

02 May 2018

**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 Malta Medicines Authority, Pfizer Hellas S.A, together with other marketing authorisation holders of azithromycin containing medicines authorised in Malta, would like to inform you of the following:

**Summary**

- **A clinical trial ALLOZITHRO<sup>1</sup> which investigated long-term azithromycin to prevent bronchiolitis obliterans syndrome (BOS) in patients who underwent allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for haematological 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 haematological 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 **authorised** 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 allogeneic hematopoietic stem cell transplantation*” (N<sup>o</sup> 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 haematological malignancy. The enrolment 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 26<sup>th</sup> December 2016 i.e. at thirteen 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 haematological 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 allogeneic HSCT for haematological 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.

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<sup>1</sup> 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

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 haematological 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**

Healthcare professionals are reminded to report suspected adverse reactions associated with azithromycin containing medicines in accordance with the national spontaneous system. Any suspected adverse reactions and medication errors can be reported via the national Adverse Drug Reactions (ADRs) reporting system. Report forms can be downloaded from [www.medicinesauthority.gov.mt/adrportal](http://www.medicinesauthority.gov.mt/adrportal) and posted to Malta Medicines Authority Post-licensing, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta or sent by email to [postlicensing.medicinesauthority@gov.mt](mailto:postlicensing.medicinesauthority@gov.mt)

### **Company contact points**

Alternatively, suspected adverse reaction may also be reported to the marketing authorisation holders using the details provided below.

If you have further questions or require additional information, please contact:

| Company                             | Product name  | Email   | Phone  | Fax               |
|-------------------------------------|---|---|--|-------------------|
| Actavis Group PTC ehf               | Actazith 500mg, film-coated Tablets   | <a href="mailto:PHVMALTA@actavis.com">PHVMALTA@actavis.com</a>  | +30<br>2118805156  | +30<br>2118805107 |
| Alet Pharmaceuticals S.A.           | Azithrin Tablets  | <a href="mailto:PHVMALTA@actavis.com">PHVMALTA@actavis.com</a>  | +30<br>2118805156  | +30<br>2118805107 |
| Central Procurement & Supplies Unit | Azithromycin 500mg Film-coated tablets  | <a href="mailto:richard.despott@gov.mt">richard.despott@gov.mt</a>  | +356<br>79600000;<br>+356 23439150                       | N/A               |
| Mint Health Ltd.                    | Azithromycin 500mg Tablets  | <a href="mailto:samantha@mint.com.mt">samantha@mint.com.mt</a>  | +356 2098<br>9800  | N/A               |
| Neofarma Pharmaceuticals Ltd        | Azithromycin 500mg Film-coated Tablets  | RP - Sylvania Galea<br><a href="mailto:galea.sylvania@gmail.com">galea.sylvania@gmail.com</a><br><br>Managing Director - Paul Camilleri<br><a href="mailto:info@neofarma.com.mt">info@neofarma.com.mt</a> | +356 20109494  | +356 21441852     |
| PharmaMT Ltd                        | Azithromycin Clonmel Tablet, film coated 250mg  | <a href="mailto:info@pharmamt.com">info@pharmamt.com</a>  | +356 21337008  | +356 21337004     |
| Teva Pharma B.V.                    | Azithromycin Teva Tablet, film coated 250mg   | <a href="mailto:PHVMALTA@actavis.com">PHVMALTA@actavis.com</a>  | +30<br>2118805156  | +30<br>2118805107 |
| PIAM Farmaceutici S.p.A.            | Azitredil   | <a href="mailto:terrire@piamfarmaceutici.com">terrire@piamfarmaceutici.com</a><br><br>Local contact:<br><a href="mailto:aparis@prohealth.com.mt">aparis@prohealth.com.mt</a>                              | +39 010<br>518621<br><br>Local contact:<br>+356 23385313 | +39 010 355734    |
| Pfizer Hellas S.A.                  | Zithromax Capsules 200 mg(s)/5 ml Powder for Oral Suspension<br><br>Zithromax Suspension<br>Azithromycin 250 mg(s) Hard Capsule | Local contact:<br><a href="mailto:regvjsp@vjsalomone.com">regvjsp@vjsalomone.com</a>  | +356 99644126<br>+356 21220174                           | +356 21243026     |
| Cherubino Ltd                       | Zithroplus Tablet, film coated 500mg  | <a href="mailto:annalisa@cherubino.com.mt">annalisa@cherubino.com.mt</a>  | +356 21343270  | +356 21330916     |

Yours sincerely,

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Greece, Cyprus and Malta