Zithracin®

1 NAME OF THE MEDICINAL PRODUCT

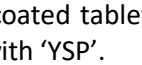
Zithracin® Film Coated Tablet 250 mg
Zithracin® Film Coated Tablet 500 mg
Zithracin® Powder for Oral Suspension 200 mg/5 mL

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

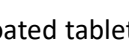
Zithracin® Film Coated Tablet 250 mg contain Azithromycin dihydrate equivalent to Azithromycin 250mg
Zithracin® Film Coated Tablet 500 mg contain Azithromycin dihydrate equivalent to Azithromycin 500mg
Each 5 mL of Zithracin® Powder for Oral Suspension 200 mg/5 mL contain Azithromycin dihydrate equivalent to 200 mg

Excipients with known effect
Zithracin® Film Coated Tablet 250 mg: Each film coated tablet contains 3.5 mg lactose (as monohydrate) and less than 1 mmol (23 mg) sodium.
Zithracin® Film Coated Tablet 500 mg: Each film coated tablet contains 7 mg lactose (as monohydrate) and less than 1 mmol (23 mg) sodium.

3 PHARMACEUTICAL FORM

Zithracin® Film Coated Tablet 250 mg:
A white colour film coated tablet in the shape of 

, one side impressed with 'YSP'.

Zithracin® Film Coated Tablet 500 mg:
A white colour film coated tablet in the shape of 

, one side impressed with 'YSP 50', another side impressed with a score.

Zithracin® Powder for Oral Suspension 200 mg/5 mL:
Before reconstitution: A white to yellowish brown granular powder with fruity flavour.
After reconstitution: A white to yellowish brown suspension with fruity flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Azithromycin is indicated for infections caused by susceptible organisms; in lower respiratory tract infections including bronchitis and pneumonia, in skin and soft tissue infections, in acute otitis media and in upper respiratory tract infections including sinusitis and pharyngitis/tonsillitis. (Penicillin is the

usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. Azithromycin is generally effective in the eradication of streptococci from the oropharynx; however, data establishing the efficacy of azithromycin and the subsequent prevention of rheumatic fever are not available at present.)
In sexually transmitted diseases in men and women, azithromycin is indicated for the treatment of uncomplicated genital infections due to *Chlamydia trachomatis*. It is also indicated for the treatment of chancroid due to *Haemophilus ducreyi* and uncomplicated genital infections due to non-multiresistant *Neisseria gonorrhoeae*; concurrent infection with *Treponema pallidum* should be excluded.

4.2 Posology and method of administration

Posology

Azithromycin Oral

Oral azithromycin should be administered as a single daily dose. The period of dosing with regard to infection is given below.

Azithromycin tablets, powder for oral suspension can be taken with or without food.

In adults

For the treatment of sexually transmitted diseases caused by *Chlamydia trachomatis* and *Haemophilus ducreyi*, or susceptible *Neisseria gonorrhoeae*, the dose is 1000 mg as a single oral dose.

For patients who are allergic to penicillin and/or cephalosporins, prescribers should consult local treatment guidelines.

For all other indications in which the oral formulation is administered, the total dosage of 1500 mg should be given as 500 mg daily for 3 days. As an alternative, the same total dose can be given over 5 days with 500 mg given on Day 1, then 250 mg daily on Days 2 to 5.

In children

The maximum recommended total dose for any treatment is 1500 mg for children.

In general, the total dose in children is 30 mg/kg. Treatment for pediatric streptococcal pharyngitis should be dosed at a different regimen (see below).

The total dose of 30 mg/kg should be given as a single daily dose of 10 mg/kg daily for 3 days, or given over 5 days with a single daily dose of 10 mg/kg on Day 1, then 5 mg/kg on Days 2-5.

As an alternative to the above dosing, treatment for children with acute otitis media can be given as a single dose of 30 mg/kg.

For pediatric streptococcal pharyngitis, azithromycin given as a single dose of 10 mg/kg or 20 mg/kg for 3 days has been shown to be effective; however, a daily dose of 500 mg must not be exceeded. In clinical trials comparing these two dosage regimens, similar clinical efficacy was observed but greater bacteriologic eradication was evident at the 20 mg/kg/day dose. However, penicillin is the usual drug of choice for the treatment of *Streptococcus pyogenes* pharyngitis, including prophylaxis of rheumatic fever.

For children weighing less than 15 kg, azithromycin suspension should be measured as closely as possible. For children weighing 15 kg or more, azithromycin suspension should be administered according to the guide provided below.

Azithromycin Suspension 30 mg/kg Total Treatment Dose		
Weight (kg)	**3-Day Regimen**	**5-Day Regimen**
<15	10 mg/kg once daily on Days 1-3.	10 mg/kg on Day 1, then 5 mg/kg once daily on Days 2-5.
15-25	200 mg (5 ml) once daily on Days 1-3.	200 mg (5 ml) on Day 1, then 100 mg (2.5 ml) once daily on Days 2-5.
26-35	300 mg (7.5 ml) once daily on Days 1-3.	300 mg (7.5 ml) on Day 1, then 150 mg (3.75 ml) once daily on Days 2-5.
36-45	400 mg (10 ml) once daily on Days 1-3.	400 mg (10 ml) on Day 1, then 200 mg (5 ml) once daily on Days 2-5.
>45	Dose as per adults.	Dose as per adults.

Azithromycin tablets should only be administered to children weighing more than 45 kg.

Special populations:

In the Elderly

The same dosage as in adult patients is used in the elderly. Elderly patients may be more susceptible to the development of torsades de pointes arrhythmia than younger patients.

In Patients with Renal Impairment
No dose adjustment is necessary in patients with GFR 10-80 ml/min. Caution should be exercised when azithromycin is administered to patients with GFR <10 ml/min.
In Patients with Hepatic Impairment
The same dosage as in patients with normal hepatic function may be used in patients with mild to moderate hepatic impairment.

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 excipient.

4.4 Special warnings and precautions for use
Hypersensitivity
As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), Dermatologic reactions including Acute Generalized 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.

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP)], Zithracin® should be discontinued immediately and appropriate treatment should be urgently initiated.

Hepatotoxicity
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. Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue

azithromycin immediately if signs and symptoms of hepatitis occur.

Infantile hypertrophic pyloric stenosis (IHPS)
Following the use of azithromycin in neonates (treatment up to 42 days of life), infantile hypertrophic pyloric stenosis (IHPS) has been reported. Parents and caregivers should be informed to contact their physician if vomiting or irritability with feeding occurs.

Ergot derivatives
In patients receiving ergot derivatives, ergotism has been precipitated by co-administration 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 co-administered.

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

Clostridium difficile-associated diarrhoea
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 2 months after the administration of antibacterial agents.

Renal impairment
In patients with GFR <10 mL/min, a 33% increase in systemic exposure to azithromycin was observed.

Diabetes
Azithromycin 40 mg/mL powder for oral suspension:
Caution in diabetic patients: 5 ml of reconstituted suspension contains 3.24 g of sucrose.

Due to the sucrose content (3.24 g/5 mL of reconstituted suspension), this medicinal product is not indicated for persons with fructose intolerance (hereditary fructose intolerance), glucose-galactose malabsorption or saccharase-isomaltase deficiency.

Prolongation of the QT interval

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. Prescribers should consider the risk of QT prolongation, which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including:

- Patients with congenital or documented QT prolongation
- Patients currently receiving treatment with other active substances known to prolong QT interval, such as antiarrhythmics of Classes IA and III, antipsychotic agents, antidepressants, and fluoroquinolones
- Patients with electrolyte disturbance, particularly in cases of hypokalemia and hypomagnesemia
- Patients with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency
- Elderly patients: elderly patients may be more susceptible to drug-associated effects on the QT interval

Myasthenia gravis

Exacerbations of the symptoms of myasthenia gravis have been reported in patients receiving azithromycin therapy.

Excipients

Excipients

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium

Zithracin® Film Coated Tablet contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

Aspartame

Unsuitable for phenylketonurics.

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 24%. 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 20 mg cetirizine 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 six HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared to placebo.

Digoxin and colchicine: 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-glycoprotein substrates, such as digoxin are administered concomitantly, the possibility of elevated serum digoxin concentrations should be considered. Clinical monitoring, and possibly serum digoxin levels, during treatment with azithromycin and after its discontinuation are necessary.

Ergot: There is a theoretical possibility of interaction between azithromycin and ergot derivatives.

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.

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). 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.

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 dose of 15 mg 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 were then administered a single 10 mg/kg oral dose of cyclosporin, the resulting cyclosporin C_{max} 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, cyclosporin levels should be monitored and the dose adjusted accordingly.

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

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.

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 500 mg/day azithromycin for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single dose of 15 mg 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 was 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.

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 C_{max} 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.

Triazolam: In 14 healthy volunteers, co-administration of 500 mg azithromycin 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 DS (160 mg/800 mg) for 7 days with 1200 mg azithromycin 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of harm to the fetus due to azithromycin was found. There is a large amount of data from observational studies performed in several countries on exposure to azithromycin during pregnancy, compared to no antibiotic use or use of another antibiotic during the same period. While most studies do not suggest an association with adverse fetal effects such as major congenital malformations or cardiovascular malformations, there is limited epidemiological evidence of an increased risk of miscarriage following azithromycin exposure in early pregnancy. Azithromycin should only be used during pregnancy if clinically needed and the benefit of treatment is expected to outweigh any small increased risks which may exist.

Breast-feeding

Limited information available from published literature indicates that azithromycin is present in human milk at an estimated highest median daily dose of 0.1 to 0.7 mg/kg/day. No serious adverse effects of azithromycin on the breast-fed infants were observed. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

In fertility studies conducted in rats, 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.

4.8 Undesirable effects

Blood and Lymphatic System Disorders: Transient episodes of mild neutropenia have occasionally been observed in clinical trials.

Ear and Labyrinth Disorders: Hearing impairment (including hearing loss, deafness and/or tinnitus) has been reported in some patients receiving azithromycin. Many of these have been associated with prolonged use of high doses in investigational studies. In those cases where follow-up information was available, the majority of these events were reversible.

Gastrointestinal Disorders: Nausea, vomiting, diarrhoea, loose stools, abdominal discomfort (pain/cramps), and flatulence.

Hepatobiliary Disorders: Abnormal liver function.

Skin and Subcutaneous Tissue Disorders: Allergic reactions including rash and angioedema, Frequency not known: severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP).

Additional undesirable effects that have been reported in post-marketing experience:

Infections and Infestations: Moniliasis and vaginitis.

Blood and Lymphatic System Disorders: Thrombocytopenia.

Immune System Disorders: Anaphylaxis (rarely fatal).

Metabolism and Nutrition Disorders: Anorexia.

Psychiatric Disorders: Aggressive reaction, nervousness, agitation, and anxiety.

Nervous System Disorders: Dizziness, convulsions, headache, hyperactivity, hypoesthesia, paresthesia, somnolence, and syncope. There have been rare reports of taste/smell perversion and/or loss.

Ear and Labyrinth Disorders: Deafness, tinnitus, hearing impaired, and vertigo.

Cardiac Disorders: Palpitations and arrhythmias including ventricular tachycardia have been reported. There have been

rare reports of QT prolongations and torsades de pointes (See Warnings & Precautions).
Vascular Disorders: Hypotension.
Gastrointestinal Disorders: Vomiting/diarrhoea (rarely resulting in dehydration), dyspepsia, constipation, pseudomembranous colitis, pancreatitis, rare reports of tongue discoloration, and infantile hypertrophic pyloric stenosis.
Hepatobiliary Disorders: Hepatitis and cholestatic jaundice have been reported, as well as rare cases of hepatic necrosis and hepatic failure, which have resulted in death.
Skin and Subcutaneous Tissue Disorders: Allergic reactions including pruritus, rash, photosensitivity, edema, urticaria, and angioedema. Frequency not known: severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP).
Musculoskeletal and Connective Tissue Disorders: Arthralgia.
Renal and Urinary Disorders: Interstitial nephritis and acute renal failure.
General Disorders and Administration Site Conditions: Asthenia, fatigue, and malaise.

Azithromycin is well tolerated with a low incidence of side effects.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

General Properties
Pharmacotherapeutic group: Macrolides. ATC code: J01FA10.

Mode of action
Azithromycin is the first of a subclass of macrolide antibiotics, known as azalides, and is chemically different from erythromycin. Chemically it is derived by insertion of a nitrogen atom into the lactone 11 ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl-9ahomoerythromycin A. The molecular weight is 749.0. Azithromycin binds to the 23S rRNA of the 50S ribosomal subunit. It blocks protein synthesis by inhibiting the

transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit.

Antibacterial spectrum

The prevalence of acquired resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive isolates. As discussed above, some ribosomal modifications determine cross-resistance with other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin), and the streptogramin B (which include, for example, the quinupristin component of quinupristin/dalfopristin). A decrease in macrolide susceptibility over time has been noted in particular in *Streptococcus pneumoniae* and *Staphylococcus aureus*, and has also been observed in viridans streptococci and *Streptococcus agalactiae*.

Organisms that are commonly susceptible to azithromycin include:

Aerobic and facultative gram-positive bacteria (erythromycin-susceptible isolates): *S. aureus, Streptococcus agalactiae,* S. pneumoniae,* Streptococcus pyogenes,** other β-hemolytic streptococci (Groups C, F, G) and viridans streptococci. Macrolide-resistant isolates are encountered relatively frequently among aerobic and facultative gram-positive bacteria, in particular among methicillin-resistant *S. aureus* (MRSA) and penicillin-resistant *S. pneumoniae* (PRSP).

Aerobic and facultative gram-negative bacteria: *Bordetella pertussis, Haemophilus ducreyi,* Haemophilus influenzae,* Haemophilus parainfluenzae,* Legionella pneumophila, Moraxella catarrhalis,** and *Neisseria gonorrhoeae.* Pseudomonas spp.* and most *Enterobacteriaceae* are inherently resistant to azithromycin, although azithromycin has been used to treat *Salmonella enterica* infections.

Anaerobes: *Clostridium perfringens, Peptostreptococcus spp.* and *Prevotella bivia*.

Other bacterial species: *Borrelia burgdorferi, Chlamydia trachomatis, Chlamydophila pneumoniae,* Mycoplasma pneumoniae,* Treponema pallidum*, and *Ureaplasma urealyticum*.

Opportunistic pathogens associated with HIV infection: *Eukaryotic microorganisms Pneumocystis jirovecii* and *Toxoplasma gondii*.

* The efficacy of azithromycin against the indicated species has been demonstrated in clinical trials.

5.2 Pharmacokinetic properties

Absorption

Following oral administration in humans, azithromycin is widely distributed throughout the body; bioavailability is approximately 37%. The time taken to peak plasma levels is 2 to 3 hours.

Distribution

In animal studies, high azithromycin concentrations have been observed in phagocytes. In experimental models, higher concentrations of azithromycin are released during active phagocytosis than from non-stimulated phagocytes. In animal models, this results in high concentrations of azithromycin being delivered to the site of infection. Pharmacokinetic studies in humans have shown markedly higher azithromycin levels in tissues than in plasma (up to 50 times the maximum observed concentration in plasma), indicating that the drug is heavily tissue bound. Concentrations in target tissues, such as lung, tonsil and prostate, exceed the MIC_{90} for likely pathogens after a single dose of 500 mg.

Elimination

Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. Approximately 12% of an intravenously administered dose is excreted in the urine over 3 days as the parent drug, the majority in the first 24 hours. Biliary excretion of azithromycin is a major route of elimination for unchanged drug following oral administration. Very high concentrations of unchanged drug have been found in human bile, together with 10 metabolites, formed by N- and O- demethylation, hydroxylation of the desosamine and aglycone rings, and cleavage of the cladinose conjugate. Comparison of HPLC and microbiological assays in tissues suggests that metabolites play no part in the microbiological activity of azithromycin.

Pharmacokinetics in special patient groups

Elderly

In elderly volunteers (>65 years), slightly higher AUC values were seen after a 5-day regimen than in young volunteers (<40 years), but these are not considered clinically significant, and hence no dose adjustment is recommended.

Renal Impairment
The pharmacokinetics of azithromycin in subjects with GFR 10 – 80 ml/min were not affected following a single 1 gram dose of immediate-release azithromycin. Statistically significant differences in AUC_{0-120} (8.8 μg·h/ml vs. 11.7 μg·h/ml), C_{max} (1.0 μg/ml vs. 1.6 μg/ml) and CLr (2.3 ml/min/kg vs. 0.2 ml/min/kg) were observed between the group with GFR <10 ml/min and GFR >80 ml/min.

Hepatic Impairment
In patients with mild (Class A) to moderate (Class B) hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to those with normal hepatic function. In these patients, urinary clearance of azithromycin appears to increase, perhaps to compensate for reduced hepatic clearance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Zithracin® Film Coated Tablet

Tablet core

Calcium Phosphate, Dibasic Dihydrate
Croscarmellose Sodium
Lactose Monohydrate
Magnesium Stearate
Pregelatinized Starch
Sodium Lauryl Sulfate

Film coating

Hydroxypropyl Methylcellulose
Triacetin
Titanium Dioxide

Zithracin® Powder for Oral Suspension 200 mg/5 mL

Aspartame
Basic Butylated Copolymer
Cellulose
Icing Sugar
Methacrylate Sodium Lauryl Sulfate
Silicon Dioxide
Sodium Phosphate
Stearic Acid Fine Powder
Tutti Fruity Flavour and Purified Water
Xanthan Gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Zithracin® Film Coated Tablet: 3 years.
Zithracin® Powder for Oral Suspension 200 mg/5 mL: 2 years

6.4 Special precautions for storage

Zithracin® Film Coated Tablet: Store at temperature below 30°C. Protect from light and moisture.
Zithracin® Powder for Oral Suspension 200 mg/5 mL: Store below 30°C for the powder and the reconstituted suspension. Use within 5 days after reconstitution. Protect from light and moisture.

6.5 Nature and contents of container

Zithracin® Film Coated Tablet 250 mg
PVDC white blister packing: 6's x 1

Zithracin® Film Coated Tablet 500 mg
PVDC white blister packing: 3's x 1

Zithracin® Powder for Oral Suspension 200 mg/5 mL
HDPE translucent bottle of 20 mL

6.6 Special precautions for disposal and other handling

Zithracin® Powder for Oral Suspension 200 mg/5 mL
Tap and shake the bottle to loosen powder. Add 10 mL of water to give 20 mL suspension. Shake vigorously to disperse powder.
Shake well before use.

7 PRODUCT REGISTRATION HOLDER

Y.S.P. INDUSTRIES (M) SDN. BHD. (199001001034)
Lot 3, 5, 7, 12 & 14, Jalan P/7, Section 13,
Kawasan Perindustrian Bandar Baru Bangi,
43000 Kajang, Selangor, Malaysia.
Ordering Line: 1 800 88 3027
Product Info: 1 800 88 3679

8 DATE OF REVISION OF THE TEXT

29/12/2025