Package leaflet: Information for the patient

Anexate® 500 micrograms/5 ml solution for injection or infusion

Flumazenil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or pharmacist or nurse.
- If you get any side effects, talk to your doctor, or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Anexate is and what it is used for

Anexate contains a medicine called flumazenil. It is used to wake you up after you have been made sleepy by a medicine called a 'benzodiazepine'.

Anexate reverses the effects of the 'benzodiazepine' medicine. It is used to:
- Wake you up after an operation or medical test.
- Help you to breathe for yourself and wake up if you have been on a ventilator in intensive care.
- Reverse any unexpected effects of benzodiazepine treatment
- Treat benzodiazepine overdose
- Help find the reason for loss of consciousness in unconscious patients.

Anexate is also used in children (more than 1 year old) to wake them up after they have been given a 'benzodiazepine' medicine to make them sleepy during a medical procedure.

2. What you need to know before you are given Anexate

You must not be given Anexate if you are allergic (hypersensitive) to:
- Flumazenil or any of the other ingredients of Anexate (listed in section 6).
- 'Benzodiazepine' medicines. These include diazepam, midazolam and temazepam.

You must not be given Anexate if any of the above apply to you. If you are not sure, talk to your doctor or nurse before having Anexate.

You must not be given Anexate if:
- You are already taking a 'benzodiazepine' medicine to treat a very serious illness (such as raised intra-cranial pressure or status epilepticus).
- You have taken a 'benzodiazepine' medicine and certain anti-depressant medicines at the same time and this has made you ill. These anti-depressant medicines (known as tricyclic or tetracyclic anti-depressants) include medicines such as amitriptyline, imipramine and dothiepin hydrochloride.

You must not be given Anexate if any of the above apply to you. If you are not sure, talk to your doctor or nurse before having Anexate.

Warnings and precautions
Talk to your doctor or nurse before having Anexate if:
- You have a head injury.

- You have epilepsy and are being treated with a 'benzodiazepine' medicine.
- You are very nervous about having your operation or medical test.
- You have a history of anxiety.
- You have heart disease or liver problems.

If any of the above apply to you, or if you are not sure, talk to your doctor or nurse before you have Anexate.

Other medicines and Anexate
Tell your doctor or nurse if you are taking or have recently taken any other medicines. This includes medicines that you buy without a prescription and herbal medicines. This is because Anexate can affect the way some other medicines work. Also some other medicines can affect the way Anexate works.

In particular, tell your doctor or nurse if you are taking any of the following medicines:
- 'Benzodiazepine' medicines, even if you have not taken them in the last few weeks. These include diazepam, midazolam and temazepam.
- Zopiclone (used to help you sleep).
- Medicines that change your mood or behaviour. These include medicines called tranquillisers, anti-depressants and sedatives.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, or are breast-feeding, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
- Do not drive or use any tools or machines for at least 24 hours after having Anexate.
- Do not do anything that is physically or mentally demanding for at least 24 hours after having Anexate.

This is because the effects of the 'benzodiazepine' medicine may return and you may start to feel sleepy again.

Anexate contains sodium
Anexate contains 0.16 mmol (approx. 3.67 mg) sodium per millilitre which is less than 1 mmol sodium (23 mg) per usual dosage (300 – 600 micrograms flumazenil), that is to say essentially ´sodium free´. Doses in excess of 600 micrograms flumazenil contain more than 1 mmol of sodium (23 mg).
A dose of 1 mg of flumazenil contains 36.7 mg sodium, equivalent to approximately 1.9% of the maximum daily sodium intake of 2 g recommended by the WHO for an adult.

3. How Anexate will be given

Anexate will be given to you by a doctor. It will be given to you as a slow injection into one of your veins.

The dose of Anexate varies from one patient to another. It depends on your age, weight, how well your liver and kidneys are working and what you need the medicine for. The doctor will work out how much to give you.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines Anexate can cause side effects, although not everybody gets them.

See your doctor straight away if you get the following side effects:

Allergic reactions (unknown: frequency cannot be estimated from the available data):
- Sudden swelling of the throat, face, lips or mouth. This can make it difficult to breathe or swallow.
- Sudden swelling of the hands, feet or ankles.
- Skin rash or itching.

Breathing problems (very rare, affect less than 1 in 10,000 people):

- Respiratory arrest. Early signs include suddenly noisy, difficult and uneven breathing. Your skin may become blue.

Heart and circulation (very rare, affect less than 1 in 10,000 people):
- A sudden change in blood pressure and heart rate (Haemodynamic shock). Early signs include feeling confused, faint and unwell.

Other possible side effects:

Common (affect less than 1 in 10 people):
- Feeling sick or being sick especially if you have also had any opiate drugs (e.g. morphine).

Uncommon (affect less than 1 in 100 people):
- Being aware of your heart rate (palpitations).
- Feeling anxious or frightened.
- These effects are most likely to happen if you have woken up too quickly.

Unknown (frequency of people affected unknown):
- Panic attacks (in people who have had panic attacks in the past).
- Abnormal crying.
- Feeling agitated.
- Being aggressive.
- Convulsions (seizures). These are more likely in people who already have epilepsy or severe liver problems or in people who have taken 'benzodiazepine' medicines for a long time. Convulsions are also more likely in people given Anexate after an overdose of more than one medicine, including at least one 'benzodiazepine', especially if taken with certain anti-depressants.
- Increased blood pressure on waking up (short lived).
- Increased heart rate on waking up (short lived).
- Feeling cold (most likely to happen if you have woken up too quickly).
- Redness of the face and neck (flushing).
- Withdrawal symptoms, for example:
  - Feeling agitated, anxious, confused, dizzy, sweaty,
  - Having mood swings, distorted senses, an increased heart rate.

  Withdrawal symptoms usually happen if you are given high doses of Anexate quickly and/or when you have recently taken 'benzodiazepine' medicines (for example to help you sleep or to treat anxiety). This may happen even if you stopped taking these medicines a few days or weeks before having Anexate.

The side effects seen in children are similar to those seen in adults. If Anexate has been used to wake up children after a medical test it may cause them to cry abnormally, feel agitated or be aggressive.

If any of the side effects become serious or troublesome, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

Reporting of side effects

If you get any side effects, talk to your doctor or, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

HPRA Pharmacovigilance
Website: www.hpra.ie

5. How Anexate is stored

- Your doctor or pharmacist is responsible for storing Anexate. They are also responsible for disposing of any unused Anexate correctly.
- Keep out of the sight and reach of children.
- Do not use after the expiry date which is stated on the pack.
- Anexate does not need any special storage conditions.

6. Contents of the pack and other information

What Anexate contains
The active substance in Anexate 500 micrograms/5 ml solution for injection or infusion is flumazenil. Each millilitre (ml) of liquid medicine contains 100 micrograms of flumazenil. Each ampoule (small glass bottle) contains 500 micrograms of flumazenil (in 5 ml of liquid).

The other ingredients are disodium edetate, glacial acetic acid (E260), sodium chloride, sodium hydroxide (E524) (for pH adjustment) and water for injections.

What Anexate looks like and contents of the pack
Anexate is a clear almost colourless liquid ('solution for injection or infusion'). This liquid may be further diluted to make it weaker before it is given to you.

Anexate is supplied in clear glass ampoules in packs of 5.

Marketing Authorisation Holder
CHEPLAPHARM Arzneimittel GmbH
Ziegelhof 24
17489 Greifswald
Germany

Manufacturer
CHEPLAPHARM Arzneimittel GmbH
Ziegelhof 23-24
17489 Greifswald
Germany

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This information is intended for medical or healthcare professionals only:
The tear-off portion above is intended for the patient

INFORMATION FOR HEALTHCARE PROFESSIONALS

Anexate® 500 micrograms/5 ml solution for injection or infusion
Flumazenil

Please refer to the Summary of Product Characteristics for full prescribing information.

Presentation
Clear glass 5 ml ampoules. Excipients are disodium edetate, glacial acetic acid (E260), sodium chloride, sodium hydroxide (E524) (for pH adjustment) and water for injections. The solution is clear and almost colourless. Cartons of 5 ampoules.

Posology and method of administration
Flumazenil must be administered intravenously by an anaesthetist or a doctor with experience in anaesthesiology and in a unit having the appropriate facilities available. Flumazenil may be administered either undiluted or diluted.

It can be administered together with other reanimation measures.

Anaesthesiology
The initial dose is 200 micrograms administered intravenously in 15 seconds. If the desired degree of consciousness is not obtained within 60 seconds, a second dose of 100 micrograms can be administered. This may be repeated at 60 second intervals where necessary, up to a maximum total dose of 1 mg. The usual dose is 300–600 micrograms.

Intensive care
The recommended initial dose of flumazenil is 300 micrograms intravenously. If the desired level of consciousness is not obtained within 60 seconds, a repeat dose of 100 micrograms may be administered. If necessary, this may be repeated at 60 second intervals up to a total dose of 2 mg. If drowsiness recurs, a second bolus injection of flumazenil may be administered. An intravenous infusion of 100–400 micrograms per hour has also been shown to be useful. The dosage and rate of infusion should be individually adjusted to achieve the desired level of sedation.

Hepatic impairment
Since flumazenil is primarily metabolized in the liver, careful titration of dosage is recommended in patients with impaired hepatic function.

Use in renal insufficiency
No dosage adjustments are necessary in patients with renal impairment.

Children above 1 year of age
For the reversal of conscious sedation induced with benzodiazepines in children > 1 year of age, the recommended initial dose is 10 micrograms/kg (up to 200 micrograms) administered intravenously over 15 seconds. If the desired level of consciousness is not obtained after waiting an additional 45 seconds, further injection of 10 micrograms/kg may be administered (up to 200 micrograms) and repeated at 60 second intervals where necessary (a maximum of 4 times) to a maximum total dose of 50 micrograms/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 flumazenil to children for re-sedation.

Elderly
No specific data are available on the use of Anexate in the elderly, but it should be remembered that this population is more sensitive to the effects of benzodiazepines and should be treated with due caution.

The individually titrated, slow injections or infusions of Anexate should not produce withdrawal symptoms, even in patients exposed to high doses of benzodiazepines and/or for long periods of time. If, however, unexpected signs of stimulation occur, an individually titrated dose of diazepam (Valium) or midazolam (Hypnovel) should be given by slow intravenous injection.

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

Instructions for use
Anexate ampoule solution may be diluted with Sodium Chloride Intravenous Infusion BP or Dextrose 5% Intravenous Infusion BP.

Anexate infusion should be administered within 24 hours of preparation.

No preparations other than those recommended should be added to the Anexate ampoule or mixed with the Anexate infusion solution.

For single use only. Discard any unused contents.

Shelf life
Unopened: 5 years.

Once opened: The product should be used immediately after opening.

Once diluted: Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature.

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.

Special precautions for storage
Unopened: This medicinal product does not require any special storage conditions.

Once diluted: See section (Shelf life) above for storage conditions of the diluted product.

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