NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC

E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 31 of Directive 2001/83/EC to the PRAC made by the Hungarian Medicines Agency:

Active Substance, Strength(s) and Pharmaceutical Form(s)	All hydroxyzine hydrochloride containing products (all strengths and formulations)
Marketing Authorisation Holder(s)	Various

Hydroxyzine hydrochloride (Atarax) is authorized nationally in 24 member states across the EU. It is indicated in all member states for the treatment of preoperative anxiolysis, anxiety disorders, pruritus, and in addition in some member states for the treatment of sleep disorders. Hungary acts as lead Member State for signals for this active ingredient.

On 7th March 2014, UCB informed the Hungarian competent authority (GYEMSZI-OGYI) of its intention to delete two approved indications (preoperative anxiolysis and sleep disorders) and decrease the highest recommended daily dose for adults from 300 mg to 100 mg in the remaining indications. The proposed measures follow a benefit-risk assessment of hydroxyzine conducted by UCB in response to results obtained from non-clinical studies and pharmacovigilance data received on the suspected pro-arrhythmogenic potential of the active substance.

In July 2011, a cumulative safety review of reports describing QT prolongation and/or torsade de pointes (TdP) in patients treated with hydroxyzin conducted by MAH concluded that there is a potential risk for developing QT prolongation and/or TdP after exposure to hydroxyzine, leading to the contraindication of Atarax in patients with known prolonged QT-interval. In September 2011, a publication pointed out that hydroxyzine could block hERG channels and prolong the cardiac action potential duration at concentrations lower than previously shown.

New relevant safety information was detected in the article published in September 2011 by Lee and coworkers. In this publication, the authors concluded that hydroxyzine could block the hERG channels and prolong the cardiac action potential duration at concentrations lower than previously shown. On the other hand, these results were not in line with a previous study performed in 2008 by Sakaguchi and coworkers. In order to clarify discrepancies in the literature, UCB conducted a GLP hERG study and a cardiac channelogram that did not reveal a pro-arrhythmogenic potential at the lowest therapeutic dose of 50 mg, i.e. the value of cardiac safety index was within the commonly acceptable safety margin regarding the risk of arrhythmia. Evaluation of cardiac safety index for higher doses remained incomplete at this stage. Furthermore, UCB conducted a cumulative review on QT-prolongation and TdP associated with hydroxyzine. The risk of QT interval prolongation and of TdP was not identified during the clinical development program of hydroxyzine. One phase IV clinical trial that investigated the efficacy and safety of hydroxyzine in the treatment of preoperative anxiety revealed a slight QT lengthening on the ECG; however, the QTc analysis did not point to a clinically significant risk. Analysis of post-marketing data revealed that cases were confounded by the presence of one or more other risk factors for QT prolongation which was in accordance with the concept of repolarization reserve which requires multiple risk factors conjointly to become exhausted leading to the development of cardiac electrophysiological disturbances. The number of cases retrieved from UCB database was 41 and 184 based on the type of MedDRA query used, torsade de pointes/QT prolongation SMQ narrow or broad, respectively. From among the 184 cases, 61 had a fatal outcome. Beside the risk of cardiac abnormalities, UCB has reviewed the evidence available for the benefit of hydroxyzine per indication. The review concluded that the benefits of hydroxyzine treatment no longer outweigh the risks in the indications of preoperative anxiolysis and sleep disorders. In the opinion of UCB the benefit-risk balance remains positive in the second line treatment of anxiety and in the symptomatic treatment of pruritus. However, no clinical study has been presented to demonstrate effectiveness of treatment for the latter indication; the use is justified on the grounds of current scientific knowledge. Dose reduction in anxiety disorders is based upon the finding that no clear evidence for incremental efficacy could be demonstrated at doses exceeding 50 mg; whereas an increased risk of torsade de pointes is expected at doses exceeding 100 mg based upon theoretical and preclinical facts; although no clinical evidence has been found yet to support this theoretical risk.

Based on the above, the Hungarian competent authority is of the view that a thorough EU review of the benefit-risk balance of hydroxyzine hydrochloride-containing products and in particular the pro-arrhythmogenic potential of hydroxyzine needs to be conducted in all the authorized indications and target populations.

In view of the elements described above and the potential need for action at EU level, the GYEMSZI-OGYI considers that it is in the interest of the Union to refer the matter to the Pharmacovigilance Risk Assessment Committee (PRAC) and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC on whether any regulatory measures should be taken on the marketing authorisations of hydroxyzine hydrochloride-containing products.

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Hilda Kőszegi Szalai PhD
Deputy Director
GYEMSZI-OGYI

25 April 2014