PRAC recommendation
Azithromycin – Signal of potentially fatal heart events

This is a recommendation from the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA).

1. Administrative details

<table>
<thead>
<tr>
<th>Substance (invented name)</th>
<th>Azithromycin</th>
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<tbody>
<tr>
<td>Authorisation procedure</td>
<td>Non-centralised</td>
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<tr>
<td>Signal (EPITT No)</td>
<td>Signal: Risk of cardiovascular death (EPITT Ref 16156)</td>
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<tr>
<td>PRAC meeting date</td>
<td>7-10 July 2014</td>
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<td>Signal identifier</td>
<td>Finland</td>
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<td>PRAC rapporteur(s)</td>
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<td>N/A</td>
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<td>Rodrigo Postigo</td>
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<tr>
<td>Status</td>
<td>Follow-up discussion</td>
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<td>Date of adoption</td>
<td>10 July 2014</td>
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2. Prioritisation and recommendation

Evidence evaluated and prioritisation/public health importance

An assessment of the risk of developing potentially fatal arrhythmias following the administration of oral or intravenous azithromycin was performed in 2013 within the PSUR Work Sharing procedure.
This assessment took into account the study published in May 2012 by Ray et al regarding the risk of cardiovascular death. The authors concluded that during 5 days of azithromycin therapy, there was a small absolute increase in cardiovascular deaths (47 per 1 million prescriptions), which was most pronounced (245 per 1 million prescriptions) among patients with a high baseline risk of cardiovascular disease. The EU reference date for azithromycin is 04 April 1991. The innovator product (Zithromax, Zithromax IV) from Pfizer is available in 130 countries, and the exposure between 2003 and 2011 has been > 300 million prescriptions for the innovator product alone. There are several generics products in the EU market. In the US approximately 1/8 of the population is exposed to azithromycin annually (Mosholder et al. NEJM 02 May 2013). If azithromycin use in the EU equals to that estimated in the US, more than 60 million patients are exposed to azithromycin in EU every year.

Pfizer, the Marketing Authorisation Holder (MAH) for the innovator product (Zithromax, Zithromax IV) provided a thorough review of this topic including an assessment of the mentioned publication and concluded that the risk of cardiovascular death is not confirmed.

As an outcome of the PSUR Work Sharing procedure, the Core Safety Profile (CSP) was updated to include information and warnings related to the risk of developing cardiac arrhythmias and torsades de pointes (TdP). The respective variations to update the SmPC were due by 01 July 2013. The text includes the following warnings concerning QT prolongation, TdP and cardiac death:

**Section 4.2**

The same dosage as in adult patients is used in the elderly. Since elderly patients can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes. (see Section 4.4 Special warnings and precautions for use).

**Section 4.4**

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides including azithromycin (See Section 4.8 Undesirable effects). Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients:

- With congenital or documented QT prolongation
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of class IA (quinidine and procainamide ) and class III (dofetilide amiodarone and sotalol), cisapride and terfenadine; antipsychotic agents such as pimozide; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency

**Section 4.8 ADR Table, frequency “unknown”**

- Torsades de pointes (see section 4.4)
- Arrhythmia (see section 4.4) including ventricular tachycardia
- Electrocardiogram QT prolonged (see section 4.4)
In May 2013, Svanström et al published an epidemiological study on azithromycin and deaths from cardiovascular causes, performed in the Danish Civil Registration System. This study represents a European population and also included less frequently patients with significant cardiovascular risk factors than the US population studied by Ray et al. Svanström et al were not able to confirm increased risk of cardiac mortality associated to azithromycin use (compared to users of V-penicillin) in general population but they were not able to exclude such possibility among those who have significant cardiovascular risk factors. The exact risk groups are still to be identified. This further emphasizes the importance of gathering new data aimed to fill the gap in understanding the effects of azithromycin among those who have potential risk factors such as proarrhythmic conditions.

Pfizer evaluated the Ray et al. and Svanström et al. findings in the context of other available cardiovascular safety data on azithromycin’s benefits and risks and concluded that the benefit-risk balance of the drug remains positive. However, further investigations, with sufficient power and adequate control of confounding (particularly of indication of use), are necessary to confirm this signal.

Pfizer intends to perform an observational study using large electronic healthcare records with the aim to examine the acute effect of azithromycin on cardiac deaths, including sudden cardiac deaths as compared to the appropriate comparisons groups. A feasibility study report showed that US Kaiser Permanente Northern California (KPNC) would be best suited database to examine the research question of interest. Two less optimal alternatives were also identified: US Department of Defense; and the Danish National Health Service Register. Moreover, it was confirmed that Pfizer had discussions with the FDA which proposed to engage also the US Kaiser Permanente of Southern California (KPSC) database and subsequently Pfizer submitted a feasibility analysis to assess the statistical power of KPNC and KPNC-KPSC to examine the acute effects of azithromycin use on cardiovascular deaths in the future observational study.

A feasibility analysis in the Veterans Affairs (VA) database has been contemplated by Pfizer upon request by the FDA, but due to a delay in the accessibility of the data beyond the control of Pfizer, the FDA has requested to begin the contracting process with the Kaiser Permanente to conduct a full study. Pfizer has therefore begun this process, which includes drafting the protocol.

Pfizer is intended to submit the draft protocol for the study in the Kaiser Permanente databases to the PRAC in August 2014 and the final protocol in January 2015. The final study report is envisaged for submission in November 2016.

The PRAC in May and October 2013 adopted the following recommendations:

- To discuss future strategies to identify and characterise possible risk groups, focusing not only in the arrhythmogenics effect, but also taking into consideration long-term ischaemic cardiac events as a risk factor and also as an outcome.
- The study should also examine the use of concomitant/interacting medication including statins and calcium channel blockers.
- The analysis should not exclude and should not be focused in any specific mechanism.
- The study should include an analysis of the other non-cardiac causes of death (besides cardiovascular and all-cause mortality), so that if the non-cardiac causes of death have no increased risks in the azithromycin cohort but cardiovascular deaths are increased, it provides reassurance that the increased cardiovascular mortality is due to the adverse cardiovascular profile of the drug, rather than confounding by the indication.
- The use of an instrumental variable approach (using physician prescribing preference) in order to overcome confounding by indication in the proposed observational study.
To consider the non-medication treatments of those with lower respiratory tract infections in the analysis in the proposed study (e.g. treatments involving the use of non-invasive ventilation methods with positive airways pressures).

To address the issue of the long-term safety of azithromycin and ischemic cardiovascular events, Pfizer presented data from two large, randomised and controlled clinical trials (ACES and WIZARD). The data demonstrates no long-term cardiovascular risk in patients with stable coronary artery disease. To further address this issue, Pfizer submitted an independent expert review of the data and provided an assessment of the mentioned WIZARD and ACES clinical trials plus the ACADEMIC trial by Anderson et al in 1999 and the AZACS trial by Cercek et al in 2003. The expert review concluded that the gathered data from randomised clinical trials did not either confirm or refute the association between azithromycin and harmful cardiac affects and therefore further information may be available upon conduction of the observational study. The PRAC agreed with the conclusion in May 2014.

Pfizer submitted a feasibility analysis to measure the statistical power of KPNC and KPNC-KPSC to examine the acute effects of azithromycin use on cardiovascular deaths in the future observational study. Based on this feasibility analysis, KPNC appears sufficiently powered to significantly detect relatively small effects, overall and within high baseline cardiovascular risk subgroups. However, given the inevitable decrease in cardiovascular deaths due to death adjudication in the planned observational study, a KPNC-KPSC collaborative study will certainly provide greater assurance of power, particularly in the smaller (and therefore more vulnerable to loss of power), high cardiovascular risk populations. Pfizer proposes that the future observational study be conducted within a KPNC-KPSC combined data source.

Moreover, a feasibility analysis in the Veterans Affairs database will be performed upon the availability of the data and Pfizer expects to submit this analysis to PRAC in October 2014.

Pfizer submitted a review of the new publication by Rao et al, 2014<sup>1</sup> on the use of azithromycin and levofloxacin and increased risk of cardiac arrhythmia and death and concluded that the data published does not change the benefit-risk balance of azithromycin.

The PRAC rapporteur has also performed an assessment of a recent publication by Khosropour et al, 2014<sup>2</sup> on the lack of association between azithromycin and death from cardiovascular causes and concluded that the study published does not directly suggest an increased risk of cardiac mortality associated to short term azithromycin use in the relatively young and healthy population studied. However, the size of the population exposed and the fact that no cardiovascular deaths were detected in this material limits further conclusions.

**Recommendation**

The PRAC endorsed the proposal from Pfizer to perform the planned observational study in the Kaiser Permanente Northern California and Kaiser Permanente of Southern California databases and agrees that a feasibility analysis within the Veterans Affairs database should be conducted once the data is available.

The draft study protocol is expected by end of August 2014 and the PRAC should be kept informed if the plan for the development of the observational study needs to be modified in the future. Pfizer is

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recommended to consider including the aspects in the previous PRAC Recommendations, including an analysis of the other non-cardiac causes of death (besides cardiovascular and all-cause mortality) to provide reassurance that the increased cardiovascular mortality is due to the adverse cardiovascular profile of the drug, rather than confounding by the indication.

The PRAC agrees with the Pfizer’s assessment of the publication by Rao et al, 2014 that the data does not provide a solid evidence for a causal association and there are no changes in the benefit-risk balance of azithromycin based on the data published.

The PRAC acknowledged the limitations of the study published by Khosropour et al, 2014 and noted that the outcome of the study does not directly suggest an increased risk of cardiac mortality associated to short term azithromycin use in the relatively young and healthy population studied.

Relevant updates of the product information should be considered upon completion of the observational study or if new data becomes available.