

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Valoid 50 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50mg of cyclizine hydrochloride.

Excipient with known effect:

Lactose (60mg/tablet)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, biconvex, uncoated tablet, scored; coded T4A.

The scoreline is to facilitate breaking for ease of swallowing and to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Valoid is indicated in adults and children aged 6 years and over for the prevention and treatment of nausea and vomiting, including:-

- Motion sickness.
- Nausea and vomiting caused by narcotic analgesics and by general anaesthetics in the post-operative period.
- Vomiting associated with radiotherapy, especially for breast cancer since cyclizine does not elevate prolactin levels.

Valoid may be of value in relieving vomiting and attacks of vertigo associated with Meniere's disease and other forms of vestibular disturbance.

4.2 Posology and method of administration

Posology

To prevent motion sickness Valoid Tablets should be taken about one to two hours before departure.

Older people

There have been no specific studies of Valoid Tablets in the elderly. Experience has indicated that normal adult dosage is appropriate.

Paediatric population

Children less than 6 years of age:

Valoid Tablets are not recommended for children less than 6 years of age.

Children 6 to 12 years of age:

25 mg orally, which may be repeated up to three times a day.

Children over 12 years of age:

50 mg orally, which may be repeated up to three times a day.

Adults

50 mg orally, which may be repeated up to three times a day.

Method of Administration

Oral

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Cyclizine is contraindicated in the presence of acute alcohol intoxication. The anti-emetic properties of cyclizine may increase the toxicity of alcohol.

4.4 Special warnings and precautions for use

As with other anticholinergic agents, Valoid Tablets may precipitate incipient glaucoma and should be used with caution and appropriate monitoring in patients with glaucoma, urinary retention, obstructive disease of the gastrointestinal tract, hepatic disease, phaeochromocytoma, hypertension, epilepsy and in males with possible prostatic hypertrophy.

Cyclizine should be used with caution in patients with severe heart failure or acute myocardial infarction. In such patients, cyclizine may cause a fall in cardiac output associated with increases in heart rate, mean arterial pressure and pulmonary wedge pressure.

Cyclizine should be avoided in porphyria.

There have been reports of abuse of cyclizine, either oral or intravenous, for its euphoric or hallucinatory effects. The concomitant misuse of Valoid Tablets with large amounts of alcohol is particularly dangerous, since the antiemetic effect of cyclizine may increase the toxicity of alcohol (see also sections 4.3. and 4.5.).

Case reports of paralysis have been received in patients using intravenous cyclizine. Some of the patients mentioned in these reports had an underlying neuromuscular disorder. Thus intravenous cyclizine should be used with caution in all patients in general, and in patients with underlying neuromuscular disorders in particular.

Valoid contains lactose.

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

4.5 Interaction with other medicinal products and other forms of interaction

Valoid Tablets may have additive effects with alcohol and other central nervous system depressants e.g. hypnotics, tranquillisers, anaesthetics, antipsychotics, barbiturates.

Valoid Tablets enhance the soporific effect of pethidine.

Valoid Tablets may counteract the haemodynamic benefits of opioid analgesics.

Because of its anticholinergic activity, cyclizine may enhance the side-effects of other anticholinergic drugs, and have an additive antimuscarinic action with other antimuscarinic drugs, such as atropine and some antidepressants (both tricyclics and MAOIs).

Valoid Tablets may mask the warning signs of damage caused by ototoxic drugs such as aminoglycoside antibacterials.

4.6 Fertility, pregnancy and lactation

Pregnancy

In the absence of any definitive human data, the use of Valoid in pregnancy is not advised.

Breast-feeding

Cyclizine is excreted in human milk, however, the amount has not been quantified

Fertility

In a study involving prolonged administration of cyclizine to male and female rats, there was no evidence of impaired fertility after continuous treatment for 90-100 days at dose levels of approximately 15 and 25 mg/kg/day. There is no experience of the effect of cyclizine hydrochloride on human fertility.

4.7 Effects on ability to drive and use machines

Studies designed to detect drowsiness did not reveal sedation in healthy adults who took a single oral therapeutic dose (50 mg) of cyclizine.

Patients should not drive or operate machinery until they have determined their own response.

Although there are no data available, patients should be cautioned that Valoid may have additive effects with alcohol and other central nervous system depressants, e.g. hypnotics and tranquillisers.

4.8 Undesirable effects

The incidence of the below adverse effects is unknown:

Blood and lymphatic system disorders

Agranulocytosis, leucopenia, haemolytic anaemia, thrombocytopenia.

Immune system disorders

Hypersensitivity reactions, including anaphylaxis and hypersensitivity hepatitis have occurred

Psychiatric disorders

Disorientation, restlessness, nervousness, euphoria, insomnia and auditory and visual hallucinations have been reported, particularly when dosage recommendations have been exceeded.

Nervous system disorders

Effects on the central nervous system have been reported with cyclizine these include somnolence, drowsiness, incoordination headache, dystonia, dyskinesia, extrapyramidal motor disturbances, tremor, convulsions, dizziness, decreased consciousness, transient speech disorders, paraesthesia and generalised chorea.

There have been rare case reports of patients experiencing depressed levels of consciousness/loss of consciousness. The use of cyclizine has been associated with cases of paralysis following administration of the intravenous formulation of the medicine. The onset of paralysis is usually within minutes of administration, affects the limbs, and fully resolves within hours of discontinuation of the medicine (see also Section 4.4).

Eye disorders

Blurred vision, oculogyration

Ear and labyrinth disorders

Tinnitus.

Cardiac disorders

Tachycardia, palpitations, arrhythmias

Vascular disorders
Hypertension, hypotension

Respiratory, thoracic and mediastinal disorders
Bronchospasm, apnoea

Gastrointestinal disorders
Dryness of the mouth, nose and throat, constipation, increased gastric reflux.
Nausea, vomiting, diarrhoea, stomach pain.
Loss of appetite

Hepatobiliary disorders
Hepatic dysfunction including hepatitis due to hypersensitivity. Cholestatic jaundice and cholestatic hepatitis have occurred in association with cyclizine.

Skin and subcutaneous tissue disorders
Urticaria, drug rash, angioedema, allergic skin reactions, fixed drug eruption, photosensitivity

Musculoskeletal and connective tissue disorders
Twitching, muscle spasms

Renal and urinary disorders
Urinary retention

General disorders and administration site conditions
Asthenia

IV formulation only:
Blisters at the site of injection and pruritus, as well as sensation of heaviness, chills, agitation and hypotension have been reported.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms:

Symptoms of acute toxicity from cyclizine arise from peripheral anticholinergic effects and effects on the central nervous system.

Peripheral anticholinergic symptoms include dry mouth, nose and throat, blurred vision, tachycardia and urinary retention. Central nervous system effects include drowsiness, dizziness, incoordination, ataxia, weakness, hyperexcitability, disorientation, impaired judgement, hallucinations, hyperkinesia, extrapyramidal motor disturbances, convulsions, hyperpyrexia and respiratory depression.

An oral dose of 5mg/kg is likely to be associated with at least one of the clinical symptoms stated above. Younger children are more susceptible to convulsions. The incidence of convulsions in children less than 5 years is about 60% when the oral dose ingested exceeds 40mg/kg.

Management:

In the management of acute overdosage with Valoid Tablets, gastric lavage and supportive measures for respiration and circulation should be performed if necessary. Convulsions should be controlled in the usual way with parenteral anticonvulsant therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: R06AE

Pharmacotherapeutic Group: Piperazine derivatives

Mechanism of action

Cyclizine is a histamine H₁ receptor antagonist of the piperazine class, which is characterised by a low incidence of drowsiness. It possesses anticholinergic and antiemetic properties. The exact mechanism by which cyclizine can prevent or suppress both nausea and vomiting from various causes is unknown. Cyclizine increases lower oesophageal sphincter tone and reduces the sensitivity of the labyrinthine apparatus. It may inhibit the part of the midbrain known collectively as the emetic centre.

Pharmacodynamic effects

Cyclizine produces its antiemetic effect within 2 hours and lasts approximately 4 hours.

5.2 Pharmacokinetic properties

Absorption

H₁-blockers are well absorbed from the GI tract. Following oral administration effects develop within 30 minutes, are maximal within 1-2 hours and last, for cyclizine, for 4-6 hours.

Distribution

In healthy adult volunteers the administration of a single oral dose of 50 mg cyclizine resulted in a peak plasma concentration of approximately 70 ng/mL occurring at about two hours after drug administration. The plasma elimination half-life was approximately 20 hours.

Biotransformation

The N-demethylated derivative, norcyclizine, has been identified as a metabolite of cyclizine. Norcyclizine has little antihistamine (H₁) activity compared to cyclizine. It is widely distributed throughout the tissues and has a plasma elimination half-life of approximately 20 hours.

Elimination

After a single dose of 50 mg cyclizine given to a single adult male volunteer, urine collected over the following 24 hours contained less than 1% of the total dose administered.

5.3 Preclinical safety data

A. Mutagenicity:

Cyclizine was not mutagenic in a full Ames test, including use of S9-microsomes but can nitrosate in vitro to form mutagenic products.

B. Carcinogenicity:

No long term studies have been conducted in animals to determine whether cyclizine has a potential for carcinogenesis. However, long-term studies with cyclizine administered with nitrate have indicated no carcinogenicity.

C. Teratogenicity:

Some animal studies are interpreted as indicating that Cyclizine may be teratogenic at dose levels up to 25 times the clinical dose level. In another study, cyclizine was negative at oral dose levels up to 65 mg/kg in rats and 75 mg/kg in rabbits. The relevance of these studies to the human situation is not known.

D. Fertility:

In a study involving prolonged administration of cyclizine to male and female rats there was no evidence of impaired fertility after continuous treatment for 90-100 days at dose levels of approximately 15 and 25 mg/kg/day. There is no

experience of the effect of Valoid Tablets on human fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Potato starch
Acacia
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Amber glass or polyethylene bottles with polyethylene tamper-evident caps for pack size 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Amdipharm Limited
Temple Chambers
3 Burlington Road
Dublin 4
Ireland.

8 MARKETING AUTHORISATION NUMBER

PA1142/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation : 01 April 1979

Date of last renewal: 01 April 2009

10 DATE OF REVISION OF THE TEXT

April 2015