EU RISK MANAGEMENT PLAN (EU-RMP)

HYDROXYZINE 25 mg, scored film-coated tablets

Active substance(s) (INN or common name):	Hydroxyzine hydrochloride
Pharmaco-therapeutic group (ATC Code):	N05BB01, Anxiolytics
Name of Marketing Authorisation Holder or Applicant:	EQL Pharma AB
Number of medicinal products to which this RMP refers:	• 1
Product(s) concerned (brand name(s)):	Hydroxyzine EQL Pharma 25 mg film-coated tablets

Data lock point for this RMP: 31.03.2013

Version number: 1.1

Date of final sign off: 07.01.2014

EQL Pharma AB

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

The drug hydroxyzine is intended to be used for the symptomatic treatment of anxiety, agitation, urticaria and pruritus.

Anxiety means excessive worry where the person finds it difficult to control the worry. It is also associated with restlessness or feeling keyed up, being easily fatigued, difficulty concentrating, irritability, muscle tension and sleep disturbance. A study found that lifetime prevalence rates in the Western countries range from 13.6% to 28.8% for anxiety. Further studies in the United States have found a lifetime prevalence of anxiety of 5.1% to 11.9%. In general, anxiety disorders develop relatively early in life. In 80–90% of cases, the disorder manifests before the age of 35, and the time between 10 and 25 years seems to be a high-risk period for the development of anxiety disorders. Epidemiological research has revealed that comorbidity is very important in understanding the distribution of anxiety disorders (Baldwin D; Michael T; Eaton W).

Urticaria or pruritus, commonly known as ‘itch’ or ‘rash’, is a very common dermatological condition. It is the most impressive reactions of skin that is experienced by most people at some point in their lives. They are principally harmless, but can be particularly unpleasant and sometimes even painful. Data on the epidemiology of urticaria vary a great deal. Studies carried out more recently have shown a prevalence of 0.6 - 4.8% in German population. These considerable variations are probably due to geographical and methodical differences in the parameters of the studies. In total, prevalence of acute itch in general population is found to be 8.4% (Magerl M; Dalgard F).

VI.2.2 Summary of treatment benefits

In psychiatry, the anxiolytic efficacy of hydroxyzine has been confirmed by numerous open and controlled clinical studies in anxiety states. Numerous clinical trials in the 1960s and 1970s have attested to the anxiolytic efficacy of hydroxyzine and its beneficial effect on sleep, as well as in reducing stress and anxiety associated with coronary disease. Experience with hydroxyzine has also shown a lack of organ toxicity and an absence of dependency. Hydroxyzine showed both efficacy and safety in the treatment of generalised anxiety disorder and appears to be an effective alternative treatment to benzodiazepine prescription.

Hydroxyzine is also used as an adjunct to pre- and post-operative medication. Anaesthesia with sevoflurane leads to a high prevalence of emergence agitation in paediatric patients. The

incidence of sevoflurane-induced emergence agitation was significantly lower in children pre-medicated with a midazolam and hydroxyzine combination compared to those pre-medicated with midazolam only. Furthermore, the midazolam and hydroxyzine combination provided better premedication quality than midazolam alone.

Antihistamine effects (relief of allergies) of hydroxyzine have been demonstrated experimentally and confirmed clinically; it is highly effective in alleviating pruritus. The antipruritic effects of hydroxyzine were studied in 12 children with severe dermatitis, each given a single oral dose. Pruritis was significantly suppressed from 1 to 24 hours after the administration of the dose, with greater than 85% suppression from 2 to 12 hours. (Ferreri and Hantouche 1998, Guaiana et al 2010, Huh et al 2011, Lader and Scotto 1998, Llorca et al 2002, Köner et al 2011, Simons et al 1984b)

VI.2.3 Unknowns relating to treatment benefits

None currently

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Changes in Electrocardiogram (Cardiac dysrhythmias/ QT prolongation)	The drug is having potential to cause changes in electrocardiogram suggestive of abnormal heart rhythm. The QT wave of electrocardiogram is prolonged which can later lead to 'Torsade de pointes', a severe form of heart arrhythmia. In this condition, the heart beats very fast and without any proper rhythm. This is a life-threatening condition. Existing such abnormality, reduced heart rate or pre-existing cardiovascular conditions are risk factors for development of 'Torsade de pointes' (Yap YG).	The risk of serious adverse reactions can be reduced by monitoring for early symptoms. Caution is advised when treating patients with severe reduction in heart rate, cardiovascular disease and with a hereditary QT interval prolongation. Concomitant use with other antipsychotic medicinal products should be avoided. Caution is also required in patients with a predisposition to cardiac rhythm disturbances, including electrolyte disturbances (low potassium, low magnesium). Other treatments should be considered.
Convulsions	Involuntary motor activity including rare instances of tremor and convulsions has been reported with this drug,	Hydroxyzine should be administered with caution to patients with increased risk of

Risk	What is known	Preventability
	usually with doses considerably higher than those recommended. Younger children are more susceptible to side effects in relation to nervous system stimulation. Tremors are more frequently reported in children than in adults.	convulsions/tremors. The drug should be used as per dosage prescribed and recommended.
Anti-cholinergic effect	Anticholinergic effects are physical symptoms resulting from agents (e.g. medications) that counter the action of acetylcholine, a neurotransmitter (chemical within the nervous system) that is involved in many major bodily functions. These anticholinergic effects typically include constipation, dry mouth, blurred vision, dizziness, and slowing of urination. Hydroxyzine is known to cause these effects.	Due to potential anti-cholinergic effects, caution is required in the treatment of elderly patients, patients with glaucoma, urinary retention, reduced gastrointestinal motility, myasthenia gravis and dementia.
Changes in effect when taken with alcohol (Interaction with alcohol)	Alcohol, when taken along with Hydroxyzine, increases the effect of this drug. Hydroxyzine has moderate influence on the ability to drive and use machines. Patients should be warned that their ability to perform activities requiring mental alertness or physical coordination such as operating machinery or driving a vehicle may be impaired. Simultaneous use of hydroxyzine hydrochloride with alcohol or other central nervous system depressants should be avoided as this may aggravate these effects.	Concomitant use of Hydroxyzine and alcohol should be avoided.
Use in patients with moderate or severe renal impairment	In patients with renal impairment the time for elimination of the drug in the body is prolonged which will lead to an increased concentration. It was shown that the metabolism of the drug is altered in these patients	In order to avoid any important accumulation of the cetirizine metabolite following multiple doses of hydroxyzine, the daily dose of hydroxyzine should be reduced in subjects with impaired renal function.
Use in patients with hepatic impairment	In the patients with hepatic impairment, the time for elimination of the drug in the body is prolonged which will lead to an increased concentration. It was shown that the metabolism of the drug is altered in these patients	As hydroxyzine elimination is impaired in patients with hepatic dysfunction, daily dose or dose frequency should be reduced in patients with impaired liver function. In patients with hepatic impairment, it is recommended to reduce the daily dose by 33 %.
Use in elderly	In elderly patients the time for	In elderly patients, it is

Risk	What is known	Preventability
patients	elimination of the drug in the body is prolonged which will lead to an increased concentration. This might be due to decreased renal and hepatic function. For both patient groups (hepatic or renal impairment) it was shown that the metabolism of the drug is altered.	recommended to reduce the dose to 50% due to prolonged action, and the possible effect of age-related changes on pharmacologic functions, including hepatic metabolism and renal excretion. The duration of the treatment should be as short as possible. The results and need for treatment should be continuously assessed.
Use in patients with electrolyte imbalances	Caution is required in patients with a predisposition to cardiac dysrhythmias, including electrolyte disturbances (hypokalaemia, hypomagnesaemia), with existing cardiac disorders or who are concomitantly treated with a potentially arrhythmogenic drug. Other treatments should be considered.	Simultaneous use of active substances that may cause electrolyte disturbances, such as thiazide diuretics (hypokalaemia), should be avoided as they increase the risk of malignant arrhythmias.
Allergic reaction (Hypersensitivity)	Most allergic reactions are minor, such as rash or sneezing. The type of reaction depends on the person's immune system response, which is sometimes unpredictable. In rare cases, an allergic reaction can be life-threatening (known as anaphylaxis).	Previous allergic reaction to Hydroxyzine, cetirizine, other piperazine derivatives, aminophylline or ethylene-diamine or to any of the excipients should be discussed with a physician or pharmacist. The risk of serious adverse reactions can be mitigated by monitoring for early symptoms.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Stroke in patients having risk factors for stroke (Cerebrovascular events in patients with risk of stroke)	An approximately 3 times increased risk of stroke has been observed in clinical trials of some antipsychotics in patients with dementia. The underlying mechanism for this is unknown. No confirmed evidence has been generated, but an increased risk with hydroxyzine, other antipsychotics or other patient population cannot be excluded.

Missing information

Risk	What is known
Use in children under 5 years of age	Hydroxyzine EQL Pharma should not be used in paediatric patients under the age of 5 years.

VI.2.5 Summary of additional risk minimisation measures by safety concern

Not applicable. No additional risk minimisation measures are proposed for Hydroxyzine 25 mg film-coated tablets.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Table 1. Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.1	29/11/2013	Identified risks: - QT prolongation - Convulsions - Anticholinergic effect - Interaction with alcohol - Use in patients with moderate or severe renal impairment - Use in patients with hepatic impairment - Use in elderly patients - Use in patients with electrolyte imbalances - Hypersensitivity Potential risks: - Cerebrovascular events in patients with risk of stroke Missing information: - Use in children under 5 years of age	None