Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Valoid 50 mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml ampoule contains 50mg cyclizine lactate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection

Clear, colourless solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Valoid is indicated in adults for the prevention and treatment of nausea and vomiting, including:-

- Motion sickness, when the oral route cannot be used.
- 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 Injection, by the intravenous route, is also indicated pre-operatively in patients undergoing emergency surgery in order to reduce the hazard of regurgitation and aspiration of gastric content during induction of general anaesthesia.

Valoid may be of value in relieving vomiting and attacks of vertigo associated with Menière's disease and other forms of vestibular disturbance when the oral route cannot be used.

4.2 Posology and method of administration

Posology

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

Adults
50 mg intramuscularly or intravenously up to three times daily.

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

Cyclizine given intravenously, in half the recommended dose, increases the lower oesophageal sphincter tone and thereby reduces the hazard of regurgitation and aspiration of gastric contents if given to patients, undergoing emergency surgery, before induction of general anaesthesia.

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

Paediatric population
Not licensed for use in children.

Method of Administration:
Intramuscularly or intravenously.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Valoid Injection 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 may precipitate incipient glaucoma and it 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. Valoid Injection may have a hypotensive effect.

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 with large amounts of alcohol is particularly dangerous, since the antiemetic effect of cyclizine may increase the toxicity of alcohol (see also Section 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

Valoid enhances the soporific effect of pethidine.

Valoid Injection may counteract the haemodynamic benefits of opioid analgesics.

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

Valoid 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 Valoid Injection 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, 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 tranquilizers.

4.8 Undesirable effects

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: Very common: (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Not known: cannot be estimated from the available data.

The following undesirable effects have been reported with a frequency of Not known:

System Organ Class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Not known	Agranulocytosis, leucopenia, Haemolytic anaemia, thrombocytopenia
Cardiac disorders	Not known	Tachycardia, palpitations, arrhythmias
Ear and labyrinth disorder	Not known	Tinnitus
Eye disorders	Not known	Blurred vision, oculogyration
Gastrointestinal disorders	Not known	Dryness of the mouth, nose and throat, constipation increased gastric reflux. Nausea, vomiting, diarrhoea stomach pain Loss of appetite
General disorders and administration site conditions	Not known	Asthenia, malaise

Hepatobiliary disorders	Not known	Hepatic dysfunction including hepatitis due to hypersensitivity. Cholestatic jaundice and cholestatic hepatitis have occurred in association with cyclizine.
Immune system disorders	Not known	Hypersensitivity reactions, including anaphylaxis and hypersensitivity hepatitis have occurred.
Musculoskeletal and connective tissue disorders	Not known	Twitching, muscle spasms
Nervous system disorders	Not known	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*
Psychiatric disorders	Not known	Disorientation, restlessness, nervousness, euphoria, insomnia and auditory and visual hallucinations have been reported, particularly when dosage recommendations have been exceeded
Renal and urinary disorders	Not known	Urinary retention
Respiratory, thoracic and mediastinal disorders	Not known	Bronchospasm, apnoea
Skin and subcutaneous tissue disorders	Not known	Urticaria, pruritus, drug rash, angioedema, allergic skin reactions, fixed drug eruption, photosensitivity
Vascular disorders	Not known	Hypertension, hypotension

* 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).

IV formulation only:
Blisters at the site of injection and pruritus, as well as sensation of heaviness, chills, agitation, flushing and hypotension have been reported.
Rapid IV administration can lead to symptoms similar to overdose.

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 5 mg/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 five years, is about 60% when the oral dose ingested exceeds 40 mg/kg.

Management:
In the management of acute overdosage with Valoid 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

Pharmacotherapeutic Group: Piperazine derivatives

ATC Code: R06AE03

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 anti-emetic effect within two hours and lasts approximately four hours.

5.2 Pharmacokinetic properties

Distribution
In healthy adult volunteers the administration of a single oral dose of 50mg cyclizine resulted in the peak plasma concentration of approximately 70ng/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 antihistaminic (H_1) activity compared to cyclizine 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 Injection on human fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactic acid
Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25°C.
Keep the ampoule in the outer carton in order to protect it from direct sunlight.

6.5 Nature and contents of container

1 ml neutral glass ampoules. Five ampoules in a carton.

6.6 Special precautions for disposal and other handling

For single use only. Discard any unused contents.

7 MARKETING AUTHORISATION HOLDER

Amdipharm Limited
Temple Chambers
3 Burlington Road
Dublin 4
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1142/001/001

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

July 2018