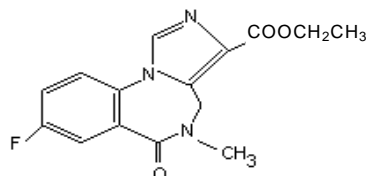


NAME OF THE MEDICINE

ANEXATE®

(*flumazenil*)



CAS registry number: 78755-81-4

DESCRIPTION

ANEXATE is a colourless to almost colourless clear liquid.

The active ingredient of ANEXATE belongs to the chemical group of 1,2- imidazo benzodiazepines and is ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo- 4H-imidazo [1,5-a] [1,4] benzodiazepine -3-carboxylate (flumazenil). It has a molecular weight of 303.3.

Ampoules contain 0.5 mg active ingredient in 5 mL aqueous solution (for intravenous administration) and also the following ingredients: disodium edetate, acetic acid, sodium chloride, sodium hydroxide in water for injections adjusted to pH 4.0.

PHARMACOLOGY

ANEXATE, an imidazobenzodiazepine, is a benzodiazepine antagonist which specifically blocks the central effects of agents acting through the benzodiazepine receptor by competitive inhibition. In animal experiments the effects of compounds showing no affinity for the benzodiazepine receptor, e.g. barbiturates, ethanol, meprobamate, GABA mimetics, adenosine receptor agonists and other agents were not affected by ANEXATE, but those of nonbenzodiazepine agonists of benzodiazepine receptors, such as cyclopyrrolones (e.g. zopiclone) and triazolopyridazines were blocked.

ANEXATE reverses the central sedative effects of benzodiazepines.

The hypnotic-sedative benzodiazepine effects are rapidly reversed by ANEXATE after its intravenous injection (1-2 minutes) and may reappear gradually within the next few hours, depending on the half life and dose ratio of the agonist and antagonist.

ANEXATE is well tolerated even in high doses.

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 signs of withdrawal, including seizure. A similar effect was seen in adult human subjects.

Pharmacokinetics

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

Distribution

ANEXATE, a weak lipophilic base, is about 50% bound to plasma proteins. Albumin accounts for two thirds of the plasma protein binding. Flumazenil is extensively distributed in the extravascular space. The distribution phase of flumazenil is approximately 4 minutes.

The mean volume of distribution at steady state ($V_{ss} = 0.95 \text{ L/kg}$) is close to that of structurally related benzodiazepines and indicates tissue binding and/or partitioning of the drug.

Metabolism

The carboxylic acid was identified in free and conjugated form as the main metabolite in human urine. In pharmacological tests, this main metabolite was inactive as a benzodiazepine agonist or antagonist.

Elimination

The average elimination half-life of flumazenil is 53 minutes.

ANEXATE is almost completely (99%) nonrenally eliminated. 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 ANEXATE is on average 1 L/min and can be attributed almost entirely to hepatic clearance. The low renal clearance rate suggests an effective reabsorption of the drug after glomerular filtration.

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.

When administered together with the benzodiazepines midazolam, flunitrazepam or lorazepam, the basic pharmacokinetic parameters of ANEXATE were not affected.

Pharmacokinetics in Special Populations

In patients with impaired liver function, the elimination half-life of flumazenil is longer and the total body clearance lower than in healthy subjects. In patients with moderate to severe hepatic impairment, clearance of flumazenil was found to be reduced by 57-74% and the elimination half-life prolonged up to 2-fold.

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

INDICATIONS

ANEXATE is indicated for use in hospitalised patients for the reversal of acute benzodiazepine effects (overdose or therapeutic). Hospitalised patients are patients admitted to hospital, inpatient care and under continued professional observation while under the influence of ANEXATE. Not to be used in outpatients or short stay patients. Not to be used as a diagnostic.

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).

In mixed intoxications with benzodiazepines and cyclic antidepressants, the toxicity of the antidepressants can be masked by protective benzodiazepine effects. In the presence of autonomic (anticholinergic), neurological (motor abnormalities) or cardiovascular symptoms of severe intoxication with tricyclics/tetracyclics, ANEXATE should not be used to reverse benzodiazepine effects.

PRECAUTIONS

Flumazenil blocks the effects of benzodiazepines in animals and can precipitate benzodiazepine withdrawal at high doses (also see *Pharmacology, Interactions with Other Drugs and Adverse Reactions*).

ANEXATE should be administered cautiously to patients with known or suspected benzodiazepine dependency or who have been treated with high doses of benzodiazepines for the weeks preceding the treatment. In such cases the reversal of benzodiazepine effects may precipitate withdrawal symptoms or convulsions. Titration of the dose may help to reduce this risk. In case of unexpected signs of withdrawal a slow i.v. injection of 5 mg diazepam or 5 mg midazolam should be given.

ANEXATE may remove the protective effect of benzodiazepines in multiple drug overdose. There have been several reports of tachyarrhythmia (the pathogenesis of which is unclear) following ANEXATE administration in the presence of known arrhythmogenic drug overdose. Convulsions in epileptics previously treated with benzodiazepines may occur.

Consideration should be given to the possibility of resedation, respiratory depression or other residual benzodiazepine effects following the use of ANEXATE. These patients should be monitored for an appropriate period based on the dose and duration of effect of the benzodiazepine employed.

The use of ANEXATE in intensive care units for the interruption of long term/over sedation is not recommended because of a relative lack of clinical experience.

ANEXATE should not be used as a routine empirical means of assessing unconscious patients in settings where resuscitation equipment and expertise to deal with complications are not immediately to hand.

Patients with head injury (and/or unstable intracranial pressure) treated with ANEXATE to reverse the effects of benzodiazepines may develop raised intracranial pressure. In addition, ANEXATE may be capable of precipitating convulsions or altering cerebral blood flow in patients with head injury receiving benzodiazepines.

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.

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

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

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

When used in anaesthesiology at the end of the operation, ANEXATE should not be injected before the effect of peripheral muscle relaxants has disappeared.

Effects on the Ability to Drive and Use Machinery

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 sedation and drowsiness may occur.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

No long-term animal studies on the carcinogenic potential of flumazenil have been performed.

Mutagenesis

Flumazenil was not mutagenic in bacterial (*Salmonella typhimurium* or *Saccharomyces cerevisiae*) or mammalian (V79) cells *in vitro* nor clastogenic in human lymphocytes *in vitro* or rat micronuclei *in vivo*. Flumazenil caused a slight increase in unscheduled DNA synthesis in rat hepatocytes *in vitro* while no induction of DNA repair was observed in mouse germ cells *in vivo*.

Impairment of Fertility

Flumazenil did not affect fertility in female and male rats at oral doses up to 125 mg/kg/day (>300 times the clinical exposure at the maximum recommended i.v. dose of 2 mg, based on AUC).

Use in Pregnancy

PREGNANCY CATEGORY B3

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

No evidence of teratogenicity was observed in pregnant rats or rabbits given oral doses of flumazenil up to 150 mg/kg/day throughout the period of organogenesis. These doses represented > 300 to 1700-fold the clinical exposure at the maximum recommended i.v. dose of 2 mg, based on AUC. In rabbits, embryotoxicity (increased resorptions) was observed at oral doses \geq 50 mg/kg/day (>500 times the clinical exposure, based on AUC). The no-effect dose was 15 mg/kg/day (170 times the clinical exposure, based on AUC).

Because animal reproduction studies are not always predictive of human response, flumazenil should be used during pregnancy only if clearly needed.

Use in Lactation

Caution should be exercised when deciding to administer flumazenil to a breastfeeding woman because it is not known whether flumazenil is excreted in human milk.

Oral administration of flumazenil to pregnant rats at 125 mg/kg/day from late gestation through weaning was associated with decreased pup survival, increased pup liver weight and retarded physical development (delayed incisor eruption and ear opening). This dose represented > 300-fold the clinical exposure at the maximum recommended dose of 2 mg, based on AUC. The no-effect dose was 25 mg/kg/day (65 times the clinical exposure, based on available AUC data).

Use in Children

An uncontrolled, single arm study has been conducted in children aged 1-17 years (n = 107) who were given weight based titration doses (see *Dosage and Administration*) after undergoing various procedures (such as GI endoscopy and bronchoscopy) under midazolam. Agitation and aggressive reactions were seen in 3 % and 2 % children respectively. The pharmacokinetic data from a subset of 27 children showed high variability in pharmacokinetic parameters, although the mean clearance was similar to that in historical control data in adults.

Interactions with Other Medicines

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. Interactions with other CNS depressant substances have not been observed.

The pharmacokinetics of benzodiazepines are unaltered in the presence of the antagonist ANEXATE.

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 the benzodiazepine effect by ANEXATE.

ADVERSE EFFECTS

ANEXATE was systemically and locally well tolerated. Nausea and/or vomiting was reported in clinical trials with ANEXATE. This occurred more frequently when ANEXATE was given as a single high dose to reverse anaesthesia and when opioids and other anaesthetic agents were used as a component of the anaesthesia. These reactions occurred rarely in volunteer studies or when benzodiazepines alone were used for sedation.

Infrequently reported adverse events included dizziness, vertigo, anxiety, palpitation, fearfulness, depressed mood, and tearfulness with or without agitation. These may be related to reversal of the anaesthetic.

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.

DOSAGE AND ADMINISTRATION

ANEXATE should be administered intravenously by an anaesthetist or experienced physician.

The use of ANEXATE should be balanced against the risk of precipitating withdrawal symptoms (see PRECAUTIONS). The desirability of retaining a degree of sedation in the early postoperative period should be considered.

ANEXATE may be diluted in glucose 5% in water or 0.9% NaCl for infusion and may also be used concurrently with other resuscitative procedures. In order to reduce microbial contamination hazards, infusion should be commenced as soon as practicable after preparation. Infusion should be completed within 24 hours of preparation and any residue discarded.

ANEXATE is for use in one patient only. Discard any remaining contents.

Reversal of benzodiazepine effects at therapeutic doses (anaesthesia or sedation)

The recommended initial dose is 0.2 mg administered i.v. within 15 seconds. If the desired degree of consciousness is not obtained within 60 seconds following the first i.v. administration, a second dose of 0.1 mg can be injected and 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.

Children > 1 year of age (see Precautions: Use in Children): The recommended initial dose is 0.01 mg/kg (or up to 0.2 mg, whichever is lower) administered intravenously over 15 seconds. If the desired level of consciousness is not obtained after waiting for 60 seconds, further injections of 0.01 mg/kg (or up to 0.2 mg, whichever is lower) can be administered and repeated at 60 second intervals where necessary 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. The patients should be observed for at least 2 hours after treatment with flumazenil.

When using flumazenil, consideration should be given to the potential impact of rapid reversal of sedation and anxiolysis, and the risk of precipitating withdrawal symptoms. The safety and efficacy of flumazenil for reversal of prolonged sedation, such as in an intensive care unit, has not been studied.

Reversal of benzodiazepine effects at overdose, known or suspected

The recommended initial i.v. dose is 0.3 mg. If the desired degree 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, an i.v. infusion of 0.1 - 0.4 mg/h has been shown to be useful. The rate of the infusion should be individually adjusted up to the desired level of arousal.

OVERDOSAGE

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

Even when given at a dosage of 100 mg i.v., no symptoms of overdosage were observed. For withdrawal symptoms attributable to the agonist, see under *Precautions*.

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.

Contact the Poisons Information Centre for advice on management of overdosage.



PRESENTATION AND STORAGE CONDITIONS

ANEXATE ampoules 0.5 mg/5 mL are available in packs of 5.

ANEXATE should be protected from light and kept in a cool dry place where the temperature stays below 30 °C.

SPONSOR

ROCHE PRODUCTS PTY LIMITED
ABN 70 000 132 865
4-10 INMAN ROAD
DEE WHY NSW 2099

Date of TGA Approval: 6 December 2004

Date of Most Recent Amendment: 9 January 2007