

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

HYDROXYZINE 25 EQUITY film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

HYDROXYZINE 25 EQUITY contains 25 mg hydroxyzine hydrochloride per tablet.

Contains sugar.

HYDROXYZINE 25 EQUITY contains 69,80 mg lactose anhydrous per tablet.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Off-white to white, oblong, biconvex film-coated tablets with score line on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HYDROXYZINE 25 EQUITY is indicated in the short-term (not more than 4 months) management of anxiety, tension and psychomotor agitation in conditions of emotional stress.

HYDROXYZINE 25 EQUITY is also useful for alleviating the manifestations of anxiety and tension in situations in which the causative stress is temporary, as in the preparation for dental and other minor surgical procedures.

In addition, it has been used as adjunctive therapy in allergic conditions with strong emotional overlay, as in urticaria and pruritus.

4.2 Posology and method of administration

Posology

HYDROXYZINE 25 EQUITY should be used at the lowest effective dose and for the shortest possible duration.

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

Since the tablet cannot be halved, other appropriate strengths and dosage forms containing hydroxyzine should be administered in case a lower dose is required.

Anxiety:

Adults: 50-100 mg daily in divided doses.

Other indications:

Adults: 25-100 mg daily in divided doses.

For pruritus a starting dose of 25 mg at night increasing as necessary to 25 mg three or four times daily.

Pre- and postoperative adjunctive medication:

Adults: 50-100 mg.

Special populations

Elderly

In the elderly, the maximum daily dose is 50 mg per day (see section 4.4).

A reduced dose is advised. This is due to a possible increase in the volume of distribution, prolonged action and the possible effect of age-related changes on pharmacologic functions, including hepatic metabolism and renal excretion (see section 5.2).

Hepatic impairment

The total daily dose should be reduced by 33 % in patients with mild and moderate (Child –Pugh class A and B) liver disease. Use in patients with severe (Child-Pugh class C) liver disease should be avoided (see section 4.4).

Renal impairment

For patients with moderate or severe renal impairment, it is recommended that the total daily dosage should be reduced by 50 % due to decreased excretion of its metabolite cetirizine (see section 4.4).

Paediatric population

HYDROXYZINE 25 EQUITY should not be used in children under 6 years of age.

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

Pre- and postoperative adjunctive medication:

Children over 40 kg in weight: 0,6 mg/kg body weight to a maximum of 100 mg daily.

Other indications:

For children over 40 kg in weight, starting at 15-25 mg and increasing to 50-100 mg daily in divided doses adjusted according to the child's weight. Maximum daily dose in children up to 40 kg in bodyweight is 2 mg/kg/day.

Method of administration

Oral use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients in HYDROXYZINE 25 EQUITY (see section 6.1), to cetirizine, to other piperazine derivatives, to aminophylline, or to ethylenediamine.
- 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 (see section 4.4).
- Concomitant use with medicine known to prolong the QT interval and/or induce Torsade de Pointes (see section 4.5).
- Asthmatics who have previously experienced a serious antihistamine-induced adverse bronchopulmonary effect.
- Respiratory failure.

- Porphyria.
- Pregnancy and breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

Cardiovascular effects

HYDROXYZINE 25 EQUITY 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 25 EQUITY should be used at the lowest effective dose and for the shortest possible duration.

Treatment with HYDROXYZINE 25 EQUITY should be stopped if signs and symptoms occur that may be associated with cardiac dysrhythmia, and the patients should seek immediate medical attention.

Patients should be advised to promptly report any cardiac symptoms.

Patients with hepatic impairment

Due to its sedative properties, use of HYDROXYZINE 25 EQUITY should be avoided in patients with severe liver disease (Child -Pugh class C) due to an increased risk of coma, and in patients with hepatic failure due to hepatic encephalopathy.

HYDROXYZINE 25 EQUITY elimination is impaired in patients with hepatic dysfunction secondary to primary biliary cirrhosis. Dosage should be modified for patients with hepatic impairment (see section 4.2 Special populations).

Patients with renal impairment

HYDROXYZINE 25 EQUITY should be used with caution in patients with impaired renal function (see

section 4.2 Special populations). It is uncertain whether the medicine may accumulate or have other adverse effects in such patients. HYDROXYZINE 25 EQUITY is completely metabolised and one of the metabolites is the active metabolite cetirizine. Cetirizine is renally excreted and clearance is reduced in patients with moderate renal impairment and on dialysis compared to normal volunteers.

Elderly

HYDROXYZINE 25 EQUITY 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 section 4.2 Special populations & 4.8). In elderly patients, it is recommended to reduce the dose of HYDROXYZINE 25 EQUITY due to a possible increase in the volume of distribution, prolonged action, and the possible effect of age-related changes on pharmacologic functions, including hepatic metabolism and renal excretion (see section 4.2 Special populations and 5.2).

Because of its potential antimuscarinic actions, HYDROXYZINE 25 EQUITY should be used with caution in patients suffering from angle-closure glaucoma, urinary retention, prostatic hyperplasia, or pyrodoodenal obstruction.

Caution is required in patients suffering from the following conditions:

- seizure disorders including epilepsy
- myasthenia gravis
- dementia
- decreased gastrointestinal motility
- bladder outflow obstruction
- stenotic peptic ulcer
- patients with breathing problems (e.g., emphysema, chronic bronchitis)
- increased intraocular pressure (e.g., closed-angle glaucoma)
- hyperthyroidism
- cardiovascular disease

- hypertension

Dosage adjustments may be required if HYDROXYZINE 25 EQUITY is used simultaneously with other central nervous system depressants or with medicines having antimuscarinic properties (see section 4.5).

The concomitant use of alcohol and HYDROXYZINE 25 EQUITY should be avoided (see section 4.5).

Treatment should be stopped for one week before skin testing for allergy is undertaken, and for 96 hours prior to a methacholine test.

Elderly patients are more susceptible to many adverse effects of HYDROXYZINE 25 EQUITY, including antimuscarinic effects, sedation and hypotension.

Patients should be warned of impaired judgement and dexterity.

Important information regarding the excipients in this medicine

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take HYDROXYZINE 25 EQUITY.

Paediatric population

HYDROXYZINE 25 EQUITY should not be given to children under the age of 6 years (see section 4.2).

Children are more susceptible to adverse effects.

4.5 Interaction with other medicines and other forms of interaction

Associations contraindicated

Co-administration of HYDROXYZINE 25 EQUITY with medicine known to prolong the QT interval and/or induce Torsade de Pointes e.g. class IA (e.g. quinidine, disopyramide) and III antidysrhythmic (e.g. amiodarone, sotalol), some antihistamines, some antipsychotics (e.g. haloperidol), some antidepressants (e.g. citalopram, escitalopram), some antimalarial medicines (e.g. mefloquine), some antibiotics (e.g. erythromycin, levofloxacin, moxifloxacin), some medicines used to treat—cancer (e.g., toremifene,

vandetanib), methadone, increase the risk of cardiac dysrhythmia. Therefore, the combination is contraindicated (see section 4.3).

Associations requiring precaution of use

Caution with bradycardia and hypokalaemia-inducing medicines.

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 medicine known to be potent inhibitors of these enzymes.

Methacholine test

Treatment should be stopped for 96 hours prior to a methacholine test, to avoid effects on the test results (see section 4.4).

Skin testing for allergy

Treatment should be stopped at least one week before skin testing for allergy to avoid effects on the test results (see section 4.4).

Central Nervous System depressants

Patients should be warned that HYDROXYZINE 25 EQUITY may enhance their response to alcohol, barbiturates, benzodiazepines, hypnotics, opioids, anxiolytics, antipsychotics, antidepressants, antiemetics, antiepileptics, other antihistamines, phenothiazines, skeletal muscle relaxants, sedatives, anaesthetics and other central nervous system depressants (see section 4.4).

Antimuscarinics

Antimuscarinic side effects (both peripheral and central) may be increased if HYDROXYZINE 25 EQUITY is given with antimuscarinics such as atropine and some antidepressants (both tricyclic antidepressants and monoamine oxidase inhibitors [MAOIs]) (see section 4.4).

Anticholinergic agents

Additive anticholinergic effects may occur if HYDROXYZINE 25 EQUITY is administered concomitantly with other anticholinergic medicines.

Anticholinesterase medicine

HYDROXYZINE 25 EQUITY may antagonise the effects of anticholinesterase medicines.

Betahistine

HYDROXYZINE 25 EQUITY may antagonise the effects of betahistine.

Cimetidine

Cimetidine, 600 mg twice a day, has been shown to increase the serum concentrations of hydroxyzine by 36 % (as contained in HYDROXYZINE 25 EQUITY) and to decrease peak concentrations of the metabolite cetirizine by 20 %.

CYP2D6 & Cytochrome P450

Hydroxyzine (as contained in HYDROXYZINE 25 EQUITY) is an inhibitor of CYP2D6 and may cause medicine interactions with CYP2D6 substrates. Cetirizine does not interact with other medicine via cytochrome P450.

Medicines that affect the hepatic microsomal enzyme system

Metabolism may be reduced in patients concomitantly receiving medicines that affect the hepatic microsomal enzyme system. Decreased metabolism may result in accumulation of potentially toxic concentrations of unchanged antihistamine.

Ototoxic medicines

It has been suggested that some sedating antihistamines could mask the warning signs of damage caused by ototoxic medicines such as aminoglycoside antibiotics.

Porter-Silber reaction or the Glenn-Nelson method

Hydroxyzine (as contained in HYDROXYZINE 25 EQUITY) has been reported to cause falsely elevated urinary concentrations of 17-hydroxycorticosteroids when the Porter-Silber reactions or the Glenn-Nelson method is used.

When anticoagulants are administered, it is recommended that haemostasis be controlled at the beginning of treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy

HYDROXYZINE 25 EQUITY should not be used during pregnancy (see section 4.3).

Breastfeeding

HYDROXYZINE 25 EQUITY should not be used during breastfeeding (see section 4.3).

4.7 Effects on ability to drive and use machines

Hydroxyzine may cause tiredness, dizziness, sedation, visual disturbances and thereby may have moderate to major influence on the ability to react and to concentrate, in particular at higher doses and/or if alcohol or sedative medicines are co-administered.

Patients should be warned that HYDROXYZINE 25 EQUITY may impair their ability to perform activities requiring mental alertness or physical co-ordination such as operating machinery or driving a vehicle. Concomitant use of HYDROXYZINE 25 EQUITY with alcohol or other central nervous system depressants should be avoided as this may aggravate these effects (see section 4.5).

4.8 Undesirable effects

The most common adverse 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 headache, psychomotor impairment and antimuscarinic effects.

System organ class	Frequency	Adverse Reaction
Blood and lymphatic system disorders	Frequency unknown	Blood disorders, including agranulocytosis, leukopenia, haemolytic anaemia, and thrombocytopenia, hypertension
Immune system disorders	Frequency unknown	Hypersensitivity reactions, anaphylaxis, angioedema
Metabolism and nutrition disorders	Frequency unknown	Porphyria, anorexia
Psychiatric disorders	Frequency unknown	Agitation, confusion, disorientation, hallucinations, sleep disturbances, depression, increased anxiety, nightmares
Nervous system disorders	Frequency unknown	Dyskinesia ⁴ , insomnia, sedation, drowsiness, dizziness, weakness, headache, tremor ¹ convulsions ² , psychomotor impairment, paraesthesia, extrapyramidal effects, seizure, coma, somnolence, disturbance in attention, involuntary motor activity ³ , ataxia, slurred speech, bitter taste in mouth, faintness
Eye disorders	Frequency unknown	Accommodation disorder, blurred vision
Ear and labyrinth disorders	Frequency unknown	Tinnitus, labyrinthitis, vertigo
Cardiac disorders	Frequency unknown	Ventricular dysrhythmias (e.g. Torsade de Pointes), QT interval prolongation (see section 4.4), tachycardia, palpitation
Vascular disorders	Frequency unknown	Hypotension, flushing
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Bronchospasm, thickened respiratory tract secretions, wheezing, nasal stuffiness, dryness of throat
Gastrointestinal disorders	Frequency unknown	Constipation, dryness of the mouth, nausea, vomiting, increased gastric reflux, diarrhoea, epigastric pain, increased

		GI peristalsis
Hepato-biliary disorders	Frequency unknown	Liver dysfunction, jaundice
Skin and subcutaneous tissue disorders	Frequency unknown	Dermatitis, fixed medicine eruption, pruritis, erythema, papular rash, sweating increased, urticaria, hair loss, eczema, acute generalised exanthematous pustulosis (AGEP), toxic epidermal necrolysis, photosensitivity
	Less frequent	Stevens-Johnson syndrome, erythema multiforme
Musculoskeletal and connective tissue disorders	Frequency unknown	Myalgia
Renal and urinary disorders	Frequency unknown	Urinary retention, dysuria
Reproductive system and breast disorders	Frequency unknown	Priapism, impotence, early menses
General disorders and administration site conditions	Frequency unknown	Fatigue, malaise, lassitude, pyrexia, dryness of respiratory mucosae, asthenia, tightness of chest, irritability, chills
Investigations	Frequency unknown	Liver function tests abnormal

Footnotes

^{1, 2, 3} reported usually with doses considerably higher than those recommended. Continuous therapy with over 1g/day has been employed in some patients without these effects having been encountered.

⁴ dyskinesia may follow termination of prolonged antihistamine therapy.

Children and the elderly are more susceptible to adverse effects.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued

monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Overdosage with sedating antihistamines is associated with antimuscarinic, extrapyramidal, and central nervous system (CNS) effects. If CNS stimulation predominates over CNS depression, ataxia, excitement, seizures, tremors, psychosis, hallucinations, convulsions and hyperpyrexia can occur. Coma and cardiorespiratory collapse may follow. CNS stimulation is more likely in children and elderly. In adults, CNS depression is more common with drowsiness, postictal depression, coma, and convulsions, progressing to respiratory failure and cardiovascular collapse. In children and adults, cerebral oedema and upper nephron nephrosis, a deepening coma, tachycardia, QRS widening, heart block, cardiorespiratory collapse/arrest, cardiogenic shock, and death may occur.

Common features include excessive sedation, nausea, vomiting, flushing, dilated pupils, dry mouth and tongue, hot dry skin, fever, sinus tachycardia, hypertension, ataxia, nystagmus, delirium, agitation, psychosis and visual hallucinations. Uncommon systemic features include myoclonic jerking, muscle rigidity, coma, convulsions, cardiac conduction abnormalities, QT prolongation and dysrhythmias, cardiovascular collapse, paralytic ileus, urinary retention, hyperkalaemia, metabolic acidosis and rhabdomyolysis.

Peak concentrations occur approximately two hours post ingestion, and elimination half-life has been reported approximately 14 hours and 20 hours post ingestion (see section 5.2)

There is no specific antidote. It is doubtful whether haemodialysis or peritoneal dialysis has any value in the treatment of overdosage with HYDROXYZINE 25 EQUITY. However, if other medicines such as barbiturates have been ingested concomitantly, dialysis may be indicated.

Consider activated charcoal only if the patient presents within 1 hour of ingestion of a potentially toxic amount.

General supportive care, including frequent monitoring of the vital signs and close observation of the patient is indicated. Clear airways should be maintained, and there should be adequate ventilation. Assisted ventilation is indicated if hypercapnia is present. Observation for 6 hours after ingestion, without any other specific treatment, will be sufficient for the majority of patients. Monitor BP, pulse and body temperature. In

symptomatic patients measure urea, electrolytes and creatine kinase. Perform a 12-lead ECG and monitor cardiac rhythm. Patients who have been unconscious may be hypothermic.

Hypotension, though unlikely, may be controlled with intravenous fluids. In adults, if severe hypotension persists, determine the cause and consider treatment with the following; if hypotension is mainly due to decreased systemic vascular resistance, medicine such as noradrenaline or high dose dopamine may be beneficial, if hypotension is due to reduced cardiac output dobutamine, or in severe cases adrenaline may be beneficial. However it should be noted that hydroxyzine has been shown to inhibit and reverse the vasopressor effect of adrenaline (epinephrine).

Analeptic medicines should not be used since they may cause seizures.

As in the management of overdosage with any medicine, it should be borne in mind that multiple-medicines may have been taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.6.3 Tranquillisers: Diphenylmethane derivatives

ATC class: N05B B01

Mechanism of action

Hydroxyzine is a first generation antihistamine, a piperazine derivative. Hydroxyzine has antimuscarinic and sedative properties.

First-generation H₁ antagonists easily cross the blood-brain barrier, consequently producing well-documented sedative and anticholinergic effects.

First-generation antihistamines also have affinity for 5-HT receptors, alpha-adrenoreceptors, and muscarinic receptors. They also reduce cyclic GMP concentrations, increase atrioventricular nodal conduction, and inhibit activation of airway vagal afferent nerves.

5.2 Pharmacokinetic properties

Absorption

Hydroxyzine is rapidly absorbed from the gastrointestinal tract.

After a single oral dose of hydroxyzine, 0,7 mg/kg (mean dose 39,0 +/- 5,4 mg) a mean maximum serum hydroxyzine concentration of 72.5 +/- 11,1 ng/ml has been shown to occur at a mean time of 2,1 +/- 0,4 hours.

Distribution

Distribution of hydroxyzine into human body tissues and fluids has not been fully characterised.

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

First-generation H₁ antagonists easily cross the blood-brain barrier.

Elimination

Hydroxyzine is extensively metabolised and the elimination half-life is about 20 hours.

Hydroxyzine is metabolised in the liver. Metabolites include cetirizine, which has antihistaminic activity.

Cetirizine is formed from hydroxyzine via an oxidative biotransformation step.

Hydroxyzine is eliminated by hepatic metabolism in humans. Cetirizine is mainly renally excreted.

Elderly patients

Hydroxyzine has a long mean serum elimination half-life value, a large volume of distribution and a prolonged pharmacodynamics effect (suppressive effect on wheal and flare response to histamine) in the elderly.

In the elderly a number of age-related biological and physiological changes may have an effect on the pharmacology of hydroxyzine and its metabolite, cetirizine. These changes may impact upon the pharmacologic functions of absorption, distribution, metabolism, excretion, and receptor sensitivity. Dosage reduction may be appropriate in elderly patients (see section 4.2 'Posology and Method of Administration')

Hepatic impairment

Hydroxyzine elimination was found to be impaired in patients with primary biliary cirrhosis.

Dosage should be adjusted in patients with hepatic impairment (see section 4.2).

Renal impairment

Reduced renal clearance of cetirizine (active metabolite of hydroxyzine) may be of clinical importance in patients with renal failure.

Dosage should be adjusted in patients with renal impairment (see section 4.2).

Paediatric population

The elimination half-life values increased with increasing age. Dosage should be adjusted in the paediatric population (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose anhydrous

Microcrystalline cellulose PH 112

Colloidal anhydrous silica

Magnesium Stearate

Opadry white OY-58900 consisting of hypromellose, titanium dioxide and macrogol 400.

6.2 Incompatibilities

None.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

Store in the blisters in the original container until required to use.

6.5 Nature and contents of container

HYDROXYZINE 25 EQUITY scored film-coated tablets are packed into the following packs:

Alu/PVC and Al/PVC/PVDC blister strips. The blister strips are packed in a cardboard box.

Pack sizes: 28, 30 & 84; 100 film-coated tablets.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd.

100 Sovereign Drive, Route 21 Corporate Park

Nellmapius Drive

Irene, South Africa

8. REGISTRATION NUMBER(S)

56/2.6/0508

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

3 December 2024

10. DATE OF REVISION OF THE TEXT

To be allocated

An electronic copy of the translated Professional Information (PI) is available on the Equity website:

<http://www.equitypharmaceuticals.co.za>