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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Hydroxyzine-containing medicinal products

INN: hydroxyzine

Procedure number: EMEA/H/A-31/1400

Note

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. Background information on the procedure

On 25 April 2014, further to evaluation of data resulting from pharmacovigilance activities, the Hungarian Competent Authority (Gyógyszerészeti és Egészségügyi Minőség- és Szervezetfejlesztési Intézet) informed the European Medicines Agency, pursuant to Article 31 of Directive 2001/83/EC of a request to review the benefit-risk balance of hydroxyzine-containing products taking into account the potential risk for developing QT interval prolongation and Torsades de Pointes after exposure to hydroxyzine, and that it was in the interest of the European Union (EU) to refer the matter to the PRAC.

2. Scientific discussion

2.1. Introduction

Hydroxyzine is a first generation antihistamine with a large spectrum of action first authorised in the 1950s and available in 24 EEA member states as film-coated tablets, oral syrup, a gel or a solution for injection. 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 the outcome of a benefit-risk assessment of hydroxyzine carried out by UCB, the marketing authorisation holder (MAH) of the originator product in response to results obtained from non-clinical studies and pharmacovigilance data received on the pro-arrhythmogenic potential of hydroxyzine. In July 2011, a cumulative safety review of reports describing QT interval prolongation and/or Torsades de Pointes (TdP) in patients treated with hydroxyzine conducted by the MAH concluded that there is a potential risk for developing QT interval prolongation and/or TdP after exposure to hydroxyzine, leading to a contraindication in patients with known prolonged QT interval. In September 2011, a publication (Lee et al., 2011) pointed out that hydroxyzine could block hERG channels and prolong the cardiac action potential duration at concentrations lower than previously shown. These results were conflicting with results previously obtained (Sakaguchi et al., 2008) and in order to clarify discrepancies in the literature, the originator MAH conducted a GLP hERG study (NCD2366, 2013) and a cardiac channelogram, the results of which indicated an acceptable safety margin regarding pro-arrhythmia risk.

Although the potential risk of QT interval prolongation with hydroxyzine was already known and reflected in the product information of some nationally-approved products, the Hungarian competent authority therefore considered it 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 issued a list of questions and a list of outstanding issues to the MAHs and also consulted the EMA Paediatric Committee (PDCO) and the Geriatric Expert Group (GEG). In addition, the PRAC reviewed the results of a EudraVigilance analysis on case reports of QT interval prolongation where hydroxyzine is a suspect or interacting substance as well as data generated from a call to European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) for information and data for hydroxyzine and its pro-arrhythmogenic potential. This report presents a summary of the relevant data for the procedure.

At the start of the procedure, the PRAC reviewed the current product information (PI) of the nationally-approved products, where provided by the MAHs and noted the wide range of indications approved, including preoperative sedation, the treatment of anxiety disorders, skin conditions such as pruritus, dermatitis or urticaria, and the treatment of sleep disorders. The maximum daily dose ranged from 75 mg to 400 mg, with the majority of member states having a maximum daily dose of 300 mg. Regarding the treatment duration, the PIs either lacked any specifics regarding treatment duration or included a statement that the duration of treatment should be based on the individual patient's response and should therefore be determined by the treating physician. Most PIs referred to the paediatric population, but with varying upper and lower age limits and without any information on the maximum dose. Many but not all products were contraindicated in patients with pre-existing prolonged QT interval together with warnings and precautions for patients with a known risk factor to cardiac arrhythmia, including electrolytes imbalance (hypokalaemia, hypomagnesaemia), who have pre-existing heart disease, or who are concomitantly treated with other potentially arrhythmogenic drugs. Similarly, the relevant adverse drug reactions QT interval prolongation and TdP were generally present in most member states.

2.2. Efficacy data

Data on efficacy was submitted by the MAHs and reviewed by the PRAC.

2.2.1. Evidence of efficacy

Treatment of anxiety

The PRAC noted that the anxiolytic effect of hydroxyzine in adults was assessed by a number of placebo-controlled clinical trials carried out between 1956-1998 and more recently by a randomised, double-blind, parallel group, multicentre study (Hindmarch et al., 2001) sponsored by the originator MAH. This study enrolled 80 patients aged 18-65 and the primary objective of the study was to compare the effects of hydroxyzine with lorazepam on the cognitive functions of out-patients suffering from generalised anxiety disorder (GAD) without associated severe depressive symptoms. Although the PRAC noted that the studied indication differed from the "symptomatic treatment of anxiety" indication approved for hydroxyzine and that lorazepam is not indicated in GAD per se, the study revealed no difference in efficacy of hydroxyzine and lorazepam as measured by the primary outcome variable at daily dosage of 50mg of hydroxyzine. Regarding paediatric patients, no clinical trial data or recommendations in guidelines were identified, although it was noted that anxiety problems affects many children and adolescents in western countries, 2.9-4.6% of children and adolescents in the USA affected by GAD (Hoge et al., 2004). The PRAC also reviewed a meta-analysis (Guaiana et al., 2010) which included five studies with a total of 884 participants. According to the authors, hydroxyzine was shown to be more effective than placebo for generalised anxiety disorder and also acceptable and tolerable. Compared to other anxiolytic agents (benzodiazepines and buspirone), hydroxyzine was equivalent in terms of efficacy, acceptability and tolerability. In terms of side effects, hydroxyzine was associated with a higher rate of sleepiness/drowsiness than the active comparators. Finally hydroxyzine is the only first generation antihistamine used in the treatment of anxiety disorders and clinical studies indicate that hydroxyzine is not addictive and does not adversely affect memory and attention in this indication (De Brabander, 1990; Lednard, 1999), which is of relevance considering the risk of addiction associated with alternative therapies.

Treatment of sleep disorders in children

The sedative effect of hydroxyzine is considered to be well-known and well characterised. While considered as a potential adverse event in some indications, it is also considered to be a useful effect in the treatment of paediatric insomnia (Mindell et al., 2006). Sleep disorders are common in a number of forms in childhood and adolescence and hydroxyzine is known to be well tolerated in children, with sedation as the most frequent adverse event (Simons et al., 2002) and hydroxyzine had comparable somnolence rates to diphenhydramine in children aged from 6 to 12 years (Simons et al., 1996). In France, hydroxyzine was considered to fill an unmet medical need in the treatment of sleep onset insomnia and in the treatment of sleep maintenance (related to its 7-hour half-life elimination duration) in children, due to the suitable pharmacokinetic profile, the well-documented sedative effect in children, the documented efficacy in minor manifestations of anxiety, the existence of a formulation adapted for children and reassuring pharmacovigilance data (in particular a significant amount of data gathered in children). As a result, in the context of a 2003 national review by the French Health Agency of the efficacy and safety data on hydroxyzine, an extension of the indication was agreed in children older than 6 years as second-line treatment of sleep onset insomnia, despite the absence of clinical trials. Furthermore, according to the results of a survey (Owens et al., 2003) of community-based paediatricians in the United States (3424 physicians in 6 US cities) on the medication used in the treatment of paediatric insomnia, over-the-counter antihistamines were the most commonly reported non-prescription medication for sleep, used by more than two thirds of practitioners, varying from 34% to 58% depending on the age group.

Premedication in surgery

Regarding the indication premedication in surgery, the PRAC noted that clinical studies investigating hydroxyzine in premedication have been reviewed and discussed in a clinical expert opinion (Martini, 1984) commissioned by the originator MAH. In addition, a second clinical expert review (Niklson, 2002) covering the period 1985-2001 reviewed 72 published studies dealing with the use of hydroxyzine in the pre- and post-operative management of adult patients and treatment of children before dental interventions. The most relevant studies included 11 trials on the use of hydroxyzine monotherapy in adults patients undergoing surgical interventions, 3 comparative studies of sedative anxiolytic efficacy of hydroxyzine versus benzodiazepines, 11 published reports of the use of hydroxyzine in combination with other pre-medications, 12 published reports on hydroxyzine monotherapy in the premedication in children, usually dental interventions (9 double-blind studies but among them only one placebo-controlled study) and 19 published studies referring to the combined treatment of hydroxyzine with other drugs. The review concluded that with few exceptions, the published findings favoured the use of hydroxyzine as premedication, particularly in the combination with other drugs, due to desirable combination of its sedative-calming and somatic effects (prevention of nausea and vomiting, gastric secretion etc.). Also the findings in children show, almost without exception, beneficial effect of hydroxyzine in reducing agitation and uncooperative behaviour, which hampers, specifically, dental interventions.

A new study (N01108) was initiated in 2002 by the originator MAH and finalised in August 2008 with a clinical study report entitled *"A double-blind, placebo controlled, randomized, parallel groups, multicenter phase IV trial: Evaluation of the efficacy and of the safety of hydroxyzine dihydrochloride 100mg oral tablet (single dose) in treatment of preoperative anxiety on subjects undergoing a Premedication before general anaesthesia for ambulatory surgery".* This study included 300 adult subjects randomly assigned to one of the 2 treatment groups (152 on placebo and 148 on hydroxyzine). The efficacy results for the primary parameter failed to show a statistically significant reduction of preoperative anxiety with hydroxyzine compared to placebo, however, a significant

difference in favour of hydroxyzine was observed in the secondary efficacy parameters: the anxiety visual analogue scale (p=0.049) and the 5- point anxiety scale (p=0.008, Wilcoxon rank sum test), which were evaluated by the subject and investigator, respectively. Furthermore, significantly more subjects in the hydroxyzine group exhibited a mild level of sedation compared to the placebo group (45.9% versus 15.1%). Based on these sedation results, hydroxyzine was considered as a potential alternative anxiolytic premedication option. Moreover, no safety issues were identified from adverse events, physical examination findings or vital signs.

In addition, a recent randomised double-blind parallel group clinical trial (Köner et al., 2011) studied the addition of hydroxyzine to midazolam for sedation before anaesthesia induction in 84 children 1-7 years of age. The objective was to reduce emergence agitation, which was evaluated with the PAED score (Paediatric Anesthesia Emergence Delirium). The median PAED score of the midazolam group (15) was higher than that of the midazolam and hydroxyzine group (11; $P < 0.001$) and the number of children with PAED scores above 16 was also higher in midazolam group (n = 16) compared to the midazolam and hydroxyzine group (n = 2; $P < 0.001$). The study was considered to show the efficacy of hydroxyzine to induce sedation during general anaesthesia and that the midazolam plus hydroxyzine provided a better premedication efficacy compared to midazolam alone. A further single-blinded randomised clinical trial study (Fallah et al., 2014) compared the efficacy of hydroxyzine to midazolam for sedation prior to MRI in infant aged less than 8 year-old. Sixty children (28 girls and 32 boys with the mean age of 2.72±1.58 years) were studied. Adequate sedation and completion of MRI were achieved in 76.7% of hydroxyzine group. The two treatment arms showed equal effectiveness in paediatric MRI sedation but the hydroxyzine treatment was found to be safer.

Skin disorders (such as pruritus, urticaria, dermatitis)

No clinical trials were identified in the pruritus indication; however the efficacy of hydroxyzine in the treatment of pruritus caused by various allergens has been investigated in human pharmacology studies in adults and children. Using objective measures of the extent of cutaneous reactions induced by various allergens, hydroxyzine was shown to be more effective than a number of other antihistamine drugs. In addition, the high efficacy of hydroxyzine was accompanied by an acceptable level of tolerability and sedation is the most common adverse reaction. In this context, a controlled study (Rhoades et al., 1975) demonstrated that hydroxyzine resulted in a 750-fold increase in the dose of histamine required to elicit itch. This compared to five-fold increase following both cyproheptadine and placebo and ten-fold increase following diphenhydramine. Similarly, hydroxyzine was significantly more effective in reducing histamine-induced pruritus than neuroleptics (Arnold et al., 1979). Finally, a pharmacokinetic study (Simons, 1984) in 12 children with atopic dermatitis (4 males, 8 females), aged from 1-14.4 years demonstrated that both single (0.7mg/kg) and multiple doses (0.7-1.4mg/kg, three times a day) of hydroxyzine had a benefit in alleviating pruritus. These observations are supported by the European Dermatology Forum (EDF) Guidelines on Chronic Pruritus (Weisshaar et al., 2012) which proposes antihistamines as the first-line treatment for pruritus associated with different systemic diseases. In particular, hydroxyzine is the most commonly used first generation antihistamine showing sedative, anxiolytic and antipruritic activities in adults and children. In some member states, hydroxyzine is indicated in urticaria.

Because urticaria is characterised by well-circumscribed areas of erythema and oedema involving the dermis and epidermis that are very pruritic, the evidence of benefit shown in pruritus can be considered to relevant also to urticaria. In the absence of recent clinical studies with hydroxyzine in histamine-mediated pruritus, the PRAC reviewed the latest updated guidelines and noted that the EAAC/GA^{2}LEN/EDF/WAO guidelines updated in 2014 (Zuberbier et al., 2014) on chronic urticaria and chronic pruritus state that sedating antihistamines can be recommended at night time for sleep

improvement and that hydroxyzine is the first choice of the majority of physicians to control chronic pruritus but its sedative effect may contraindicate its use in the elderly. It was also noted that the American Academy of Allergy, Asthma & Immunology (Bernstein, 2014 - The diagnosis and management of acute and chronic urticaria: 2014 update) recommends antihistamines as first-line therapy with use of second-generation antihistamines to avoid sedative effect and impaired motor skills. In chronic urticaria, second-generation antihistamines are safe and effective therapies in patients with chronic urticaria and are considered first-line agents and first-generation antihistamines can be considered in patients who do not achieve control of their condition with a higher dose of second-generation antihistamines.

2.2.2. Overall discussion on efficacy

In conclusion, the PRAC considered that the available efficacy data did not raise any new concerns.

2.3. Safety data

The PRAC reviewed all available safety information, in particular data related to QT interval prolongation associated with the use of hydroxyzine, including information provided by the MAHs.

2.3.1. Non-clinical data

The main non-clinical evidence consisted of a number of studies of hydroxyzine's human Ether-à-go-go-Related Gene (hERG) current inhibitory effects in hERG-transfected cells, and its potential pro-arrhythmic risk. The first study investigated the blockade in vitro of the hERG channel with a heterologous expression in the Xenopus oocytes. The concentration producing a 50% decrease (IC50) in the current generated on activation of the patched cell was 10.7 µM (Taglialatela et al., 2000). A second study, performed in 2008 using a patch-clamp technique at 37°C with hERG-transfected Chinese Hamster Ovary (CHO) cells observed an IC50=0.62µM (Sakaguchi et al., 2008). Two further studies using human embryonic kidney 293 (HEK293) cells provided IC50 values of 0.16 µM at room temperature (Lee et al., 2011) and 0.36µM (n=4) at room temperature and 0.39µM (n=4) at 35°C (NCD2366, 2013).

The PRAC considered hERG patch-clamp assays to be the gold-standard method for the assessment of a drug's effect on the potassium channel function and QT interval in vitro (Murphy et al., 2006), although it was noted that limitations remain with regard to extrapolating non-clinical data to the clinical situation. Not all drugs causing TdP are potent hERG blockers, and hERG blockade is not necessarily associated with TdP (Yang et al., 2001). Also, there is no fixed relationship between the extent of QT interval prolongation and the risk of TdP (Gintant et al., 2008). The PRAC also noted that hERG tests are very sensitive to the choice of cell material used and to temperature, voltage and other experimental conditions (Gintant et al., 2006; Hancox et al., 2008). The PRAC concluded that a dose-effect on hERG channel blockade could be observed and that the variability of the IC50 results (between 0.16 µM and 10.7 µM) could be attributed to different experimental conditions. hERG studies performed close to physiological temperature and with mammalian cells (CHO and HEK293) were therefore considered of most relevance while the IC50 estimated by Taglialatela et al. in Xenopus oocytes was disregarded as less suitable.

The PRAC also reviewed a non-GLP manual patch-clamp assay conducted on 7 human cardiac ion channels (study NCD2367), which showed that hydroxyzine blocked cardiac sodium channels in a concentration and state-dependent manner, with reported IC50 values of 0.32µM in the fast inactivated state, 5.8µM in the slow inactivated state, and 13.3µM in the resting state. Hydroxyzine

also concentration-dependently blocked other cardiac channels (calcium and non hERG potassium), although the impact of these different channels blockade on the QT interval prolongation is unclear. Study NCD2367 confirmed the multi-ion blocker effect of the hydroxyzine previously suspected in a dog Purkinje fibre study (RRLE00B0403, 2003), which was negative at 30 times the therapeutic free plasma concentration for a dose of 50 mg.

Based on the results of study NCD2366 (0.39µM in HEK293 cells at 35°C), the MAH calculated a Cardiac Safety Index (CSI) at the lowest therapeutic dose of 50mg hydroxyzine of 39 (CSI=hERG IC50 [0.39µM]/free Cmax at a dose of 0.7mg/kg [0.01µM]), which is above the commonly recommended ratio of 30 to ensure an acceptable safety margin regarding pro-arrhythmia risk, as proposed in a review investigating the relative value of pre-clinical cardiac electrophysiology data (in vitro and in vivo) for predicting the risk of TdP in clinical use (Redfern et al., 2003).

The PRAC reviewed the CSI calculation carried out by the MAH, noting that the therapeutic free plasma concentration (free Cmax) value of 0.01µM used by the MAH was calculated from the healthy subjects in the clinical study performed by Simons et al in 1984, following a 0.7 mg/kg single dose, which correspond to a 50 mg dose in a 70 kg patient. However, the PRAC noted that the CSI decreases with higher free Cmax and with lower IC50. Hence, if the IC50 value from the Lee study is considered, the CSI calculation provided by the MAH underestimates the CSI. Similarly, the CSI is underestimated if a higher dose than 0.7 mg/kg is considered. In addition, the MAH did not provide human pharmacokinetic data at higher dosage and as a result, the extrapolation to the 100 mg dose was not considered justified.

Based on the available non-clinical data, the PRAC therefore concluded that hydroxyzine has the potential to block hERG channels and other types of cardiac channels with an observed dose effect, which results in a potential risk of QT interval prolongation and cardiac arrhythmia events. Although no effect on QT interval prolongation has been observed during in vivo pre-clinical studies, these data are not necessarily applicable to human and no thorough QT study has been performed in human.

Concept of repolarisation reserve

The PRAC noted that published data indicates that even though the ability of a particular drug to block the IKr potassium channel is confirmed, this does not translate necessarily into a real and significant risk of TdP, because several factors are involved, as presented in the concept of repolarisation reserve. This concept proposes that when the repolarisation reserve is reduced, it is likely that further added stress, e.g., IKr blocking drug or a subtle genetic defect, is sufficient to precipitate a TdP in individual patients. In summary, loss of one component ordinarily would not lead to failure of repolarisation (i.e. marked QT interval prolongation), instead 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 (Roden, 1998). Factors reducing the repolarisation reserve can therefore be identified as risk factors for the induction of QT interval prolongation. The PRAC therefore concluded that these risk factors are key in the evaluation and prevention of the risk of cardiac electrophysiological disturbances such as QT interval prolongation and TdP in humans.

2.3.2. Clinical data

The originator MAH stated that the risk of QT interval prolongation and TdP was not identified during the clinical development of hydroxyzine and that no thorough QT study was therefore performed. However, the results of the previously discussed study N01108, performed in 300 subjects, were considered of relevance for this assessment. The PRAC focused its review on the slight QT interval prolongation effect observed (using the ICH E14 guideline definition of a QT interval prolongation as a

baseline change above 30 ms) to identify risk factors for QT interval prolongation. In the placebo group (n=152), 10 patients had a change from baseline between 30 and 60 ms and one patient presented a change from baseline higher than 60 ms. In the hydroxyzine group (n=148), 14 subjects had a change from baseline between 30 and 60 ms and were considered to have a potential risk factor for risk of QT interval prolongation and TdP due to relevant medical history, concomitant medication potentially associated with the induction of prolongation of QT interval, polymedication or had undergone voluntary abortion (oxytocin, which has been associated with QT interval prolongation, is usually used for voluntary abortion). The patients who experienced a QT interval prolongation were between 19.1 and 64 year-old with a median at 31.7 year-old. Having reviewed the case reports and noted the identified risk factors, the PRAC considered that the short time to onset of QT prolongation strongly suggests a causal relationship with hydroxyzine. Only one case did not clearly identify a risk factor, in the others a risk factor for QT interval prolongation, especially concomitant medication known to prolong the QT interval was identified. The PRAC therefore concluded that the at-risk population can clearly be identified as the patients with predisposing factors for QT interval prolongation and that appropriate risk minimisation measures should be implemented in order to address this issue. The PRAC considered this finding to be in line with the concept of repolarisation reserve.

2.3.3. Post-marketing data

A review of post-marketing data was carried and the PRAC reviewed all cases reported in the broad standardised MedDRA query (SMQ) TdP/QT prolongation with hydroxyzine, with a data-lock point of 31 May 2014. All were spontaneous reports with 55% reported by health care professionals. A total of 190 cases (of which 64 cases were fatal) with 226 events of the 20 preferred terms belonging to the broad SMQ for TdP/QT prolongation were retrieved from the safety database. From these 190 broad SMQ cases, 42 were listed with the narrow SMQs TdP (16 cases), QT prolongation (21 cases) and ventricular tachycardia (5 cases). Descriptions were provided for all relevant cases and the PRAC noted that all cases reported in narrow SMQs included risk factors for QT interval prolongation and TdP (cardiac disorders, hypokalaemia, long QT syndrome, bradycardia, concomitant drugs which are known to prolong the QT interval). Of these 42 cases, 10 cases were reported after a dose ≤ 100 mg/day, 4 cases were reported after a dose > 100 to ≤ 300 mg/day, 8 cases were reported after a dose >300 mg/day, 11 cases were reported after an intake of hydroxyzine with unknown dosage and nine cases were reported in the pre-medication indication. The PRAC noted that the cases involved individuals between 15 and 89 year-old with a median at 50 years and most of these are female (62%). These data are in agreement with the suggestion that females are more at risk of QT interval prolongation. Only one of the cases for which the age was specified is reported in a patient under 18 year-old (15 year-old). This non-fatal case was reported in a context of intentional overdose. No conclusion on the treatment indication could be drawn given the number of cases in which the indication was not reported and due to the lack of exposure data by indications. Only 9 cases are reported in the premedication indication. For 7 cases a voluntary intoxication is reported. The time to onset (TTO) is specified in 50% of cases and for these cases the median TTO is 2 days. This TTO may suppose a relationship with the drug for the risks of QT interval prolongation, TdP or ventricular tachycardia.

Of the 64 fatal cases reported, 6 cases were in narrow SMQs. Excluding a large number of reports (39 cases, 61%) describing suicide attempts (including 36 poorly documented literature cases of voluntary intoxication with many other concomitant drugs, reported from 3 publications), the remaining 25 fatal cases included 4 poorly documented cases and 21 cases with at least one risk factor for TdP and/or QT interval prolongation (cardiac disorders, hypokalaemia, long QT interval syndrome, bradycardia, concomitant drugs which are known to prolonged QT interval and sometimes with overdose). Of these, 10 cases (~40%) had a TTO ≤ 2 days, 9 cases (~36%) had a TTO > 2 days and 6 cases (~24%) did

not report a TTO. The dose was reported in 15 of the 64 cases: 10 cases with a dose ≤100 mg, 3 cases with a dose >100 - ≤300 mg and 2 cases with a dose >300 mg. In most cases, hydroxyzine seems to have been another contributor to the event on top of other already known risk factors. The involved individuals were between 2.9 and 87 years of age with a median at 41.5 years and, where age was reported with an equal gender distribution. Four of the cases for which the age was specified are reported in patients under 18 year-old (30 months, 6, 13 and 16 year-old). Other cause of death is identified in these 4 children cases (infection, tachycardia and arterial hypertension in a child with polymedication, accidental exposure to methadone, intentional overdose). The TTO was specified in only 27% of cases and for these cases the median TTO is 3 days.

Regarding the 90 cases remaining after having removed narrow SMQs and fatal cases from the total 190 broad SMQ cases, 7 cases reported a preferred term that may be potentially related to the adverse events of interest, including 3 cases of ventricular fibrillation, 1 case of ventricular arrhythmia, 1 case of cardiac fibrillation, 1 case of electrocardiogram repolarisation abnormality and 1 poorly documented case of electrocardiogram U-wave abnormality. The PRAC noted that possible confounding factors were present in 5 cases (general anaesthesia, chest discomfort before hydroxyzine administration, negative dechallenge, medical history of multiple supraventricular extrasystoles, cannabis) including one case reported in a patient under 18 year-old. One case was poorly documented and little information was provided for the case of ventricular arrhythmia. The PRAC therefore considered that no additional evidence could be obtained from these cases. The other cases included 11 cases of cardiac arrest, 9 cases of cardiorespiratory arrest, 49 cases of loss of consciousness and 14 cases of syncope. In many of these cases there was no evidence of the occurrence of the event of interest QT prolonged and a number of cases presented other risk factors related to QT interval prolongation.

Eight cases of positive dechallenge for hydroxyzine were also retrieved using narrow SMQs in individuals between 34 and 89 years of age. Several indications were involved (urticaria and pruritus in 1 case, depression in 1 case, drug allergy in 1 case, premedication in 1 case, and not reported in 4 cases) but all eight cases presented clear risk factors which could explain the onset of the event following the administration of hydroxyzine, including a relevant medical cardiac history and/or concomitant medications associated with an increased risk of QT interval prolongation. All cases followed the discontinuation of multiple drugs, including six cases involving drugs that are known to induce QT interval prolongation/TdP. Three reports described corrective interventions that could have had a relevant contribution for the resolution of the events, including the placement of an implantable pacemaker. Some cases were reported with a concomitant medication known to inhibit the CYP3A4 enzyme. As hydroxyzine is metabolised by this cytochrome, this interaction could potentially be associated with an increased risk of QT interval prolongation and TdP. The PRAC concluded that a causal relationship between the discontinuation of hydroxyzine and the positive outcome was only confirmed for one case, while all patients had risk factors such as concomitant medication known to prolong the QT interval, cardiac disease or a genetic hERG mutation. Although hERG channels blockage is usually dose dependent, no clear dose effect was observed.

The PRAC also carried out a targeted review of all cases reported with a hydroxyzine dose equal or lower than 100 mg to quantify and discuss the risk of QT interval prolongation/ TdP associated with the use of this dose. Of the 190 total cases, 74 cases (39%) reported a dosage ≤100mg/daily, in patients aged between 5 months and 94 years. Five cases involved children and the reported time to onset ranged from a few minutes to 6 years. Cases were reported in all indications, with 36 cases in approved indications (22 of which were in the premedication indication), 18 cases in other indications and 20 cases in an unspecified indication. According to the MAH, the 22 cases in premedication represent a potential for risk factors for the events in question as the patients may have an altered

medical condition before the administration of hydroxyzine and these cases were therefore reviewed separately.

The 22 cases in the premedication indication included 7 cases describing specifically the events of Electrocardiogram QT prolonged (2 cases), TdP (2), Ventricular Tachycardia (2) and TdP/Ventricular Tachycardia (1). The cases described at least 2 risk factors, including medical history/ ongoing medical conditions associated with cardiovascular disorders, and concomitant medications associated with QT interval prolongation or associated inhibition of CYP3A4. It was noted that for the 7 key cases, all patients experienced the reported events in a short period after the intake of hydroxyzine (4 cases within between 30 minutes and a few hours after the intake of hydroxyzine) and 3 cases between 1 and 4 days after the intake of hydroxyzine. All cases reported relevant medical history associated with cardiac disorders or electrolyte imbalance and subsequently with the risk of TdP/QT interval prolongation. The 52 cases not in the premedication indication included 6 cases of Electrocardiogram QT prolonged, 2 cases of TdP and 3 cases of Electrocardiogram QT prolonged/ TdP and were all medically confirmed. The analysis of the risk factors demonstrated that all patients who experienced the events TdP / QT interval prolongation reported at least 2 risk factors among medical history/ ongoing medical conditions associated with cardiovascular disorders, reported concomitant medications associated with QT interval prolongation, genetic mutation related to a cardiac channel, elderly age, polymedication and female gender.

Conclusions on post-marketing data

In conclusion, having reviewed the post-marketing data, the PRAC considered that the post-marketing cases of QT interval prolongation, TdP and ventricular tachycardia confirm the findings of the hERG studies suggesting that hydroxyzine blocks hERG channels. No difference in the risk of QT interval prolongation could be observed based on the indication or the age of the subject. In addition, despite the pre-clinical data suggesting a dose effect, no such dose effect was observed in the post-marketing data. In fact, the data revealed that the risk of QT interval prolongation is not excluded with a dose of 100 mg and cases were reported with a dose lower or equal dose to 100 mg although causality with hydroxyzine was unclear. The PRAC further noted that all patients who experienced narrow SMQs events TdP/QT interval prolongation after an intake of hydroxyzine ≤100mg/daily presented potentially risk factors for QT interval prolongation in the form of multiple risk factors (such as cardiac medical history and concomitant medications associated with QT interval prolongation, electrolytes imbalance). This increased the risk for the patient to experience an adverse event related to TdP, which is in line with the repolarisation reserve concept.

2.3.4. Consultations and other data

Consultation of the Paediatric Committee (PDCO)

The PRAC requested the Paediatric Committee (PDCO) to give its opinion on the efficacy and safety of hydroxyzine in the paediatric population, specifically on the therapeutic role of hydroxyzine in the approved indications, on off-label use and on alternative therapeutic options. The view of the PDCO was that in European clinical practice, hydroxyzine is authorised in children but is not widely used. The paediatric indications are country specific, with high heterogeneity and variability in terms of use by paediatricians. Very little evidence of off-label use was identified. The PDCO was of the view that hydroxyzine is not a high priority need medicine in the paediatric population and that therapeutic alternatives are available, however these are country-specific and likely to have different mechanisms of action and different pharmacological effects and potential safety risks.

Consultation of the Geriatric Expert Group (GEG)

The PRAC also consulted the Geriatric Expert Group (GEG) on the use of hydroxyzine in elderly. The GEG was of the view that the use of hydroxyzine in the elderly patient population is not recommended, taking into account the mechanism of action of hydroxyzine and the available alternative therapeutic options available. Taking into consideration a number of factors, such as changes in the pharmacokinetics of hydroxyzine in the elderly, resulting in a higher volume of distribution (from 16 L/Kg in the young to 22.5 L/Kg in the older population) which, in turn, leads to an prolonged t1/2 (29h) as well as the safety profile of the medicine and the potential concomitant use of QT interval prolonging drugs, the presence of an active metabolite (cetirizine), a decreased renal function in this population and the availability of safer alternatives, the GEG was of the opinion that the daily dose in the elderly should be reduced to 25mg, with a maximum daily dose of 50mg. The GEG also considered that the addition of a warning statement to the product information, while potentially useful, must be accompanied by other measures, such as its inclusion in computerised prescribing systems, and the performance of a drug utilisation study. In conclusion, the GEG recommended that hydroxyzine should be contraindicated in the elderly with the potential exception of the treatment of pruritus in urticaria, when sedation is needed and when other alternatives have been considered and deemed unsuitable. The GEG also considered that of all indications, anxiety is the most concerning due to its high prevalence among the elderly and, therefore, the heightened risk of coadministration with other QT-prolonging medicines.

The PRAC reviewed the GEG position but noted that the available alternatives by indications in this population were not discussed, especially in the anxiety indication and that some alternative treatments may not represent safer treatment options in this population. The PRAC also noted the proposed recommended daily dose (25 mg with the option to increase to a maximum of 50mg), which is in line with the originator MAH recommendation to start with half of the recommended adult dose. Hydroxyzine half-life in adults is approximately 14 hours and the elimination half-life of hydroxyzine is prolonged to 29 hours in elderly (Simons et al., 1989). As a result, a maximum daily dose in elderly of half the maximum daily dose in adults is appropriate. The PRAC also considered that a warning regarding the use in elderly should be added in section 4.4 of the SmPC due to the greater risk of adverse events especially due to the anticholinergic effect and to the decrease of hydroxyzine elimination in this population as compared to adults.

EMA EudraVigilance analysis

The EMA carried out an analysis of EudraVigilance case reports of QT interval prolongation where hydroxyzine is a suspect or interacting substance. All cases mentioning hydroxyzine for the broad SMQ “Torsades de Pointes/QT prolongation” up until the 31 July 2014 were retrieved. Summary tabulations of counts of case reports stratified by individual MedDRA preferred terms within the SMQ and by age were produced and for the purpose of individual case review, only fatal cases were retained. Considering that the broad SMQ “Torsades de Pointes/QT prolongation” includes disorders that may be the result of several different aetiologies (e.g. cardiac arrest following anaphylaxis), the individual case reports were clinically reviewed to determine the primary cause of death. Cases where the fatal outcome was a result of disorders not considered directly related to TdP or QT interval prolongation were not presented. Cases due to intentional self-harm, misuse or abuse were excluded from the individual review of cases except if hydroxyzine was the only reported suspect drug.

A total of 369 case reports (including duplicates) were retrieved of which 213 were reported as fatal cases. The most commonly reported MedDRA preferred terms among the cases retrieved were cardiac arrest (90) and cardio-respiratory arrest (95), which relate to disorders that have different aetiologies (e.g. pulmonary embolism, anaphylaxis, etc.), hence may not necessarily imply that they are a result of rate and rhythm disorder. From the 213 fatal cases, 80 unique individual case safety reports were

identified and 39 of these were selected for individual review, including one suicide report involving hydroxyzine only. 5 cases were considered to have information directly related to QT interval prolongation, TdP or ventricular fibrillation, while the remaining cases, although describing cases with fatal cardiac outcomes, were considered as not presenting information that could indicate a QT interval prolongation mechanism underpinning the adverse reaction. A review of the 5 cases revealed potential alternative causes and risk factors for QT interval prolongation, TdP or ventricular fibrillation (underlying cardiovascular disease, other co-medication as clomipramine, hydroxychloroquine, risperidone or saquinavir, diseases and co-morbidities). The PRAC therefore considered that this analysis did not identify any additional information relevant to the procedure.

Data obtained through ENCePP

In the context of this review, a call was issued to the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) for relevant information and data for hydroxyzine and its pro-arrhythmogenic potential. In response, a preliminary study report was submitted with a descriptive analysis of QT interval prolongation in patients ≥ 65 years-old treated with hydroxyzine who attended an emergency department at the Pisa University Hospital in Italy. These data was extracted from the ANCESTRAL database which is a programme of pharmacologic counselling for elderly patients referred to the emergency department. The programme started in May 2012 and is currently ongoing. Thirty four patients treated with hydroxyzine were identified (20 males and 14 females). The preliminary findings showed that 10 patients (9 males, 1 female) exposed for 2 weeks or longer (group 1) or < 2 weeks (group 2) presented with an abnormal QT interval (abnormal value : 451 – 500 ms for men and 471 – 500 ms for women). These 10 patients were at risk for QT interval prolongation either from concomitant disease or from concomitant drugs or both. No patient displayed a QT interval over 500 ms. The reported doses were between 12.5 mg and 25 mg per day although the maximum daily dose in Italy is 100 mg. A control group is in the process of being evaluated to assess the relative risk. Of note, prolonged QT interval in these patients had not been considered drug-related, since nobody had correlated the prolonged QT interval with any of the treatment taken by patients. In addition, an overview of five cases involving hydroxyzine reported to the Netherlands Pharmacovigilance Centre (Lareb) up to 20 July 2014 was also submitted. Four cases reported palpitations and one case reported bradycardia. The PRAC noted that none of these cases was serious and that two patients were also treated with beta-blockers and two cases were poorly documented. In addition, the reported preferred terms did not belong to the SMQ broad “Torsades de Pointes/QT prolongation”.

The PRAC did not consider that the information obtained through ENCePP raised any additional information relevant to the procedure.

2.3.5. Overall discussion on safety

Having reviewed all available safety data, including input from the PDCO and the GEG as well as pre-clinical, clinical and post-marketing safety data, the PRAC considered that there is evidence that hydroxyzine blocks hERG channels and is associated with a risk of QT interval prolongation and TdP. The risk did not differ between indications and no dose effect was observed, despite pre-clinical data suggesting that hydroxyzine has a dose-dependent hERG inhibitory effect. However, the data identified risk factors for QT interval prolongation in the form of risk factors such as cardiac medical history and concomitant medications associated with QT interval prolongation, electrolytes imbalance and the PRAC therefore reviewed possible risk minimisation measures which could be taken in order to minimise the risk of QT interval prolongation and TdP.

Regarding treatment duration, the PRAC considered that a short term treatment is associated with less risk of QT interval prolongation than a long term treatment as the occurrence of a risk factor for QT interval prolongation may be more frequent with long term use. The PRAC therefore recommended that the treatment duration should be as short as possible.

Regarding dosage, the PRAC noted that despite post-marketing data suggesting that the risk of QT interval prolongation in patients with risk factors hydroxyzine is not dose-dependent, hERG blockage appears to be concentration dependent and by extrapolation so does the risk for QT interval prolongation. The PRAC therefore considered it appropriate to recommend the use of hydroxyzine at the lowest effective dose as a risk minimisation measure. The PRAC also specified maximum daily doses in all populations.

The PRAC reviewed the posology with the aim of determining an appropriate maximum daily dose. A 100 mg dose of hydroxyzine was investigated in a number of trials, including study N01108 and publications by Schapira and al., 2004; Rickels et al., 1970, Goldberg et al., 1973 and Guaiana et al., 2010, which found the dose efficacious and well-tolerated. A 100 mg maximum daily dose is also recommended in a number of guidelines, such as the European Dermatology Forum (EDF) Guidelines on Chronic Pruritus (Weisshaar, 2012) and pruritus guidelines such as the EAAC/GA²LEN/EDF/WAO guidelines updated in 2014 (Zuberbier et al., 2014) and the American Academy of Allergy, Asthma & Immunology recommendation (Bernstein, 2014 - The diagnosis and management of acute and chronic urticaria: 2014 update). Overall, the PRAC was therefore of the opinion that the available evidence indicates that a maximum daily hydroxyzine dose of 100 mg is efficacious and well-tolerated in adults.

Regarding the maximum daily dose in children, the PRAC noted that hydroxyzine has a higher clearance in children (32.08 ± 11.05 ml/min/kg) compared to adults (9.78 ml/min/kg) (Simons et al., 1984). Meanwhile, the volume of distribution is considered to be equal across the two groups (18.5 ± 8.6 L/kg in children vs 16.0 ± 3.0 L/kg in adults). On the other hand, studies with hydroxyzine in a paediatric population, both with single and repeat dosing (Simons et al., 1984), have demonstrated that the half-life of hydroxyzine in plasma increases with age between 0-16 years. The half-life of the drug in adults, based upon multiple studies (Simons et al., 1984, Gengo et al., 1987; Simons et al., 1995; Salo et al.' 1986), is established at approximately 14 hours. Paediatric studies report a half-life of 4 hours in patients at 12 months of age and 11 hours in patients at 14 years of age. As a consequence, an increased dose is required in children to maintain plasma levels of drug at efficacious concentrations. The PRAC therefore considered that a doubled maximum daily dose in terms of mg/kg body weight in the paediatric population compared to adults to be supported by the available data. In line with the recommendation in adults, the PRAC recommended a maximum daily dose in paediatric patients of 2 mg/kg body weight for children up to 40 kg. The PRAC was also of the view that an appropriate measuring device should be made available for products with a paediatric formulation.

Regarding the maximum daily dose in the elderly, the PRAC noted while the hydroxyzine half-life in adults is approximately 14 hours, the elimination half-life in the elderly is prolonged to 29 hours in elderly (Simons et al., 1989) and therefore determined that the maximum daily dose in the elderly should be half the maximum daily dose in adults.

The PRAC also considered that the use of hydroxyzine should be reduced in the at-risk populations for QT interval prolongation and TdP and that the risk factors should be clearly identified and mentioned in the product information in order to avoid concomitant risk factors. Based on the available data, the PRAC therefore 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 TdP.

The PRAC also noted that hydroxyzine is metabolised by alcohol dehydrogenase and CYP3A4/5, an increase in hydroxyzine blood concentrations may be expected when hydroxyzine is co-administered with drugs known to be potent inhibitors of these enzymes. Administration of a concomitant drug, inhibitor of alcohol dehydrogenase or CYP3A4/5, could therefore change the pharmacokinetics of hydroxyzine, increasing its plasma concentration and consequentially the potential block of the IKr potassium channel. However, little evidence was made available for review and given the uncertainty regarding this interaction, the PRAC agreed on a precautionary statement.

2.4. Changes to the product information

The PRAC revised section 4.2 to recommend that hydroxyzine should be used at the lowest effective dose and for the shortest possible duration. The PRAC also revised the recommendation on the maximum daily dose in all populations, based on the available data, recommending the following maximum daily doses: 100 mg per day in adults, 2 mg/kg body weight per day in paediatric patients up to 40 kg and 50 mg per day in the elderly.

The PRAC also considered that the use of 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 TdP.

The PRAC further revised section 4.4 to reflect the above information in order to reinforce the message. In addition, information was added to advise patients to seek medical attention in case of signs or symptoms of cardiac arrhythmia and to promptly report any cardiac symptoms. A statement that the use of hydroxyzine in elderly patients is not recommended because of a decrease of hydroxyzine elimination in this population as compared to adults and because of the greater risk of adverse reactions especially due to the anticholinergic effect was also added to this section.

The PRAC also revised section 4.5, as it was considered essential that the interactions at risk of QT interval prolongation, such as drugs known to prolong the QT interval are clearly mentioned in the SmPC and therefore listed the contraindicated associations, with examples. In addition, a precaution for use was added to mention the interaction with bradycardia or hypokalaemia-inducing drugs (bradycardia and hypokalaemia are well identified as risk factors for QT interval prolongation). The PRAC also agreed on a precautionary statement regarding the potential interaction with alcohol dehydrogenase and CYP3A4/5, to be added to section 4.5. In addition, ventricular arrhythmias (e.g. Torsades de Pointes) and QT interval prolongation were listed in section 4.8 as undesirable effect.

The package leaflet was revised accordingly.

2.5. Risk minimisation activities

The PRAC, having considered the data submitted in the application is of the opinion that in addition to the previously discussed changes to the product information, the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

- The Marketing Authorisations Holders of products which are approved in a paediatric indication shall ensure that an appropriate measuring device is made available when a paediatric formulation exists.

2.6. Pharmacovigilance activities

- The Marketing Authorisation Holders should assess the effectiveness of the risk minimisation measures. The risks of QT interval prolongation, Torsades de Pointes, ventricular arrhythmia, sudden death and cardiac arrest should continue to be closely monitored in periodic safety update reports (PSUR) and the PSUR frequency should be changed to 18 months.

2.7. Communication plan

As part of this referral procedure, the MAHs and the PRAC agreed the wording of a 'Direct healthcare professional' communication designed to inform prescribers of the risks associated with hydroxyzine and the amendments of the marketing authorisation, to be sent to relevant health care professionals according to the agreed communication plan.

2.8. Overall benefit-risk assessment

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.

3. Overall conclusion and grounds for the recommendation

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.