NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Cyclizine Lactate 50 mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 50 mg cyclizine lactate (corresponds to 37.35 mg of cyclizine).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to slightly yellow solution and free from visible particles. pH 3.3-3.7

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated 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 postoperative period
- vomiting associated with radiotherapy, especially for breast cancer since cyclizine does not elevate prolactin levels.

Intravenous cyclizine is indicated pre-operatively in patients undergoing emergency surgery to reduce the hazard of regurgitation and aspiration of gastric contents during induction of general anaesthesia.

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

4.2 Dose and method of administration

For adult administration only.

The recommended dose is 50 mg administered intramuscularly (IM) or intravenously (IV), which may be repeated up to three times a day.

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

To prevent post-operative vomiting the first dose should be given by slow IV injection 20 minutes before the anticipated end of surgery.

Cyclizine given IV, in half the recommended dose, increases the lower oesophageal sphincter tone thus reducing the hazard of regurgitation and aspiration of gastric contents when given to patients undergoing emergency surgery before the induction of general anaesthesia.

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

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, cyclizine 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, pheochromocytoma, hypertension, epilepsy and in males with possible prostatic hypertrophy. Cyclizine 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 cyclizine 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 case reports had an underlying neuromuscular disorder. Thus intravenous cyclizine, should be used with caution in all patients and with particular care in patients with underlying neuromuscular disorders.

4.5 Interaction with other medicines and other forms of interaction

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

Cyclizine enhances the soporific effect of pethidine.

Cyclizine 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).

Cyclizine 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 cyclizine in pregnancy is not advised.

Breastfeeding

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 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 cyclizine may have additive effects with alcohol and other central nervous system depressants, e.g. hypnotics and tranquillisers.

4.8 Undesirable effects

Blood and lymphatic system disorders

Agranulocytosis, leucopenia, haemolytic anaemia, thrombocytopenia.

Immune system disorders

Hypersensitivity reactions, including anaphylaxis have occurred.

Psychiatric disorders

Disorientation, restlessness or agitation, 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, restless legs syndrome, tremor, convulsions, dizziness, decreased consciousness, transient speech disorders, paraesthesia, paralysis*and generalised chorea.

*Case reports of paralysis have been received in patients using intravenous cyclizine. Some of the patients mentioned in these case reports had an underlying neuromuscular disorder (see section 4.4).

Eye disorders

Blurred vision, oculogyric crisis.

Ear and labyrinth disorders

Tinnitus.

There have been rare case reports of patients experiencing depressed levels of consciousness/loss of consciousness.

Cardiac disorders

Tachycardia palpitations, arrhythmias (see section 4.4).

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 (see section 4.4), hypersensitivity hepatitis, cholestatic jaundice and cholestatic hepatitis have occurred in association with cyclizine.

Skin and subcutaneous tissue disorders

Urticaria, pruritus, 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.

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

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

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 https://nzphvc.otago.ac.nz/reporting/

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

Management

In the management of acute overdosage with cyclizine, 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Piperazine derivatives, ATC code: R06AE

Mechanism of action

Cyclizine is a histamine H_1 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 two hours and lasts approximately four hours.

5.2 Pharmacokinetic properties

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 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

Mutagenicity

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

Carcinogenic potential

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.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactic acid
Water for injections

6.2 Incompatibilities

None known.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened: 2 years

Diluted solution:

Chemical and physical in-use stability has been demonstrated 24 hours at 25°C for the diluted solution.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.

Keep the ampoules in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

1 ml colourless glass one-point-cut (OPC) ampoules type I containing 1 ml solution for injection.

Each pack contains 5 or 10 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product can be diluted to a concentration of 5 mg/ml with glucose 50 mg/ml (5%), sodium chloride 9 mg/ml (0.9%) or water for injections.

The solution should be examined visually following dilution and immediately prior to administration and should not be used if any cloudiness or particulate matter is present.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

17 October 2019

10 DATE OF REVISION OF THE TEXT

15 June 2021

SUMMARY TABLE OF CHANGES

Date of Revision	Section Changed	Summary of new information
19/12/2019	6.5	• Addition of 5 ampoule pack size.
14 April 2020	3 6.3	• Amend solution colour • Extend shelf life to 2 years.
15 June 2021	4.8 8	• Nervous system disorders: addition of restless legs syndrome • PO box update