

NEW ZEALAND DATA SHEET

ANEXATE® 0.5mg/5mL, solution for injection

Flumazenil

1 PRODUCT NAME

Anexate, 0.5mg/5mL, solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 0.1mg flumazenil

1 ampoule with 5 mL contains 0.5mg flumazenil

For full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Solution for injection. Anexate is a colourless to almost-colourless, sterile, clear liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Anexate is indicated for reversal of the centrally sedative effects of benzodiazepines. It should therefore be used in anaesthesia and intensive care in the following indications:

In anaesthesia

- Termination of general anaesthesia induced and maintained with benzodiazepines in inpatients.
- Reversal of benzodiazepine sedation in short diagnostic and therapeutic procedures in both inpatients and outpatients.
- Reversal of paradoxical reactions due to benzodiazepines.

In intensive care and in the management of unconsciousness of unknown origin

- For the diagnosis and/or management of benzodiazepine overdose due to self-poisoning or accidental overdose.
- As a diagnostic measure in unconsciousness of unknown origin to differentiate between involvement of benzodiazepines, other medicines or drugs or brain damage.
- Anexate may also be used for specific reversal of the central effects of benzodiazepines in drug or medicine overdose (return to spontaneous respiration and consciousness in order to render intubation unnecessary or allow extubation).

4.2 Dose and method of administration

Anexate is recommended for intravenous (IV) use only and should be administered by an anaesthesiologist or experienced physician.

For instructions on handling Anexate, see Section 6.6.

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Dosage should be titrated for the intended effect. Since the duration of action of some benzodiazepines may exceed that of Anexate, repeated doses may be required if sedation recurs following awakening.

In anaesthesia

The recommended initial dose of Anexate is 0.2 mg administered IV over 15 seconds. If the desired degree of consciousness is not obtained within 60 seconds, a second dose of 0.1 mg can be injected; this may be repeated at 60-second intervals where necessary, up to a total dose of 1 mg. The usual dose is 0.3-0.6 mg, but individual requirements may vary considerably, depending on the dose and duration of effect of the benzodiazepine administered and patient characteristics.

In intensive care and in the management of unconsciousness of unknown origin

The recommended initial dose of Anexate is 0.3 mg IV. If the desired level of consciousness is not obtained within 60 seconds, Anexate may be injected repeatedly until the patient awakes or up to a total dose of 2 mg. If drowsiness recurs, Anexate may be administered as one or more bolus IV doses as above, or as an IV infusion of 0.1-0.4 mg per hour. The rate of infusion should be individually adjusted to the desired level of arousal.

If a significant improvement in consciousness or respiratory function is not obtained after repeated doses of Anexate, a non-benzodiazepine aetiology must be assumed.

In the intensive care unit, in patients treated with high doses of benzodiazepines and/or for long periods of time, the individually titrated injections of Anexate, slowly administered, should not produce withdrawal syndromes. If unexpected symptoms occur, diazepam or midazolam could be carefully titrated intravenously according to patient response (see Section 4.4).

Special dosage instructions

Children >1 year-of-age

For the reversal of conscious sedation induced with benzodiazepines in children above one year-of-age, the recommended initial dose is 0.01 mg/kg (up to 0.2 mg) administered IV over 15 seconds. If the desired level of consciousness is not obtained after waiting an additional 45 seconds, further injections of 0.01 mg/kg (up to 0.2 mg) can be administered and repeated at 60-second intervals where necessary (up to a maximum of four additional times) to a maximum total dose of 0.05 mg/kg or 1 mg, whichever is lower. The dose should be individualised based on patient response. No data are available on the safety and efficacy of repeated administration of Anexate to children for re-sedation.

Hepatic Impairment

Since Anexate is primarily metabolised in the liver, careful titration of dosage is recommended in patients with impaired hepatic function.

4.3 Contraindications

Anexate is contraindicated in patients with known hypersensitivity to the medicine.

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Anexate is contraindicated in patients who have been given a benzodiazepine for control of a potentially life-threatening condition (e.g. control of intracranial pressure or status epilepticus).

4.4 Special warnings and precautions for use

Particular caution is necessary when using Anexate in cases of mixed-substance overdose since the toxic effects (such as convulsions and cardiac dysrhythmias) of other medicines taken in overdose (especially cyclic antidepressants) may emerge with the reversal of benzodiazepine effects by Anexate.

The use of Anexate is not recommended in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Although Anexate exerts a slight intrinsic anticonvulsant effect, its abrupt suppression of the protective effect of a benzodiazepine agonist can give rise to convulsions in epileptic patients.

Patients who have received Anexate for the reversal of benzodiazepine effects should be monitored for re sedation, respiratory depression or other residual benzodiazepine effects for an appropriate period based on the dose and duration of effect of the benzodiazepine employed. As patients with underlying hepatic impairment may experience delayed benzodiazepine effects, an extended observation period may be required.

When Anexate is used with neuromuscular-blocking agents, it should not be injected until the effects of neuromuscular blockade have been fully reversed.

Anexate should be used with caution in patients with head injury as it may be capable of precipitating convulsions or altering cerebral blood flow in patients receiving benzodiazepines.

Rapid injection of Anexate should be avoided in patients with high dose and/or long-term exposure to benzodiazepines ending at any time within the weeks preceding Anexate administration as it may produce withdrawal symptoms, including agitation, anxiety, emotional lability as well as mild confusion and sensory distortions (see Section 4.2).

Anexate is not recommended either as a treatment for benzodiazepine dependence or for the management of protracted benzodiazepine abstinence syndromes.

Anexate should be used with caution for the reversal of conscious sedation in children below the age of one year, for the management of overdose in children, for resuscitation of the newborn and for reversal of the sedative effects of benzodiazepines used for induction of general anaesthesia in children, as experience is limited (see Section 4.2).

Paediatric Use

See Section 4.4 above.

Hepatic Impairment

See Section 4.2 and Section 4.4 above.

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4.5 Interaction with other medicines and other forms of interaction

Anexate blocks the central effects of benzodiazepines by competitive interaction at the receptor level. The effects of non-benzodiazepine agonists at benzodiazepine receptors, such as zopiclone, triazolopyridazines and others, are also blocked by Anexate.

The pharmacokinetics of benzodiazepine agonists are unaltered in the presence of Anexate and vice versa.

There is no pharmacokinetic interaction between ethanol and flumazenil.

4.6 Fertility, pregnancy and lactation

Pregnancy

Although in-vitro and animal studies using high doses of Anexate have not shown evidence of mutagenicity, teratogenicity or impairment of fertility, the safety of Anexate in human pregnancy has not been established. Therefore, the benefits of medication during pregnancy should be weighed against possible risks to the foetus.

Breastfeeding

Parenteral administration of Anexate in emergencies is not contraindicated during lactation.

Fertility

Animal studies using high doses of Anexate have not shown evidence of impairment of fertility.

4.7 Effects on ability to drive and use machines

Patients should be warned against engaging in hazardous activities requiring complete mental alertness (such as operating dangerous machinery or driving a motor vehicle) during the first 24 hours after administration since the effect of the originally ingested or administered benzodiazepine (for example, sedation) may occur.

4.8 Undesirable effects

Anexate is well tolerated in adults and children. In adults, Anexate is well tolerated even at doses exceeding those recommended.

Hypersensitivity reactions, including anaphylaxis, have been observed.

Complaints such as feelings of anxiety, palpitations and fear have been infrequently observed after rapid injection of Anexate. These adverse effects usually do not necessitate special treatment.

Seizures have been reported in patients known to suffer from epilepsy or severe hepatic impairment, particularly after long-term treatment with benzodiazepines or in cases of mixed-substance overdose.

In cases of mixed-substance overdose, particularly with cyclic antidepressants, toxic effects (such as convulsions and cardiac dysrhythmias) may emerge with the reversal of benzodiazepine effects by Anexate.

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Withdrawal symptoms may occur following rapid injection of Anexate in patients with long-term exposure to benzodiazepines ending at any time within the weeks preceding Anexate administration.

Anexate has been reported to provoke panic attacks in patients with a history of panic disorders.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

There is very limited experience of acute overdose in humans with Anexate.

There is no specific antidote for overdose with Anexate. Treatment of an overdose with Anexate should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

Even when given at doses exceeding those recommended, no symptoms of overdosage were observed. For withdrawal symptoms attributable to the agonist, see Section 4.2.

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: Benzodiazepine antagonist.

ATC code: V03AB25

Anexate, an imidazobenzodiazepine derivative, is a benzodiazepine antagonist. It competitively inhibits agents that act via benzodiazepine receptors, specifically blocking their central nervous effects. In animal experiments, the effects of compounds showing affinity for benzodiazepine receptors were blocked. In healthy volunteers, IV Anexate has been shown to antagonise the sedation, amnesia and psychomotor impairment produced by benzodiazepine agonists. Hypnotic-sedative benzodiazepine effects are rapidly reversed by Anexate after IV injection (1-2 minutes) and may then reappear gradually within the next few hours depending on the half-life and dose ratio of the agonist and antagonist.

Anexate may possess some weak intrinsic agonistic (e.g. anticonvulsant) activity.

In animals pre-treated with high doses of benzodiazepines over several weeks, Anexate elicited symptoms of benzodiazepine withdrawal, including seizures. A similar effect was seen in adult human subjects.

5.2 Pharmacokinetic properties

Absorption

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The pharmacokinetics of flumazenil is dose-proportional within and above the therapeutic range (up to 100 mg).

Distribution

Flumazenil, a weak lipophilic base, is about 50% bound to plasma proteins. Albumin accounts for two-thirds of plasma protein binding. Flumazenil is extensively distributed in the extravascular space. Plasma concentrations of flumazenil decrease with a half-life of 4-11 minutes during the distribution phase. The volume of distribution at steady state is 0.9-1.1 L/kg.

Biotransformation

Flumazenil is extensively metabolised in the liver. The carboxylic acid metabolite is the main metabolite in plasma (free form) and urine (free form and its glucuronide). This main metabolite shows no benzodiazepine agonist or antagonist activity in pharmacological tests.

Elimination

Flumazenil is almost completely (99%) eliminated by non-renal routes. Practically no unchanged flumazenil is excreted in the urine, suggesting complete metabolic degradation of the medicine. Elimination of radiolabelled substance is essentially complete within 72 hours, with 90-95% of the radioactivity appearing in urine and 5-10% in the faeces. Elimination is rapid, as shown by a short elimination half-life of 40-80 minutes. The total plasma clearance of flumazenil is 0.8-1.0 L/hr/kg and can be attributed almost entirely to hepatic clearance.

Ingestion of food during an intravenous infusion of flumazenil results in a 50% increase in clearance, most likely due to the increased hepatic blood flow that accompanies a meal.

Pharmacokinetics in special populations

In patients with impaired liver function, the elimination half-life of flumazenil is longer (1.3 hours in moderate impairment and 2.4 hours in severely impaired patients) and the total body clearance is lower than in healthy subjects. The pharmacokinetics of flumazenil are not significantly affected in the elderly, by gender, haemodialysis or renal failure.

The elimination half-life in children over one year of age is more variable than in adults, averaging 40 minutes and generally ranging from 20-75 minutes. Clearance and volume of distribution, normalised for body weight, are in the same range as is seen in adults.

5.3 Preclinical safety data

In-vitro and animal studies using high doses of Anexate have not shown evidence of mutagenicity, teratogenicity or impairment of fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate, glacial acetic acid, sodium chloride, sodium hydroxide, sterile water for injections.

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6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in Section 6.6.

6.3 Shelf life

5 years. This medicine should not be used after the expiry date (EXP) shown on the pack.

Also see Section 6.6.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Anexate ampoules contain 0.5 mg flumazenil in 5 mL aqueous solution for intravenous (IV) administration. Anexate is a colourless to almost-colourless, sterile, clear liquid stored in 5 mL glass ampoules. Anexate ampoules are supplied in packs of five.

6.6 Special precautions for disposal and other handling

When Anexate is drawn into a syringe or diluted with normal saline, lactated Ringer's or 5% dextrose, it should be discarded after 24 hours (see Section 4.2).

For optimum sterility, Anexate should remain in the ampoule until just before use.

7 MEDICINE SCHEDULE

Prescription medicine.

8 SPONSOR

Pharmaco (NZ) Ltd
4 Fisher Crescent
Mt Wellington
Auckland 1060
Telephone: 0800 804 079

9 DATE OF FIRST APPROVAL

30 April 1987

10 DATE OF REVISION OF THE TEXT

11 July 2018

[CDS 5.0]

NEW ZEALAND DATA SHEET

SUMMARY TABLE OF CHANGES

| Section changed | Summary of new information |
|-----------------|---|
| All | September 2016 data sheet reformatted to new SPC format |
| 5.3 | Information regarding mutagenicity, impairment of fertility and teratogenicity added to align with CDS. |