

FDA Drug Safety Communication: Azithromycin (Zithromax or Zmax) and the risk of potentially fatal heart rhythms

Safety Announcement

[3-12-2013] The U.S. Food and Drug Administration (FDA) is warning the public that azithromycin (Zithromax or Zmax) can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm. Patients at particular risk for developing this condition include those with known risk factors such as existing QT interval prolongation, low blood levels of potassium or magnesium, a slower than normal heart rate, or use of certain drugs used to treat abnormal heart rhythms, or arrhythmias. This communication is a result of our review of a study by medical researchers as well as another study by a manufacturer of the drug that assessed the potential for azithromycin to cause abnormal changes in the electrical activity of the heart.

The [azithromycin drug labels](#) have been updated to strengthen the *Warnings and Precautions* section with information related to the risk of QT interval prolongation and torsades de pointes, a specific, rare heart rhythm abnormality. Information has also been added regarding the results of a clinical QT study which showed that azithromycin can prolong the QTc interval. (see Data Summary)

Health care professionals should consider the risk of fatal heart rhythms with azithromycin when considering treatment options for patients who are already at risk for cardiovascular events (see Additional Information for Health Care Professionals below). FDA notes that the potential risk of QT prolongation with azithromycin should be placed in appropriate context when choosing an antibacterial drug: Alternative drugs in the macrolide class, or non-macrolides such as the fluoroquinolones, also have the potential for QT prolongation or other significant side effects that should be considered when choosing an antibacterial drug.

FDA released a [statement on May 17, 2012](#), about a *New England Journal of Medicine (NEJM)* study that compared the risks of cardiovascular death in patients treated with the antibacterial drugs azithromycin, amoxicillin, ciprofloxacin (Cipro), and levofloxacin (Levaquin), or no antibacterial drug.¹ The study reported an increase in cardiovascular deaths, and in the risk of death from any cause, in persons treated with a 5-day course of azithromycin (Zithromax) compared to persons treated with amoxicillin, ciprofloxacin, or no drug. The risks of cardiovascular death associated with levofloxacin treatment were similar to those associated with azithromycin treatment.

FDA will update health care professionals and the public with any relevant information that becomes available about azithromycin and the risk of abnormal heart rhythms.

FACTS ON ZITHROMAX (azithromycin)

- Azithromycin is marketed under the brand names Zithromax and Zmax.
- FDA-approved indications for azithromycin include:
 - Acute bacterial exacerbations of chronic obstructive pulmonary disease
 - Acute bacterial sinusitis
 - Community-acquired pneumonia
 - Pharyngitis/tonsillitis
 - Uncomplicated skin and skin structure infections
 - Urethritis and cervicitis
 - Genital ulcer disease
- In 2011, approximately 40.3 million individuals in the U.S. received an outpatient prescription for the macrolide azithromycin.²

Additional Information for Patients

- Do not stop taking azithromycin without talking to your health care professional.
- Discuss any questions or concerns about azithromycin or other antibacterial drugs with your health care professional.
- Seek immediate care if you experience an irregular heartbeat, shortness of breath, dizziness, or fainting while taking azithromycin.
- Report any side effects you experience to your health care professional and the FDA MedWatch program using the information in the “Contact FDA” box at the bottom of the page.

Additional Information for Health Care Professionals

- Health care professionals should consider the risk of torsades de pointes and fatal arrhythmia when considering treatment options with azithromycin or alternative antibacterial drugs. Groups at higher risk include:
 - 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 and patients with cardiac disease may be more susceptible to the effects of arrhythmogenic drugs on the QT interval.

- The potential risk of QT prolongation should be placed in appropriate context when choosing an antibacterial drug: Alternative drugs in the macrolide or fluoroquinolone drug classes also have the potential for QT prolongation or other significant side effects that should be considered when choosing an antibacterial drug.
- Report adverse events involving azithromycin to the FDA MedWatch program using the information in the “Contact FDA” box at the bottom of the page.

Data Summary

The study published in NEJM suggested a higher risk of cardiovascular deaths and deaths from any cause in persons treated with a 5-day course of azithromycin compared to persons treated with amoxicillin, ciprofloxacin, or no drug.¹

The study has important limitations. First, patients were not randomized to the antibacterial drugs studied, so patients who received different drugs might have differed in ways that could have biased the results. Second, the study only examined antibacterial drugs used in an outpatient setting, so it is likely that few patients were being treated for severe or life-threatening infections. Third, cardiovascular deaths were determined using death certificates rather than full medical records. Fourth, there were also some limitations to the statistical methods used.

On balance, however, the study was methodologically sound and supports the validity of the overall finding. The estimated excess risk of cardiovascular death compared with amoxicillin varied considerably with the patients’ baseline cardiovascular risk, from roughly 1 in 111,000 among healthier patients to 1 in 4,100 among high-risk patients. The duration of the elevated risk of all-cause mortality and of cardiovascular death corresponded to the duration of azithromycin therapy. The increase in total deaths was due to cardiovascular deaths and not due to an increase in deaths from other causes. The excess risk of cardiovascular death, especially of sudden death, is consistent with arrhythmias from drug-related QT prolongation.

FDA also evaluated the results of a clinical QT study conducted by the manufacturer assessing the effects of azithromycin on the QT interval in adults. The results of the study indicated that azithromycin prolonged the QTc interval. Information regarding the results of the QT study has been added to the [Zithromax drug label](#).

References

1. Ray WA, Murray KT, Hall K, et al. Azithromycin and the risk of cardiovascular death. N Engl J Med 2012;366:1881-1890. <http://www.nejm.org/doi/full/10.1056/NEJMoa1003833>

2.Source: IMS Health Vector One National Total Patient Tracker