SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Atarax 25mg Film-coated tablets

2. Qualitative and quantitative composition

Each film-coated tablet contains 25 mg of hydroxyzine dihydrochloride

3. Pharmaceutical form

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

4. Clinical Particulars

4.1 Therapeutic Indications

- the symptomatic relief of anxiety in adults,
- the symptomatic relief of pruritus,
- premedication before surgery.

4.2 Posology and Method of Administration

Atarax should be used at the lowest effective dose and for the shortest possible duration *(see Section Warnings and Precautions).*

For oral use.

Adults

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

For symptomatic treatment of anxiety

50 mg/day in 3 separate administrations of 12.5-12.5-25 mg; in more severe cases doses of up to 100 mg/day can be used.

For symptomatic treatment of pruritus

Starting dose of 25 mg at night, increasing as necessary to 25 mg three or four times daily.

For premedication before surgery

50 to 100 mg/day in 1or 2 administrations: single administration 1 hour before surgery, which may be preceded by 1 administration the night before anaesthesia.

Children (from 12 months) (*see Section Warnings and Precautions*)

For symptomatic treatment of pruritus

- from 12 months 1 mg/kg/day up to 2 mg/kg/day in divided doses.

In children up to 40 kg in weight, the maximum daily dose is 2 mg/kg/day in divided doses. In children over 40 kg in weight, the maximum daily dose is 100 mg/day.

For premedication before surgery

Single administration of 1 mg/kg 1 hour before surgery, which may be preceded by 1mg/kg the night before anaesthesia.

Special Populations

The dosage should be adapted within the recommended dose range accordingly to the patient's response to therapy.

Elderly

Use of hydroxyzine in the elderly is not recommended. However, if needed, it is advised to start with half the recommended dose due to a prolonged action.

In the elderly, the maximum daily dose is 50 mg per day *(see Sections Warnings and Precautions).*

Renal impairment

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

Hepatic impairment

In patients with hepatic dysfunction, it is recommended to reduce the daily dose by 33%.

4.3 Contra-indications

Hydroxyzine is contraindicated in:

- patients with a history of hypersensitivity to hydroxyzine or any of the excipients, to cetirizine, to other piperazine derivatives, to aminophylline, or to ethylenediamine,
- pregnancy and lactation (*see Section Pregnancy and Lactation*),
- patients with porphyria,
- patients with 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: Warnings and Precautions, Interactions).*

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 or concomitant treatment that may have been contributory *(see Section Adverse Reactions)*.

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.

Convulsions
Hydroxyzine 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.

Elderly
Hydroxyzine is not recommended in elderly patients because of a decrease of hydroxyzine elimination in this population as compared to adults and greater risk of adverse reactions (e.g. anticholinergic effects) *(see Section Adverse Reactions).*

Hydroxyzine anticholinergic effects
Because of its potential anticholinergic effects, hydroxyzine 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 hydroxyzine 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 hydroxyzine should be avoided (*see Section Interactions*).
Hepatic and renal impairment
Hydroxyzine dosage should be reduced in patients with hepatic dysfunction and in patients with moderate or severe renal impairment.

Tablets
Lactose
Hydroxyzine film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interactions

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 gastrointestinal medicines (e.g. prucalopride), some medicines used in cancer (e.g. toremifene, vandetanib), methadone, increase the risk of cardiac arrhythmia. Therefore, the combination is contraindicated *(see Section Contraindications).*

Associations requiring precaution of use
Caution with bradycardia and hypokalaemia-inducing drugs.

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 drugs known to be potent inhibitors of these enzymes.

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 hydroxyzine.

Betahistine and anticholinesterase drugs
Hydroxyzine antagonises the effects of betahistine and anticholinesterase drugs.

Tests results
The treatment should be stopped at least 5 days before allergy testing or methacholine 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 b.i.d. 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 (Ki : 3.9 µM ; 1.7 µg/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 P450 2C9/C10, 2C19 and 3A4 isoforms at concentrations (IC_{50} : 19 to 140 µM ; 7 to 52 µg/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.

4.6 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 contraindicated 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.

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

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 ≥1/10

Common ≥1/100 to <1/10

Uncommon ≥1/1000 to <1/100

Rare ≥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, QT interval prolongation, venticular arrhythmias (e.g. Torsade de Pointes) *(see Section Warnings and Precautions)*

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.

4.9 Overdose

Symptoms and signs

Symptoms observed after an important overdose are mainly associated with excessive anticholinergic load, Central Nervous System (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 an 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.

5 Pharmacological Properties

5.1 Pharmacodynamic Properties

Phramacotherapeutic 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.

5.2 Pharmacokinetic Properties

Absorption

Hydroxyzine is rapidly absorbed from the gastro-intestinal 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 14 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 (mean 6.1 ± 4.6 yrs; 22.0 ± 12.0 kg) following a single oral dose of 0.7 mg/kg. The apparent plasma clearance was approximately 2.5 times that in adults. The half-life was shorter than in adults. It was approximately 4 hours in the 1 year-old patients and 11 hours in the 14 year-old-patients. 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 hours and the apparent volume of distribution was increased to 22.5 l/kg. It is recommended to reduce by half the daily dose of hydroxyzine in elderly patients (*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*).

Clinical Studies

Not relevant for this product.

5.3 Preclinical Safety Data

The safety pharmacology, acute, sub-acute and chronic toxicity studies did not raise significant safety concerns from data in rodents, dogs and monkeys. Lethal doses 50 (LD50) in rats and mice are respectively 690 and 550 mg/kg per os whereas these are 81 and 56 mg/kg intra venous (i.v.).

Single oral doses of 80 mg/kg and above induced signs of depression, ataxia, convulsions and tremors in dogs. In monkeys, at oral doses exceeding 50 mg/kg, some vomiting occurred without any other signs up to 400 mg/kg, whereas i.v. doses of 15 mg/kg caused transient ataxia and convulsions, with complete recovery within 5 minutes after dosing. Intra-arterial injections lead to important local tissue lesions in rabbits.

In isolated canine Purkinje fibres, hydroxyzine at 3µM increased action potential duration suggesting that there was an interaction with potassium channels involved with the repolarisation phase. At a higher concentration, 30µM, 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 (I_{Kr}) current in human ether –a-go-go-related gene (hERG) channels expressed in mammalian cells, with an IC50 of 0.62µM, a concentration that is between 10 and 60-fold higher than therapeutic concentrations. Moreover, 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 a first dog telemetry study, hydroxyzine (21 mg/kg po) 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 concern. 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.

In rats, hydroxyzine administered for 30 days was well tolerated at 20 mg/kg/day s.c., but some mortalities occurred at 200 mg/kg/day per os.
Chronic toxicity was tested in rats at oral doses up to 50 mg/day in 100 g food for 24 weeks without clinical signs or histopathological abnormalities. Doses of 10 mg/kg/day for 70 days reduced the concentration and the viability of spermatocytes in male rats.

In dogs, oral doses up to 20 mg/kg/day during 6 months were not associated with any histopathological changes.

Teratogenicity was assessed in pregnant rodents: foetal malformations and foetal abortions were associated with doses over 50 mg/kg of hydroxyzine, this being due to the accumulation of norchlorcyclizine metabolite. Teratogenic doses are much higher than those used in man for therapeutic purpose. No mutagenic activity was shown in the Ames test. A mouse lymphoma study showed marginal increases in mutations of low magnitude in the presence of S9 at $\geq$ 15 µg/ml. This was close to the maximum level of toxicity for this study. A study for micronuclei induction in rats was negative. As only very marginal effects were noted in the *in vitro* study and the *in vivo* study was negative, it is considered that hydroxyzine is not a mutagen.

Animal carcinogenicity studies have not been undertaken with hydroxyzine. However, the drug is not mutagenic and has not been associated with any overt increased tumorgenic risk during several decades of clinical use.

6 Pharmaceutical Particulars

6.1 Excipients

Tablet core:

Lactose monohydrate 54,80 mg
Microcrystalline cellulose 28,00 mg
Magnesium stearate 1,50 mg
Colloidal anhydrous silica 0,70 mg

Tablet coating:

Opadry® Y-1-7000 3,30 mg (titane dioxyde 0,21 mg, Hypromellose 2,06 mg, macrogol 400 1,03 mg).

6.2 Incompatibilities

There are no relevant data available.

6.3 Shelf life

60 months

6.4 Storage conditions

Store in dry place, below 25°C

6.5 Nature and contents of container

25 tablets in PVC - aluminium foil blister. 1 blister with leaflet insert inside of carton.

6.6 Special precautions for disposal

There are no special requirements for use or handling of this product.

7 Manufacturer (name, address, company)

UCB Pharma S. A., Chemin du Foriest, B-1420 Braine-I'Alleud, Belgium

8 Marketing Authorisation Holder

GlaxoSmithKline Export Limited, 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK

9. Date of final revision of the text

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