SUMMARY OF PRODUCTS CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

ZIMYCIN DRY SYRUP
Azithromycin for Oral Suspension USP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml reconstituted suspension contains:
Azithromycin Dihydrate USP
Eq. to Azithromycin……..200 mg
Flavoured Syrupy base…..……. Q.S.
Colour: Erythrosine
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder for oral 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 - 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 ongoingproarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes.

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

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.

4.3 Contraindications
The use of this product is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or Ketolide Antibiotic.

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 exanthematouspustulosis (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 ongoingproarrhythmic conditions (especially women and elderly patients) such as patients:

• With congenital or documented QT prolongation
• With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesemia

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.

4.6 Fertility, pregnancy and lactation

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

Breastfeeding
Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in breastfeeding 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 azithromycin. 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 azithromycin may have an effect on a patient's ability to drive or operate machinery. Visual impairment and vision blurred 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 postmarketing surveillance by system organ class and frequency.
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.

Adverse reactions possibly or probably related to azithromycin based on clinical trial experience and post-marketing surveillance:

	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**
Blood and Lymphatic System Disorders			Leukopenia Neutropenia Eosinophilia		Thrombocytopenia Haemolytic anaemia
Immune System Disorders			Angioedema Hypersensitivity		Anaphylactic reaction
Metabolism and Nutrition Disorders			Anorexia		
Psychiatric Disorders			Nervousness Insomnia,	Agitation	Aggression Anxiety Delirium Hallucination
Nervous System Disorders		Headache	Dizziness Somnolence Dysgeusia Paraesthesia		Syncope, convulsion Hypoestheia Psychomotor hyperactivity Anosmia Ageusia Parosmia Myasthenia gravis
Eye Disorders					Visual impairment, blurred vision
Ear and Labyrinth Disorders			Ear disorder Vertigo		Hearing impairment including deafness and/or tinnitus
Cardiac Disorders			Palpitations		Torsades de pointes Arrhythmia including ventricular tachycardia Electrocardiogram QT prolonged
Vascular Disorders			Hot flush		Hypotension
Respiratory, thoracic and mediastinal disorders			Dyspnoea, Epistaxis		

Gastrointestinal Disorders	Diarrhea	Vomiting Abdominal pain Nausea	Constipation Flatulence Dyspepsia, Gastritis dysphagia Abdominal distension Dry mouth Eructation Mouth ulceration Salivary hypersecretion		Pancreatitis Tongue discolouration
Hepatobiliary Disorders				Hepatic function abnormal Jaundice cholestatic	Hepatic failure (which has rarely resulted in death) Hepatitis fulminant Hepatic necrosis
Skin and Subcutaneous Tissue Disorders			Rash Pruritus Urticaria, Dermatitis Dry skin Hyperhidrosis	Photosensitivity reaction Acute generalised exanthematouspustulosis (AGEP)	Stevens-Johnson syndrome Toxic epidermal necrolysis Erythema multiforme
Musculoskeletal and Connective Tissue Disorders			Osteoarthritis, Myalgia Back pain Neck pain		Arthralgia
Renal and Urinary Disorders			Dysuria Renal pain		Renal failure acute Nephritis interstitial
Reproductive system and breast disorders			Metrorrhagia, Testicular disorder		

4.9 Overdose

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. In the event of over dosage, general symptomatic and supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use; macrolides; azithromycin, **ATC code:** J01FA10

Mode of action

Azithromycin is an azalide, a sub-class of the macrolide antibiotics. By binding to the 50S-ribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented.

PK/PD relationship
For azithromycin the AUC/MIC is the major PK/PD parameter correlating best with the efficacy of azithromycin.

Mechanism of resistance
Resistance to azithromycin may be inherent or acquired. There are three main mechanisms of resistance in bacteria: target site alteration, alteration in antibiotic transport and modification of the antibiotic.
Complete cross resistance exists among *Streptococcus pneumoniae*, betahaemolytic streptococcus of group A, *Enterococcus faecalis* and *Staphylococcus aureus*, including methicillin resistant *S. aureus* (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

5.2 Pharmacokinetic properties

Absorption
The biological availability of azithromycin after oral administration is approximately 37%. Peak plasma levels are achieved 2-3 hours after taking the medicinal product.

Distribution
After oral administration, azithromycin is distributed throughout the entire body. Pharmacokinetic studies have shown clearly higher azithromycin levels in the tissues than in the plasma (up to 50 times the maximum observed concentration in plasma). This indicates that the substance is bound in the tissues in considerable quantities.
Concentrations in the infected tissues, such as lungs, tonsil and prostate are higher than the MRC90 of the most frequently occurring pathogens after a single dose of 500 mg.
The protein binding of azithromycin in serum is variable and varies, depending on the serum concentration, from 52% at 0.05 mg/l to 12% at 0.5 mg/l. The steady state distribution volume is 31.1 l/kg.

Elimination
The terminal plasma-elimination half-life closely follows the tissue depletion half-life from 2 to 4 days. Approximately 12% of an intravenously administered dose of azithromycin is, over a period of 3 days, excreted unchanged in the urine. High concentrations of unchanged azithromycin were found in human bile. In this, ten metabolites were also detected (formed by N- and O- desmethylation, by hydroxylation of the desosamin and aglycon rings and by splitting the cladinose conjugate). A comparison of fluid chromatography and

microbiological assessment methods shows that the metabolites are microbiologically inactive.
In animal models high concentrations of azithromycin were found in phagocytes. Also it has been shown that during active phagocytosis higher concentrations of azithromycin are released than during inactive phagocytosis. In animal models this process was shown to contribute to the accumulation of azithromycin in infectious tissue.

Pharmacokinetics in special populations

Renal insufficiency

Following a single oral dose of azithromycin 1 g, 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, the mean C_{max} and AUC_{0-120} increased 61% and 33% respectively compared to normal.

Hepatic insufficiency

In patients with mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to normal hepatic function. In these patients, urinary recovery of azithromycin appears to increase perhaps to compensate for reduced hepatic clearance.

Elderly

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.

Infants, toddlers, children and adolescents

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 ug/l in children aged 0.6-5 years and after 3 days dosing and 383 ug/l in those aged 6-15 years. The $t_{1/2}$ of 36 h in the older children was within the expected range for adults.

5.3 Preclinical Safety Data

In animal studies using exposures 40 times those achieved at the clinical therapeutic dosages, azithromycin was found to have caused reversible phospholipidosis, but as a rule there were no associated toxicological consequences. The relevance of this finding to humans receiving azithromycin in accordance with the recommendations is unknown.
Electrophysiological investigations have shown that azithromycin prolongs the QT interval.

Carcinogenic potential:

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenic potential:
There was no evidence of a potential for genetic and chromosome mutations in in-vivo and in-vitro test models.
Reproductive toxicity:
Teratogenic effects were not observed in rat reproductive toxicity studies. At slight maternally toxic doses retardation in foetal ossification was seen. In peri- and postnatal studies in rats mild retardations in physical and reflex development were noted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Name of Material	Specification
Sodium Benzoate	BP
Colloidal Anhydrous Silica	BP
Flavour Strawberry Dry	IHS
Ecocool DT	IHS
Aspartame	BP
Tri sodium phosphate (Dodecahydrate)	IHS
Sucralose	BP
Colour Erythrosin Supra	IHS
Sodium Chloride	BP
Magnesium oxide (light)	BP
Xanthan gum	USP-NF
Dextrose anhydrous	BP

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C. Protected from light.
KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

15ml and 30ml HDPE bottle

7. MARKETING AUTHORISATION HOLDER

Ahmedabad
Gujarat, India.
E-mail: info@sagalabs.com
URL: www.sagalabs.com

8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

08480/09347/NMR/2021

9. DATE OF FIRSHT AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/03/2023

10. DATE OF REVISION OF THE TEXT

01 April 2026