-2010

3. INFORMATION ON THE RATIONAL USE OF DRUGS

- This medicine was prescribed by your doctor for your specific health problem. You should not administer it to others or use it yourself for other health problems, without prior consent from your doctor.
- Inform immediately your doctor or pharmacist if a problem appears during the treatment.
- If you have any questions regarding the medicine that you are taking or you need further information on your health problem, do not hesitate to contact your doctor or pharmacist and ask for additional information.
- The medicine that was prescribed to you is safe and effective only when administered according to your doctor or pharmacist instructions.
- It is important for your safety and your health to read carefully all information regarding the medicine that was prescribed to you.
- Do not store medicines in bathroom closets since heat and humidity may alter them and render them hazardous for your health.
- Do not store medicines that have already expired or are no more useful to you.
- For more safety keep medicines in a secure place away from children

4. MODE OF ADMINISTRATION
This medicine may only be administered with a doctor's prescription