Annex II

Scientific conclusions and grounds for variation to the terms of the marketing authorisations and detailed explanation of the scientific grounds for the differences from the PRAC recommendation

Scientific conclusions and detailed explanation of the scientific grounds for the differences from the PRAC recommendation

Hydroxyzine hydrochloride is a first generation antihistamine first authorised in the 1950s and available in 24 EEA member states. The products are nationally authorised as prescription-only medicines, for use in a number of indications including the treatment of anxiety disorders, skin conditions (such as pruritus, dermatitis or urticaria) for preoperative sedation and for the treatment of sleep disorders.

On 7th March 2014, the Hungarian competent authority was informed of new data on the potential risk for developing QT interval prolongation and/or Torsades de Pointes after exposure to hydroxyzine. The Hungarian competent authority considered it to be in the interest of the Union to refer the matter to the Pharmacovigilance Risk Assessment Committee (PRAC) under Article 31 of Directive 2001/83/EC. The PRAC was requested to review the benefit-risk balance of hydroxyzine-containing products, in particular giving consideration to their pro-arrhythmogenic potential in all authorised indications and target populations and to give its recommendation on whether any regulatory measures should be taken on the marketing authorisations. In the context of the review, the PRAC consulted the EMA Paediatric Committee (PDCO) and the Geriatric Expert Group (GEG).

The PRAC reviewed all available data, including pre-clinical data, clinical efficacy and safety data and post-marketing safety data, as well as input from the PDCO and the GEG, in the context of its review of the potential risk for developing QT interval prolongation and Torsades de Pointes after exposure to hydroxyzine. The PRAC considered that the efficacy data did not raise any new concerns. Based on the available non-clinical data, the PRAC concluded that hydroxyzine has the potential to block hERG channels and other types of cardiac channels, resulting in a potential risk of QT interval prolongation and cardiac arrhythmia events. This potential risk was confirmed by clinical and post-marketing data, which also identified the at-risk population as consisting of patients with risk factors for QT interval prolongation, such as cardiac medical history, concomitant medications associated with QT interval prolongation and electrolyte imbalance. This is in line with the concept of the repolarisation reserve, which proposes that the concomitant action of multiple factors is required for the exhaustion of the repolarisation reserve, opening the way to the occurrence of cardiac electrophysiological disturbances.

The risk did not differ between indications and no dose effect could be observed based on post-marketing data, despite pre-clinical data suggesting that hydroxyzine has a dose-dependent hERG inhibitory effect. The PRAC considered that the potential risk of QT interval prolongation and Torsades de Pointes can be adequately minimised through appropriate risk minimisation measures targeting the identified risk factors and restricting the use of hydroxyzine, in particular in the at-risk populations. A maximum daily dose of 100 mg was found to be efficacious and well-tolerated and the PRAC therefore recommended restricting the maximum daily dose to 100 mg per day in adults, with corresponding changes in the paediatric and elderly populations, based on pharmacokinetic data. The PRAC also recommended that the treatment duration should be as short as possible. The PRAC recommended that hydroxyzine should be contra-indicated in patients with a known acquired or congenital QT interval prolongation as well as in patients with a known risk factor to QT interval prolongation including a known cardiovascular disease, significant electrolytes imbalance (hypokalaemia, hypomagnesaemia), family history of sudden cardiac death, significant bradycardia, concomitant use with other drugs known to prolong the QT interval and/or induce Torsades de Pointes. In addition, further changes to the product information were implemented, including a revision of the posology and a warning that use in the elderly is not

recommended due to the anticholinergic effects. The PRAC also requested the MAHs to circulate a 'Direct healthcare professional' communication (DHPC), assess the effectiveness of the risk minimisation measures and continue to monitor the risks of QT interval prolongation, Torsades de Pointes, ventricular arrhythmia, sudden death and cardiac arrest.

The PRAC concluded that the benefit-risk of the hydroxyzine-containing products remains positive, provided that the agreed changes to the product information and the additional risk minimisation measures are implemented.

Overall conclusion and grounds for the variation to the Marketing Authorisations

Whereas

- The Pharmacovigilance Risk Assessment Committee (PRAC) considered the procedure under Article 31 of Directive 2001/83/EC;
- The PRAC reviewed the totality of the available data in relation to the potential risk for developing QT interval prolongation and/or Torsades de Pointes after exposure to hydroxyzine, including pre-clinical data, clinical efficacy and safety data and post-marketing safety data, the MAHs' submissions as well as reports from the Paediatric Committee and the Geriatric Expert Group;
- The PRAC considered that the available efficacy data did not raise any new concerns;
- The PRAC considered that the available safety data confirms the potential risk of QT interval prolongation associated with the use of hydroxyzine;
- The PRAC considered the known risk factors for QT interval prolongation and was of the opinion that the potential risk for QT interval prolongation can be adequately minimised by restricting the use of hydroxyzine, particularly in at-risk patient populations;
- The PRAC agreed on measures including a revision of the posology, contraindications in patients with a known acquired or congenital QT interval prolongation and patients with a known risk factor to QT interval prolongation, a warning that use in the elderly is not recommended due to the anticholinergic effect and a request to the MAHs to assess the effectiveness of the risk minimisation measures.

The PRAC, as a consequence, concluded that the benefit-risk balance of the hydroxyzine-containing products identified in Annex I remains favourable, subject to the agreed amendments to the product information and additional pharmacovigilance activities and additional risk minimisation measures.

The PRAC therefore recommended the variation to the terms of the marketing authorisation for the medicinal products referred to in Annex I and for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III of the PRAC recommendation.

2 – Detailed explanation of the scientific grounds for differences from the PRAC recommendation

Having reviewed the PRAC recommendation, the CMDh agreed with the overall scientific conclusions and grounds for recommendation. However, the CMDh considered that additional changes were necessary to the wording proposed for the Summary of Product Characteristics (SmPC) and the Package Leaflet, to provide appropriate guidance on the recommendation

regarding the maximum daily dose in children and adolescents over 40 kg of body weight but below 18 years of age. The CMDh noted that the pharmacokinetic data reviewed during the procedure indicates that the half-life of hydroxyzine appears to display a linear increase with age (the half-life in children 12 months of age is 4 hours, compared to 11 hours for children aged 14 years, 14 hours in adults and 29 hours in the elderly). As the recommendation in children below 40 kg in weight is 2 mg/kg/day, the maximum daily dose in this population is 80 mg per day. Because 40 kg in weight is generally considered to be the weight of a child aged 12 years, the CMDh considered that based on the available pharmacokinetic data, the adult maximum daily dose of 100 mg per day would be considered appropriate also for children over 40 kg in weight. The CMDh amended the product information accordingly, revising the wording of Section 4.2 of the SmPC as follows: "*In adults and children over 40 kg in weight, the maximum daily dose is 100 mg per day*" and clarifying the wording of the recommendation in children up to 40 kg in weight. The wording of Section 3 of the Package Leaflet was amended accordingly.

In addition, the CMDh agreed that when implementing the agreed changes to the product information, the MAHs should also revise the posology section as appropriate to introduce any changes consequential to the revised maximum daily dose recommendations. These amendments should be submitted within a Type IB variation.

For products with a paediatric formulation (syrup or oral solution), consideration should be given to making available an appropriate measuring device.

CMDh agreement

The CMDh, having considered the PRAC recommendation, agrees with the overall scientific conclusions by the PRAC and agrees that the marketing authorisations for hydroxyzine-containing medicinal products should be varied.