

Atarax™

Hydroxyzine Hydrochloride

Atarax™ 10 mg film-coated tablet

Atarax™ 25 mg film-coated tablet

Atarax™ 2 mg/ml Syrup



QUALITATIVE AND QUANTITATIVE COMPOSITION

Hydroxyzine hydrochloride, 10 mg, film-coated tablet

Each film-coated tablet contains 10 mg of hydroxyzine hydrochloride.

Hydroxyzine hydrochloride, 25 mg, film-coated tablet

Each film-coated tablet contains 25 mg of hydroxyzine hydrochloride.

Hydroxyzine hydrochloride, 10 mg/5 ml, syrup

Each ml of syrup contains 2 mg of hydroxyzine hydrochloride.

Excipients

Hydroxyzine hydrochloride, 10 mg, film-coated tablet

Lactose, Starch, Calcium stearate, Talc, PVP, Eudragit, PEG, Titanium dioxide

Hydroxyzine hydrochloride, 25 mg, film-coated tablet

Lactose monohydrate, Microcrystalline cellulose, Magnesium stearate, Colloidal anhydrous silica, Titanium dioxide (E171), H.P.M.C. 2910 5cP, Macrogol 400, Opadry Y-1-7000

Hydroxyzine hydrochloride, 10 mg/5 ml, syrup

Ethyl alcohol, Sucrose, Sodium benzoate, Menthol, Hazelnut flavour, Water

PHARMACEUTICAL FORM

Hydroxyzine hydrochloride, 10 mg, film-coated tablet

White, round, film-coated tablet.

Hydroxyzine hydrochloride, 25 mg, film-coated tablet

White, oblong, film-coated tablet, with a bisect line.

Hydroxyzine hydrochloride, 10 mg/5 ml, syrup

Clear, colourless solution.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group

Anxiolytics; Diphenylmethane derivatives

ATC Code

N05BB01

Mechanism of Action

Hydroxyzine is a first generation antihistamine that crosses the blood/brain barrier extensively and has a high affinity for histaminic receptors into the brain, thereby producing sedative-anxiolytic effects.

Pharmacodynamic effects

Antihistaminic and bronchodilator activities have been demonstrated experimentally and confirmed clinically. An antiemetic effect, both by the apomorphine test and the veriloid test, has been demonstrated. Pharmacological and clinical studies indicate that hydroxyzine at therapeutic dosage does not increase gastric secretion or acidity and in most cases has mild antisecretory activity. Wheal and flare reduction have been demonstrated in adult healthy volunteers and in children after intradermal injections of histamine or antigens. Hydroxyzine has also revealed its efficacy in relieving pruritus in various forms of urticaria, eczema and dermatitis.

Onset of action

The antihistaminic effect begins approximately after 1 hour with oral pharmaceutical forms. The sedative effect starts after 5-10 minutes with oral liquid and after 30-45 minutes with tablets.

Hydroxyzine has a weak affinity for muscarinic receptors.

Pharmacokinetics

Absorption

Hydroxyzine is rapidly absorbed from the gastrointestinal tract. The peak plasma level (C_{max}) is reached approximately two hours after oral intake. After single oral doses of 25 mg and 50 mg in adults, C_{max} concentrations are typically 30 and 70 ng/ml, respectively.

The rate and extent of exposure to hydroxyzine is very similar when given as tablet or as a syrup. Following repeat administration once a day, concentrations are increased by 30%. The oral bioavailability of hydroxyzine with respect to intramuscular (IM) administration is about 80%. After a single 50 mg IM dose, C_{max} concentrations are typically 65 ng/ml.

Distribution

Hydroxyzine is widely distributed in the body and generally more concentrated in the tissues than in plasma. The apparent volume of distribution is 7 to 16 l/kg in adults.

Hydroxyzine enters the skin following oral administration. Skin concentrations of hydroxyzine are higher than serum concentrations, following both single and multiple administration. Hydroxyzine crosses the blood-brain and placental barriers leading to higher foetal than maternal concentrations.

Metabolism

Hydroxyzine is extensively metabolised. The formation of the major metabolite cetirizine, a carboxylic acid metabolite (approximately 45% of the oral dose), is mediated by alcohol dehydrogenase. This metabolite has significant peripheral H1-antagonist properties. The other metabolites identified include a N-dealkylated metabolite, and an O-dealkylated metabolite with a plasma half-life of 59 hours. These pathways are mediated principally by CYP3A4/5.

Elimination

Hydroxyzine half-life in adults is approximately 12 ± 5 hours (range: 7 - 20 hrs). The apparent total body clearance calculated across studies is 13 ml/min/kg. Only 0.8% of the dose is excreted unchanged in urine. The major metabolite cetirizine is excreted mainly unchanged in urine (25% and 16 % of the hydroxyzine oral and IM dose, respectively).

Special patient populations**Children**

The pharmacokinetics of hydroxyzine was evaluated in 12 paediatric patients aged 1 to 14 years (mean 6.1 ± 4.6 yrs) with severe atopic dermatitis. A 0.7 mg/kg single dose of hydroxyzine was administered orally. The mean peak serum concentration was 47 ± 17 ng/ml and occurred at a mean time of 2.0 ± 0.9 h after the dose. The mean plasma clearance was higher than in adults (32 ± 11 ml/min/kg). The half-life was shorter than in adults and increased with age from 4 hours at 1 year of age to 11 hours at 14 years of age. No data was available regarding the metabolite cetirizine.

Like in adults, the antipruritic effect lasted longer than anticipated for the half-life as pruritus was significantly suppressed from 1 to 24 hours post-dose with >85% suppression from 2 to 12 hours.

Dosage should be adjusted in paediatric population (*see Section Dosage and Administration*).

Elderly

The pharmacokinetics of hydroxyzine was investigated in 9 healthy elderly subjects (69.5 ± 3.7 years) following a single 0.7 mg/kg oral dose. The elimination half-life of hydroxyzine was prolonged to 29 ± 10 hours (range 20-53 hours) and the apparent volume of distribution was increased to 22 ± 6 l/kg (range 13-31 l/kg). In view of the longer $t_{1/2}$ and of the prolonged Pharmacodynamic effect (suppression of the wheal and flare response to histamine), it is advised to start with half the recommended dose (*see Section Dosage and Administration*).

Renal impairment

The pharmacokinetics of hydroxyzine was studied in 8 severe renally impaired subjects (Creatinine clearance: 24 ± 7 ml/min). The extent of exposure (AUC) to hydroxyzine was not altered in a relevant manner while that to the carboxylic metabolite, cetirizine, was increased. This metabolite is not removed efficiently by haemodialysis. 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 (*see Section Dosage and Administration*).

Hepatic impairment

In subjects with hepatic dysfunction secondary to primary biliary cirrhosis, total body clearance was approximately 66% that of normal subjects. The half-life was increased to 37 hours and the serum concentrations of the carboxylic metabolite, cetirizine, were higher than in young patients with a normal liver function. Daily dose or dose frequency should be reduced in patients with impaired liver function (*see Section Dosage and Administration*).

INDICATIONS

- For symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested.

- As a sedative used as premedication
- As symptomatic relief in atopic pruritus

The effectiveness of hydroxyzine as an antianxiety agent for long term use, that is more than 4 months, has not been assessed by systematic clinical studies. The physician should reassess periodically the usefulness of the drug for the individual patient.

Hydroxyzine may potentiate meperidine and barbiturates, so their use in pre-anaesthetic adjunctive therapy should be modified on an individual basis. Atropine and other belladonna alkaloids are not affected by the drug. Hydroxyzine is not known to interfere with the action of digitalis in any way and it may be used concurrently with this agent.

DOSAGE AND ADMINISTRATION

The maximum single dose in adults should not exceed 200 mg whereas the maximum daily dose should not exceed 300 mg.

- In adults:
In general practice: 30 to 100 mg per day in divided doses during the day or at night.
In neuropsychiatry: 100 to 300 mg per day
In anaesthesiology: 100 to 200 mg per day. ATARAX when used as a premedication is usually given the night before surgery instead of barbiturates.
- In children:
30 months to 15 years of age: 1 mg/kg/day in divided doses.
The dosage of ATARAX must be adapted to the patient's response.
For a shorter effect half the usual dose can be given.

CONTRA-INDICATIONS

- History of hypersensitivity to hydroxyzine or to any of the excipients, to cetirizine, to other piperazine derivatives, to aminophylline, or to ethylenediamine.
- Patients with porphyria
- Pregnancy and lactation
- Patients with pre-existing prolonged QT interval
- ATARAX Syrup 2 mg/ml includes 0.75 g of sucrose per ml. Patients with rare hereditary problems of fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take this medicine.
- ATARAX tablets include lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose mal-absorption should not take this medicine.

WARNINGS AND PRECAUTIONS

Convulsions

ATARAX should be administered cautiously in patients with increased potential for convulsions.

Children

Young children are more susceptible to develop adverse events related to the central nervous system (*see Section Adverse Reactions*). In children, convulsions have been more frequently reported than in adults.

Hydroxyzine anticholinergic effects

Because of its potential anticholinergic effects, ATARAX should be used cautiously in patients suffering from glaucoma, bladder outflow obstruction, decreased gastro-intestinal motility, myasthenia gravis, or dementia.

Co-administration with CNS depressants

Dosage adjustments may be required if ATARAX is used simultaneously with other central nervous system depressant drugs or with drugs having anticholinergic properties (*see Section Interactions*).

Alcohol

The concomitant use of alcohol and ATARAX should be avoided (*see Section Interactions*).

Cardiac disorders

Caution is needed in patients who have a known predisposing factor to cardiac arrhythmia, including electrolytes imbalance (hypokalemia, hypomagnesaemia), who have pre-existing heart disease, or who are concomitantly treated with a potentially arrhythmogenic drug. In these patients use of alternative treatments is to be considered.

Elderly

In the elderly, it is advised to start with half the recommended dose due to a prolonged action.

Hepatic and renal impairment

ATARAX dosage should be reduced in patients with hepatic dysfunction and in patients with moderate or severe renal impairment.

Test results

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

Syrup

Sucrose

This product contains sucrose. At a dose higher than 6.5 ml of ATARAX Syrup 2 mg/ml, the sucrose content should be taken into consideration in patients with diabetes mellitus. Sucrose may be harmful to the teeth.

Ethanol

ATARAX Syrup 2 mg/ml contains small amounts (0.1 vol %) of ethanol (alcohol). The concentration of alcohol after the administration of 100 ml syrup (equivalent to 200 mg of hydroxyzine) will be up to 100 mg, equivalent to 2 ml beer or 1 ml wine. This has to be taken into account for patient suffering from alcoholism, children, and high-risk groups such as patients with liver disease, or epilepsy.

INTERACTIONS

CNS depressants

Patients should be informed that hydroxyzine may potentiate the effects of barbiturates, other CNS depressants or drugs having anticholinergic properties.

Alcohol

Alcohol also potentiates the effects of ATARAX.

Betahistine and anticholinesterase drugs

Hydroxyzine antagonises the effects of betahistine and anticholinesterase drugs.

Test results

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

Monoamine oxidase inhibitors

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

Epinephrine

Hydroxyzine counteracts the pressor action of epinephrine.

Phenytoin

In rats, hydroxyzine antagonised the anticonvulsant action of phenytoin.

Cimetidine

Cimetidine 600 mg bid 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 cytochrome P450 2D6 (K_i : 3.9 μM ; 1.7 $\mu\text{g/ml}$) and may cause at high doses drug-drug interactions with CYP2D6 substrates.

Effect on other drug metabolism

Hydroxyzine has no inhibitory effect at 100 μM on UDP-glucuronyl transferase isoforms 1A1 and 1A6 in human liver microsomes. It inhibits cytochrome P₄₅₀2C9/C10, 2C19 and 3A4 isoforms at concentrations (IC_{50} : 19 to 140 μM ; 7 to 52 $\mu\text{g/ml}$) well above peak plasma concentrations. The metabolite cetirizine at 100 μM has no inhibitory effect on human liver cytochrome P₄₅₀ (1A2, 2A6, 2C9/C10, 2C19, 2D6, 2E1, and 3A4) and UDP-glucuronyl transferase isoforms. Therefore, hydroxyzine is unlikely to impair the metabolism of drugs which are substrates for these enzymes.

Potent inhibitors of liver enzymes

As hydroxyzine is metabolised in the liver, an increase in hydroxyzine blood concentrations may be expected when hydroxyzine is co-administered with drugs known to be potent inhibitors of liver enzymes.

Potentially arrhythmogenic drugs

Co-administration of hydroxyzine with a potentially arrhythmogenic drug may increase the risk of QT prolongation and Torsade de Pointes.

PREGNANCY AND LACTATION

Fertility

There are no relevant data available.

Pregnancy

Hydroxyzine is contraindicated during pregnancy (*see Section Contraindications*).

Animal studies have shown reproductive toxicity.

Hydroxyzine crosses the placental barrier leading to higher foetal than maternal concentrations.

To date, no relevant epidemiological data are available relating to exposure to hydroxyzine 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.

Lactation

Hydroxyzine is contra-indicated during lactation (*see Section Contraindications*). Breast-feeding should be stopped if hydroxyzine therapy is needed.

Cetirizine, the principal metabolite of hydroxyzine, is excreted in human milk.

Although no formal studies have been performed on the excretion of hydroxyzine in human milk, severe adverse effects have been shown in breastfed newborns/infants of hydroxyzine treated mothers.

ABILITY TO PERFORM TASKS THAT REQUIRE JUDGEMENT, MOTOR OR COGNITIVE SKILLS

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.

ADVERSE REACTIONS

Undesirable effects are mainly related to CNS depressant or paradoxical CNS stimulation effects, to anticholinergic activity, or to hypersensitivity reactions.

Adverse reactions are ranked under headings of frequency using the following convention:

Very common $\geq 1/10$

Common $\geq 1/100$ to $< 1/10$

Uncommon $\geq 1/1000$ to $< 1/100$

Rare $\geq 1/10000$ to $< 1/1000$

Very rare $< 1/10000$

Not known (cannot be estimated from the available data).

Clinical Trial Data

The following undesirable effects were reported in placebo-controlled clinical trials for hydroxyzine and including 735 subjects exposed to hydroxyzine up to 50 mg daily.

Nervous system disorders

Very common: somnolence

Common: headache

Uncommon: dizziness, insomnia, disturbance in attention

Gastrointestinal disorders

Common: dry mouth

Uncommon: constipation, nausea

General disorders and administration site conditions

Common: fatigue

Uncommon: asthenia

Post Marketing Data

Immune system disorders

Not known: hypersensitivity, anaphylactic shock

Psychiatric disorders

Not known: agitation, confusion, disorientation, hallucination

Nervous system disorders

Not known: sedation, tremor, convulsions, dyskinesia

Eye disorders

Not known: accommodation disorder, vision blurred

Cardiac disorders

Not known: tachycardia, electrocardiogram QT prolonged, torsades de pointes

Vascular disorders

Not known: hypotension

Respiratory, thoracic and mediastinal disorders

Not known: bronchospasm

Gastrointestinal disorders

Not known: vomiting

Hepatobiliary disorders

Not known: liver function tests abnormal

Skin and subcutaneous tissue disorders

Not known: pruritus, erythematous rash, maculo-papular rash, urticaria, dermatitis, angioneurotic oedema, hyperhidrosis, fixed drug eruption, acute generalized exanthematous pustulosis, erythema multiforme, Stevens-Johnson syndrome

Renal and urinary disorders

Not known: urinary retention

General disorders and administration site conditions

Not known: malaise, pyrexia

The following adverse reactions have been observed with cetirizine, the principal metabolite of hydroxyzine: thrombocytopenia, aggression, depression, tic, dystonia, paraesthesia, oculogyric crisis, diarrhoea, dysuria, enuresis, asthenia, oedema, weight increased and could potentially occur with hydroxyzine.

OVERDOSAGE

Symptoms and Signs

Symptoms observed after an important overdose are mainly associated with excessive anticholinergic load, CNS depression or CNS paradoxical stimulation. They include nausea, vomiting, tachycardia, pyrexia, somnolence, impaired pupillary reflex, tremor, confusion, or hallucination. This may be followed by depressed level of consciousness, respiratory depression, convulsions, hypotension, or cardiac arrhythmia. Deepening coma and cardiorespiratory collapse may ensue.

Treatment

Airway, breathing and circulatory status must be closely monitored with continuous ECG recording and adequate oxygen supply should be available. Cardiac and blood pressure monitoring should be maintained until the patient is free of symptoms for 24 hours. Patients with altered mental status should be checked for simultaneous intake of other drugs or alcohol and should be given oxygen, naloxone, glucose and thiamine if deemed necessary.

Norepinephrine or metaraminol should be used if vasopressor is needed. Epinephrine should not be used.

Syrup of ipecac should not be administered in symptomatic patients or those who could rapidly become obtunded, comatose or convulsing, as this could lead to aspiration pneumonitis. Activated charcoal may be left in the stomach but there are scant data to support its efficacy.

It is doubtful that haemodialysis or haemoperfusion would be of any value.
There is no specific antidote.

Literature data indicate that, in the presence of severe, life-threatening, intractable anticholinergic effects unresponsive to other agents, a therapeutic trial dose of physostigmine may be useful. Physostigmine should not be used just to keep the patient awake. If cyclic antidepressants have been co-ingested, use of physostigmine may precipitate seizures and intractable cardiac arrest. Also avoid physostigmine in patients with cardiac conduction defects.

SHELF LIFE

The expiry date is indicated on the packaging.

STORAGE

Tablets and syrup: store below 25°C.

HOW SUPPLIED

Oral preparations:

CONFIDENTIAL

- 500 film-coated tablets of hydroxyzine 10 mg
- 500 film-coated tablets of hydroxyzine 25 mg
- 200 ml of syrup, 10 mg hydroxyzine per 5 ml
This form contains as preservative: sodium benzoate 1.5 mg/5ml.

Version number: NCDS02(SI)

Version date: 17 June 2013

Manufacturer for syrup:
NEXTPHARMA SAS
LIMAY - FRANCE

Manufacturer for tablets:
UCB Pharma S.A.
BRAINE-L'ALLEUD - BELGIUM