

Attachment 1: Product information for AusPAR Valoid cyclizine lactate Link Medical Products Pty Ltd PM-2010-03573-3-1 Final 15 January 2013. This Product Information was approved at the time this AusPAR was published.

VALOID cyclizine lactate
Injection 50mg/mL

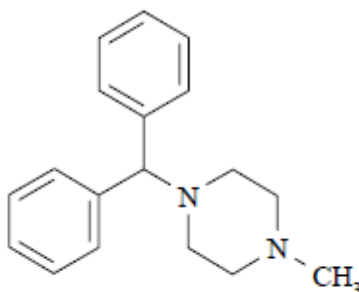
Product Information

Product Information

VALOID™

Name of the Medicine

VALOID injection contains 50mg cyclizine lactate and has the following structural formula



Molecular formula C₁₈H₂₂N₂
Molecular weight 266
CAS no. 82-92-8

Description

Cyclizine is a piperazine-derivative antihistamine used as an anti-emetic agent when given as cyclizine lactate solution by intravenous injection. Cyclizine is a water soluble, bitter, white crystalline, solid, with pKa₁ = 2.16 and pKa₂ = 8.05. VALOID injection is a clear, colourless solution for injection with a pH of 3.3 to 3.7 which contains cyclizine, lactic acid and water for injection. Each 1 mL ampoule contains 50 mg cyclizine lactate.

Pharmacology

Pharmacokinetics:

In healthy adult volunteers the following data were obtained from 6 subjects given a single bolus intravenous 25mg dose of cyclizine lactate.

Subject	AUC _{0-∞} mcg/L*h	MRT h	λ ₂ h ⁻¹	t _{1/2} h	V _{ss} L/kg	V _z L/kg	Cl _{TOT} L/h/kg	Cl _g	% dose in urine
Mean	273.53	15.46	0.0537	13.53	13.43	16.50	0.870	0.00418	0.55
SD	32.53	2.40	0.0077	2.33	2.51	3.33	0.105	0.00244	0.25

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The N-demethylated derivative, norcyclizine, has been identified as a metabolite of cyclizine.

Norcyclizine has little antihistaminic (H₁) activity compared to cyclizine and has a plasma elimination half life of approximately 14 hours.

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

Pharmacodynamics/Mechanism of action:

ATC Code: R60AE03

Pharmacotherapeutic Group: Piperazine derivatives

Cyclizine is a histamine H₁ receptor antagonist of the piperazine class. 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.

Clinical Trials

The principal studies were conducted in young female patients only and may include data from older studies that may not align with current anaesthetic regimens and practice.

A Cochrane review of Drugs for Preventing Post-operative Nausea and Vomiting (PONV) was conducted. This systematic review included randomised, controlled trials that compared a drug with placebo or another drug prevention of PONV, or compared doses or timing of administration and reported PONV as an outcome. Studies of treatment for established PONV were excluded. Study drug could be given pre-operatively, at induction of anaesthesia, intra-operatively or post-operatively (before nausea and vomiting had occurred). Studies in the review could include participants undergoing general anaesthesia, regional anaesthesia or sedation. Overall the review included 737 studies involving 103,237 people. 60 different medications were identified, including cyclizine. A medication was considered effective if it achieved statistically significant benefits when compared to placebo for all four of the following outcomes: nausea, vomiting, nausea or vomiting; and use of rescue anti-emetic.

Efficacy in prevention of PONV was demonstrated for 8 of these 60 drugs, including cyclizine. The review included 10 studies that assessed the efficacy and safety of cyclizine. Compared with placebo, cyclizine had a Relative Risk of 0.65 (95% CI 0.47-0.90) for nausea, 0.57 (95% CI 0.43-0.75) for vomiting and 0.68 (95% CI 0.58-0.80) for nausea or vomiting and 0.27 (95% CI 0.14-0.62) for rescue antiemetic.

Summary Results on the Prevention of drug therapy related nausea and vomiting

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A study was carried out to compare the effectiveness of standard single-dose dexamethasone (n=30) and cyclizine (n=30) on PONV in women receiving spinal morphine and fentanyl for caesarean section under general anaesthesia. In relation to nausea severity scales, cyclizine was found to be superior to placebo (n=30) at 3 and 6 hours and superior to dexamethasone. With respect to vomiting episodes, cyclizine was found to be superior at 3 and 6 hours versus placebo and at 3 hours versus dexamethasone.

A study was carried out to examine the anti-emetic effect of cyclizine compared to droperidol when included in a patient-controlled analgesia regime. No statistically significant differences between groups was found, results were closely similar and better than historical controls leading to author conclusion that "... we have shown cyclizine to be as effective as droperidol in the prevention of PONV when included in a PCA infusion of morphine."

A prospective randomised, double-blind study compared the (antiemetic) effects of cyclizine and perphenazine in reducing the emetic effects of morphine and pethidine. Cyclizine reduced sickness after pethidine pre-operatively $p < 0.0001$. Cyclizine reduced post-operative vomiting and nausea after morphine 10 mg, $p < 0.001$ and pethidine 100 mg, $p < 0.0001$. Cyclizine reduced PONV after morphine 15 mg ($p < 0.0005$).

Indications

VALOID is indicated for the prevention of nausea and vomiting in the post-operative period

Contraindications

VALOID should not be given to individuals with known hypersensitivity to cyclizine.

VALOID should not be given to patients who have severe heart failure. In such patients, cyclizine may cause a fall in cardiac output associated with increases in heart rate, mean arterial pressure and pulmonary wedge pressure.

Precautions

Anticholinergic effects

Cyclizine has anticholinergic effects and may precipitate pre-existing conditions that are likely to be exacerbated by anticholinergic activity, such as urinary retention or obstruction, angle-closure glaucoma, untreated intraocular hypertension, or uncontrolled primary open-angle glaucoma. It may also exacerbate gastrointestinal obstructive disorders and cause dry mouth and constipation.

It has been suggested that the anticholinergic effect of antihistamines such as cyclizine may reduce the volume and cause thickening of bronchial secretions, resulting in obstruction of

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respiratory tract. Cyclizine should be administered cautiously in patients with asthma or chronic obstructive pulmonary disease.

Cardiovascular effects

Cyclizine should not be used in patients with severe heart failure. In such patients, cyclizine may cause a fall in cardiac output associated with increases in heart rate, mean arterial pressure and pulmonary wedge pressure.

Use in porphyria

Cyclizine should be avoided in porphyria.

Nervous system

Nervous system side effects of cyclizine have included drowsiness and sedation in many patients. Motor skills may be impaired. Cyclizine may also cause restlessness, excitation, nervousness and insomnia. Extrapyrimal effects may occur and dystonic reactions have been reported after single doses of cyclizine

There have been reports of abuse of cyclizine, either oral or intravenous, for its euphoric or hallucinatory effects. The concomitant misuse of VALOID with large amounts of alcohol is particularly dangerous, since the antiemetic effect of cyclizine may increase the toxicity of alcohol.

There have been isolated case reports of transient paralysis occurring in patients using intravenous cyclizine. Two 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.

Studies designed to detect drowsiness did not reveal sedation in healthy adults who took a single oral therapeutic dose (50 mg) of cyclizine lactate. Sedation of short duration was reported by subjects receiving intravenous 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.

In studies in which atropine has been used as part of the anaesthetic regime, cyclizine has been found to be not effective in treating PONV. This may be due to the central anti-cholinergic activity of atropine affecting the anti-emetic effect of cyclizine.

Effects on fertility

The effects of cyclizine on human fertility are unknown. There are no adequate nonclinical studies of the effects of cyclizine on fertility.

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Use in pregnancy (Category B3)

Administration of cyclizine to rat, mice and rabbits during gestation was associated with malformations including cleft palate and various cephalic abnormalities; the no-effect doses determined in rats and rabbits were 50 and 25 mg/kg/day, respectively. There has been no systematic assessment of the safety of cyclizine in pregnancy in humans therefore the use of VALOID in pregnancy is not recommended.

Use in lactation

It is not known whether cyclizine and/or its metabolites are excreted in human milk. The use of VALOID in breastfeeding women is not recommended.

Paediatric Use

The safety and effectiveness of cyclizine in the treatment of post-operative nausea and vomiting has not been assessed. Children may be more sensitive to the anticholinergic side effects of cyclizine. Use is not recommended.

Use in the Elderly

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

Genotoxicity

In bacterial reverse mutation assays, cyclizine *per se* was negative in all tested strains, while nitrosated cyclizine was positive in some strains. No other genotoxicity studies have been conducted with cyclizine.

Effects on ability to drive and operative machines

Patients given intravenous cyclizine 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. anaesthetic agents, hypnotics and tranquillizers.

Interaction with other medicines

VALOID may have additive effects with alcohol and other central nervous system depressants e.g. hypnotics, tranquilisers, anaesthetics.

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VALOID enhances the soporific effect of pethidine. In nonclinical studies, cyclizine potentiated the antiemetic effects of pentazocine and morphine in rodents.

Because of its anticholinergic activity, cyclizine may enhance the side-effects of other anticholinergic drugs.

In studies in which atropine has been used part of the anaesthetic regime, cyclizine has been found to be not effective in treating PONV. This may be due to the central anti-cholinergic activity of atropine affecting the anti-emetic effect of cyclizine.

In vitro studies using human liver preparations identified a weak inhibitory effect of cyclizine on CYP2D6 (IC₅₀ 109µM) which is unlikely to be clinically relevant, and moderate inhibitory activity on estrone sulfotransferase at a concentration (IC₅₀ 0.44µM) close to clinical plasma concentrations, although the clinical significance is not known.

Adverse effects

The incidence of adverse effects due to cyclizine alone has not been examined in clinical trials and the incidence of adverse events listed in this section has not been accurately determined.

Blood and lymphatic system disorders

Agranulocytosis

Cardiac disorders

Tachycardia

Eye disorders

Blurred vision, oculogyric crisis

Gastrointestinal system disorders

Dryness of the mouth, nose and throat, constipation

General disorders and administration site conditions

Asthenia

Injection site reactions including vein tracking, erythema, pain, thrombophlebitis and blisters. A sensation of heaviness, chills and pruritus have been reported rarely.

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Anaphylaxis has been recorded following intravenous administration of cyclizine co-administered with propanidid in the same syringe.

Hepatobiliary disorders

Hepatic dysfunction, hypersensitivity hepatitis, cholestatic jaundice and cholestatic hepatitis have occurred in association with cyclizine.

Immune system disorders

Hypersensitivity reactions, including anaphylaxis have occurred.

Musculoskeletal and connective tissue disorders

Twitching, muscle spasms

Nervous system disorders

Effects on the central nervous system have been reported with cyclizine. These include somnolence, 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 transient 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.

Psychiatric disorders

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

Renal and urinary disorders

Urinary retention

Respiratory, thoracic and mediastinal disorders

Bronchospasm, apnoea

Skin and subcutaneous tissue disorders

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Urticaria, pruritus, drug rash, angioedema, allergic skin reactions, fixed drug eruption

Vascular disorders

Hypertension, hypotension

Dosage and administration

Treatment with VALOID should commence within first 24 hours of surgery and should not continue beyond 48 hours.

There are no data on the use of VALOID in the treatment of established post-operative nausea and vomiting.

Route of Administration: intravenous

Adults

50 mg intravenously up to three times daily.

When used intravenously, VALOID should be injected slowly into the bloodstream, with only minimal withdrawal of blood into the syringe.

For the prevention of postoperative nausea and vomiting, administer the first dose by slow intravenous injection 20 minutes before the anticipated end of surgery.

Overdosage

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.

Treatment

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

In case of overdose, immediately contact the Poisons Information Centre (in Australia, call 13 11 26 for advice).

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Presentation and storage conditions

1mL neutral glass ampoules. Five ampoules in a carton.
Each mL contains 50 mg cyclizine lactate

Shelf Life

Four years

Special Precautions for Storage

Store below 25°C
Protect from light, keep the ampoule in the outer carton.

AUST R 180894

Name and address of sponsor

Link Medical Products Pty Ltd
5 Apollo St.
Warriewood, NSW 2102

Poison schedule of the medicine

Prescription only medicine - S4

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG)

19 June 2012