Anexate®

Flumazenil

Benzodiazepine antagonist

Composition

Active ingredient: flumazenil

Excipients: sodium edetate, acetic acid, sodium chloride, water for injection qs 5 ml.

Pharmaceutical form and quantity of active substance per unit

Solution for injection containing 0.1 mg flumazenil per 1 ml.

Indications and potential uses

Anexate is indicated for 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 the anesthesia induced and maintained with benzodiazepines in hospitalised patients.

Reversal of benzodiazepine-induced sedation in short diagnostic and therapeutic procedures in ambulant or hospitalised patients.

In intensive care

Anexate is used to provide diagnostic information on or to exclude intoxication with benzodiazepines.

As a diagnostic measure in unconsciousness of unknown cause in order to determine whether benzodiazepines or other drugs are involved or whether brain damage is present.

As specific treatment to reverse the central effects of benzodiazepines in drug overdosage (to restore spontaneous respiration and consciousness and thereby avoid the need for intubation or to permit extubation).

Dosage and administration

Standard dosage

Anexate is for intravenous use only and should be administered i.v. by an anesthetist or an experienced physician.

For administration by infusion, Anexate can be diluted in 5% glucose (in water), lactated Ringer's solution or normal saline solution.

Once drawn up into a syringe or diluted with one of the solutions referred to above, Anexate should be discarded after 24 hours.

The dose should be titrated in accordance with the desired effect.

As the action of some benzodiazepines can be more prolonged than that of Anexate, repeated doses of Anexate may be required if sedation recurs after waking.

The drug can also be used in combination with other resuscitative measures.

In anesthesia

The recommended initial dose is 0.2 mg i.v. and it should be administered within 15 seconds. If the desired level of consciousness is not obtained within 60 seconds of the first i.v. dose, a second dose of 0.1 mg can be injected. If necessary, this procedure can be repeated at 60-second intervals up to a total dose of 1 mg. The usual dose is in the range 0.3–0.6 mg.

In the intensive care unit

An initial dose of 0.3 mg i.v. is recommended. If the desired level of consciousness is not obtained within 60 seconds, further doses of Anexate can be injected until the patient wakes up or a total dose of 2 mg has been administered. If drowsiness recurs, an i.v. infusion of 0.1–0.4 mg per hour can be useful. The rate of infusion should be individually adjusted to the desired level of consciousness.

In the intensive care unit, individually titrated slow injection of Anexate should not produce withdrawal symptoms in patients who have received benzodiazepines in high doses and/or for long periods of time. If unexpected signs of overstimulation occur, 5 mg diazepam or 5 mg midazolam can be given i.v., carefully titrated to individual patient response.

If the level of consciousness or respiratory function does not improve after repeated doses of Anexate, a non-benzodiazepine etiology must be assumed.

Special dosage instructions

When used in anesthesia at the end of an operation, Anexate should not be injected before the effect of peripheral muscle relaxants has worn off.

Pediatrics (children over 1 year of age):

For reversal of benzodiazepine-induced sedation, the recommended initial dose is 0.01 mg/kg body-weight (up to 0.2 mg) administered i.v. over 15 seconds. If there is no response within 45 seconds, further doses can be given at one-minute intervals. The total dose must not exceed 0.05 mg/kg body-weight or 1 mg.

Because of limited experience, Anexate should be used with caution in the following cases:

- Children under 1 year of age for reversal of sedation

- In all pediatric age groups to reverse the sedative properties of benzodiazepines in anesthesia, for management of overdose and for resuscitation

Contraindications

Anexate is contraindicated in patients with known hypersensitivity to the drug. Anexate is contraindicated in patients who have received a benzodiazepine to treat a potentially life-threatening condition (e.g. control of intracranial pressure after severe head injury or status epilepticus).

Warnings and precautions

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.

In mixed intoxications with benzodiazepines and cyclic antidepressants, the toxicity of the antidepressants can be masked by the protective benzodiazepine effect. Therefore, in the presence of autonomic (anticholinergic), motor or cardiac manifestations of severe intoxication with tricyclics/tetracyclics, the benzodiazepine effect should not be reversed with Anexate.

Patients who have been given Anexate to reverse the effect of benzodiazepines should be monitored for resedation, respiratory depression and other residual benzodiazepine effects for an appropriate period of time which will depend upon the dose and duration of action of the benzodiazepines used.

When used with muscle relaxants, Anexate should only be injected after the effects of the neuromuscular blockade have been completely reversed.

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

Rapid injection of Anexate should be avoided in patients who have received benzodiazepines in high doses immediately or for up to a week before administration of Anexate and/or over a prolonged period of time, since this can lead to withdrawal phenomena such as agitation, anxiety, emotional lability, mild confusion and sensory distortions (see *Dosage and administration*).

Interactions

Anexate blocks the central effects of benzodiazepines by competitive interaction at the receptor level. Non-benzodiazepines that act via the benzodiazepine receptor, such as zopiclone, triazolopyridazines and others, are also blocked by Anexate

Particular caution is required when Anexate is used in cases of acute mixed drug overdose, since the toxic effects (for example, convulsions and cardiac arrhythmias) of other medications also taken in overdose (especially cyclic antidepressants) may emerge

after reversal of the benzodiazepine effect. The pharmacokinetics of benzodiazepine agonists are unaffected by Anexate and vice versa.

No interaction is known to occur between alcohol and flumazenil.

Pregnancy and lactation

Pregnancy

Although studies in animals given high doses of Anexate revealed no evidence of teratogenicity, no controlled studies on pregnant women are available. The general medical principle of administering drugs in early pregnancy only if absolutely necessary should therefore be observed.

Lactation

Parenteral administration of Anexate during lactation is not contraindicated in acute cases. It is not known whether flumazenil is excreted in human milk.

Effects on ability to drive and use machines

Although patients remain alert and conscious after administration of Anexate, they should refrain from hazardous activities that demand complete mental alertness (e.g. operating dangerous machinery or driving a motor vehicle) for 24 hours after administration, since the effect of the originally ingested or administered benzodiazepine may return.

Undesirable effects

Rare cases of flushing, nausea and/or vomiting have been reported with use in anesthesia. In isolated cases patients complained of anxiety, palpitations and fearfulness after rapid injection of Anexate. These undesirable effects required no specific treatment.

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

In cases of mixed drug overdose, particularly with cyclic antidepressants, reversal of the benzodiazepine effect by Anexate can lead to undesirable effects (such as convulsions and cardiac arrhythmias).

Rapid injection of Anexate can lead to benzodiazepine agonist withdrawal phenomena in patients who have received benzodiazepines over a prolonged period of time ending immediately or in the weeks preceding administration of Anexate. These phenomena should disappear after slow i.v. injection of 5 mg diazepam or 5 mg midazolam

Undesirable effects in clinical studies

Adverse events most frequently associated with flumazenil alone were dizziness, injection site pain, increased sweating, headache, and abnormal or blurred vision.

Psychiatric disorders

Common: Agitation (anxiety, nervousness, dry mouth, tremor, palpitations, insomnia, dyspnea, hyperventilation), emotional lability (abnormal weeping, depersonalisation, euphoria, increased tears, depression, dysphoria, paranoia).

Very rare: Fear, panic attacks in patients with a history of panic disorders.

Withdrawal symptoms may occur following rapid injection of Anexate in patients receiving long-term treatment with benzodiazepines.

Nervous system

Very common: Dizziness (vertigo, ataxia) (10%).

Common: Headache, paresthesia (abnormal sensation, hypoesthesia).

Rare: Confusion (poor concentration, delirium), convulsions (see *Warnings and precautions*), somnolence (stupor).

Eyes

Common: Abnormal vision (visual field defect, diplopia).

Ear and inner ear

Rare: Abnormal hearing (transient hearing impairment, hyperacusis, tinnitus).

Vascular disorders

Common: Cutaneous vasodilation (sweating, flushing, hot flushes).

Gastrointestinal disorders

Very common: Vomiting (11%).

Common: Nausea.

General disorders

Common: Fatigue (asthenia, malaise), pain at the injection site (thrombophlebitis, skin changes, rash).

Overdosage

There is limited experience of acute overdose with Anexate.

There is no specific antidote for overdose with Anexate. Treatment of an overdose with Anexate consists of general emergency medicine measures, including monitoring and stabilisation of vital signs and observation of the clinical status of the patient.

Even with i.v. doses of 100 mg, no effects of overdosage have been observed. Regarding withdrawal phenomena attributable to the agonist, see *Standard dosage*.

Properties and effects

ATC code: V03AB25

Mechanism of action

Flumazenil, an imidazobenzodiazepine derivative, antagonises the effect of benzodiazepines on the central nervous system. It competitively inhibits the activity at the benzodiazepine recognition site on the GABA/benzodiazepine receptor complex. This antagonistic action has been demonstrated in studies with 17 different benzodiazepine derivatives. In animal experiments the effects of compounds that show no affinity for the benzodiazepine receptor, e.g. barbiturates, ethanol, meprobamate, GABA-mimetics, adenosine receptor agonists and other agents, were not affected by Anexate, whereas those of non-benzodiazepine agonists of benzodiazepine receptors, such as cyclopyrrolones (e.g. zopiclone) and triazolopyridazines, were similarly antagonised by Anexate. The hypnotic-sedative effects of benzodiazepines are rapidly reversed (within 1 to 2 minutes) by intravenous injection of Anexate and may reappear gradually within the next few hours, depending on the half-life and dose ratio of the agonist and antagonist.

Flumazenil is a weak partial agonist in some animal models of activity, but has little or no agonist activity in man.

In animals pretreated with high doses of benzodiazepines over several weeks, Anexate elicited signs of withdrawal. A similar effect was also seen in adult humans.

Pharmacodynamics

The duration and degree of reversal of sedative benzodiazepine effects are related to the dose and plasma concentrations of flumazenil. Generally, doses of approximately 0.1 mg to 0.2 mg Anexate (corresponding to peak plasma concentrations of 3 to 6 ng/ml) produce partial antagonism, whereas higher doses in the range 0.4 to 1 mg (with peak plasma levels of 12 to 28 ng/ml) usually produce complete antagonism in the treatment of patients who have received the usual sedating doses of benzodiazepines. Reversal of the benzodiazepine effect is usually evident within 1 to 2 minutes after the injection of Anexate. Eighty percent response will be reached within 3 minutes, with the peak effect of Anexate occurring at 6 to 10 minutes. The duration and degree of reversal of the benzodiazepine effect are related to the plasma concentration of the sedating benzodiazepine as well as the dose of Anexate given.

In healthy volunteers Anexate did not alter intraocular pressure when given alone and reversed the decrease in intraocular pressure seen after administration of midazolam.

Clinical efficacy

Anexate has been administered to adults to reverse the effects of benzodiazepines in conscious sedation, general anesthesia, and the management of suspected benzodiazepine overdose. Limited information from uncontrolled studies in children is available regarding the use of Anexate to reverse the effects of benzodiazepines in conscious sedation only.

Conscious sedation (adults)

Anexate was studied in four trials in 970 patients who received an average of 30 mg diazepam or 10 mg midazolam for sedation (with or without a narcotic) in conjunction

with both inpatient and outpatient diagnostic or surgical procedures. Anexate was an effective drug in reversing the sedating and psychomotor effects of the benzodiazepine; however, amnesia was less completely and less consistently reversed. In these studies, Anexate was administered as an initial dose of 0.4 mg i.v. (two doses of 0.2 mg), with additional 0.2 mg doses as needed (up to a maximum dose of 1 mg) to achieve complete awakening.

Seventy-eight percent of patients receiving flumazenil responded by becoming completely alert. Of those patients, approximately half responded to doses of 0.4 mg to 0.6 mg, while the other half required doses of 0.8 mg to 1 mg. Adverse effects occurred infrequently in patients who received Anexate at doses of 1 mg or less, although injection site pain, agitation and anxiety did occur. Reversal of sedation was not associated with any increase in the frequency of inadequate analgesia or increase in narcotic demand in these studies. While most patients remained alert throughout the 3-hour postprocedure observation period, resedation was observed in 3% to 9% of patients, and was most common in patients who had received high doses of benzodiazepines (see *Warnings and precautions*).

General anesthesia in adults

Anexate was studied in four trials in 644 patients who received midazolam as an induction and/or maintenance agent in balanced or inhalational anesthesia. Midazolam was generally administered in doses ranging from 5 mg to 80 mg, alone or in conjunction with muscle relaxants, nitrous oxide, regional or local anesthetics, narcotics and/or inhalational anesthetics. Flumazenil was given as an initial dose of 0.2 mg i.v., with additional 0.2 mg doses as needed to reach a complete response (up to a maximum dose of 1 mg). These doses were effective in reversing sedation and restoring psychomotor function, but did not completely restore memory as tested by picture recall. Anexate was not as effective in the reversal of sedation in patients who had received multiple anesthetic agents in addition to benzodiazepines.

Eighty-one percent of patients sedated with midazolam responded to flumazenil by becoming completely alert or just slightly drowsy. Of these patients, 36% responded to doses of 0.4 mg to 0.6 mg, while 64% required doses of 0.8 mg to 1 mg.

Resedation in patients who responded to Anexate occurred in 10% to 15% of patients studied and was more common after high doses of midazolam (>20 mg), long procedures (>60 minutes) and use of neuromuscular blocking agents (see *Warnings and precautions*).

Management of suspected benzodiazepine overdose in adults

Anexate was studied in two trials in 497 patients who were presumed to have taken an overdose of a benzodiazepine, either alone or in combination with a variety of other agents. In these trials, 299 patients were proven to have taken a benzodiazepine as part of the overdose, and 80% of the 148 patients who received Anexate responded by an improvement in level of consciousness. Of the patients who responded to flumazenil, 75% responded to a total dose of 1 mg to 3 mg.

Reversal of sedation was associated with an increased frequency of symptoms of central nervous system excitation. Of the patients treated with flumazenil, 1% to 3% required additional treatment for agitation or anxiety. Serious adverse effects were uncommon, but 6 seizures were observed in 446 patients treated with flumazenil in these studies. Four of these six patients had ingested high doses of cyclic antidepressants, which increased the risk of seizures (see *Warnings and precautions*).

Pediatric use

The safety of flumazenil for reversing benzodiazepine-induced sedation has been studied in pediatric patients aged 1 year and above (107 pediatric patients aged 1–17 years). The patients received up to 5 injections of 0.01 mg/kg flumazenil up to a maximum total dose of 1.0 mg at a rate not exceeding 0.2 mg/min.

Of 60 patients who were fully alert at 10 minutes, 7 experienced resedation. None of these patients (aged 1 to 5 years) returned to the baseline level of sedation. The undesirable effects in these pediatric patients were similar in type and frequency to those previously observed in adults.

The safety and efficacy of flumazenil for reversal of sedation in pediatric patients under 1 year of age have not been established.

The safety and efficacy of flumazenil have not been established in pediatric patients for the other indications approved in adults.

Pharmacokinetics

The pharmacokinetics of flumazenil are 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, of which albumin accounts for two thirds. Flumazenil is extensively distributed in the extravascular space. Plasma concentrations of flumazenil decrease with a half-life of 4 to 11 minutes during the distribution phase. The mean volume of distribution at steady state (V_{ss}) is 0.95 l/kg and is thus similar to that of structurally related benzodiazepines.

Metabolism

Unchanged flumazenil is metabolised mostly in the liver. The carboxylic acid metabolite is the main metabolite in plasma (free form).

The main metabolite in the urine is the carboxylic acid (free form and glucuronide). This main metabolite showed no benzodiazepine agonist or antagonist activity in pharmacological studies.

Elimination

Flumazenil is eliminated almost exclusively (99%) by nonrenal routes. Practically no unchanged flumazenil is excreted in the urine, suggesting complete metabolic degradation of the drug.

Elimination of radiolabelled flumazenil is essentially complete within 72 hours, with 90–95% of the radioactivity appearing in the urine and 5–10% in the feces, accounted for by the metabolites.

Mean total plasma clearance is approximately 1 l/min and can be attributed almost entirely to hepatic clearance. The low contribution of renal clearance indicates effective reabsorption of the drug after glomerular filtration. The mean elimination half-life of the drug is 50–60 minutes.

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

Pharmacokinetics in special patient groups

In patients with impaired liver function the elimination half-life of flumazenil is longer and total body clearance lower than in healthy subjects. The pharmacokinetics of flumazenil are not significantly influenced by advanced age, gender, hemodialysis or renal failure.
The elimination half-life in children (1–17 years) is more variable than in adults, averaging 40 minutes (range 20–75 minutes). Clearance and volume of distribution, normalised for body-weight, are in the same range as in adults.

Preclinical data

Acute toxicity

The results of acute toxicity studies with flumazenil showed intravenous LD_{50} values of 160 mg/kg in the mouse and 120 and 160 mg/kg in male and female rats, respectively.

Mutagenicity and carcinogenicity

No evidence of mutagenic potential was observed in six out of seven test systems. A weak DNA change effect was observed in an in vitro system, but only at a cytotoxic concentration. Two further studies, including one in vivo, failed to confirm this effect.

Reproductive toxicity

Reproductive toxicity studies showed no evidence of impairment of fertility or reproductive behaviour.

Additional information

Stability

This medicinal product must not be used after the expiry date (EXP) shown on the pack.

Instructions for use and handling

When Anexate is drawn into a syringe or diluted with 5% dextrose (in water), lactated Ringer’s or normal saline (0.9% sodium chloride), any unused solution should be discarded after 24 hours.

Packs

Ampoules (5 ml) with 0.5 mg	5, 25
Ampoules (10 ml) with 1 mg	5, 25

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

Current at January 2009

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland
by CENEXI SAS, Fontenay-sous-Bois, France