

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hydroxyzine Orifarm 10 mg film-coated tablets

Hydroxyzine Orifarm 25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet, 10 mg contains 10 mg hydroxyzine hydrochloride.

One film-coated tablet, 25 mg contains 25 mg hydroxyzine hydrochloride.

Excipients with known effect:

10 mg: Lactose monohydrate 56 mg

25 mg: Lactose monohydrate 140 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

10 mg: White to off-white, circular (diameter 5.3-5.7 mm, thickness 2.7-3.3 mm), biconvex film-coated tablets and plain on both sides.

25 mg: White to off-white, circular (diameter 7.8-8.2 mm, thickness 3.5-4.1 mm), biconvex film-coated tablets with breakline on one side. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hydroxyzine Orifarm is intended for:

- symptomatic treatment of anxiety in adults aged 18 years and above
- symptomatic treatment of pruritus in adults, adolescents and children aged 6 years and above.

4.2 Posology and method of administration

Posology

Hydroxyzine Orifarm should be used at the lowest effective dose and for the shortest possible duration.

All indications

Since the 10 mg tablet cannot be divided into two equal doses, other appropriate strengths and dosage forms containing hydroxyzine should be administered in case a dose below 10 mg are required. Other dosage forms containing hydroxyzine are recommended for patients who cannot swallow tablets.

Adults

- *For symptomatic treatment of anxiety in adults (≥ 18 years):*
50 mg/day divided in 3 single doses of 12.5 mg, 12.5 mg, 25 mg, where the highest dose can be taken in the evening. In more severe cases, doses up to 100 mg/day can be used. The maximum daily dose is 100 mg/day.
- *For symptomatic treatment of pruritus in adults (≥ 18 years):*
The starting dose is 25 mg in the evening (approximately one hour before bedtime) and later if necessary up to 25 mg in total 3-4 times a day. The maximum daily dose is 100 mg/day.

Special populations

The dose should be adjusted within the recommended dose range and in relation to the patient's response to treatment.

Pediatric population

- *For symptomatic treatment of pruritus in children and adolescents (≥ 6 years):*
1 mg/kg/day to 2 mg/kg/day in divided doses (see section 5.2). The maximum daily dose in children up to 40 kg in bodyweight is 2 mg/kg/day. The maximum daily dose in children with bodyweight of 40 kg or above is 100 mg/day.

Hydroxyzine Orifarm film-coated tablets are not recommended to children under 6 years of age since they may have difficulty swallowing tablets. The safety and efficacy of hydroxyzine in children under 12 months of age have not yet been established. No data are available.

Elderly

In the elderly, it is advised to start with half the recommended dose due to the prolonged action. The lowest possible dose should be selected in the treatment of elderly patients. The maximum daily dose in elderly is 50 mg/day (see section 4.4). The results and need for treatment should be continuously assessed.

Patients with renal impairment

Caution is advised in patients with renal impairment and dose reduction should be considered. See table below and adjust the dose accordingly.

Dose adjustments for adult patients with renal impairment:

Group	eGFR (mL/min)	Percentage of recommended dose
Mild renal impairment	60-<90	100%
Moderate renal impairment	30-<60	50%
Severe renal impairment	15-<30	25%
Terminal renal failure (ESRD)	<15	25% 3 times per week

The dose reductions aim to avoid overexposure to the antipruritic metabolite cetirizine. The anxiolytic effect mediated by hydroxyzine can be affected by dose reduction. Individual evaluation is recommended after dose reduction.

Patients with hepatic impairment

Caution is required in patients with hepatic impairment, and a reduction of the dose should be considered.

Method of administration

The tablets should be swallowed with a sufficient amount of water. The tablets can be taken with or without food.

4.3 Contraindications

Hydroxyzine Orifarm should not be used in patients with:

- Hypersensitivity to the active substance, cetirizine, other piperazine derivatives, aminophylline, ethylenediamine or any of the excipients listed in section 6.1.
- Porphyria.
- Pregnancy and breast-feeding (see section 4.6).
- Patients with a known acquired or congenital QT interval prolongation.
- 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 drugs known to prolong the QT interval and/or induce Torsade de Pointes (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Hydroxyzine Orifarm should be administered with caution to patients with increased risk of convulsions. Younger children are more susceptible to side effects in relation to CNS stimulation (see section 4.8). Convulsions are more frequently reported in children than in adults.

Due to potential anticholinergic effects, caution is required in the treatment of:

- elderly patients
- patients with glaucoma
- urinary retention
- reduced gastrointestinal motility
- myasthenia gravis
- dementia

Cardiovascular effects

Hydroxyzine has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been cases of QT interval prolongation and torsade de pointes in patients taking hydroxyzine. Most of these patients had other risk factors, electrolyte abnormalities and concomitant treatment that may have been contributory (see section 4.8).

Hydroxyzine should be used at the lowest effective dose and for the shortest possible duration.

Treatment with hydroxyzine should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should seek immediate medical attention.

Patients should be advised to promptly report any cardiac symptoms.

An approximately 3 times increased risk of cerebrovascular events have been observed in randomised, placebo-controlled clinical trials of some atypical antipsychotics in patients with dementia. The underlying mechanism for this is unknown. An increased risk with other antipsychotics or other patient population cannot be excluded. Administer hydroxyzine hydrochloride with caution in patients with a risk of stroke.

Hydroxyzine is not recommended in elderly patients because of a decrease of hydroxyzine elimination in this population as compared to adults and the greater risk of adverse reactions (e.g. anticholinergic effects) (see sections 4.2 and 4.8). If used in elderly patients, it is recommended to begin treatment with half of the recommended dose due to prolonged action (see section 4.2).

The dose of Hydroxyzine Orifarm should be reduced in patients with decreased hepatic function and in patients with moderate to severe renal impairment (see section 4.2). In particular, caution should be exercised when adjusting the dose in patients with end-stage renal disease (ESRD) as there are limited clinical data regarding safety and efficacy.

High doses might result in dry mouth. The patient should be informed about this and the importance of having a good oral and dental hygiene during treatment with hydroxyzine hydrochloride. The prescriber should discuss the anticipated duration of treatment with the patient and inform about the initial adverse reactions.

Dose adjustments may be required if Hydroxyzine Orifarm is used simultaneously with other CNS depressants or with drugs having anticholinergic properties (see section 4.5).

Concomitant use of Hydroxyzine Orifarm and alcohol should be avoided (see section 4.5).

Treatment should be stopped at least 5 days before skin testing for allergy or bronchial provocation testing with methacholine to avoid effects on the test results (see section 4.5).

Hydroxyzine Orifarm contains lactose. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Associations contraindicated:

Co-administration of hydroxyzine with drugs known to prolong the QT interval and/or induce Torsade de Pointes e.g. class IA (e.g. quinidine, disopyramide) and III antiarrhythmics (e.g. amiodarone, sotalol), some antihistamines, some antipsychotics (e.g. haloperidol), some antidepressants (e.g. citalopram, escitalopram), some antimalarial drugs (e.g. mefloquine, hydroxychloroquine), some antibiotics (e.g. erythromycin, levofloxacin, moxifloxacin), some antifungal agents (e.g. pentamidine), some gastro-intestinal medicines (e.g. prucalopride), some medicines used in cancer (e.g., toremifene, vandetanib), methadone, increase the risk of cardiac arrhythmia. Therefore, the combination is contra-indicated (see section 4.3).

Associations not recommended:

Betahistine and anticholinesterase drugs

Hydroxyzine antagonises the effects of betahistine and of anticholinesterases.

Allergy testing

The treatment should be stopped at least 5 days before allergy testing or methacholine bronchial challenge, to avoid effects on the test results.

MAO-inhibitors

Simultaneous administration of hydroxyzine with monoamine oxidase inhibitors should be avoided.

Associations requiring precaution of use:

Bradycardia and hypokalaemia-inducing drugs

Caution with bradycardia and hypokalaemia-inducing drugs.

CNS depressants

Patients should be informed that hydroxyzine may potentiate the effects of CNS depressants or active substances having anticholinergic properties. Dose should be adapted on an individual basis.

Alcohol

Alcohol potentiates the effects of hydroxyzine.

Adrenaline

Hydroxyzine counteracts the adrenaline pressor action of adrenaline.

Phenytoin

In rats, hydroxyzine antagonised the anticonvulsant action of phenytoin.

Cimetidine

Cimetidine 600 mg twice daily has been shown to increase the serum concentrations of hydroxyzine by 36 % and to decrease peak concentrations of the metabolite cetirizine by 20 %.

CYP2D6 substrates

Hydroxyzine is an inhibitor of CYP2D6 (Ki: 3.9 µM; 1.7 µg/ml) and may at high doses cause drug interactions with CYP2D6 substrates:

- beta blockers (metoprolol, propafenone, timolol)
- SSRIs (fluoxetine, fluvoxamine)
- antidepressants (amitriptyline, clomipramine, desipramine, duloxetine, imipramine, paroxetine, venlafaxine)
- antipsychotics (aripiprazole, haloperidol, risperidone, thioridazine)
- codeine, dextromethorphan, flecainide, mexiletine, ondansetron, tamoxifen, tramadol

UDP-glucuronyl transferase and cytochrome P450

Hydroxyzine is unlikely to impair the metabolism of drugs which are substrates for cytochrome P450 2C9, 2C19 and 3A4 and UDP-glucuronyl transferases.

CYP3A4/5 inhibitors

Hydroxyzine is metabolized by alcohol dehydrogenase and CYP3A4/5 and an increase in hydroxyzine blood concentrations may be expected when hydroxyzine is co-administered with active substances known to be potent inhibitors of these enzymes. Examples of potent inhibitors of CYP3A4/5 are telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, and certain HIV protease inhibitors, including atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, lopinavir/ritonavir, saquinavir/ritonavir, and tipranavir/ritonavir and examples of potent inhibitors of alcohol dehydrogenase are disulfiram and metronidazole. No interaction with CYP3A4/5-substrate is expected with hydroxyzine.

Thiazide diuretics

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 (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of hydroxyzine hydrochloride in pregnant women. Hydroxyzine hydrochloride crosses the placental barrier which may lead to higher foetal than maternal

concentrations. The following events were observed immediately after or only a few hours after birth in neonates whose mothers received hydroxyzine hydrochloride during pregnancy and/or birth; hypotonia, movement disorders including extrapyramidal disorders, clonic movements, CNS depression, neonatal hypoxia or urinary retention. Animal studies have shown reproductive toxicity (see section 5.3). Hydroxyzine Orifarm is therefore contraindicated during pregnancy.

Breastfeeding

Cetirizine, the main metabolite of hydroxyzine hydrochloride is excreted in human milk. Although no formal studies of excretion of hydroxyzine hydrochloride in human milk have been conducted, serious effects have been observed in nursed neonates/infants whose mothers were treated with hydroxyzine hydrochloride. Hydroxyzine Orifarm is therefore contraindicated during breastfeeding. Breastfeeding must be stopped if therapy with Hydroxyzine Orifarm is needed.

Fertility

There is no information concerning the influence of hydroxyzine hydrochloride on fertility.

4.7 Effects on ability to drive and use machines

Hydroxyzine Orifarm 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.

4.8 Undesirable effects

The most common undesirable effect of the sedating antihistamines is CNS depression. Effects vary from slight drowsiness to deep sleep, and include lassitude, dizziness, and incoordination. Paradoxical stimulation may occasionally occur, especially at high doses and in children and the elderly. If sedative effects occur, they may diminish after a few days of treatment. Other common adverse effects include anti-cholinergic activity, hypersensitivity reactions, headache, psychomotor impairment and antimuscarinic effects.

A Clinical trials

Oral administration of hydroxyzine hydrochloride:

The table below shows undesirable effects reported from placebo-controlled studies with a frequency of at least 1 % for hydroxyzine hydrochloride. The studies include 735 patients that received hydroxyzine hydrochloride in doses up to 50 mg daily, and 630 patients that received placebo.

Side effect	% side effects of hydroxyzine	% side effects of placebo
Sleepiness	13.74	2.70
Headache	1.63	1.90
Tiredness	1.36	0.63
Dry mouth	1.22	0.63

B Post-marketing experience

The table below shows those undesirable effects reported while hydroxyzine was marketed.

Undesirable effects are listed by MedDRA System Organ Classes. In each frequency class the undesirable effects are reported according to a decreasing order of seriousness. Assessment of undesirable effects is based on the following frequency groupings:

Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1,000$), Very rare ($< 1/10,000$), Not known (cannot be estimated from the available data)

System Organ Class	Frequency	Undesirable effects
<i>Blood and lymphatic system disorders</i>	Not known	Thrombocytopenia
<i>Immune system disorders</i>	Rare	Hypersensitivity reactions
	Very Rare	Anaphylaxis
<i>Psychiatric disorders</i>	Uncommon	Agitation, confusion
	Rare	Disorientation, hallucinations
	Not known	Aggression, depression, tics
<i>Nervous system disorders</i>	Common	Sedation
	Uncommon	Dizziness, insomnia, tremor
	Rare	Seizures, dyskinesia
	Not known	Dystonia, paraesthesia, syncope
<i>Eye disorders:</i>	Rare	Accommodation disorders, blurred vision
	Not known	Oculogyric crisis
<i>Cardiac disorders</i>	Rare	Cardiac arrest, ventricular fibrillation, ventricular tachycardia
	Not known	QT interval prolongation (see section 4.4), ventricular arrhythmias (e.g. Torsade de Pointes)
<i>Vascular disorders</i>	Rare	Hypotension
<i>Respiratory, thoracic and mediastinal disorders</i>	Very rare	Bronchospasm
<i>Gastrointestinal disorders</i>	Uncommon	Nausea
	Rare	Constipation, vomiting
	Not known	Diarrhoea
<i>Hepatobiliary disorders</i>	Rare	Increase in transaminases, alkaline phosphatase, bilirubin and glutamyl
	Not known	Hepatitis
<i>Skin and subcutaneous tissue disorders</i>	Rare	Pruritus, erythema, papular rash, urticaria, dermatitis
	Very rare	Angioedema, increased sweating, fixed drug eruption, acute generalised pustolosis (AGEP), erythema multiforme, Stevens-Johnson syndrome
	Not known	Bullous condition e.g. toxic epidermal necrolysis, pemphigoids
<i>Renal and urinary disorders</i>	Rare	Urinary retention
	Not known	Dysuria, enuresis

<i>General disorders and administration site conditions</i>	Uncommon	Malaise, fever
	Not known	Asthenia, oedema
<i>Investigations</i>	Not known	Weight gain

Treatment with antipsychotic medicines may result in QT interval prolongation and cardiac arrhythmias. Cases of sudden death that may be cardiac related (see section 4.4) have been reported during the treatment with such medicines.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Toxicity

60–100 mg hydroxyzine hydrochloride given to a 2 year old child resulted in none to mild intoxication and 300 mg hydroxyzine given to a 2 year old child resulted in a severe intoxication. 1–1.5 g hydroxyzine given to adults caused mild intoxication. 1.5–2.5 g hydroxyzine hydrochloride given to adults resulted in a moderate intoxication.

Symptoms

Symptoms observed after a large hydroxyzine hydrochloride overdose have mainly been associated with strong anticholinergic effects, CNS depression or paradoxical CNS stimulation. The symptoms include nausea, vomiting, tachycardia, pyrexia, somnolence, altered pupillary reflexes, tremors, confusion or hallucinations. These effects may be followed by reduced consciousness, respiratory depression, convulsions, hypotension or cardiac arrhythmia including bradycardia. Coma, cardiovascular collapse and respiratory failure may occur. QT interval prolongation and cases of fatal arrhythmias have been reported with the overdose of neuroleptics.

Treatment

Symptomatic and supportive treatment is indicated. Gastric lavage with endotracheal intubation may be performed if a clinically significant amount of medicine has been ingested. Activated charcoal should be considered, but there is few data that supports the effect. Airways, respiratory and circulatory status must be closely monitored with continuous ECG recordings and adequate oxygen supply must be available. Monitoring of heart rate and blood pressure must be done until the patient is free of symptoms for 24 hours. It is doubtful whether haemodialysis or peritoneal dialysis has any value.

There is no specific antidote. According to literature, a therapeutic dose of physostigmine may lead to serious, life-threatening anticholinergic effects that are hard to treat and does not respond to other compounds. Physostigmine should not be used to keep a patient awake. If cyclic antidepressants have been taken, administration of physostigmine may lead to convulsions and cardiac arrest. Physostigmine should also be avoided in patients with conduction disorders.

Patients with changes in mental status should be examined to determine simultaneous use of other drugs or alcohol, and be given oxygen, naloxone, glucose and thiamine, if needed.

Noradrenaline or metaraminol should be administered when a need for a blood pressure stimulant exist. Do not give adrenaline.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, anxiolytics, diphenylmethane derivatives, ATC code: N05BB01

The active substance, hydroxyzine hydrochloride, is a diphenylmethane derivative, which does not belong to the same chemical group as phenothiazines, reserpine, meprobamate and benzodiazepines.

Hydroxyzine hydrochloride is a fast-acting H_1 -receptor antagonist with potent antipruritic and anti-allergic properties. Effect is reached after about 1 hour and remains for at least 24 hours.

Hydroxyzine hydrochloride also has a calming effect, due to its effect on the reticular formation. The effect is noticeable after about 15 minutes and remains for about 12 hours. Hydroxyzine hydrochloride also has anticholinergic, spasmolytic and adrenolytic effect.

Mechanism of action

Hydroxyzine hydrochloride is not a cortical depressant, but its effect may be due to CNS suppression of the activity of certain key subcortical areas.

Pharmacodynamic effects, clinical efficacy and safety

Hydroxyzine hydrochloride has been experimentally found to have antihistaminic and bronchodilatory effects and the effects are confirmed clinically. In addition, an anti-emetic effect has been demonstrated in both the apomorphine test and the veriloid test. Pharmacological and clinical studies indicate that hydroxyzine hydrochloride in therapeutic dose does not increase gastric secretion or acidity and in most cases provides mild antisecretory benefits. Healthy volunteer adults' and children's hives and reddening has been shown to decrease when the skin is first injected with histamine or antigens. Hydroxyzine hydrochloride has also proven effective in reducing itching for various types of urticaria, eczema and dermatitis.

In the case of hepatic failure, the effect of one dose of antihistamine can last as long as 96 hours after dosing.

EEG studies conducted in healthy volunteers have shown that the medicinal product has an anxiolyticsedative profile. An anxiolytic effect was confirmed by a variety of classical psycho-metric tests. It was found in polygraphic sleep studies on patients suffering from anxiety and insomnia that the total duration of sleep was increased, total time of nocturnal wakeups decreased, and the time to go to sleep was reduced, after both the 50 mg single dose and repeated dosing. Muscle tension was found to decrease in over-anxious patients using a daily dose of 3 x 50 mg. Memory disturbances were not observed. Patients with anxiety did not show any symptoms of withdrawal after 4 weeks of treatment.

Paediatric population

The pharmacokinetics and antipruritic effects of hydroxyzine hydrochloride were studied in 12 children (mean age 6.1 ± 4.6 years) with severe atopic dermatitis, each given a single 0.7 mg/kg 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. The potent antipruritic effect persists even when serum concentrations of the active substance are low (only 10 % of the maximum levels achieved). In children, the biological effects of hydroxyzine hydrochloride appear to be much more prolonged than would be predicted from the half-life values.

5.2 Pharmacokinetic properties

Absorption

Hydroxyzine hydrochloride is rapidly absorbed from the gastrointestinal tract. Maximum plasma concentration (C_{max}) has been shown to occur after around 2 hours (t_{max}) after oral administration. After

single doses of 25 mg and 50 mg in adults, C_{max} is normally 30 respective 70 ng/ml. Rate and extent of exposure to hydroxyzine hydrochloride are about the same as if given as a tablet or syrup. After repeated once daily dosing, the concentration increases about 30 %. Oral bioavailability of hydroxyzine hydrochloride compared with intramuscular (IM) administration is about 80 %.

Distribution

Hydroxyzine hydrochloride is widely distributed in the body and is generally more concentrated in tissues than in plasma. The apparent volume of distribution is 7-16 l/kg in adults. Hydroxyzine hydrochloride is taken up in the skin after oral administration. The hydroxyzine concentrations in the skin are higher than serum concentrations after both single and multiple dose administration.

Hydroxyzine hydrochloride crosses the placental barrier which may lead to higher foetal than maternal concentrations.

Biotransformation

Hydroxyzine hydrochloride is extensively metabolised. The formation of the main metabolite cetirizine, a carboxylic acid (about 45 % of oral dose), is mediated by alcohol dehydrogenase. This metabolite has significant peripheral H1-antagonist properties. Other identified metabolites include N-dealkylated and Odealkylated metabolites with a plasma half-life of 59 hours. These metabolic pathways are mediated primarily by CYP3A4/5.

Elimination

Hydroxyzine's half-life in adults is about 14 hours (7-20 h). Half-life of the main metabolite cetirizine in adults is approximately 10 hours. Plasma clearance (CL/F) calculated after an oral dose from studies, is 13 ml/min/kg. Only 0.8 % of the dose is excreted unchanged in urine after an oral dose. Cetirizine is mainly excreted unchanged in urine (25 % of oral hydroxyzine hydrochloride dose).

Special populations

Elderly

Hydroxyzine's pharmacokinetics in elderly was investigated in 9 healthy elderly subjects (69.5 ± 3.7 years) after a single dose of 0.7 mg/kg. Hydroxyzine's half-life increased to 29 hours and the apparent volume of distribution volume rose to 22.5 l/kg. Reduction of daily dose is recommended in elderly patients (see section 4.2).

Paediatric population

Hydroxyzine's pharmacokinetics was evaluated in 12 children (6.1 ± 4.6 years; 22.0 ± 12.0 kg) after an oral dose of 0.7 mg/kg. Oral plasma clearance per kg was about 2.5 times higher than in adults. The half-life was shorter than in adults. It was about 4 hours in 1 year old infants and 11 hours in 14 year old adolescents and increases with age. Dosage should be adjusted to the child (see section 4.2).

Hepatic impairment

In subjects with hepatic impairment secondary to primary biliary cirrhosis, plasma clearance (CL/F) was approximately 66 % of that in normal subjects. Half-life was increased to 37 hours and serum concentrations of the carboxylic acid metabolite cetirizine were higher than in young subjects with normal hepatic function.

Renal impairment

Hydroxyzine's pharmacokinetics was studied in 8 subjects with severe renal impairment (creatinine clearance 24 ± 7 ml/min). The exposure (AUC) of hydroxyzine hydrochloride did not change significantly, while it increased about 5 times for the carboxylic acid metabolite cetirizine. This metabolite was not removed efficiently by dialysis. To avoid significant accumulation of cetirizine after repeated dose of

hydroxyzine hydrochloride, the daily dose of hydroxyzine hydrochloride should be reduced in patients with renal impairment (see section 4.2).

5.3 Preclinical safety data

Administration of 50 mg/kg hydroxyzine hydrochloride in rats and rabbits showed deformations and abortions of foetuses.

Increased duration of action potential in isolated Purkinje fibres from dogs at 3 µM hydroxyzine hydrochloride may suggest an interaction with potassium channels involved in the repolarisation phase. A higher concentration, 30 µM, showed a significant decrease in the duration of the action potential suggesting a possible interaction with calcium and/or sodium currents. Hydroxyzine hydrochloride had an inhibitory effect on the potassium (I_{Kr})-flow in human ether-a-go-go-related genes (hERG)-channels expressed in mammal cells with an IC₅₀ of 0.62 µM, which is between 10-60 times higher than therapeutic concentrations. Further, the concentrations of hydroxyzine hydrochloride needed to affect cardiac electrophysiology are 10-100 times higher than those needed to block H₁- and 5HT₂-receptors. Dogs monitored with telemetry, not restrained and conscious, showed hydroxyzine hydrochloride and its enantiomers similar cardiovascular profiles, although with some minor differences. An initial telemetry study with dogs showed that hydroxyzine hydrochloride (21 mg/kg orally) slightly increased the heart rate and shortened the PR and QT intervals. No effect on QRS and QTc intervals were seen and therefore it is not likely that these minor changes are clinically significant at normal therapeutic doses.

Similar effects on heart rate and PR interval were observed in another telemetry study with dogs, where it was confirmed that a single dose hydroxyzine hydrochloride of up to 36 mg/kg had no effect on the QTc interval.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Lactose monohydrate, calcium phosphate tribasic, pregelatinised starch, sodium laurilsulfate, colloidal anhydrous silica, magnesium stearate.

Film-coating:

Macrogol, hypromellose, titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

PVC/PVDC/aluminium blisters: 25, 100 tablets

HDPE container with a polypropylene lid: 250 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2024-05-22