VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Hydroxyzine is indicated for symptomatic treatment of urticaria and pruritus and symptomatic treatment of anxiety in adults where no alternative medication is indicated. Hydroxyzine Orifarm is indicated in adults, adolescents and children of 5 years and above.

The listed indications are generally common.

The listed indications are not specific for any population or pattern.

VI.2.2 Summary of treatment benefits

The beneficial aspects of the proposed medicinal product (Hydroxyzine 10 mg and 25 mg tablets), and its place in the proposed indications, have been established in the many years of clinical use of the product and are supported by clinical data.

The SmPC proposed by the applicant takes the pharmacodynamic, pharmacokinetic, and clinical evidences into account, and it complies with the current knowledge about the active ingredient with regard to the proposed indications and with the reference product's SmPC.

In conclusion, the assessment of the available clinical evidence on the proposed medicinal product in terms of pharmacological and clinical documentation, favours the benefit of this medicinal product in the proposed indications with an acceptable level of safety and established efficacy.

VI.2.3 Unknowns relating to treatment benefits

None.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
• Allergic reactions (Hypersensitivity reactions)	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 ethylenediamine 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.
• Changes in electrocardiogram (Cardiac dysrhythmias/ QT prolongation)	The drug is having potential to cause changes in electro-cardiogram suggestive of abnormal heart rhythm. The QT wave of electro-cardiogram 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'.	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.
• 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, reduction of the dose should be considered.
• Use in elderly	In elderly patients the time for 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.	In elderly patients, it is recommended to reduce the initial 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

Risk	What is known	Preventability
		treatment should be continuously assessed.
• Convulsions	Involuntary motor activity including rare instances of tremor and convulsions has been reported with this drug, usually with doses considerably higher than those recommended. Younger children are more susceptible to side effects in relation to nervous system stimulation. Convulsions are more frequently reported in children than in adults.	Hydroxyzine should be administered with caution to patients with increased risk of convulsions/tremors. The drug should be used as per dosage prescribed and recommended.
• Anticholinergic 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 anticholinergic 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 to major 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 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 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 drug that can induce arrhythmias. 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.

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 Orifarm should not be used in children under the age of 5 years.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Hydroxyzine Orifarm can be found in the Hydroxyzine Orifarm's EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

None.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable as this is the initial risk management plan.