Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml ampoule contains 500 micrograms of flumazenil (100 micrograms per ml).
Excipient(s) with known effect: Sodium 3.7 mg/ml

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection and infusion.
A clear, almost colourless, sterile aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Anexate is indicated for the complete or partial reversal of the central sedative effects of benzodiazepines. It may therefore be used in the following situations:

Termination of general anaesthesia induced and/or maintained with benzodiazepines.

Reversal of benzodiazepine sedation in short diagnostic and therapeutic procedures.

Reversal of paradoxical reactions due to benzodiazepines.

For the diagnosis and/or management of deliberate or accidental benzodiazepine overdosage.

As a diagnostic measure in unconsciousness of unknown origin, to differentiate between involvement of benzodiazepines and other aetiologies.

For the specific reversal of the central effects of benzodiazepines, to allow return to spontaneous respiration and consciousness, in patients in intensive care.

For the reversal of conscious sedation induced with benzodiazepines in children > 1 year of age.

4.2 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.

For dilution, see section 6.6.

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.

4.3 Contraindications

Flumazenil is contra-indicated in patients:

o with hypersensitivity to the active substance, benzodiazepines or any of the excipients.
o who have been administered benzodiazepines for the treatment of a potentially life-threatening condition (e.g. increased intracranial pressure or status epilepticus).

4.4 Special warnings and precautions for use

Until sufficient data are available, flumazenil should only be administered to children below the age of 1 year if the risks to the patient (especially in the case of accidental overdose) have been weighed up against the benefits of the treatment.

Elimination may be delayed in patients with hepatic impairment.

The antagonistic effect of flumazenil is specific to benzodiazepines; an effect is therefore not to be expected if the 'non-awakening' is caused by other substances. If flumazenil is administered for anesthesiology at the end of the operation, the effect of any peripheral muscle relaxants must first have disappeared. Because flumazenil generally has a shorter duration of action than the benzodiazepines and therefore sedation can re-occur, the clinical state of the patient must be monitored, preferably in the intensive care unit, until the effect of flumazenil is eliminated.

In high-risk patients, the benefits of a benzodiazepine-induced sedation should be weighed against the risks of a rapid return to consciousness. In patients (e.g. with cardiac problems), maintenance of a certain degree of sedation during the early post-operative period may be preferable to complete consciousness.

Rapid injection of flumazenil should be avoided. In patients with high dose and/or long-term exposure to benzodiazepines ending at any time within the weeks preceding flumazenil administration, rapid injection of doses equal to or higher than 1 mg

has led to withdrawal symptoms, including palpitations, agitation, anxiety, emotional lability as well as mild confusion and sensory distortions.

In patients who are anxious during the pre operative phase or in patients who are known to suffer from chronic or transient anxiety, the dosage of flumazenil should be adjusted carefully.

However, after major surgery, the post operative pain should be considered and it may be preferable to keep the patient lightly sedated.

For patients who have been treated chronically with high doses of benzodiazepines, the advantages of the use of flumazenil should be carefully weighed up against the risk of withdrawal symptoms; if, despite careful dosing, withdrawal symptoms occur, treatment with low doses of benzodiazepines, titrated intravenously according to the patient's response, may be considered if necessary.

Use of the antagonist is not recommended in patients with epilepsy who have been treated with benzodiazepines for a prolonged period. Although flumazenil exerts a slight intrinsic anticonvulsant effect, the abrupt suppression of the protective effect of a benzodiazepine agonist can induce convulsions in epileptic patients.

In patients with severe brain injury (and/or instable intracranial pressure) who are being treated with flumazenil – to antagonise the effects of benzodiazepines – increased intracranial pressure may develop.

Particular caution is necessary when using flumazenil in cases of mixed-drug overdose. In particular in the case of an intoxication with benzodiazepines and cyclic antidepressants, certain toxic effects such as convulsions and cardiac arrhythmias, which are caused by these antidepressants but which emerge less readily on concomitant administration with benzodiazepines, are exacerbated on administration of flumazenil.

Patients who have received flumazenil for the reversal of benzodiazepine effects should be monitored for resedation, 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 effects as described above, an extended observation period may be required.

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

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.

4.5 Interaction with other medicinal products and other forms of interactions

Flumazenil antagonises the central effects of benzodiazepines by competitive interaction at the receptor.The effects of non-benzodiazepine agonists that acting via the benzodiazepine receptor, such as zopiclone, triazolopyridazine and others are also blocked by flumazenil. Interactions with other centrally acting substances have not been observed. The pharmacokinetics of benzidiazeines are not influenced by the antagonist flumazenil.

On administering flumazenil concomitantly with the benzodiazepines midazolam, flunitrazepam and lormetazepam, the pharmacokinetic parameters of flumazenil were unaffected.

However, particular caution is necessary when using Anexate in cases of intentional overdosage since the toxic effects of other psychotropic drugs (especially tricyclic antidepressants) taken concurrently may increase with the subsidence of the benzodiazepine effect.

There is no pharmacokinetic interaction between ethanol and flumazenil.

4.6 Fertility, pregnancy and lactation

<u>Pregnancy</u>

There are insufficient data on use in human pregnancy for an assessment of possible harmful effects and efficacy in the foetus. Caution is therefore required. To date, there is no evidence of harmful effects in animal studies. The efficacy in the foetus has not been investigated in animal studies.

Breast-feeding
It is unknown whether flumazenil is excreted in human milk. In emergency situations, however, the parenteral administration of flumazenil to a patient who is breastfeeding is not contraindicated.

4.7 Effects on ability to drive and use machines

Although patients are awake and conscious after administration of flumazenil, they should be advised not to operate dangerous machinery or drive a vehicle during the first 24 hours because the effect of the earlier administered benzodiazepine may recur.

4.8 Undesirable effects

The adverse events listed below have been reported. Adverse events usually subside rapidly without the need for special treatment.

Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); unknown (cannot be estimated from the available data).

Immune System Disorders
Unknown: Hypersensitivity reactions, including anaphylaxis, may occur.

Psychiatric disorders
Uncommon: anxiety, fear: following rapid injection, generally did not require treatment.
Unknown: Withdrawal symptoms (e.g., agitation, anxiety, emotional lability, confusion, sensory distortions, tachycardia, dizziness, sweating), following rapid injection of doses of 1 mg or more in patients with high-dose and/or long-term exposure to benzodiazepines ending at any time within the weeks preceding flumazenil administration (see section 4.4); panic attacks (in patients with a history of panic reactions); abnormal crying, agitation, aggressive reactions (the side effect profile in children is generally similar to that in adults. When flumazenil has been used for the reversal of conscious sedation, abnormal crying, agitation and aggressive reactions have been reported).

Nervous system disorders
Unknown: Seizures: particularly in patients known to suffer from epilepsy or severe hepatic impairment, mainly after long-term treatment with benzodiazepines or in cases of mixed-drug overdose (see section 4.4).

Cardiac disorders
Uncommon: Palpitations: following rapid injection, generally did not require treatment.
Very rare: haemodynamic shock
Unknown: Transient increases in heart rate (on awakening).

Respiratory disorders
Very rare: respiratory arrest

Vascular disorders
Unknown: Transient increased blood pressure (on awakening).

Gastrointestinal disorders
Common: Nausea: vomiting: during post-operative use, particularly if opiates have also been used.

Skin and subcutaneous tissue disorders
Unknown: Flushing.

General disorders and administration site conditions
Unknown: Chills: following rapid injection, generally did not require treatment.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via: HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971; Fax: +353 1 6762517 ;Website: www.hpra.ie;e-mail: medsafety@hpra.ie

4.9 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 flumazenil.

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

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

Even at dosages of 100 mg i.v., no symptoms of overdosage were observed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: benzodiazepine antagonist; ATC code: V03AB25

Mechanism of action
Anexate, an imidazobenzodiazepine, is a specific competitive inhibitor of substances which act via the benzodiazepine receptors, specifically blocking their central effects.

The hypnotic-sedative effects of the agonist are rapidly reversed by Anexate and may then reappear gradually within a few hours, depending on the half-life and dose ratio of the agonist and antagonist.

5.2 Pharmacokinetic properties

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. 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 showed no benzodiazepine agonist or antagonist activity in pharmacological tests.

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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 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 lower than in healthy subjects. The pharmacokinetics of flumazenil are not significantly affected in the elderly, by gender, haemodialysis or renal failure.

Paediatric population
In children above one year of age , the half- life elimination is shorter and the variability is higher than in adults (approximately 40 min with a range of 20 to 75 min respectively). Clearance and volume of distribution, by kg of body weight are the same as in adults.

5.3 Preclinical safety data

Other than preclinical information provided under *section 4.6*, no further information is relevant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Glacial acetic acid (E260)
Sodium chloride
Sodium hydroxide(E524) (for pH adjustment)
Water for injections

6.2 Incompatibilities

No preparations other than those recommended in section 6.6 should be added to the Anexate ampoule or mixed with the Anexate infusion solution.

6.3 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.

6.4 Special precautions for storage

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

Once diluted: See section 6.3 for storage conditions of the diluted product.

6.5 Nature and contents of container

5 ml, clear, type I glass ampoule. Pack of 5

6.6 Special precautions for disposal and other handling

Diluents
Anexate ampoule solution may be diluted with Sodium Chloride Intravenous Infusion BP, or Dextrose 5% Intravenous Infusion BP.

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

For single use only.

Discard any unused contents.

7 MARKETING AUTHORISATION HOLDER

Cheplapharm Arzneimittel GmbH
Ziegelhof 24
17489 Greifswald
Germany

8 MARKETING AUTHORISATION NUMBER

PA1868/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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