Rx Prescription only

Azicine

1. Name of the medicinal product

Azicine

2. Special notice and recommendation

Keep out of reach of children

Read the package insert carefully before use

3. Composition

Each hard gelatin capsule contains azithromycin 250 mg (as azithromycin dihydrate 262 mg).

4. Pharmaceutical form

Hard gelatin capsule.

Hard gelatin capsule size No.0, white cap and white body, imprinted logo "" on cap and "Azicine" on the body with edible black ink, containing white powder.

5. 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 in the treatment of uncomplicated genital infections due to *Chlamydia trachomatis*. It is also indicated in the treatment of chancroid due to *Haemophilus ducreyi*; and uncomplicated genital infection due to non-multiresistant *Neisseria gonorrhoea*; concurrent infection with *Treponema pallidum* should be excluded. Azithromycin is indicated, either alone or in combination with rifabutin, for prophylaxis against *Mycobacterium avium-intracellulare complex* (MAC) infection, an opportunistic infection prevalent in patients with advanced human immunodeficiency virus (HIV). Azithromycin is indicated in combination with ethambutol for the treatment of disseminated MAC (DMAC) infection in patients with advanced HIV infection.

6. Administration and dosage

Administration

Azicine is administered orally, should be taken at least 1 hour before or 2 hours after food.

Dosage

Adults

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

– 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.

– For prophylaxis against MAC infections in patients infected with the human immunodeficiency virus (HIV), the dose is 1200 mg once per week.

– For the treatment of DMAC infections in patients with advanced HIV infection, the recommended dose is 600 mg once a day. Azithromycin should be administered in combination with other antimycobacterial agents that have shown *in vitro* activity against MAC, such as ethambutol at the approved dose.

In children under 45 kg body weight

Azithromycin capsules are not suitable for children under 45 kg.

Elderly

The same dosage as in adult patients is used in the elderly.

Patients with renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (glomerular filtration rate 10 - 80 ml/min). Caution should be exercised when azithromycin is administered to patients with severe renal impairment (glomerular filtration rate < 10 ml/min).

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.

7. Contraindications

The use of this product is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic.

8. Special warnings and precautions for use

– 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.

– 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.

– 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.

– In patients with severe renal impairment (glomerular filtration rate <10 ml/min) a 33% increase in systemic exposure to azithromycin was observed.

– QT prolongation

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. Cases of torsades de pointes have been spontaneously reported during post-marketing surveillance in patients receiving azithromycin. Providers 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 known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmias or uncompensated heart failure.
+ Patients on drugs known to prolong the QT interval.
+ Patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents.
+ Elderly patients may be more susceptible to drug-associated effects on the QT interval.

– 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) and acute generalised exanthematous pustulosis (AGEP)], Azicine should be discontinued immediately and appropriate treatment should be urgently initiated.

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

9. Pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women.

Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

Lactation

There are no data on secretion in breast milk. As many drugs are excreted in human milk, azithromycin should not be used in the treatment of a lactating woman unless the physician feels that the potential benefits justify the potential risks to the infant.

10. Effects on ability to drive and use machines

There is no evidence to suggest that azithromycin may have effect on the patient's ability to drive or operate machinery.

11. Drug interactions

– *Antacids*

No effect on overall bioavailability was seen although peak serum concentrations were reduced by approximately 25%. In patients receiving both oral azithromycin and antacids, the drugs should not be taken simultaneously.

– *Digoxin*
Some of the macrolide antibiotics have been reported to impair the microbial metabolism of digoxin in the gut in some patients. In patients receiving concomitant azithromycin, a related azalide antibiotic and digoxin the possibility of raised digoxin levels should be borne in mind.
– *Zidovudine*
Single 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients.
– *Ergot*
Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended.
Pharmacokinetic studies have been conducted between azithromycin and the following drugs known to undergo significant cytochrome P450 mediated metabolism.
– *Cyclosporin*
Caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.
– *Rifabutin*
Coadministration 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.
– *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.

12. Adverse reactions

– *Infections and infestations:* Uncommon: Candidiasis, vaginal infection, pneumonia, fungal infections, bacterial infection, pharyngitis, gastroenteritis, respiratory disorder, rhinitis, oral candidiasis.
– *Blood and lymphatic system disorders:* Uncommon: Leukopenia, neutropenia, eosinophilia.
– *Immune system disorders:* Uncommon: Angioedema, hypersensitivity.
– *Metabolism and nutrition disorders:* Uncommon: anorexia.
– P*sychiatric disorders:* Uncommon: Nervousness, insomnia.
– *Nervous system disorders:* Common: Headache; Uncommon: dizziness, somnolence, dysgeusia, paraesthesia.
– *Eye disorders*: Uncommon: Visual impairment.
– *Ear and labyrinth disorders:* Uncommon: Ear disorder, vertigo.
– *Cardiac disorders:* Uncommon: Palpitations.
– *Vascular disorders:* Uncommon: Hot flush.
– *Respiratory, thoracic and mediastinal disorders:* Uncommon: Dyspnoea, epistaxis.
– *Gastrointestinal disorders:* Very common: Diarrhea; Common: vomiting, abdominal pain, nausea; Uncommon: Constipation, flatulence, dyspepsia, gastritis dysphagia, abdominal distension, dry mouth, eructation, mouth ulceration, salivary hypersecretion.
– *Skin and subcutaneous tissue disorders:* Uncommon: rash, pruritus, urticaria, dermatitis, dry skin, hyperhidrosis. Not known: Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP).
– *Musculoskeletal and connective tissue disorders:* Uncommon: Osteoarthritis, myalgia, back pain, neck pain.
– *Renal and urinary disorders:* Uncommon: Dysuria, renal pain.
– *Reproductive system and breast disorders:* Uncommon: Metrorrhagia, testicular disorder.
– *General disorders and administration site condition:* Uncommon: Oedema, asthenia, malaise, fatigue, face edema, chest pain, pain, peripheral edema.
– *Investigations:* Common: Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased, basophils increased, monocytes increased, neutrophils increased; Uncommon: 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:* Uncommon: Post procedural complication.

Postmarketing experience:

– *Gastrointestinal disorders:* Infantile hypertrophic pyloric stenosis.
– *Cardiac disorders:* Palpitations and arrhythmias including ventricular tachycardia have been reported. There have been rare reports of QT prolongation and torsades de pointes (see 8. Special warnings and precautions for use).
– *Skin and subcutaneous tissue disorders:* Allergic reactions including pruritus, rash, photosensitivity, edema, urticaria, and angioedema. Rarely, serious cutaneous adverse reactions including erythema multiforme, SJS, TEN and DRESS have been reported.

13. Overdosage and management

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.

14. Pharmacodynamic properties

Azithromycin is a marcrolide antibiotic belonging to the azalide group. The molecule is constructed by adding a nitrogen atom to the lactone ring of erythromycin A. The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis by binding to the ribosomal 50s sub-unit and inhibition of peptide translocation.
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.

15. 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 2-3 hours.

Distribution

Orally administered azithromycin is widely distributed throughout the body. In pharmacokinetic studies it has been demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (as much as 50 times) than those measured in plasma, which indicates that the agent strongly binds to tissues. The mean volume of distribution at the steady state (VVss) has been calculated to be 31.1 l/kg.

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 within the following three days as the parent drug. Particularly high concentrations of unchanged drug 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 cleavage of the cladinose conjugate. Comparison of liquid chromatography and microbiological analyses in tissues suggests that metabolites play no part in the microbiological activity of azithromycin.

16. Packaging

Blister of 6 capsules. Box of 1 blister.

17. Storage condition, shelf-life

Protect from light. Do not store above 30°C.
The expiry date of this pack is printed on the box. Do not use this pack after this date.

18. Name, address of manufacturer

STELLAPHARM J.V. CO., LTD. – BRANCH 1
(A Joint Venture Company of Auxilto GmbH, Germany)
No. 40 Tu Do Avenue, Vietnam - Singapore Industrial Park,
An Phu Ward, Thuan An Town, Binh Duong Province, Vietnam
Tel: (+84 274) 3767 470 Fax: (+84 274) 3767 469

STELLA

1/....

PI261023

Date of revision: October 26th, 2023