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New restrictions to minimise the risks of effects on heart rhythm with hydroxyzine-containing medicines

Use to be avoided in patients at greatest risk and doses to be kept low

The CMDh[1] has agreed by consensus new measures to minimise the risk of effects on heart rhythm with medicines containing the antihistamine hydroxyzine. The measures include restricting use of hydroxyzine in patients at high risk of heart rhythm problems and using the medicine at the lowest effective dose for as short a time as possible.

Hydroxyzine medicines are available in most EU countries. Their approved uses (indications) vary between countries and may include use to treat anxiety disorders, for relief of pruritus (itching), as premedication before surgery, and treatment of sleep disorders.

Recommendations for these new measures were originally made by EMA's Pharmacovigilance Risk Assessment Committee (PRAC), which confirmed a previously known risk of QT interval prolongation and torsades de pointes, alterations in the electrical activity of the heart that can lead to abnormal heart rhythms and cardiac arrest (stopping of the heart). Having assessed the available evidence, including published studies and data from regular safety monitoring, the PRAC concluded that the risk did not differ between indications and that such events are most likely to occur in patients who have risk factors. The PRAC therefore recommended that the risk be managed by restricting hydroxyzine use in those most at risk of heart rhythm problems and reducing exposure to the medicine.

As the CMDh has now agreed the PRAC measures by consensus, the measures will be directly implemented by the Member States where the medicines are authorised, according to an agreed timetable. In particular, the product information of hydroxyzine-containing medicines will be updated with new dosing recommendations and warnings on use in patients who have risk factors for heart rhythm disturbances or who are taking certain other medicines.

[1] The CMDh is a medicines regulatory body representing the European Union (EU) Member States, Iceland, Liechtenstein and Norway.

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Information to patients

- Medicines containing the antihistamine hydroxyzine are available in most EU countries. The approved uses are different in different countries, but may include treatment of anxiety, relief of itching, use as one of the medicines given before an operation (premedication) or treatment of sleep problems.
- There is a small risk of altered electrical activity of the heart when taking these medicines, which can lead to abnormal heart rhythm or even cause the heart to stop (cardiac arrest). The risk is mostly seen in patients who already have heart rhythm problems or have risk factors for these problems.
- To reduce the risk to a minimum, new measures have been agreed for these medicines to ensure they are used for as short a time as possible at the lowest effective dose, and that their use is avoided in those at higher risk.
- The dose in adults should not add up to more than a total of 100 mg a day. Elderly patients should not use these medicines, but if they do the maximum dose should be 50 mg a day.
- In countries where the medicines are approved for use in children, the maximum dose depends on their weight, and the daily total should not be more than 2 mg per kg of body weight in children weighing up to 40 kg (children over 40 kg should be given the adult dose).
- Hydroxyzine must not be taken by patients who already have disturbances of heart rhythm or are taking other medicines that can cause similar effects on the heart. It should be used with care if taking certain other medicines that slow the heart rate or decrease the level of potassium in the blood.
- The package leaflet and other product information for these medicines will be updated to take account of the new measures. In the meantime, patients who have any concerns should speak to their doctor or pharmacist.

Information to healthcare professionals

- 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. Most cases had other risk factors, electrolyte abnormalities or concomitant treatment that may have been contributory.
- The potential risk of QT interval prolongation and torsades de pointes can therefore be adequately minimised through measures targeting the identified risk factors and restricting the use of hydroxyzine to the lowest effective dose for the shortest possible duration.
- The maximum dose in adults should be a total of 100 mg daily; in the elderly, if use cannot be avoided the maximum daily dose should be 50 mg.
- The maximum daily dose in children up to 40 kg in weight should be 2 mg/kg/day; children over 40 kg should be given the adult dose.
- Use of hydroxyzine is contraindicated in patients with known acquired or congenital QT interval prolongation, or with a known risk factor for QT interval prolongation such as cardiovascular disease, significant electrolyte imbalance (hypokalaemia, hypomagnesaemia), family history of

sudden cardiac death, significant bradycardia, or concomitant use of drugs known to prolong the QT interval and/or induce torsades de pointes.

- Use is not recommended in elderly patients, due to reduced elimination of hydroxyzine in these patients and greater vulnerability to anticholinergic effects and other adverse reactions. The medicine should be used with caution in patients with bradycardia, or who are taking hypokalaemia-inducing medicines. Care is also required when hydroxyzine is co-administered with drugs known to be potent inhibitors of alcohol dehydrogenase or CYP3A4/5.

The above risk minimisation measures were taken following an assessment of the available evidence, including published studies and data from regular safety monitoring. The data showed that the risk did not differ between indications. It was considered appropriate to restrict the maximum daily dose in adults, with corresponding changes in the paediatric and elderly populations based on pharmacokinetic data, in order to minimise exposure. For similar reasons, it was recommended that the treatment duration should be as short as possible.

The new measures will now be implemented according to an agreed timetable in the individual EU countries. A letter explaining the changes will be sent to healthcare professionals. The SmPC and package leaflet of the affected medicines will be amended accordingly.

More about the medicine

Hydroxyzine-containing medicines have been authorised by national procedures in 22 Member States of the EU (Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Malta, Netherlands, Poland, Portugal, Slovakia, Spain, Sweden and United Kingdom) plus Norway and Iceland.

They are used generally by mouth or sometimes by injection. These medicines are available under various trade names including Atarax. Approved uses vary between countries, but may include treatment of anxiety disorders, relief of pruritus (itching) including that due to urticaria, premedication before surgery, and treatment of sleep disorders.

More about the procedure

The review of hydroxyzine was initiated on 25 April 2014 at the request of Hungary, under Article 31 of Directive 2001/83/EC.

The review was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations. As hydroxyzine-containing medicines are all authorised nationally, the PRAC recommendation was forwarded to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), for a position. The CMDh is a regulatory body representing EU Member States plus Iceland, Liechtenstein and Norway, and is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

On 25 March 2015 the CMDh adopted its position by consensus, so the measures recommended by the PRAC will be directly implemented by the Member States where the medicines are authorised, according to an agreed timetable.

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