

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hydroxyzine Bluefish 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg hydroxyzine hydrochloride.

Excipient with known effect:

Each 10 mg film-coated tablet contains 22 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, 5.0 mm round shaped, biconvex, film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of anxiety in adults.

Symptomatic treatment of pruritus associated with urticaria.

4.2 Posology and method of administration

Posology

Hydroxyzine Bluefish should be used at the lowest effective dose and for the shortest possible duration. Do not change dose without first talking to a doctor.

Symptomatic treatment of anxiety:

Adults:

10 mg – 50 mg daily, divided into 2-3 doses daily. In adults over 40 kg, the maximum daily dose is 100 mg per day.

Medicinal treatment of anxiety should always be used as adjuvant therapy. As far as possible, treatment should be initiated, supervised and discontinued by the same physician.

Symptomatic treatment of pruritus associated with urticaria:

Adults and adolescents (≥ 12 years):

25-50 mg in the evening. In adults and adolescents over 40 kg, the maximum daily dose is 100 mg per day.

Children aged 5-12 years:

10-25 mg in the evening.

In children over 40 kg, the maximum daily dose is 100 mg per day.

In children up to 40 kg, the maximum daily dose is 2 mg/kg/day.

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 or higher doses which cannot be divided by 10, e.g. 25 mg.

Dose adjustment

Dose should be adjusted within the given dose range in accordance with the treatment response in the patient.

Special populations

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:

Dose should be reduced in patients with moderate or severe renal impairment due to decreased excretion of its metabolite cetirizine.

Patients with hepatic impairment:

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

4.3 Contraindications

- Hypersensitivity to the active substance, to cetirizine, to other piperazine derivatives, aminophylline, ethylenediamine or any of the excipients listed in section 6.1.
- Patients with porphyria.
- Pregnancy and lactation (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

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.

Patients with hepatic impairment

Dosage should be reduced for patients with hepatic impairment (see section 4.2).

In patients with hepatic impairment who receive hydroxyzine regularly, liver function should be monitored.

Patients with renal impairment

Hydroxyzine should be used with caution in patients with moderate and severe renal impairment and the dose should be reduced (see section 4.2).

Elderly patients

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).

In elderly patients, it is recommended to begin treatment with half of the recommended dose due to prolonged action (see section 4.2).

Because of its potential anticholinergic effects, Hydroxyzine should be used with caution in patients suffering from glaucoma, urinary tract obstruction, decreased gastro-intestinal motility, myasthenia gravis, or dementia.

Hydroxyzine should be administered cautiously in patients with increased risk of convulsions.

Younger children are more susceptible to develop adverse events related to the central nervous system (see section 4.8). In children, convulsions have been more frequently reported than in adults.

Dosage adjustments may be required if Hydroxyzine is used concomitantly with other central nervous system depressant drugs or drugs with anticholinergic properties (see section 4.5).

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

The treatment should be stopped at least 5 days before allergy testing or methacholine bronchial challenge to avoid effects on the test results (see section 4.5).

Dry mouth may occur with high doses and patients should therefore be informed about this risk and observe good mouth and tooth hygiene.

The duration of treatment should be agreed on with the patient and the patient should be made aware of the initial adverse reactions.

An about 3-fold risk of cerebrovascular events has been observed in randomised, placebo-controlled clinical studies with certain atypical neuroleptics in patients with dementia. Background mechanism for this increased risk is not known. An increased risk with other neuroleptics and in other patient populations cannot be excluded. Therefore, hydroxyzine should be used with caution in patients with risk factors for stroke.

Hydroxyzine film-coated tablets contain lactose (see section 6.1).

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

Hydroxyzine film-coated tablets contain sodium

This medicine contains less than 1 mmol sodium (23 mg) per 10 mg tablet, that is to say essentially 'sodium-free'.

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), 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.

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 (K_i : 3.9 μ M: 1.7 μ g/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 metabolised 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 is no reliable data on the use of hydroxyzine in pregnant women. Hydroxyzine crosses the placental barrier leading to higher foetal than maternal concentrations. Animal studies have shown reproductive toxicity (see section 5.3). Therefore, hydroxyzine is contraindicated during pregnancy.

In neonates whose mothers received hydroxyzine during late pregnancy and/or labour, the following events were observed immediately or only a few hours after birth: hypotonia, movement disorders including extrapyramidal disorders, clonic movements, CNS depression, neonatal hypoxic conditions or urinary retention.

Breast-feeding

Cetirizine, the main metabolite of hydroxyzine, is excreted in human milk. Although no formal studies have been conducted concerning the excretion of hydroxyzine in human milk, serious undesirable effects have been seen in breast-fed newborns/infants of hydroxyzine-treated women. Therefore, hydroxyzine is contraindicated during breast-feeding. Breast-feeding must be discontinued if hydroxyzine treatment is necessary.

4.7 Effects on ability to drive and use machines

Hydroxyzine may impair the ability to react and to concentrate. Patients should be warned of this possibility and cautioned against driving a car or operating machinery. Concomitant use of Hydroxyzine with alcohol or other sedative drugs should be avoided as it aggravates these effects.

4.8 Undesirable effects

The undesirable effects are mainly associated with CNS depression or paradoxical CNS stimulation, with anti-cholinergic activity or hypersensitivity reactions.

A Clinical trials

Oral administration of hydroxyzine:

The following table lists the undesirable effects reported in placebo-controlled clinical trials at a rate of at least 1% for hydroxyzine. The trials included 735 patients who received hydroxyzine up to 50 mg daily and 630 patients who received placebo.

Undesirable effect (PT)	undesirable effects for hydroxyzine, %	undesirable effects for 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 lists, per system organ class and frequency, the undesirable effects reported during post-marketing use of the drug.

The frequency has been estimated using the following definitions:

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).

Blood and lymphatic system disorders:

Not known: thrombocytopenia

Immune system disorders:

Rare: hypersensitivity reactions

Very rare: anaphylactic shock

Psychiatric disorders:

Uncommon: agitation, confusion
Rare: disorientation, hallucination
Not known: aggression, depression, tics

Nervous system disorders:

Common: sedation
Uncommon: dizziness, insomnia, tremor
Rare: Seizures, dyskinesia
Not known: dystonia, paraesthesia, syncope

Eye disorders:

Rare: accommodation disorder, blurred vision
Not known: oculogyric crisis

Cardiac disorders:

Rare: cardiac arrest, ventricular fibrillation, ventricular tachycardia
Not known: ventricular arrhythmias (e.g. Torsade de Pointes), QT interval prolongation (see section 4.4).

Vascular disorders:

Rare: hypotension

Respiratory, thoracic and mediastinal disorders:

Very rare: bronchospasm

Gastrointestinal disorders:

Uncommon: nausea
Rare: constipation, vomiting
Not known: diarrhoea

Hepatobiliary disorders:

Rare: liver function tests abnormal
Not known: hepatitis

Skin and subcutaneous tissue disorders:

Rare: pruritis, erythema, papular rash, urticaria, dermatitis
Very rare: angioedema, increased sweating, fixed drug eruption, acute generalized exanthematous pustulosis (AGEP), erythema multiforme, Stevens-Johnson syndrome
Not known: Bullous condition e.g. toxic epidermal necrolysis, pemfigoids

Renal and urinary disorders:

Rare: urinary retention
Not known: dysuria, enuresis

General disorders and administration site conditions:

Uncommon: malaise, pyrexia
Not known: asthenia, oedema

Investigations:

Not known: weight increased

Treatment with neuroleptics may cause prolongation of the QT interval and cardiac arrhythmias. Cases of sudden death which may have cardiac causes (see section 4.4) have been reported during treatment with these drugs.

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 given to a 2yearold child resulted in no or mild intoxication, 300 mg hydroxyzine given to a 2yearold child resulted in severe intoxication. 1-1.5 g hydroxyzine given to adults resulted in mild intoxication. 1.5-2.5 g hydroxyzine given to adults resulted in moderate intoxication.

Symptoms:

Symptoms observed after a major overdose are mainly associated with strong anticholinergic effects, CNS depression or CNS paradoxical stimulation. The symptoms include nausea, vomiting, tachycardia, pyrexia, somnolence, impaired pupillary reflex, tremor, confusion, or hallucination. These may be followed by depressed level of consciousness, respiratory depression, convulsions or hypotension. Deepening coma and cardiorespiratory collapse may ensue. Prolonged QT interval and serious arrhythmia with fatal outcomes have been described in connection with an 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Hydroxyzine hydrochloride is a fast acting H1 receptor antagonist with strongly itch inhibiting and anti-allergic properties. Effect is reached after about 1 hour and remains for at least 24 hours. Hydroxyzine hydrochloride also has sedative properties, due to its effect on formatio reticularis. The effect is noticeable after about 15 minutes and remains for about 12 hours.

Hydroxyzine hydrochloride also has anticholinergic, spasmolytic and adrenolytic action. Hydroxyzine hydrochloride has a wide therapeutic window and does not cause drug addiction.

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 metabolized. The formation of the main metabolite cetirizine, a carboxylic acid metabolite (approximately 45% of the oral dose), is mediated by alcohol dehydrogenase. This metabolite has significant peripheral H₁-antagonistic properties. Other identified metabolites include an N-dealkylated metabolite, and an O-dealkylated metabolite 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 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

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity. No animal carcinogenicity studies have been performed with hydroxyzine.

In rats and rabbits, foetal malformations and foetal abortions were seen with hydroxyzine doses of 50 mg/kg.

In isolated canine Purkinje fibres, hydroxyzine at concentrations of 3 μ M increased action potential duration suggesting that there was an interaction with potassium channels involved with the repolarisation phase. At higher concentrations, 30 μ M, there was a marked decrease in the action potential duration suggesting a

possible interaction with calcium and/or sodium currents. Hydroxyzine produced inhibition of the potassium (IKr) current in hERG channels expressed in mammalian cells, with an IC₅₀ of 0.62 µM, a concentration that is between 10 and 60-fold higher than therapeutic concentrations. However, the hydroxyzine concentrations required to produce effects on cardiac electrophysiology are 10 to 100-fold higher than those required to block H1 and 5-HT₂ receptors. In unrestrained conscious dogs monitored by telemetry, hydroxyzine and its enantiomers produced similar cardiovascular profiles though there were some minor differences. In the first dog telemetry study, hydroxyzine (21 mg/kg orally) slightly increased heart rate and shortened PR and QT intervals. There was no effect on QRS and QTc intervals, and thus at normal therapeutic doses, these slight changes are unlikely to be of clinical relevance.

Similar effects on heart rate and PR interval were observed in a second dog telemetry study, where the absence of effects of hydroxyzine on QTc interval was confirmed up to a single oral dose of 36 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Cellulose microcrystalline
Lactose monohydrate
Croscarmellose sodium
Silica, colloidal anhydrous
Talc
Magnesium stearate

Coating:

Hypromellose 5cPs
Macrogol 400
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 Years

6.4 Special precautions for storage

PVC/PVdC- Alu blister:

This medicinal product does not require any special temperature storage conditions.

HDPE bottle:

This medicinal product does not require any special temperature storage conditions.
Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

The 10 mg film-coated tablets are supplied in PVC/PVdC - Alu blisters & HDPE bottles.

PVC/PVdC- Alu blister:

25, 30, 84, 100 and 250 tablets

HDPE bottle with Polypropylene child resistant cap with liner and silica gel desiccant:
25, 30, 84 and 100

HDPE bottle with Polypropylene cap with liner and silica gel desiccant:
250 tablets. This pack is for dose-dispensing.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local 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

20 December 2021