1. NAME OF THE MEDICINAL PRODUCT

ZITHROHEAL DRY SYRUP
Azithromycin USP 200 mg/5ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Batch Size: 105 kg **Pack size: 15 ml**

Sr. No	Ingredients	Grade	Quantity in gram/10 gram	Quantity per Batch (Kg)
1.	Azithromycin Dihydrate USP	USP	0.701	7.361
2.	Pharma grade Sugar	BP	8.7	91.35
3.	Sodium CMC	BP	0.048	0.507
4.	Sodium Citrate	BP	46	0.485
5.	Citric acid	BP	0.117	1.227
6.	Sodium Benzoate	BP	0.023	0.246
7.	Polysorbate 80	BP	0.151	1.584
8.	Avicel RC 591	USP	0.002	0.02
9.	Xanthan Gum	BP	0.037	0.391
10.	HPMC E-15	BP	0.058	0.613
11.	Aerosil	BP	0.027	0.279
12.	Colour Erythrosine	BP	0.186	1.952
13.	Flavour Dry Raspberry	BP	0.062	0.647
14.	Aspartame	BP	0.092	0.965

3. PHARMACEUTICAL FORM

Dry Syrup
Description: Light pink coloured granular powder, after reconstitution forms a pink coloured suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Azithromycin powder for oral suspension is indicated for the treatment of the following infections, when caused by micro-organisms sensitive to azithromycin (see section 4.4 and 5.1):

- Acute bacterial sinusitis (adequately diagnosed)

- Acute bacterial otitis media (adequately diagnosed)

- Pharyngitis, tonsillitis

- Acute exacerbation of chronic bronchitis (adequately diagnosed)

- Mild to moderately severe community acquired pneumonia

- Skin and soft tissue infections

- Uncomplicated *Chlamydia trachomatis* urethritis and cervicitis

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

4.2 Posology and method of administration
Adults

In uncomplicated *Chlamydia trachomatis* urethritis and cervicitis, the dose is 1,000 mg in one single oral dose.

For all other indications the dose is 1,500 mg, to be administered as 500 mg per day for three consecutive days. Alternatively the same total dose (1,500 mg) can also be given over a period of 5 days with 500 mg on the first day and then 250 mg on days 2 to 5.

To treat these patients other pharmaceutical forms are also available.

Elderly people

The same dose as in adult patients is used in the older people. Since older patients can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes (see section 4.4).

Children and adolescents (< 18 years)

The total dose in children aged 1 year and older is 30 mg/kg administered as 10 mg/kg once daily for three days, or over a period of five days starting with a single dose of 10 mg/kg on the first day, followed by doses of 5 mg/kg per day for the following 4 days, according to the tables shown below. There are limited data on use in children younger than 1 year.

Weight (kg)	3-day therapy	5-day therapy		Contents of the bottle
	Day 1-3 10 mg/kg/day	Day 1 10 mg/kg/day	Day 2-5 5 mg/kg/day	
10 kg	2.5 ml	2.5 ml	1.25 ml	15 ml
12 kg	3 ml	3 ml	1.5 ml	15 ml
14 kg	3.5 ml	3.5 ml	1.75 ml	15 ml
16 kg	4 ml	4 ml	2 ml	15 ml
17 – 25 kg	5 ml	5 ml	2.5 ml	15 ml
26 – 35 kg	7.5 ml	7.5 ml	3.75 ml	22.5 ml
36 – 45 kg	10 ml	10 ml	5 ml	30 ml
> 45 kg	12.5 ml	12.5 ml	6.25 ml	22.5 ml + 15 ml

The dose for the treatment of pharyngitis caused by *Streptococcus pyogenes* is an exception: in the treatment of pharyngitis caused by *Streptococcus pyogenes* Azithromycin has proved to be effective when it is administered to children as a single dose of 10 mg/kg or 20 mg/kg for 3 days with a maximum daily dose of 500 mg. At these two doses a comparable clinical effect was observed, even if the eradication of the bacteria was more significant at a daily dose of 20 mg/kg.

Penicillin is however the drug of first choice in the treatment of pharyngitis caused by *Streptococcus pyogenes* and the prevention of subsequent rheumatic fever.

Patients with renal impairment:

No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min) (see section 4.4).

Patients with hepatic impairment:

A dose adjustment is not necessary for patients with mild to moderately impaired liver function (see section 4.4).

Method of administration

Before use the powder should be reconstituted with water into a white to off white, homogenous suspension, see section 6.6. After reconstitution the drug can be administered using a PE/PP syringe for oral use.

After taking the suspension a bitter after-taste can be avoided by drinking fruit juice directly after swallowing. Azithromycin powder for oral suspension should be given in a single daily dose. The suspension may be taken together with food.

4.3 Contraindications

The use of this product is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients listed in section 6.1 (see also section 4.4).

4.4 Special warnings and precautions for use

Hypersensitivity

As with erythromycin and other macrolides, rare serious allergic reactions, including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

If an allergic reaction occurs, the medicinal product should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Since liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin (see section 4.8). Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

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

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.

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

In patients with severe renal impairment (GFR <10 ml/min) a 33% increase in systemic exposure to azithromycin was observed (see Section 5.2).

Cardiovascular Events

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides including azithromycin (see section 4.8). Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients:

• With congenital or documented QT prolongation

• Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmic 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

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including azithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing azithromycin.

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

Safety and efficacy for the prevention or treatment of *Mycobacterium avium* complex in children have not been established.

The following should be considered before prescribing azithromycin:

Azithromycin 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.

Azithromycin is not the first choice for the empiric treatment of infections in areas where the prevalence of resistant isolates is 10% or more (see section 5.1).

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*.

Pharyngitis/ tonsilitis

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

Acute otitis media

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

Skin and soft tissue infections

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

Infected burn wounds

Azithromycin 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.

Neurological or psychiatric diseases

Azithromycin should be used with caution in patients with neurological or psychiatric disorders.

Caution in diabetic patients: 5 ml of reconstituted suspension contain 3.70 g of sucrose.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine since it contains sucrose.

Azithromycin 200mg/5 ml contain aspartame which is a source of phenylalanine. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

Azithromycin 100mg/5 ml and Azithromycin 200mg/5 ml contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids

In a pharmacokinetic study investigating the effects of simultaneous administration of antacid with azithromycin, no effect on overall bioavailability was seen although peak serum concentrations were reduced by approximately 25%. In patients receiving both azithromycin and antacids, the medicinal products should not be taken simultaneously.

Cetirizine

In healthy volunteers, coadministration 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)

Coadministration of 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

Digoxin and colchicine (P-gp substrates)

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

Zidovudine

Single 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

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

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

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

Astemizole, alfentanil

There are no known data on interactions with astemizole or alfentanil. Caution is advised in the co-administration of these medicines with Azithromycin because of the known enhancing effect of these medicines when used concurrently with the macrolid antibiotic erythromycin.

Atorvastatin

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

Carbamazepine

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

Cisapride

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

Cimetidine

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

Coumarin-Type Oral Anticoagulants

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