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Worldwide Biopharmaceutical Businesses

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

Dear Healthcare Professional,

In agreement with the European Medicines Agency (EMA) and HPRA, Pfizer Limited would like to inform you of the following:

Summary

- **A clinical trial ALLOZITHRO[1] which investigated *long-term azithromycin 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 which exceed the anticipated benefits.**

- **Azithromycin is not authorized for prophylaxis of BOS in patients undergoing HSCT.**

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"* (N^{O} EudraCT: 2013-000499) sponsored by the French academic institution belonging to Hospitals in Paris, "Assistance publique des hopitaux 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 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 two 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 the 26th December 2016 i.e. at thirteen months after completing recruitment. Upon review of blinded

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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 HR (95%CI) = 1.6 (1.12-2.4) for azithromycin and placebo). Available data up through 26 April 2017 were analysed. 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 Aug 8;318(6):557-566.

EVALUATION OF THE SAFETY CONCERN

Analysis of all relevant available data do 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 which exceed the anticipated benefits. Safety of prophylactic long-term azithromycin treatment in this patient group is questioned.

Call for reporting
You can assist us with monitoring the safety of Azithromycin by reporting suspected adverse reactions. Suspected adverse drug reactions (ADRs) should be reported to the Health Products Regulatory Authority (HPRA):

- Online Reporting via the HPRA Website: www.hpra.ie
- Using downloadable form from the HPRA website. An adverse reaction report form can be downloaded from the HPRA Website. This can be sent by Freepost to the HPRA or by email to medsafety@hpra.ie.
- By telephoning the Pharmacovigilance Section of the HPRA, (01) 676 4971

Suspected adverse drug reactions may also be reported to Pfizer Medical Information on 1800 633 363.

For more information about Zithromax®, please contact Pfizer Medical Information at Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS or Tel: 1800 633 363 and ask for Medical Information or e-mail at EUMEDINFO@pfizer.com.

Suspected adverse reactions should also be reported to the relevant Marketing Authorisation Holders (see contact details below).
This information is being provided jointly by the following MAHs:

Marketing Authorisation Holder	Product Name	E-mail	Phone	Fax
Aspire Pharma Limited	Zedbac®	medinfo@aspirepharma.co.uk	+44 (0)1730 231148	
Krka Pharma Dublin Ltd	Azithromycin Krka	pharmacovigilance@krka.biz	0035312939180	
Teva	Azithromycin Teva or Azithromycin Actavis	medinfo@tevauk.com	+44 (0)20 7540 7117	+44 (0)207540 7349
Wockhardt UK Limited	Azithromycin 250mg Film-coated Tablets Azithromycin 500mg Film-coated Tablets	drug.safety@wockhardt.co.uk	+44 1978 669272	

Company contact point
Alternatively, suspected adverse reaction may also be reported to the marketing authorisation holders in the product information of the medicine (SmPC and Package Leaflet).

Yours sincerely,

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