Package leaflet: Information for the user

Valoid® 50 mg/1 ml Solution for Injection
(Cyclizine lactate)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

The name of your medicine is Valoid 50 mg/1 ml Solution for Injection. It will be referred to Valoid Injection for ease hereafter.

What is in this leaflet

1. What Valoid Injection is and what it is used for

Each 1 ml injection ampoule contains 50 mg of the active ingredient, cyclizine lactate.
Valoid Injection belongs to a group of medicines called antihistamines. It is used in adults to block the effects of substances called histamine and acetylcholine in your body, which can make you feel sick (nausea) or actually vomit. Valoid Injection is used for travel or motion sickness, and nausea which can be caused by radiotherapy of some medicines.

Some ear disorders, for example Menière's disease, can cause loss of balance. Valoid Injection is used to treat the dizziness and vomiting which can come with this.

Valoid injection is used to prevent and treat nausea and vomiting caused by certain painkillers (narcotic analgesics) and general anaesthetics following surgery.

Valoid Injection may be given before emergency surgery to stop this happening during the operation.

2. What you need to know before you are given Valoid Injection

Do not use Valoid Injection if you:

- are allergic to cyclizine lactate or any of the other ingredients of this medicine (listed in section 6). Allergic reactions include mild symptoms such as itching and /

or rash. More severe symptoms include swelling of the face, lips, tongue and / or throat with difficulty in swallowing or breathing
- have been drinking alcohol. The anti-vomiting properties of cyclizine may increase the toxicity of alcohol.

If any of these apply to you, or if you are not sure, speak to your doctor or nurse before being given this medicine.

Warnings and precautions
Talk to your doctor or nurse before being given Valoid Injection if you:
- suffer from glaucoma (eye disease caused by too much pressure within the eye)
- suffer from urinary retention (experience difficulty passing urine)
- suffer from stomach cramps, abdominal pains or constipation
- have any liver problems
- have a phaeochromocytoma (tumour of the medulla of the adrenal glands)
- have high blood pressure
- have epilepsy
- are a man, and suffer from an enlarged prostate gland
- are being treated for a weak heart or heart beat (heart failure)
- suffer from an inherited disorder which can lead to sensitivity to sunlight (porphyria)
- have any problems with your muscles or the nerves that control them.

Children
Valoid Injection is not recommended for use in children.

Other medicines and Valoid Injection
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines, especially the following:
- medicines for problems such as depression, anxiety or difficulty sleeping
- strong painkillers such as pethidine
- any medicine which belongs to a group of medicines called anticholinergics
- certain antibiotics called aminoglycosides such as gentamicin and neomycin.

Valoid Injection with food, drink and alcohol
Alcohol should be avoided when taking Valoid Injection.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or nurse for advice before taking this medicine. The active ingredient of Valoid Injection is excreted in breast milk.

Driving and using machines

Valoid Injection may cause drowsiness in some people. You should avoid driving until you have found out how Valoid Injection affects you. If it makes you feel sleepy, do not drive or operate machinery.

3. How Valoid Injection will be given to you

Your doctor will decide on a dose which is right for you.

Valoid Injection can be given as a slow injection into a vein (i/v) or by injection into a muscle (i/m).

The recommended dose for adults is 50 mg, up to three times a day.

For prevention of sickness during emergency surgery, half the recommended dose may be given, before the anaesthetic, injected into a vein.

For prevention of sickness after a normal operation, your doctor will give the first dose of Valoid Injection by injection into a vein, approximately 20 minutes before the end of the operation.

If you use more Valoid Injection than you should

If you think you have been given too much Valoid Injection or if someone else takes your medicine by mistake, tell a doctor or nurse at once. An overdose could cause a dry mouth nose and throat, blurred vision, a faster heart beat, difficulties when passing urine, feeling sleepy, dizziness, difficulties controlling movements, weakness, feelings of excitement, disorientation, impaired judgement, hallucinations, fits, a high fever and breathing difficulties.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you notice:

- itching or skin rashes
- swelling of the face, lips or throat
- difficulty in breathing or wheeziness.

Tell your doctor immediately. These may be signs of an allergic reaction.

Please tell your doctor if you experience any of the following while you are taking Valoid Injection.

The following side effects are reported with a not known frequency (frequency cannot be estimated from the available data)

- muscle twitches, spasms or tremors
- restlessness
- being confused, disorientated or unaware
- decrease in muscle tone that can cause irregular body movements
- unusual body movements, particularly of hand, arms or legs
- lack of coordination

- temporary difficulty in speaking
- blurred vision or involuntary rolling of the eyes
- convulsions; seizures
- dizziness
- pins and needles
- decreased consciousness/ loss of consciousness
- nervousness
- seeing or hearing things that are not really there (hallucinations)
- ringing in the ears
- euphoria
- headache
- fast heartbeat; irregular heartbeat
- high blood pressure
- drowsiness or general feelings of weakness / tiredness
- a dry mouth, nose or throat
- heartburn (reflux)
- stomach pain
- nausea
- vomiting
- diarrhoea
- loss of appetite
- difficulty passing water
- constipation
- difficulty in sleeping
- yellowing of the skin and the whites of your eyes (jaundice)
- a red or brownish patch which appears at the same spot each time you take the medicine
- inflammation of the liver (hepatitis) or problems with the liver
- reduced rate of breathing (apnoea)
- reduction in the production of a type of white blood cell making infection more likely (agranulocytosis)
- injection site reactions such as redness, pain, swelling or blistering
- sensations of heaviness, flushing, feeling cold or agitated or experiencing a decrease in blood pressure.

If you feel very tired, experience unexpected bruising or bleeding or more infections (e.g. colds and sore throats) than usual please tell your doctor. Your doctor may decide to conduct tests on your blood periodically as a result of these symptoms.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly 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.
By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Valoid Injection

Keep this medicine out of the sight and reach of children.
Store below 25ºC. Keep the ampoule in the outer carton, in order to protect it from direct sunlight.
Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month..
Do not use this medicine if there are any particles floating in it.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Valoid Injection contains

The active substance is cyclizine lactate. Each 1 ml ampoule contains 50 mg of cyclizine lactate.
The other ingredients are lactic acid and water for injections.

What Valoid Injection looks like and contents of the pack

Valoid Injection is a clear, colourless solution.
Valoid Injection is available in cartons of 5 x 1 ml glass ampoules.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Amdipharm Limited
Temple Chambers
3 Burlington Road
Dublin 4
Ireland

Manufacturer:

Famar A.V.E.
Alimos Plant, 63 Agiou,
Dimitriou Str., Alimos Attiki,
17456, Greece

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Valoid is a registered trademark of Amdipharm Mercury International Limited.

To the Medical and Pharmaceutical Professions

1. NAME OF THE MEDICINAL PRODUCT

Valoid 50 mg/ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml 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 can not 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 can not 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 side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly 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.
By reporting side effects you can help provide more information on the safety of this medicine.

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

ATC Code: R06AE03
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 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 (H1) 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

PA 1142/1/1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 1st April 1979/
Date of latest renewal: 1st April 1999

10. DATE OF REVISION OF TEXT

February 2019