

Anexate®

Flumazenil

DESCRIPTION**1.1 Therapeutic / Pharmacologic Class of Drug**

Benzodiazepine antagonist.

ATC code: V03AB25.

1.2 Type of Dosage Form

Ampoules.

1.3 Route of Administration

Intravenous injection.

1.4 Sterile / Radioactive Statement

Sterile product.

1.5 Qualitative and Quantitative Composition

Active ingredient: flumazenil.

Ampoules containing 0.5 mg active ingredient in 5 ml aqueous solution and 1 mg active ingredient in 10 ml aqueous solution.

2. CLINICAL PARTICULARS**2.1 Therapeutic Indication(s)**

Anexate is indicated for complete or partial reversal of the central sedative effects of benzodiazepines. It is therefore used in anesthesia and intensive care in the following indications:

In anesthesia

- Termination of general anesthesia induced and maintained with benzodiazepines in inpatients.
- Reversal of benzodiazepine sedation in short diagnostic and therapeutic procedures in both inpatients and outpatients.

In intensive care

- Anexate provides a diagnosis of benzodiazepine intoxication or rules out such intoxication.
- Anexate may also be used for specific reversal of the central effects of benzodiazepines in drug overdose (return to spontaneous respiration and consciousness in order to render intubation unnecessary or allow extubation).

2.2 Dosage and Administration

Anexate is recommended for intravenous use only and should be administered by an anesthesiologist or experienced physician.

For handling solution, see 4.2 Special Instructions for Use, Handling and Disposal.

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 anesthesia: The recommended initial dose of Anexate is 0.2 mg administered i.v. 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: The recommended initial dose of Anexate is 0.3 mg i.v. 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 i.v. doses as above, or as an i.v. 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 nonbenzodiazepine etiology 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's response (see 2.4.1 General (Warnings and Precautions)).

2.2.1 Special Dosage Instructions

Children > 1 year of age:

Anexate

For the reversal of conscious sedation induced with benzodiazepines in children > 1 year of age, the recommended initial dose is 0.01 mg/kg (up to 0.2 mg) administered i.v. 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 4 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 the patient's response. No data are available on the safety and efficacy of repeated administration of Anexate to children for re-sedation.

Hepatic impairment:

Since flumazenil is primarily metabolized in the liver, careful titration of dosage is recommended in patients with impaired hepatic function. (see 2.4.1 General (Warnings and Precautions)).

2.3 Contraindications

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

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).

2.4 Warnings and Precautions**2.4.1 General**

Particular caution is necessary when using Anexate in cases of mixed-drug overdose since the toxic effects (such as convulsions and cardiac dysrhythmias) of other drugs 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. Because patients with underlying hepatic impairment may experience delayed benzodiazepine effects (as described above), 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 2.2 Dosage and Administration).

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 1 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 anesthesia in children, as experience is limited (see 2.2 Dosage and Administration).

2.4.2 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.

2.4.3 Interactions with other Medicinal Products and other Forms of Interaction

Anexate blocks the central effects of benzodiazepines by competitive interaction at the receptor level. The effects of nonbenzodiazepine 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.

2.5 Use in Special Populations

2.5.1 Pregnancy

The safety of Anexate in human pregnancy has not been established. Therefore, the benefits of drug therapy during pregnancy should be weighed against possible risks to the fetus.

2.5.2 Nursing Mothers

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

2.5.3 Pediatric Use

See 2.4.1 General (Warnings and Precautions).

2.5.4 Hepatic Impairment

See 2.2.1 Special Dosage Instructions and 2.4.1 General (Warnings and Precautions).

2.6 Undesirable Effects

2.6.1 Post Marketing

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 undesirable 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-drug overdose.

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

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.

2.7 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 2.2 Dosage and Administration.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

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, intravenous 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 i.v. 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 pretreated 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.

3.2 Pharmacokinetic Properties

3.2.1 Absorption

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

See 3.2.2 Distribution

3.2.2 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.

3.2.3 Metabolism

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.

3.2.4 Elimination

Flumazenil is almost completely (99%) eliminated by nonrenal routes. Practically no unchanged flumazenil is excreted in the urine, suggesting complete metabolic degradation of the drug. Elimination of radiolabelled drug is essentially complete within 72 hours, with 90-95% of the radioactivity appearing in urine and 5-10% in the feces. 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.

3.2.5 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 lower than in healthy subjects.

The pharmacokinetics of flumazenil are not significantly affected in the elderly, by gender, hemodialysis, or renal failure.

The elimination half-life in children above 1 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.

3.3 Preclinical Safety

3.3.1 Mutagenicity

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

3.3.2 Impairment of Fertility

See 3.3.1 Mutagenicity.

3.3.3 Teratogenicity

See 3.3.1 Mutagenicity.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

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

4.2 Special Instructions for Use, Handling and Disposal

When Anexate is drawn into a syringe or diluted with normal saline or 5% dextrose, it should be discarded after 24 hours (see 2.2 Dosage and Administration). For optimum sterility, Anexate should remain in the ampoule until just before use.

4.3 Packs

Ampoules 0.5 mg in 5 ml	1, 5, 25
Ampoules 1 mg in 10 ml	1, 5, 25

Not all pack sizes may be available locally.

Medicine: keep out of reach of children

Current at March 2019

Made for CHEPLAPHARM Arzneimittel GmbH,

Greifswald, Germany

by CENEXI, Fontenay-sous-Bois, France