Azithromycin Dispersible Tablets

[Product Name]

Generic name: Azithromycin Dispersible Tablets

English name: Azithromycin Dispersible Tablets

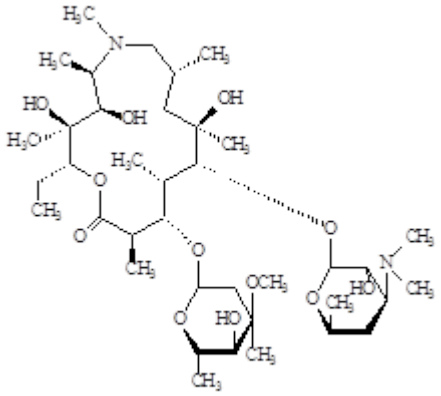
Chinese Pinyin: Aqimeisu Fensanpian

[Ingredients] The active ingredient is Azithromycin.

Chemical name:

(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one

Chemical structure:



Molecular formula: $C_{38}H_{72}N_2O_{12}$

Molecular weight: 749.00

[Description] White or off-white tablets

[Indications]

1. Acute pharyngitis and acute tonsillitis caused by Streptococcus pyogenes.
2. Sinusitis, otitis media, acute bronchitis, acute exacerbation of chronic bronchitis caused by sensitive bacteria.
3. Pneumonia caused by Streptococcus pneumoniae, Haemophilus influenzae, and Mycoplasma pneumoniae.
4. Urethritis and cervicitis caused by Chlamydia trachomatis and non-multidrug resistant Neisseria gonorrhoeae.
5. Skin and soft tissue infections caused by sensitive bacteria.

[Strength] 0.25g

[Dosage and administration] This product is a dispersible tablet, which can be taken orally or swallowed directly, or an appropriate amount of this product is put into 100ml of water, shaken and dispersed, and taken 1 hour before or 2 hours after meal.

Adult dosage: 1. For sexually transmitted diseases caused by Chlamydia trachomatis or Neisseria gonorrhoeae, only a single oral dose of 1.0g of this product is required. 2. Treatment of other infections: 0.5g/time on the first day, 0.25g/time on the 2nd to 5th day; or 0.5g/time on the first day, 3 consecutive days.

Pediatric dosage: 1. For treating otitis media and pneumonia, on the first day, take 10mg/kg/time of body weight (the maximum daily dose not exceed 0.5g), and on the second to fifth day, take 5mg/kg/time of body weight daily (the maximum daily does not exceed 0.25g). 2. For the treatment of pediatric pharyngitis and tonsillitis, take a dose of 12mg/kg/time of body weight daily (the maximum daily dose not exceed 0.5g) for 5 consecutive days.

Or as directed by doctor.

[Adverse reactions]

(1)Clinical trial experience

Because clinical trials are completed under different conditions, the adverse reaction rates of one drug observed in clinical trials cannot be directly compared with the adverse reaction rates of other drugs in clinical trials, and may not reflect the adverse reactions in practical applications rate.

In the clinical trials of azithromycin intravenous preparations for community-acquired pneumonia, 2 to 5 doses were administered intravenously. Most of the reported adverse reactions were mild to moderate, and they could be recovered after stopping the drug. Most of these clinical trials have more than one comorbidity and require other drugs. About 1.2% of patients taking this product intravenously discontinued medication, and 2.4% of patients treated with intravenous or oral azithromycin discontinued medication due to symptoms of adverse reactions or abnormal laboratory tests.

In clinical trials in patients with pelvic inflammatory diseases, after receiving 1 to 2 doses of intravenous administration of azithromycin monotherapy, 2% of patients discontinued due to clinical adverse reactions. Patients with azithromycin combined with metronidazole 4% of patients discontinued treatment due to adverse reactions.

In the above studies, the most common adverse reactions leading to drug withdrawal are gastrointestinal reactions (abdominal pain, nausea, vomiting, diarrhea, etc.) and rashes. The abnormal laboratory tests leading to drug withdrawal are mainly the rise

of aminotransferase and / or alkaline phosphatase .

In the above studies, the most common adverse reactions leading to drug withdrawal are gastrointestinal reactions (abdominal pain, nausea, vomiting, diarrhea, etc.) and rashes. The abnormal laboratory tests leading to drug withdrawal are mainly the rise of aminotransferase and / or alkaline phosphatase.

In the community-acquired pneumonia study, the most common adverse reactions of adult patients after receiving intravenous / oral preparations of this product were gastrointestinal reactions, including diarrhea or loose stools (4.3%), nausea (3.9%), and abdominal pain (2.7 %), Vomiting (1.4%). About 12% of patients experienced intravenous-related adverse reactions, the most common is pain at the injection site (6.5%) and local inflammatory reactions (3.1%).

In clinical trials of patients with pelvic inflammatory diseases, adult female patients received intravenous / oral preparations of this product. The most common adverse reactions related to treatment are also gastrointestinal reactions, of which diarrhea (8.5%) and nausea (6.6%) are common, followed by vaginitis (2.8%), abdominal pain (1.9%), anorexia (1.9%), rash and pruritus (1.9%). When azithromycin was combined with metronidazole in these studies, a higher proportion of women had nausea (10.3%), abdominal pain (3.7%), vomiting (2.8%), site-of-administration reactions, stomatitis, dizziness, and dyspnea (common 1.9%).

Azithromycin intravenous / oral multiple-dose regimens did not cause other adverse reactions of more than 1%.

Adverse reactions with an incidence of less than 1% are:

Gastrointestinal reactions: indigestion, bloating, mucositis, oral candidiasis and gastritis.

Nervous system: headache, drowsiness.

Allergic reaction: bronchospasm.

Special sensation: Incorrect taste.

(2) Experience in post-marketing applications

Oral azithromycin preparations are used in adult and / or pediatric patients after marketing. The following adverse events have been reported, but it is not certain whether they are caused by azithromycin:

Allergic reactions: joint pain, edema, urticaria, angioedema.

Cardiovascular: Arrhythmias include ventricular tachycardia, hypotension, rare QT interval prolongation, and apical torsional ventricular tachycardia.

Gastrointestinal tract: anorexia, constipation, indigestion, bloating, vomiting / diarrhea

but rarely cause dehydration, pseudomembranous enteritis, pancreatitis, oral candidiasis, pyloric stenosis, and rare tongue discoloration.

Systemic reactions: fatigue, paresthesia, fatigue, discomfort, and anaphylactic shock.

Urogenital system: interstitial nephritis, acute renal failure, vaginitis.

Hematopoietic system: thrombocytopenia.

Liver / biliary: Adverse reactions related to liver dysfunction have been reported in azithromycin post-marketing experience.

Nervous system: convulsions, dizziness, headache, drowsiness, hyperactivity, nervousness, agitation, and syncope.

Ear and labyrinth abnormalities: deafness, tinnitus, hearing impairment, dizziness.

Spirit: Aggressive response and anxiety.

Skin and accessories: itching, rare severe skin reactions including erythema multiforme, Stevens Johnson syndrome, and toxic epidermolysis necrosis.

Special sensations: Hearing disorders include hearing loss, deafness and/or tinnitus, and there are also reports of taste/olfactory abnormalities and/or loss.

Laboratory examination abnormalities:

Significant abnormal laboratory tests (whether drug-related or not) seen in clinical trials are:

Incidence rate 4% to 6%: alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine increased.

Incidence rate 1% to 3%: Lactate dehydrogenase (LDH), bilirubin increased.

The incidence is less than 1%: leukopenia, neutropenia, decreased platelet count, and elevated serum alkaline phosphatase.

Follow-up found that the laboratory abnormalities mentioned above were reversible.

In more than 750 patients taking azithromycin (intravenous/oral) multidose clinical trials, no more than 2% of patients discontinued azithromycin due to treatment-related liver enzyme abnormalities.

[Contraindications] Patients who are allergic to azithromycin, erythromycin, other macrolides or ketolactones are contraindicated. Patients with a previous history of cholestatic jaundice/liver dysfunction after azithromycin use are contraindicated.

Caution

Allergic reaction

Treatment with azithromycin causes severe allergic reactions, including angioedema, anaphylactic shock, and skin reactions, including reports of Stevens Johnson syndrome and toxic epidermal necrolysis are rare. Although rare, deaths have been reported. When allergic symptoms occur in some patients, symptomatic treatment is effective at first. If treatment is stopped prematurely, allergic symptoms can quickly recur even if azithromycin is not used. For such patients, the time for symptomatic treatment and observation needs to be extended. It is not known whether these events are related to the long half-life of azithromycin in the tissues and the longer exposure of the body to the antigen.

If an allergic reaction occurs, the drug should be discontinued immediately and appropriate treatment given. Doctors should be aware that after stopping symptomatic

treatment, allergic symptoms may recur.

Liver toxicity

Hepatic dysfunction, hepatitis, cholestatic jaundice, liver necrosis, and liver failure have been reported, and some of these cases may be fatal. If you have signs and symptoms of hepatitis, you should stop using this product immediately.

Clostridium difficile-associated diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported for almost all antibacterial applications, including this product, and its severity can range from mild diarrhea to fatal colitis. Antimicrobial treatment can cause changes in the normal flora in the colon, resulting in the overproduction of Clostridium difficile.

Clostridium difficile toxin A and toxin B are related to the pathogenesis of CDAD. Highly toxic Clostridium difficile causes increased morbidity and mortality. These infections may be difficult to treat with antimicrobials and may require colectomy. For all patients with diarrhea after antibiotic use, the possibility of CDAD must be considered. Since there have been reports of CDAD occurring more than 2 months after antimicrobial treatment, a careful medical history is required.

If CDAD is suspected or confirmed, antibiotics that are not being used against Clostridium difficile may need to be discontinued. Water, electrolytes, and proteins must be appropriately supplemented according to clinical needs, and antibiotics effective for Clostridium difficile must be given, and surgical evaluations must be performed if necessary.

[Precautions]

General matters: Since azithromycin is mainly eliminated by the liver, patients with hepatic impairment should use azithromycin with caution. Subjects with GFR <10 mL/min have limited data, and azithromycin should also be used with caution in such patients. Hepatic dysfunction, hepatitis, cholestatic jaundice, liver necrosis and liver failure have been reported, and some of these cases may be fatal. If signs and symptoms of hepatitis appear, azithromycin should be discontinued immediately.

QT interval extended

It has been reported that the use of other macrolide antibiotics, including azithromycin, can cause ventricular repolarization and prolongation of the QT interval, thereby risking arrhythmia and apical torsional ventricular tachycardia. In postmarketing monitoring of patients with azithromycin, there are spontaneous reports of cases of torsional ventricular tachycardia. When weighing the risks and benefits of azithromycin use in high-risk populations, health care providers should consider the risks of potentially fatal QT interval prolongation, which include:

Patients with known QT interval prolongation, history of apical torsional ventricular tachycardia, congenital prolonged QT interval syndrome, bradyarrhythmia, or decompensated heart failure.

Patients taking drugs known to prolong the QT interval, such as those treated with antipsychotics, antidepressants, and fluoroquinolones.

Patients with arrhythmogenic status, such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and receiving type IA (quinidine, procainamide) and type III (Dofetilide, Amiodarone, Sotalol) Patients with

antiarrhythmic drugs.
Elderly patients: Elderly patients may be more sensitive to drug-related QT interval effects.
Exacerbations of myasthenia gravis or new onset of myasthenic syndrome have been reported in azithromycin treated patients.
In the case of undiagnosed or not highly suspected bacterial infections, or without indications for prevention, the use of this product may not be beneficial to patients and increase the risk of drug-resistant bacteria.
Patients need to know:
When any signs of allergies appear, azithromycin should be stopped immediately and contact your doctor.
Patients should be informed that antibacterials, including azithromycin, can only be used to treat bacterial infections and not viral infections (such as the common cold). When using this product (azithromycin) in the treatment of bacterial infections, patients must be informed that although they usually feel better in the early stages of treatment, they should be taken precisely according to the doctor's instructions. Missing or not completing the entire course of treatment may: (1) reduce the efficacy of the current treatment; (2) increase the possibility of bacterial resistance, which will lead to the future inability of azithromycin or other antibacterial drugs to treat these resistant bacteria.
Antibiotic treatment often causes diarrhea and usually recovers when antibiotics are stopped. Sometimes after antibiotic administration, patients develop watery or bloody stools (with or without stomach cramps and fever) even 2 months or more after the last antibiotic. If this happens, the patient should contact a doctor as soon as possible.
[Pregnant and lactation] There are currently no adequate and strictly controlled clinical trials in pregnant women. Because the results of animal reproduction studies are not always predictive of human conditions, their use in pregnant women must be weighed against the pros and cons.
It is unknown whether this product is secreted in human milk. Because many drugs are secreted by human milk, women who are breastfeeding need to be careful when using it.
[Use in children] Regardless of the infection, it is recommended that the total dose of azithromycin in children does not exceed 1500 mg.
When this product is used for children body weight more than 45kg, the dosage is the same as that for adults.
The efficacy and safety of treating otitis media, community-acquired pneumonia in children less than 6 months and pharyngitis or tonsillitis in children less 2 years old have not been determined.
[Use in the elderly] It is not clear.
[Drug interactions] In the narfinavir homeostasis, co-administration of a single dose of azithromycin orally can increase the serum concentration of azithromycin.
Although it is not necessary to adjust the dose of azithromycin when co-administered

nafinavir, the known side effects of azithromycin such as liver enzyme abnormalities and hearing impairment must be monitored closely.
Spontaneous postmarketing reports suggest that co-administration of azithromycin may enhance the effect of oral anticoagulants. When patients use azithromycin in combination with oral anticoagulants, the prothrombin time should be monitored closely.
Azithromycin had no significant effect on the pharmacokinetics of atorvastatin, carbamazepine, cetirizine, didanosine, efavirenz, fluconazole, indinavir, midazolam, rifabutin, sildenafil, theophylline (intravenous and oral administration), triazolam, trimethoprim / sulfamethoxazole, or zidovudine when used within the therapeutic dose. When co-administration, efavirenz or fluconazole have little effect on the pharmacokinetics of azithromycin. When azithromycin is co-administered of any of the above drugs, there is no need to adjust the dose of any one drug.
Azithromycin has not been reported in clinical trials to interact with the following drugs. However, no special studies have been conducted to evaluate the potential interactions between azithromycin and these drugs. However, these situations have occurred when using other macrolides. Therefore, when new research data are not available, azithromycin should be observed closely when used in combination with:
Digoxin- the blood-drug concentration of Digoxin increased.
Ergotamine or dihydroergotamine-acute ergot poisoning, whose symptom are severe peripheral vasospasm and dull feeling.
The concentration of Terfenadine, cyclosporine,hexobarbital, and phenytoin increased.
Impact on laboratory tests: No reports have been found to have an impact on laboratory results.
[Overdose] Adverse drug reaction of overdose is the same as that of the he recommended dose. Once overdose is found, symptomatic and supportive treatment can be given according to the condition.
[Pharmacology and toxicology]
Pharmacology
Azithromycin is an azalactone antibiotic. Its mechanism of action is to interfere with the synthesis of its protein (without affecting nucleic acid synthesis) by binding to the 50S subunit of the ribosomes of sensitive microorganisms.
Both in vitro and clinical studies have shown that azithromycin is effective against a variety of pathogenic bacteria:

Gram-positive aerobic microorganisms: Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumoniae, Streptococcus hemolytic.
Azithromycin is cross-resistant to erythromycin-resistant Gram-positive bacteria. Most Streptococcus faecalis (enterococci) and methicillin-resistant staphylococci are resistant to this product.
Gram-negative aerobic microorganisms: Haemophilus influenzae, Moraxella catarrhalis, Chlamydia trachomatis.
Both in vitro tests and clinical studies suggest that this product can prevent diseases caused by avian intracellular mycobacterial complex (composed of avian intracellular mycobacteria and intracellular mycobacteria).
β-lactamase producing strains are not effective for this product.
Results of vitro studies have been performed on the following microorganisms, but their clinical significance is unknown, including Streptococcus (C, F, G), Streptococcus viridians, Bacillus pertussis, Haemophilus Duke, Legionella pneumophila, Bacteroides, Peptostreptococcus, Borrelia, Mycoplasma pneumoniae, Treponema pallidum, Mycoplasma urealyticum, etc.
Toxicology
Genetic Toxicology: The results of human lymphocyte test, mouse bone marrow micronucleus test and mouse vitro lymphoma cell test all confirmed that this product has no mutagenic effect.
Reproductive toxicity: Reproductive toxicity tests in rats and mice have shown that when the dosage reaches a dosage level that produces a moderate degree of maternal toxicity (ie, 200 mg / kg / day, based on body surface area, it is about 2-4 times of human medication of 500 mg / kg / day).), no teratogenic effect was found. No damage to fertility and the fetus has been found.
Carcinogenicity: There is no research data on carcinogenicity of this product for long-term use.

[Pharmacokinetics]Quickly absorbed after oral administration, bioavailability is 37%. A single dose is 0.5 g orally, the peak time is 2.5 to 2.6 hours, and the peak plasma concentration (Cmax) is 0.4 to 0.45 mg / L.This product is widely distributed in the body, the concentration in various tissues can reach 10 to 100 times of the blood concentration over the same period, the concentration is high in macrophages and fibroblasts, the former can transport azithromycin to the site of inflammation. The blood elimination half-life (t1/2β) of this product after single-dose administration is 35 to 48 hours, and more than 50% of the dose is excreted in the biliary tract in the original form, and about 4.5% is excreted in the original form in 72 hours after administration. The serum protein binding rate of this product decreases with the increase of blood drug concentration. When the blood drug concentration is 0.02 μg / ml, the serum protein binding rate is 15%; when the blood drug concentration is 2 μg / ml, the serum protein binding rate is 7%. Foreign data show that pharmacokinetic parameters of patients with mild to moderate renal insufficiency (glomerular filtration rate of 10 to 80 ml / min) have no significant change, and there is significant difference between severe renal insufficiency (glomerular filtration rate of less than 10 ml/min) and normal with a 33% increase in systemic exposure.

[Storage] Shaded, sealed and stored in a dry place.

[Package] Packing in Al-Al blister; 4 tablets/blister/box, 6 tablets/blister/box, 4 tablets×2 blisters/box, 5 tablets×2 blisters/box, and 6 tablets×2 blisters/box.

[Shelf life] 24 months

[Specification No.] Chinese Pharmacopoeia 2010 Volume II

[Approval No.] GYZZ H20066358

[Marketing Authorization Holder]

Name: CSPC Ouyi Pharmaceutical Co., Ltd.

Register Address: No.88 Yangzi Road, Economic & Technological Development Zone, Shijiazhuang, Hebei, China

[Manufacturer]

Name: CSPC Ouyi Pharmaceutical Co., Ltd.

Manufacturing Address: No.88 Yangzi Road, Economic & Technological Development Zone, Shijiazhuang, Hebei, China

Zip code: 052165

Tel: 0311-67163660 0311-87886158

Fax: 0311-87171665