Badozithro

200 mg/ 5 ml
Dry Powder For Oral Suspension

1 NAME OF THE MEDICINAL PRODUCT

Babothizro 200 mg/5 ml powder for oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of reconstituted oral suspension contains 200 mg azithromycin as dihydrate209.6
Excipients with known effect:
Each 5 ml of reconstituted oral suspension contains 3.87 g of sucrose.

3 PHARMACEUTICAL FORM

Dry powder for oral suspension.
Light yellow to yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Badozithro is indicated for the following bacterial infections induced by microorganisms susceptible to azithromycin
- Infections of the lower respiratory tract: acute bronchitis and mild to moderate community-acquired pneumonia
- Infections of the upper respiratory tract: sinusitis and pharyngitis/tonsillitis - Acute otitis media
- Infections of the skin and soft tissue of mild to moderate severity *e.g.* folliculitis, cellulites, erysipelas
- Uncomplicated *Chlamydia trachomatis* urethritis and cervicitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.
Azithromycin is not the first choice for the empirical treatment of infections in areas where the prevalence of resistant isolates is 10% or more.

4.2 Posology and method of administration

Posology

The duration of treatment in each of the infectious diseases is given below.
Paediatric population over 45 kg body weight, adults

The total dosage of Badozithro is 1500 mg which is spread over three days (500 mg once daily) . Alternatively, the dosage can be spread over five days (500 mg as a single dose on the first day and thereafter 250 mg once daily).

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

For sinusitis, treatment is aimed at adults and adolescents over 16 years of age. Other pharmaceutical forms are available to treat patients weighing more than 45 kg.

Paediatric population under 45 kg body weight

Badozithro suspension should be used for children under 45 kg. The following recommendations refer to the reconstituted 40 mg/ ml (200 mg/5ml) suspension. With as only exception the treatment of *Streptococci* pharyngitis, the total dose in children 1 year and older is 30 mg/kg, to be administered as one single daily dose of 10 mg/kg for three days. As an alternative Badothithro can also be administered over a period of 5 days with one single dose of 10 mg/kg on day 1, followed by one single daily dose of 5 mg/kg on days 2 through 5. For children with a weight of 10 to 15 kg Badothizro suspension should be

measured as accurately as possible with the assistance of the enclosed dosage syringe, which is graduated in 0.5 ml divisions, providing 20 mg of Badozithro in every division. For children who weigh more than 15 kg, Badozithro suspension should be administered with the assistance of the dosage spoon, which provides 2.5, 3.75 or 5 ml doses, corresponding to 100, 150 or 200 mg of Badozithro, respectively according to the following schedule:

Weight (kg)	*3-day treatment**	*5-day treatment**	*Content bottle*
10-15	**Once daily 10 mg/kg on days 1 through 3**	**Once daily 10 mg/kg on day 1, followed by once daily 5 mg/kg on days 2 through 5**	**15 ml**
16-25	**Once daily 200 mg (5 ml) on days 1 through 3**	**Once daily 200 mg (5 ml) on day 1, followed by once daily 100 mg (2.5 ml) on days 2 through 5**	**15 ml**
26-35	**Once daily 300 mg (7.5 ml) on days 1 through 3**	**Once daily 300 mg (7.5 ml) on day 1, followed by once daily 150 mg (3.75 ml) on days 2 through 5**	**22.5ml**
35-45	**Once daily 400 mg (10 ml) on days 1 through 3**	**Once daily 400 mg (10 ml) on day 1, followed by once daily 200 mg (5 ml) on days 2 through 5**	**30ml**
> 45	**Dose as in adults**		**37.5ml**

Separate dosage recommendations apply for streptococcal pharyngitis and are described below.
For the treatment of Streptococci pharyngitis in children aged 2 years or more: Badozithro in a single dose of 10 mg/kg or 20 mg/kg for three days, in which the maximum daily dose of 500 mg should not be exceeded. However, penicillin remains the first choice for the treatment of Streptococcus pyogenes pharyngitis, among which the prophylaxis for acute .
The maximum dosage in children correlates with the common dosage in adults
with 1500 mg Badozithro.

Sinusitis
For the treatment of sinusitis, limited data is available for the treament of children under 16 years of age.

Older people
The same dosage as in adult patients is used in the older people. Since older people can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes.

Patients with renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min) .

Patients with hepatic impairment

A dose adjustment is not necessary for patients with mild to moderately impaired liver function (Child-Pugh class A or B).

Method of administration
Badozithro suspension should be given as a single daily dose. The suspension can be taken with or without food.

4.3 Contraindications

Hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic or to any of the excipients listed**.**

- **Badozithro is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior used of Badozithro.**

4.4 Special warnings and precautions for use

Allergic reactions

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

Renal impairment

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

Hepatic impairment

Since liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to lifethreatening liver failure have been reported with Badozithro.
Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests/ investigations should be performed immediately. Badozithro administration should be stopped if liver dysfunction has emerged.

Ergot alkaloids and azithromycin

In patients receiving ergot derivatives, ergotism has been precipitated by coadministration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergot and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be coadministered.As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms, including fungi is recommended.

QT prolongation

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides, including azithromycin (see section “Undesirable effects). Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which
can lead to cardiac arrest, azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly
patients) such as patients:

- With congenital or documented QT prolongation
- Currently receiving treatment with other active substances known to prolong

QT interval such as antiarrhythmics of class IA (quinidine and procainamide) and class III (dofetilide, amiodarone and sotalol), cisapride and terfenadine; antipsychotic agents such as pimozide; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin
 With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesemia
 With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

- Badozithro have been associated with cardiovascular effects; specifically, prolongation of the QT interval. Prolongation of QT interval can lead to torsade de pointes (TdP),an abnormal heart rhythm, which can be fatal.
- Hepatotoxicity": abnormal liver function, hepatitis , cholestatic jaundice ,hepatic necrosis , hepatic failure have been reported, some of which have resuled in death.
  Discontinue badozithro immediately if signs and symptoms of hepatitis occur.

The following should be considered before prescribing Badozithro:

Badozithro powder for oral suspension is not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed.

In areas with a high incidence of erythromycin A resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other antibiotics.

As for other macrolides, high resistance rates of *Streptococcus pneumoniae* (> 30 %) have been reported for azithromycin in some European countries (see section 5.1). This should be taken into account when treating infections caused by *Streptococcus pneumoniae*.

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

Pharyngitis/tonsillitis

Badozithro is not the substance of first choice for the treatment of pharyngitis and tonsillitis caused by *Streptococcus pyogenes*. For this and for the prophylaxis of acute rheumatic fever penicillin is the treatment of first choice.

Sinusitis

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

Acute otitis media

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

Infected burn wounds

Badozithro is not indicated for the treatment of infected burn wounds.

Sexually transmitted disease

In case of sexually transmitted diseases a concomitant infection by *T. pallidum* should be excluded.

Superinfections

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

Neurological or psychiatric diseases

Badozithro should be administered with caution to patients suffering from neurological or psychiatric diseases.

Myasthenia gravis

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving Badothiro (see section 4.8).

Clostridium difficile-*associated diarrhea*

Clostridium difficile-associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial
agents alters the normal flora of the colon leading to overgrowth of *C. difficile. C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. A careful medical history is
necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Long-term use

There is no experience regarding the safety and efficacy of long-term use of azithromycin for the mentioned indications. In case of rapid recurrent infections, treatment with another antibiotic should be considered. In children aged under 6 months, evidence of the safety of Badozithro is limited. The safety and efficacy of azithromycin for the prevention or treatment of *Mycobacterium avium* complex (MAC) infection in children have not been established.

Sucrose

Caution in diabetic patients: 5 ml of reconstituted suspension contain 3.78 g of sucrose.
Badozithro 200 mg/5ml powder for oral suspension contain sucrose (3.78 g / 5 ml of reconstituted suspension). Patients with rare hereditary problems of fructose intolerance, glucose- galactose malabsorption or sucrase-isomaltase
insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids

In a pharmacokinetic study investigating the effects of simultaneous administration of antacid with Badozithro, 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. Coadministration of azithromycin prolonged-release granules for oral suspension with a single 20 ml dose of co-magaldrox (aluminium hydroxide and magnesium
hydroxide) did not affect the rate and extent of azithromycin absorption. Badozithro should be taken at least 1 hour before or 2 hours after the antacid.

Cetirizine

In healthy volunteers, coadministration of a 5-day regimen of Badozithro with cetirizine 20 mg at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

Didanosine (Dideoxyinosine)

Coadministration of 1,200 mg/day Badozithro with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

Digoxin and colchicine (P-gp substrates)

Concomitant administration of macrolide antibiotics, including azithromycin, with Pglycoprotein bstrates such as digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if Badozithro and P-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered.

Zidovudine

Single 1000 mg dose and multiple 1200 mg or 600 mg doses of Badozithro had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of Badozithro 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.

Cytochrome P450

Badozithro does not interact significantly with the hepatic cytochrome P450system. 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 Badozithro.

Ergot

Due to the theoretical possibility of ergotism, the concurrent use of Badozithro with ergot derivatives is not recommended (see section 4.4). Pharmacokinetic studies have been conducted between Badozithro and the following drugs known to undergo significant cytochrome P450 mediated metabolism.

Atorvastatin

Coadministration of atorvastatin (10 mg daily) and Badozithro (500 mg daily) did not alter the plasma concentration of atorvastatin (based on an HMG CoA-reductase inhibition assay). However, post-marketing cases of rhabdomyolysis in patients receiving Badozithro with statins have been reported.

Carbamazepine

In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

Cimetidine

In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before Badozithro, on the pharmacokinetics of Badozithro, no alteration of Badozithro pharmacokinetics was seen.

Coumarin-Type Oral Anticoagulants

In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15 mg dose of warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to coadministration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established,consideration should be given to the frequency of prothrombin time monitoring when Badozithro is used in patients receiving coumarin-type oral anticoagulants.

Ciclosporin

In a pharmacokinetic study with healthy volunteers given oral Badozithro 500 mg/day for 3 days then a single 10 mg/kg oral dose of ciclosporin, the resulting ciclosporin C_{max} and AUC_{0-5} were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these agents. If combination treatment is necessary, the ciclosporin levels should be carefully monitored and the dosage should be adjusted accordingly.

Efavirenz

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

Fluconazole

Coadministration of a single dose of 1,200 mg azithromycin did not alter the harmacokinetics of a single dose of 800 mg fluconazole. Total exposure and half-life of Badozithro were unchanged by the coadministration of fluconazole, however, a clinically insignificant decrease in Cmax (18%) of Badozithro was observed.

Indinavir

Coadministration of a single dose of 1,200 mg Badozithro had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

Methylprednisolone

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

Midazolam

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

Nelfinavir

Coadministration of azithromycin (1,200 mg) and nelfinavir at steady-state (750 mg three times daily) resulted in increased Badozithro concentrations. No clinically significant adverse effects were observed and no dose adjustment is required.

Rifabutin

Coadministration of Badozithro and rifabutin did not affect the serum concentrations of either drug. Neutropenia was observed in subjects receiving concomitant treatment of Badozithro and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established .

Sildenafil
In normal healthy male volunteers, there was no evidence of an effect of Badozithro(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 Badozithro 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. As with other macrolides, azithromycin should be administered with caution in combination with terfenadine.

Theophylline
There is no evidence of a clinically significant pharmacokinetic interaction when Badozithro and theophylline are coadministered to healthy volunteers.

Triazolam
In 14 healthy volunteers, coadministration of Badozithro 500 mg on day 1 and 250 mg on day 2 with 0.125 mg triazolam on day 2 had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

Trimethoprim/sulfamethoxazole
Coadministration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with Badozithro 1,200 mg on day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim ornsulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies.

Cisapride
Cisapride is metabolized in the liver by the enzyme CYP3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsades de pointes.

Astemizole, alfentanil
No data are available on interactions with astemizole and alfentanil. Caution should be exercised with concomitant use of these drugs and azithromycin in view of the described potentiation of its effect during concomitant use of the macrolide antibiotic erythromycin.

Substances that prolong the QT interval
Badozithro should not be used concurrently with other active substances that prolong the QT interval

4.6 Fertility, pregnancy and lactation

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

Breast-feeding
Badozithro has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in nursing women that have characterized the pharmacokinetics of azithromycin excretion into human breast milk.

Fertility
In fertility studies conducted in rat, reduced pregnancy rates were noted following administration of Badozithro. The relevance of this finding to humans is unknown.

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

4.8 Undesirable effects
The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in italics. The frequency grouping is defined using the following convention: Very common (≥1/10); Common (≥ 1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥ 1/10,000 to <1/1,000); Very Rare (< 1/10,000); and Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. About 13% of patients included in clinical trials reported adverse events, most commonly
gastro-intestinal disorders.
Adverse reactions possibly or probably related to azithromycin based on clinical trial
experience and post-marketing surveillance:

System organ class	**Very common (≥1/10)**	**Common(≥1/ 100 to < 1/10)**	**Uncommon (≥1/1000 to < 1/100)**	**Rare(≥1/10,000 to < 1/1,000)**	**Frequency Not Known**
Infections and infestations			Candidiasis Vaginal infection Pneumonia Fungal infection Bacterial infection Pharyngitis Gastroenteritis Respiratory disorder Rhinitis Oral candidiasis		Pseudomembranous colitis (see section 4.4)
Blood and lymphatic system disorders			Leukopenia Neutropenia Eosinophilia		Thrombocytopenia Haemolytic anaemia
Immune system disorders			Angioedema Hypersensitivity		Anaphylactic reaction (see section 4.4)
Metabolism and nutrition disorders			Anorexia		
Psychiatric disorders			Nervousness, Insomnia	Agitation Depersonalisation	Aggression Anxiety Delirium Hallucination

Nervous system disorders		Headache	Dizziness Somnolence, Dysgeusia Paraesthesia		Syncope Convulsion Hypoesthesia, Psychomot or hyperactivity, Anosmia, Parosmia, Ageusia, Myasthenia gravis (see section 4.4)
Eye disorders			Visual Impairment		
Ear and labyrinth disorders			Ear disorder Vertigo		hearingimpairment including deafness and/or tinnitus
Cardiac disorders			Palpitations		torsades de pointes (see section 4.4) Arrhythmia (see Section 4.4) Including ventricular tachycardia electrocard iogram QT prolonged (see section 4.4)
Vascular disorders			Hot flush		Hypotensi On
Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis		
Gastrointestinal disorders	Diarrhoea	Vomiting, Abdominal pain,	Gastritis Constipation Flatulence Dyspepsia Dysphagia Abdomminal distension Dry mouth Eructation Mouth ulceration Salivary hypersecretion Loose stools	Discolouration of the teeth	Pancreatitis Tongue discolourat ion
Hepatobiliary Disorders			Hepatitis	Hepatic function abnormal Jaundice cholestatic	Hepatic failure which has rarely resulted in death (see section 4.4) hepatitis fulminant

					hepatic necrosis
Skin and Subcutaneous Tissue Disorders			Rash, Pruritus Urticaria Dermatitis Dry skin Hyperhidrosis	Photosensitivity reaction	Stevens-Johnson Syndrome Toxic Epidermal necrolysis Erythema multiforme Maculopapular rash
Musculoskeletal and Connective Tissue Disorders			Osteoarthritis, Myalgia, Back pain, Neck pain		Arthralgia
Renal and Urinary Tract Disorders			Dysuria Renal pain		Acute renal failure Interstitial nephritis
Reproductive system and breast disorders			Metrorrhagia, Testicular disorder Vaginitis		
General disorders and administration site conditions			Oedema Asthenia Malaise Fatigue Face edema Chest pain Pyrexia Pain Peripheral edema		
Investigations		Lymphocyte count decreased Eosinophil count increased Blood bicarbonate decreased Basophils increased Monocytes increased Neutrophils increased	Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubin increased Blood urea increased Blood creatinine increased Blood potassium abnormal Blood alkaline phosphatase increased Chloride increased		

			Glucose increased Platelets increased Hematocrit decreased Bicarbonate increased Abnormal Sodium		
Injury and poisoning			Post procedural complication		

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 the prolonged release formulations, either in kind or in frequency:

	Very common (≥1/10)	**Common(≥1/100 to < 1/10)**	**Uncommon (≥1/1000 to < 1/100)**
Metabolism and Nutrition Disorders		Anorexia	
Nervous System Disorders		Dizziness Headache Paraesthesia Dysgeusia	Hypoesthesia
Eye Disorders		Visual impairment	
Ear and Labyrinth Disorders		Deafness	Hearing impaired Tinnitus
Cardiac Disorders			Palpitations
Gastrointestinal Disorders	Diarrhea Abdominal pain Nausea Flatulence Abdominal Discomfort		
Hepatobiliary Loose stools **Disorders**			Hepatitis
Skin and Subcutaneous Tissue Disorders		Rash Pruritus	Stevens-Johnson syndrome Photosensitivity reaction
Musculoskeletal and Connective Tissue		Arthralgia	
General Disorders and Administration Site Conditions		Fatigue	Asthenia Malaise

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

Adverse reactions:"Postmarketing Experience"

* Liver/Biliary : Adverse reactions related to hepatic dysfunction have been reported in postmarketing experience with Badozithro.

4.9 Overdose
Adverse events experienced in higher than recommended doses were similar to those seen at normal doses.

Symptoms
The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea.

Treatment
In cases of overdose the administration of medicinal charcoal and general symptomatic and supportive measures are indicated as required.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use; macrolides.
ATC code: J01FA10.
Badozithro 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 chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl- 9a-homo-erythromycin A. The molecular weight is 749.0.

Mechanism of action
The action mechanism of azithromycin is based upon the suppression of bacterial protein synthesis, by binding to the 50 S subunit and thus inhibiting the translocation of peptides.

5.2 Pharmacokinetic properties
Absorption

Following oral administration the bio-availability of Badozithro is approximately 37%. Peak plasma levels are reached after 2-3 hours.

Distribution
Orally administered azithromycin is widely distributed throughout the body. Pharmacokinetic studies have shown considerably higher Badozithro concentrations in the tissues (up to 50 times the maximum concentration observed in the plasma) than in the plasma. This indicates that the substance is extensively bound in the tissues (steady-state volume of distribution approximately 31 l/kg). The mean maximum concentration observed (C_{max}) after a single dose of 500 mg is approximately 0.4 µg/ml, 2-3 hours after

administration. With the recommended dosage no accumulation in the serum/plasma occurs. Accumulation does occur in the tissues where the levels are much higher than in the serum/plasma. Three days after administration of 500 mg as a single dose or in divided doses concentrations of 1.3-4.8 µg/g,0.6-2.3 µg/g, 2.0-2.8 µg/g and 0-0.3 µg/ml are found in lung, prostate, tonsil and serum respectively.

Mean peak concentrations measured in peripheral leukocytes are higher than the MIC_{90} of the most common pathogens.

In experimental *in vitro* and *in vivo* studies, Badozithro accumulates in phagocytes; release is promoted by active phagocytosis. In animal models this process appeared to contribute to the accumulation of azithromycin in the tissue.

The binding of azithromycin to plasma proteins is variable and varies from 52% at 0.005 µg/ml to 18% at 0.5 µg/ml, depending on the serum concentration.

Biotransformation and Elimination

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

Pharmacokinetics in special populations

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

Hepatic impairment
In patients with mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of Badozithro compared to normal hepatic function. In these patients, urinary recovery of Badozithro appears to increase perhaps to compensate for reduced hepatic clearance. There are no data on azithromycin use in cases of more severe hepatic impairment.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Hydroxypropyl cellulose
Sodium phosphate tribasic dodecahydrate
Xanthan gum
Quinolone yellow
Vanilla
Banana flavor

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened bottles: 36 Months store at temp not exceed 30°C in dry place
After reconstitution (for Badozithro 15 ml): 3 days
After reconstitution: store at temp. not exceed 30ºC.in dry place

6.4 Special precautions for storage

Unopened bottles: store at temp. not excess than 30ºC.

6.5 Nature and contents of container

Carton box containing 30 ml transparent plastic HDPE bottle of 12.57 gm powder with 2 LDPE plastic ampules each contains 4 ml sterile water to make gives 15 ml suspension with mulit dose cap + inner leaflet

6.6 Special precautions for disposal

Preparing suspension:
First loosen the powder by tapping well.
For 15 ml bottle: add 8 ml water.
Shake well.
Advice should be given as to whether the dose should be measured using the oral dosing Cap **.**

Manufactured by Badr Pharma for Pharmaceutical Industries