ZYSON®

Capsules/suspension

(Azithromycin USP)

زائسن®

کیپسول/سسپینشن

(ازیتھرومائی سین یو ایس پی)

COMPOSITION:
Capsules:
Each capsule Contains:
Azithromycin (As Dihydrate) USP ..... 250 mg
Suspension:
Each 5ml after reconstitution Contains:
Azithromycin (As Dihydrate) USP ..... 200 mg

DESCRIPTION:
ZYSON® (Azithromycin) contains the active ingredient Azithromycin, an azalide, a subclass of macrolide antibiotics, for oral administration. Azithromycin has the chemical name (2R , 3S , 4R , 5R , 8R , 10R , 11R , 12S , 13S , 14R)-13-[(2,6-dideoxy-3- C -methyl -3 - O -methyl-(alpha)- 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)-(beta)- D-xylo -hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is C_{38} H_{72} N_2 O_{12}, and its molecular weight is 749.00.

CLINICAL PHARMACOLOGY:
Pharmacokinetics:
Following oral administration of a single 500 mg dose (two 250 mg capsules) to 36 fasted healthy male volunteers, the mean (SD) Pharmacokinetics parameters were AUC 0-72 = 4.3 (1.2) µg•h/mL; C max = 0.5 (0.2) µg/ml; T max = 2.2 (0.9) hours.
With a regimen of 500 mg (two 250 mg capsules) on day 1, followed by 250 mg daily (one 250 mg capsule) on days 2 through 5, the Pharmacokinetics parameters of Azithromycin in plasma in healthy young adults (18-40 years of age) are portrayed in the chart below. C min and C max remained essentially unchanged from day 2 through day 5 of therapy.
In a two-way crossover study, 12 adult healthy volunteers (6 males, 6 females) received 1,500 mg of Azithromycin administered in single daily doses over either 5 days (two 250 mg capsules on day 1, followed by one 250 mg capsule on days 2-5) or 3 days (500 mg per day for days 1-3). Due to limited serum samples on day 2 (3-day regimen) and days 2-4 (5-day regimen), the serum concentration-time profile of each subject was fit to a 3-compartment model and the AUC 0-(infinity) for the fitted concentration profile was comparable between the 5-day and 3-day regimens. Median Azithromycin exposure (AUC 0-288) in mononuclear (MN) and polymorphonuclear (PMN) leukocytes following either the 5-day or 3-day regimen was more than a 1000-fold and 800-fold greater than in serum, respectively. Administration of the same total dose with either the 5-day or 3-day regimen may be expected to provide comparable concentrations of Azithromycin within MN and PMN leukocytes.
Two Azithromycin 250 mg capsules are bioequivalent to a single 500 mg capsule.

Absorption:
The absolute bioavailability of Azithromycin 250 mg capsules is 38%.
In a two-way crossover study in which 12 healthy subjects received a single 500 mg dose of Azithromycin (two 250 mg capsules) with or without a high fat meal, food was shown to increase C max by 23% but had no effect on AUC.
When Azithromycin suspension was administered with food to 28 adult healthy male subjects, C_{max} increased by 56% and AUC was unchanged.
The AUC of Azithromycin was unaffected by co-administration of an antacid containing aluminum and magnesium hydroxide with Azithromycin capsules; however, the C max was reduced by 24%. Administration of cimetidine (800 mg) two hours prior to Azithromycin had no effect on Azithromycin absorption.

Distribution:
The serum protein binding of Azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 µg/ml to 7% at 2 µg/ml.
Following oral administration, Azithromycin is widely distributed throughout the body with an apparent steady-state volume of distribution of 31.1 L/kg. Greater Azithromycin concentrations in tissues than in plasma or serum were observed. High tissue concentrations should not be interpreted to be quantitatively related to clinical efficacy. The antimicrobial activity of Azithromycin is pH related and appears to be reduced with decreasing pH.

Metabolism:
In vitro and in vivo studies to assess the metabolism of Azithromycin have not been performed.
Elimination:
Plasma concentrations of Azithromycin following single 500 mg oral and i.v. doses declined in a polyphasic pattern with a mean apparent plasma clearance of 630 ml/min and terminal elimination half-life of 68 hours. The prolonged terminal half-life is thought to be due to extensive uptake and subsequent release of drug from tissues.
Biliary excretion of Azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

INDICATIONS AND USAGE:
ZYSON® (Azithromycin) is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below.

Lower Respiratory Tract:
Acute bacterial exacerbations of chronic obstructive pulmonary disease due to Haemophilus influenzae, Moraxella catarrhalis , or Streptococcus pneumoniae .
Community-acquired pneumonia of mild severity due to Streptococcus pneumoniae or Haemophilus influenzae in patients appropriate for outpatient oral therapy.

Upper Respiratory Tract:
Streptococcal pharyngitis/tonsillitis--As an alternative to first line therapy of acute pharyngitis/tonsillitis due to Streptococcus pyogenes occurring in individuals who cannot use first line therapy.

Skin and Skin Structure:
Uncomplicated skin and skin structure infections due to Staphylococcus aureus, Streptococcus pyogenes, or Streptococcus agalactiae . Abscesses usually require surgical drainage.

Sexually Transmitted Diseases:
Non-gonococcal urethritis and cervicitis due to Chlamydia trachomatis.
ZYSON® (Azithromycin), at the recommended dose, should not be relied upon to treat gonorrhea or syphilis. Antimicrobial agents used in high doses for short periods of time to treat non-gonococcal urethritis may or delay the symptoms of incubating gonorrhea or syphilis. All patients with sexually-transmitted urethritis or cervicitis should have a serologic test for syphilis and appropriate cultures for gonorrhea performed at the time of diagnosis. Appropriate antimicrobial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

Mycobacterial Infections:

Prophylaxis of Disseminated Mycobacterium avium complex (MAC) Disease:
ZYSON® (Azithromycin) taken alone or in combination with rifabutin at its approved dose, is indicated for the prevention of disseminated Mycobacterium avium complex (MAC) disease in persons with advanced HIV infection.

CONTRAINDICATIONS:
ZYSON® (Azithromycin) is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin or any macrolide antibiotic.

WARNINGS:
Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported rarely in patients on Azithromycin therapy. Although rare, fatalities have been reported. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further Azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of Azithromycin and subsequent prolonged exposure to antigen is unknown at present.
If an allergic reaction occurs, the drug 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.
In the treatment of pneumonia, Azithromycin has only been shown to be safe and effective in the treatment of community-acquired pneumonia due to Chlamydia pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae or Streptococcus pneumoniae in patients appropriate for oral therapy. Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).
Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.
Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is a primary cause of "antibiotic-associated colitis."
After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against Clostridium difficile colitis.

PRECAUTIONS:
General: Because Azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function. Due to the limited data in subjects with GFR <10 mL/min, caution should be exercised when prescribing Azithromycin in these patients.

The following adverse events have been reported with macrolide products: ventricular arrhythmias, including ventricular tachycardia and torsade de pointes , in individuals with prolonged QT intervals.
There has been a spontaneous report from the post-marketing experience of a patient with previous history of arrhythmias who experienced torsade de pointes and subsequent myocardial infarction following a course of Azithromycin therapy.

INFORMATION FOR PATIENTS:
ZYSON® (Azithromycin) capsules and oral suspension can be taken with or without food.
Patients should also be cautioned not to take aluminum- and magnesium-containing antacids and Azithromycin simultaneously.
The patient should be directed to discontinue Azithromycin immediately and contact a physician if any signs of an allergic reaction occur.

ADVERSE REACTIONS:
In clinical trials, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. Potentially serious side effects of angioedema and cholestatic jaundice were reported rarely. Approximately 0.7% of the patients (adults and children) from the 5-day multiple-dose clinical trials discontinued **ZYSON®** (Azithromycin) therapy because of treatment-related side effects. In adults given 500 mg/day for 3 days, the discontinuation rate due to treatment-related side effects was 0.4%. In clinical trials in children given 30 mg/kg, either as a single dose or over 3 days, discontinuation from the trials due to treatment-related side effects was approximately 1%. Most of the side effects leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, or abdominal pain.

Adults:
Multiple-dose regimens: Overall, the most common treatment-related side effects in adult patients receiving multiple-dose regimens of **ZYSON®** (Azithromycin) were related to the gastrointestinal system with diarrhea/loose stools (4-5%), nausea (3%) and abdominal pain (2-3%) being the most frequently reported.
No other treatment-related side effects occurred in patients on the multiple-dose regimens of **ZYSON®** (Azithromycin) with a frequency greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:
Cardiovascular: Palpitations, chest pain.
Gastrointestinal: Dyspepsia, flatulence, vomiting, melena and cholestatic jaundice.
Genitourinary: Monilia, vaginitis and nephritis.
Nervous System: Dizziness, headache, vertigo and somnolence.
General: Fatigue.
Allergic: Rash, pruritus, photosensitivity and angioedema.
Single 1-gram dose regimen: Overall, the most common side effects in patients receiving a single-dose regimen of 1 gram of **ZYSON®** (Azithromycin) were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.
Side effects that occurred in patients on the single one-gram dosing regimen of **ZYSON®** (Azithromycin) with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), dyspepsia (1%) and vaginitis (1%).
Single 2-gram dose regimen: Overall, the most common side effects in patients receiving a single 2-gram dose of **ZYSON®** (Azithromycin) were related to the gastrointestinal system. Side effects that occurred in patients in this study with a frequency of 1% or greater included nausea (18%), diarrhea/loose stools (14%), vomiting (7%), abdominal pain (7%), vaginitis (2%), dyspepsia (1%) and dizziness (1%). The majority of these complaints were mild in nature.

Children:
Single and Multiple-dose regimens: The types of side effects in children were comparable to those seen in adults, with different incidence rates for the dosage regimens recommended in children.
Acute Otitis Media: For the recommended total dosage regimen of 30 mg/kg, the most frequent side effects (>/=1%) attributed to treatment were diarrhea, abdominal pain, vomiting, nausea and rash.
With any of the treatment regimens, no other treatment-related side effects occurred in children treated with **ZYSON®** (Azithromycin) with a frequency greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:
Cardiovascular: Chest pain.
Gastrointestinal: Dyspepsia, constipation, anorexia, enteritis, flatulence, gastritis, jaundice, loose stools and oral moniliasis.
Hematologic and Lymphatic: Anemia and leukopenia.
Nervous System: Headache (otitis media dosage), hyperkinesia, dizziness, agitation, nervousness and insomnia.
General: Fever, face edema, fatigue, fungal infection, malaise and pain.
Allergic: Rash and allergic reaction.
Respiratory: Cough increased, pharyngitis, pleural effusion and rhinitis.
Skin and Appendages: Eczema, fungal dermatitis, pruritus, sweating, urticaria and vesiculobullous rash.
Special Senses: Conjunctivitis.

DOSAGE AND ADMINISTRATION
Adults:
The recommended dose of **ZYSON®** (Azithromycin) for the treatment of community-acquired pneumonia of mild severity, pharyngitis/tonsillitis (as second-line therapy), and uncomplicated skin and skin structure infections due to the indicated organisms is: 500 mg as a single dose on the first day followed by 250 mg once daily on Days 2 through 5. The recommended dose of **ZYSON®** (Azithromycin) for the treatment of mild to moderate acute bacterial exacerbations of chronic obstructive pulmonary disease is: either 500 mg per day for 3 days or 500 mg as a single dose on the first day followed by 250 mg once daily on Days 2 through 5.
ZYSON® (Azithromycin) capsules can be taken with or without food. The recommended dose of **ZYSON®** (Azithromycin) for the treatment of genital ulcer disease due to Haemophilus ducreyi (chancroid), non-gonococcal urethritis and cervicitis due to C. trachomatis is: a single 1 gram (1000 mg) dose of **ZYSON®** (Azithromycin).
The recommended dose of **ZYSON®** (Azithromycin) for the treatment of urethritis and cervicitis due to Neisseria gonorrhoeae is a single 2 gram (2000 mg) dose of **ZYSON®** (Azithromycin).

Renal Insufficiency:
No dosage adjustment is recommended for subjects with renal impairment (GFR </=80 mL/min). The mean AUC 0-120 was similar in subjects with GFR 10-80 mL/min compared to subjects with normal renal function, whereas it increased 35% in subjects with GFR <10 mL/min compared to subjects with normal renal function. Caution should be exercised when azithromycin is administered to subjects with severe renal impairment.

Hepatic Insufficiency:
The pharmacokinetics of azithromycin in subjects with hepatic impairment have not been established. No dose adjustment recommendations can be made in patients with impaired hepatic function.
No dosage adjustment is recommended based on age or gender.

Pediatric Patients:
ZYSON® can be taken with or without food.
There is no information on children under six months of age.
Acute Otitis Media: The recommended dose of **ZYSON®** (Azithromycin) for the treatment of children with acute otitis media is 30 mg/kg given as a single dose or 10 mg/kg once daily for 3 days or 10 mg/kg as a single dose on the first day followed by 5 mg/kg/day on Days 2 through 5.
Community-Acquired Pneumonia: The recommended dose of **ZYSON®** (Azithromycin) for the treatment of children with community-acquired pneumonia is 10 mg/kg as a single dose on the first day followed by 5 mg/kg on Days 2 through 5.

STORAGE INSTRUCTIONS:
Store in a dry place below 30°C and protect from sunlight. Keep out of reach of children.

PRESENTATION:
Zyson® Capsules 250 mg: Blister pack of 1 x 10's Capsules.
Zyson® Suspension 200 mg/5ml: 15ml suspension filled in amber coloured plastic bottle

خوراک:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

خشک جگہ پر ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

بچوں کی دسترس سے دور رکھیں۔

سورج کی روشنی سے بچائیں۔

صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔

دوا تیار کرنے کا طریقہ:

۱۵ ملی لیٹر سسپینشن تیار کرنے کے لیے ۱۰ ملی لیٹر ابلا ہوا ٹھنڈا پانی

ڈبے کے اندر دیئے گئے پیمانہ سے بوتل میں ڈالیں اور اچھی طرح ہلائیں۔

استعمال سے پہلے بوتل کو اچھی طرح ہلائیں۔

استعمال کے بعد ڈھکن اچھی طرح بند کر دیں۔

تیار شدہ دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر

رکھیں اور ۱۰ دن کے اندر استعمال کر لیں۔

غیر استعمال شدہ دوا کو ضائع کر دیں۔

بچوں کی پہنچ سے دور رکھیں۔

For Prescribing information:
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An ISO 9001:2000 Certified Company