Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755

Worldwide Research & Development

August 2018

IMPORTANT INFORMATION REGARDING THE NON-AUTHORIZED USE OF AZITHROMYCIN AS A PROPHYLACTIC IMMUNOMODULATORY AGENT IN HSCT PATIENTS

Azithromycin: increased rate of relapses of haematological malignancies and mortality in hematopoietic stem cell transplantation (HSCT) patients treated with azithromycin

Dear Health Care Provider,

In agreement with the US Food and Drug Administration, Pfizer would like to inform you of the following:

Summary

- **Azithromycin is not indicated for prophylaxis of bronchiolitis obliterans syndrome (BOS) in patients undergoing HSCT.**
- **A clinical trial, ALLOZITHRO,[1] which investigated long-term azithromycin exposure to prevent bronchiolitis obliterans syndrome (BOS) in patients who underwent allogenic hematopoietic stem cell transplantation (HSCT) for hematological malignancy, was terminated early after an increased risk of relapses was seen in patients taking azithromycin compared with placebo.**
- **Although it is not clear how azithromycin could have contributed to the observed higher rate of hematological relapses, in the study, it is concluded that long-term azithromycin exposure following HSCT may include risks that exceed the anticipated benefits.**

Background on the safety concern

The French clinical trial entitled ALLOZITHRO *"Evaluation of the efficacy of azithromycin to prevent bronchiolitis obliterans syndrome after allogenic hematopoietic stem cell transplantation"* (NCT01959100) sponsored by the French academic institution belonging to hospitals in Paris, "Assistance Publique – Hôpitaux de Paris," investigated whether early prophylactic azithromycin would improve airflow decline-free survival 2 years after HSCT.

Study design: This study was a randomized, placebo-controlled, parallel-group trial conducted in 19 academic transplant centers in France. Enrolled patients were aged 16 years or older who were undergoing HSCT due to hematologic malignancy. The enrollment period was February 2014 to August 2015. A total of 480 patients were randomized: 243 patients were to receive azithromycin (250 mg) 3 times weekly for 2 years; 237 patients were to receive placebo for 2 years, starting at the time of conditioning regimen. The immunomodulating effects of azithromycin therapy were evaluated when used for the long-term prevention of BOS.

Main Outcomes & Measures: The primary efficacy end point of the ALLOZITHRO trial was airflow decline-free survival at 2 years after randomization. The main secondary endpoints were overall survival and bronchiolitis obliterans syndrome at 2 years.

Results: The ALLOZITHRO study treatments (azithromycin/placebo) were terminated on 26 December 2016, ie, at 13 months after completing recruitment. Upon review of blinded data, the independent Data and Safety Monitoring Board (DSMB) detected an unanticipated imbalance across blinded groups in the number of hematological relapses (77 versus 48 patients; adjusted hazard ratio [HR] [95%CI] = 1.6 [1.12-2.4] for azithromycin and placebo). Available data up through 26 April 2017 were analyzed. The 2-year survival rates were 57% in azithromycin-treated patients and 70% in placebo patients (unadjusted HR [95% CI] 1.5 [1.1-2.0]). The authors concluded that among patients undergoing allogenic HSCT for hematological malignancy, early administration of azithromycin as prophylaxis resulted in worse airflow decline-free survival than did placebo. The authors noted that the findings were limited by early study treatment termination and other factors. The authors concluded that the potential for harm related to relapse requires further investigation.

[1] Bergeron A et al. Effect of azithromycin on airflow decline-free survival after allogeneic hematopoietic stem cell transplant: the ALLOZITHRO randomized clinical trial. *JAMA*. 2017;318(6):557-566.

EVALUATION OF THE SAFETY CONCERN

Analysis of all relevant available data does not suggest this risk to apply to other patient populations or to approved indications in short- and long-term use.

Even though an exact potential mechanism remains unidentified, and despite the absence of other supportive data, the evidence from this randomized clinical trial is considered strong enough to assume that (off-label) long-term azithromycin exposure subsequent to HSCT may be associated with an increased relapse risk of hematological malignancies.

The long-term azithromycin exposure following HSCT may include risks that exceed the anticipated benefits. Safety of prophylactic long-term azithromycin treatment in this patient group is questioned.

Reporting Adverse Events

Health care providers and patients are encouraged to report adverse events in patients taking azithromycin to Pfizer at 1-800-438-1985. You are encouraged to report negative

side effects of prescription drugs to the FDA. Visit www.fda.gov/MedWatch, or call 1-800-FDA-1088.

You may also contact our Medical Information department at 1-800-438-1985 if you have any questions about the information contained in this letter or the safe and effective use of azithromycin.

This letter is not intended as a complete description of the benefits and risks related to the use of azithromycin. Please refer to the full Prescribing Information.

Important Safety Information for Zithromax® (azithromycin)

Contraindications:

- Known hypersensitivity to azithromycin, erythromycin, any macrolide, or ketolide drug.
- History of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin.

Warnings and Precautions:

- Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson Syndrome, and toxic epidermal necrolysis, have been reported rarely in patients on azithromycin therapy. Discontinue ZITHROMAX and initiate appropriate therapy if reaction occurs.
- Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur.
- Following the use of azithromycin in neonates (treatment up to 42 days of life), Infantile Hypertrophic Pyloric Stenosis has been reported. Direct parents and caregivers to contact their physician if vomiting or irritability with feeding occurs.
- Prolongation of QT interval and cases of torsades de pointes have been reported. This risk which can be fatal should be considered in patients with certain cardiovascular disorders including known QT prolongation or history of torsades de pointes, those with proarrhythmic conditions, and with other drugs that prolong the QT interval. Elderly patients may be more susceptible to development of torsades de pointes arrhythmias.
- *Clostridium difficile*-Associated Diarrhea: Evaluate patients if diarrhea occurs. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued.
- Exacerbations of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving azithromycin therapy.
- Close monitoring for known side effects of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted when given with Nelfinavir.
- Warfarin use with azithromycin may increase coagulation times; monitor prothrombin time.

Most common adverse reactions are diarrhea (5 to 14%), nausea (3 to 18%), abdominal pain (3 to 7%), or vomiting (2 to 7%).

ZITHROMAX is a macrolide antibacterial drug indicated for mild to moderate infections caused by designated, susceptible bacteria:

- Acute bacterial exacerbations of chronic bronchitis in adults
- Acute bacterial sinusitis in adults
- Uncomplicated skin and skin structure infections in adults
- Urethritis and cervicitis in adults
- Genital ulcer disease in men
- Acute otitis media in pediatric patients
- Community-acquired pneumonia in adults and pediatric patients
- Pharyngitis/tonsillitis in adults and pediatric patients

Limitation of Use:
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.
To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZITHROMAX (azithromycin) and other antibacterial drugs, ZITHROMAX (azithromycin) should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.

Safety and effectiveness in the treatment of patients under 6 months of age have not been established.

Please see the full Prescribing Information at www.pfizer.com/products/product-detail/zithromax.

Yours sincerely,

Pardis Tabrizi, PharmD
US Associate Medical Director

PO Box 29483
Mission, KS 66201

PRSRT STD
U.S. Postage
PAID
Pfizer Inc

IMPORTANT INFORMATION

PP-ZIT-USA-0001-02