Skip to main content

Azithromycin (Zithromax)

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Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, most of the reported adverse reactions were mild to moderate in severity and were reversible upon discontinuation of the drug. Approximately 0.7% of the patients from the multiple-dose clinical trials discontinued ZITHROMAX (azithromycin) therapy because of treatment-related adverse reactions. Serious adverse reactions included angioedema and cholestatic jaundice. Most of the adverse reactions leading to discontinuation were related to the gastrointestinal tract,].**Clinical Studies**e.g., nausea, vomiting, diarrhea, or abdominal pain [see

Multiple-dose regimen

Overall, the most common adverse reactions in adult patients receiving a multiple-dose regimen of ZITHROMAX were related to the gastrointestinal system with diarrhea/loose stools (5%), nausea (3%), and abdominal pain (3%) being the most frequently reported.

No other adverse reactions occurred in patients on the multiple-dose regimen of ZITHROMAX with a frequency greater than 1%. Adverse reactions that occurred with a frequency of 1% or less included the following:

Palpitations and chest pain. **Cardiovascular:**

Dyspepsia, flatulence, vomiting, melena, and cholestatic jaundice. **Gastrointestinal:**

Monilia, vaginitis, and nephritis. **Genitourinary:**

Dizziness, headache, vertigo, and somnolence. **Nervous System:**

Fatigue.**General:**

Rash, photosensitivity, and angioedema. **Allergic:**

Chronic therapy with 1200 mg weekly regimen

The nature of adverse reactions seen with the 1200 mg weekly dosing regimen for the prevention of Mycobacterium avium infection in severely].**Clinical Studies**immunocompromised HIV-infected patients were similar to those seen with short-term dosing regimens [see

Chronic therapy with 600 mg daily regimen combined with ethambutol

The nature of adverse reactions seen with the 600 mg daily dosing regimen for the treatment of Mycobacterium avium complex infection in severely immunocompromised HIV-infected patients were similar to those seen with short term dosing regimens. Five percent of patients experienced reversible hearing impairment in the pivotal clinical trial for the treatment of disseminated MAC in patients with AIDS. Hearing impairment has been reported with macrolide antibiotics, especially at higher doses. Other treatment-related adverse reactions occurring in > 5% of subjects and seen at any time during a median of 87.5 days of therapy include: abdominal pain (14%), nausea (14%), vomiting (13%), diarrhea (12%), flatulence (5%), headache (5%), and abnormal vision (5%). Discontinuations from treatment due to laboratory abnormalities or adverse reactions considered related to study drug occurred in 8 of 88 (9.1%) of subjects.

Single 1 gram dose regimen

Overall, the most common adverse reactions in patients receiving a single-dose regimen of 1 gram of ZITHROMAX were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.

Adverse reactions that occurred in patients on the single 1 gram dosing regimen of ZITHROMAX with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), dyspepsia (1%), and vaginitis (1%).

Post-marketing Experience

The following adverse reactions have been identified during post approval use of azithromycin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions reported with azithromycin during the postmarketing period in adult and/or pediatric patients for which a causal relationship may not be established include:

Arthralgia, edema, urticaria, and angioedema. **Allergic:**

Arrhythmias, including ventricular tachycardia, and hypotension. There have been reports of QT prolongation and torsades de pointes. **Cardiovascular:**

Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea pseudomembranous colitis, pancreatitis, oral candidiasis, pyloric stenosis, and **Gastrointestinal:** tongue discoloration.

Asthenia, paresthesia, fatigue, malaise, and anaphylaxis **General:**

Interstitial nephritis, acute renal failure, and vaginitis. **Genitourinary:**

Thrombocytopenia. **Hematopoietic:**

].**WARNINGS AND PRECAUTIONS** Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure, [see **Liver/Biliary:**

Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, agitation, and syncope. **Nervous System:**

Aggressive reaction and anxiety. **Psychiatric:**

Pruritus, and serious skin reactions including erythema multiforme, Stevens -Johnson syndrome, and toxic epidermal necrolysis. **Skin/Appendages:**

Hearing disturbances including hearing loss, deafness, and/or tinnitus, and reports of taste/smell perversion and/or loss. **Special Senses:**

Laboratory Abnormalities

Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows:

- With an incidence of 1-2%, elevated serum creatine phosphokinase, potassium, ALT (SGPT), GGT, and AST (SGOT).
- With an incidence of less than 1%, leukopenia, neutropenia, decreased platelet count, elevated serum alkaline phosphatase, bilirubin, BUN, creatinine, blood glucose, LDH, and phosphate.

When follow-up was provided, changes in laboratory tests appeared to be reversible.

In multiple-dose clinical trials involving more than 3000 patients, 3 patients discontinued therapy because of treatment-related liver enzyme abnormalities and 1 because of a renal function abnormality.

In a phase 1 drug interaction study performed in normal volunteers, 1 of 6 subjects given the combination of azithromycin and rifabutin, 1 of 7 given rifabutin alone, and 0 of 6 given azithromycin alone developed a clinically significant neutropenia (< 500 cells/mm^3).

Laboratory abnormalities seen in clinical trials for the prevention of disseminated Mycobacterium avium disease in severely immunocompromised HIV-infected]**Clinical Studies**patients [see

Chronic therapy (median duration: 87.5 days, range: 1-229 days) that resulted in laboratory abnormalities in > 5% of subjects with normal baseline values in the pivotal trial for treatment of disseminated MAC in severely immunocompromised HIV-infected patients treated with azithromycin 600 mg daily in combination with ethambutol include: a reduction in absolute neutrophils to < 50% of the lower limit of normal (10/52, 19%) and an increase to five times the upper limit of normal in alkaline phosphatase (3/35, 9%). These findings in subjects with normal baseline values are similar when compared to all subjects for analyses of neutrophil reductions (22/75, 29%) and elevated alkaline phosphatase (16/80, 20%). Causality of these laboratory abnormalities due to the use of study drug has not been established.