FLUMAZENIL 100 MICROGRAMS/ML SOLUTION FOR INJECTION OR INFUSION
PL 05827/0016

UKPAR

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LAY SUMMARY

The MHRA today granted Nordic Pharma Limited a Marketing Authorisation (licence) for the medicinal product Flumazenil 100 micrograms/ml Solution for Injection or Infusion (PL 05827/0016). This is a prescription only medicines (POM) for the partial or complete reversal of central sedative effects of benzodiazepines, to be used in anaesthesia or intensive care.

Flumazenil 100 micrograms/ml Solution for Injection or Infusion contains the active ingredient flumazenil, which acts as a pure benzodiazepine receptor blocker, which prevents benzodiazepines from binding to their receptor but does not affect the $GABA_A$ receptor.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Flumazenil 100 micrograms/ml Solution for Injection or Infusion outweigh the risks, hence a Marketing Authorisation has been granted.

FLUMAZENIL 100 MICROGRAMS/ML SOLUTION FOR INJECTION OR INFUSION

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisation for the medicinal product Flumazenil 100 micrograms/ml Solution for Injection or Infusion to Nordic Pharma Limited (PL 05827/0016) on 13th January 2006. The product is a prescription only medicine.

The application was submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming essential similarity to the original product Anexate 500 micrograms/5ml Ampoule (Roche Products Limited, UK).

The product contains the active ingredient flumazenil and is indicated for the partial or complete reversal of central sedative effects of benzodiazepines, to be used in anaesthesia or intensive care.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

INN: Flumazenil

Chemical Name: Ethyl 8-fluoro-5-methyl-6-oxo-5,6-dihydro-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate

Molecular Formula: $C_{15}H_{14}FN_30_3$

Molecular Weight: 303.3

General Properties: Flumazenil is a white or almost white crystalline powder very slightly soluble in water, freely soluble in methylene chloride, sparingly soluble in methanol.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis. No materials of animal or human origin are used in the production of the active substance.

An appropriate specification is provided for the active substance flumazenil.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof of structure has been supplied for the active pharmaceutical ingredient.

All potential known impurities have been identified and characterised.

Batch analysis data are provided that comply with the proposed specification.

The container used for storage of the active substance is satisfactory.

Appropriate stability data have been generated and no indication of instability seen. The data support a retest period of 24 months without the need for a temperature restriction. A commitment has been provided in the European Drug Master File (EDMF) that an annual batch will be added to the programme.

OTHER INGREDIENTS

Other ingredients consist of sodium chloride, disodium edetate, glacial acetic acid, sodium hydroxide, hydrochloric acid and water for injections. All excipients used comply with their relevant Ph Eur monograph.

Satisfactory specifications and Certificates of Analysis have been provided for all excipients. No materials of animal or human origin are contained in or used in the manufacture of this product. No genetically modified organisms are included in this product.

The product is presented in 5ml capacity clear Type I glass ampoules containing 5ml solution. Ampoules are supplied in packs of 5 ampoules. The ampoules have serigraphic printing. The ampoules meet the requirements of the Ph Eur for Type I glass and meet the requirements of the European Pharmacopoeial monograph *Glass Containers for Pharmaceutical Use*. Diagrams with dimensions of each ampoule have been provided. The specifications applied have been stated and satisfactory analytical certificates have been provided.

PHARMACEUTICAL DEVELOPMENT

Composition of the proposed product is based on the reference product. A satisfactory summary of product development has been provided. A justification for inclusion of the ingredients has been provided. The levels are typical for a product of this nature.

MANUFACTURE

Copies of relevant manufacturing authorisations and GMP certificates for the finished product manufacturer have been provided. A satisfactory batch formula for the manufacture of the maximum batch size has been provided.

A satisfactory method of manufacture has been provided, with adequate in-process controls and limits set. The manufacturing process is straightforward using standard techniques.

Results of pilot scale validation studies have been provided and are satisfactory. The applicant has committed to validating the process through the manufacture of three commercial-scale batches prior to releasing these batches for marketing.

CONTROL OF MEDICINAL PRODUCT

The finished product specifications at both release and shelf-life are satisfactory. Analytical methods used are satisfactory and have been suitably validated. Satisfactory batch analysis data have been provided, showing compliance with the proposed release specification.

STABILITY

Stability data have been provided supporting a shelf life of 2 years with no special storage conditions. A commitment has been provided that the first three production batches will be tested in stability studies.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC), LABELLING, PATIENT INFORMATION LEAFLET (PIL)

The SPC, PIL and labelling are satisfactory. A satisfactory Quality Overall Summary is provided by an appropriately qualified individual.

CONCLUSIONS

The requirements of essential similarity are met with respect to qualitative and quantitative content of the active substance and pharmaceutical form. Given the route of administration, it is not necessary to demonstrate bioequivalence of the proposed product to the reference product.

The pharmaceutical evaluation of the application led to the conclusion that a marketing authorisation could be granted for this product.

PRECLINICAL ASSESSMENT

This application for a generic product claims essential similarity to Anexate 500 micrograms/5ml Ampoule (Roche Products Limited, UK), which has been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

INDICATIONS
Complete or partial reversal of the central sedative effects of benzodiazepines. Flumazenil 100 micrograms/ml Solution for Injection may therefore be used in anaesthesia and intensive care in the following situations:

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

Reversal of benzodiazepine sedation in short diagnostic and therapeutic procedures.

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

The above is consistent with the SPC text for the licensed indications of the UK reference product and is, therefore, satisfactory.

DOSE & DOSE SCHEDULE
The dose advice is fully in line with the SPC for the UK reference product:

CLINICAL PHARMACOLOGY
No new data are submitted and none are required for this type of application. A bioequivalence study is not required.

EFFICACY
No new data are submitted and none are required for this type of application.

SAFETY
No new data are submitted and none are required for this type of application.

EXPERT REPORTS
A satisfactory expert report is provided by an appropriately qualified individual.

PATIENT INFORMATION LEAFLET (PIL)
The PIL is satisfactory.

LABELLING
The labelling is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
The SPC is fully in line with that for the reference product.

DISCUSSION
The SPC, PIL and labelling are fully in line with that for the reference product. A bioequivalence study is not required.

CONCLUSION

There are no medical objections to the granting of a product licence for this preparation.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Flumazenil 100 micrograms/ml Solution for Injection or Infusion are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

No new data were submitted and none are required for applications of this type.

The SPC, PIL and labelling are satisfactory and consistent with that for the reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with flumazenil is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 2nd March 2004
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 16th March 2004
3	Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 3rd December 2004.
4	The applicant responded to the MHRA's requests, providing further information on 19th May 2005.
5	The applications were determined on 13th January 2006

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

1. NAME OF THE MEDICINAL PRODUCT

Flumazenil 100 micrograms/ml Solution for Injection or Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The solution contains 100 micrograms flumazenil per ml.
Each 5ml ampoule contains 500 micrograms flumazenil.
For excipients see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion.
Ampoules containing a clear, colourless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Complete or partial reversal of the central sedative effects of benzodiazepines. Flumazenil 100 micrograms/ml Solution for Injection may therefore be used in anaesthesia and intensive care in the following situations:

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

Reversal of benzodiazepine sedation in short diagnostic and therapeutic procedures.

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

4.2. Posology and method of administration

By slow intravenous injection or infusion. Flumazenil 100 micrograms/ml Solution for Injection should only be administered under the supervision of an experienced physician. It may be used concurrently with other resuscitative procedures.

Adults

The recommended initial dose is 200 micrograms administered intravenously over 15 seconds. If the desired level of consciousness is not obtained within 60 seconds a further dose of 100 micrograms can be injected and repeated at 60 second intervals where necessary, up to a maximum total dose of 1mg or in intensive care situations, 2mg. The usual dose required is 300 - 600 micrograms.

If drowsiness recurs, an intravenous infusion of 100 - 400 micrograms per hour may be used. The rate of infusion should be individually adjusted to achieve the desired level of arousal.

Individually titrated, slow injections or infusions 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 overstimulation occur, an individually titrated dose of diazepam or midazolam should be given by slow intravenous injection.

If a significant improvement in consciousness or respiratory function is not obtained after repeated doses of flumazenil, it may be assumed that there is a non-benzodiazepine aetiology

Elderly
No specific data are available on the use of flumazenil in the elderly, but as this population is more sensitive to the effects of benzodiazepines, treatment should be given with caution.

Children
There are insufficient data to make dosage recommendations for flumazenil in children. It should, therefore, be administered only if the potential benefits to the patient outweigh the possible risks.

Use in renal and hepatic insufficiency
No dosage adjustments are necessary in patients with renal impairment. However, since flumazenil is primarily metabolised in the liver, careful titration of dosage is recommended in patients with impaired hepatic function.

4.3. Contraindications

Known hypersensitivity to benzodiazepines.

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 tricyclic and/or tetracyclic 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, flumazenil should not be used to reverse benzodiazepine effects.

4.4. Special warnings and precautions for use

Due to its short duration of action and the possible need for repeat doses of flumazenil, the patient should remain under close observation until all possible central benzodiazepine effects have subsided.

The use of flumazenil is not recommended in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Although flumazenil 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.

Flumazenil 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.

Benzodiazepines have a dependence potential when used chronically. Symptoms such as depression, nervousness, rebound insomnia, irritability, sweating and diarrhoea may arise following abrupt cessation of benzodiazepines in patients treated with high doses and/or for prolonged periods of time. Rapid injection of flumazenil in such patients may trigger these withdrawal symptoms, even in patients who stopped taking the benzodiazepine in the weeks preceding flumazenil administration (depending on the half-life of the benzodiazepine used) and should therefore be avoided. There is also a possibility of mild and transient withdrawal reactions occurring even after a short period of administration of benzodiazepines.

When flumazenil is used with neuromuscular blocking agents, it should not be injected until the effects of neuromuscular blockade have been fully reversed. In high-risk patients, the advantages of counteracting the central nervous system depression associated with benzodiazepines should be weighed against the drawbacks of rapid awakening.

The dosage of flumazenil should be adjusted individually to the needs of patients suffering from pre-operative anxiety or having a history of chronic or episodic anxiety. In anxious patients, particularly those with coronary heart disease, it is preferable to maintain a degree of sedation throughout the early post-operative period rather than bring about complete arousal.

The pain felt by patients in the post-operative period must be taken into account. Following a major intervention, it is preferable to maintain a moderate degree of sedation.
Flumazenil is not recommended either as a treatment for benzodiazepine dependence or for the management of protracted benzodiazepine abstinence syndromes.

4.5. Interactions with other medicinal products and other forms of interaction

Flumezanil blocks the central effects of benzodiazepines by competitive interaction at the receptor level; the effects of non-benzodiazepines acting via the benzodiazepine receptor, such as zopiclone, are also blocked by flumezanil. However, flumezanil is ineffective when unconsciousness is due to other substances.

Interaction with other central nervous system depressants has not been observed. However, particular caution is necessary when using flumezanil 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.

The pharmacokinetics of benzodiazepines are unaltered in the presence of flumezanil and vice versa.

4.6. Pregnancy and lactation

Flumezanil, as with other benzodiazepine compounds, is expected to cross the placenta and to enter into breast milk, although the total quantities involved would be small. There has been little human usage during pregnancy but

animal studies have shown no teratogenic potential. It is recommended that administration of flumazenil in early pregnancy is considered only when absolutely necessary.

Emergency use of flumazenil during lactation is not contra-indicated.

4.7. Effects on ability to drive and use machines

Patients who have received flumazenil to reverse the effects of benzodiazepine sedation should be warned not to drive, to operate machinery or to engage in any other physically or mentally demanding activity for at least 24 hours, since the effect of the benzodiazepine may return.

4.8. Undesirable effects

Flumazenil is generally well tolerated. In post-operative use, nausea and/or vomiting are occasionally observed, particularly if opiates have also been employed. Flushing has also been noted. If patients are awakened too rapidly, they may become agitated, anxious or fearful. Very rarely, seizures have been reported, particularly in patients known to suffer from epilepsy or severe hepatic impairment, after long-term treatment with benzodiazepines or in cases of mixed drug overdose. Transient increases in blood pressure and heart rate may occur on awakening in intensive care patients.
Any side-effects associated with flumazenil usually subside rapidly without the need for special treatment.

Excessive and/or rapidly injected doses of flumazenil may induce benzodiazepine withdrawal symptoms such as anxiety attacks, tachycardia, dizziness and sweating in patients on long-term and/or high dose benzodiazepine treatment ending at any time within the weeks preceding flumazenil administration (depending on the half-life of the benzodiazepine used). Such symptoms may be treated by slow intravenous injection of diazepam or midazolam. There is also a possibility of mild and transient withdrawal reactions occurring even after a short period of administration of benzodiazepines.

Flumazenil has been reported to provoke panic attacks in patients with a history of panic disorders.

4.9. Overdose

Symptoms of flumazenil overdosage have not been observed even when given intravenously at doses of 100mg,

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: V03A B25

Flumazenil is an imidazobenzodiazepine. It 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 flumazenil 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

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.

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.

Flumazenil is almost completely (99%) eliminated by non-renal routes. Practically no unchanged flumazenil is excreted in the urine, suggesting complete metabolic degradation of the drug. Elimination of radio-labelled 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.

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

In patients with impaired liver function, the elimination half-life of flumazenil is longer 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.

5.3. Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride
Disodium edetate
Glacial acetic acid
Sodium hydroxide
Hydrochloric acid
Water for injections

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months (unopened)

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 2-8°C unless reconstitution/dilution takes place in controlled and validated aseptic conditions.

6.4. Special precautions for storage

There are no special storage precautions.

6.5. Nature and contents of container

5ml ampoules of type I clear glass.
A pack size of 5 x 5ml ampoules is available.

6.6. Instruction for use and handling

Flumazenil 100 micrograms/ml Solution for Injection may be diluted with 5% solutions of normal saline, glucose or Ringers Lactate.

7. MARKETING AUTHORISATION HOLDER

Nordic Pharma (UK) Limited
Abbey House
1650 Arlington Business Park
Theale
Reading
RG7 4SA
United Kingdom

8. MARKETING AUTHORISATION NUMBER

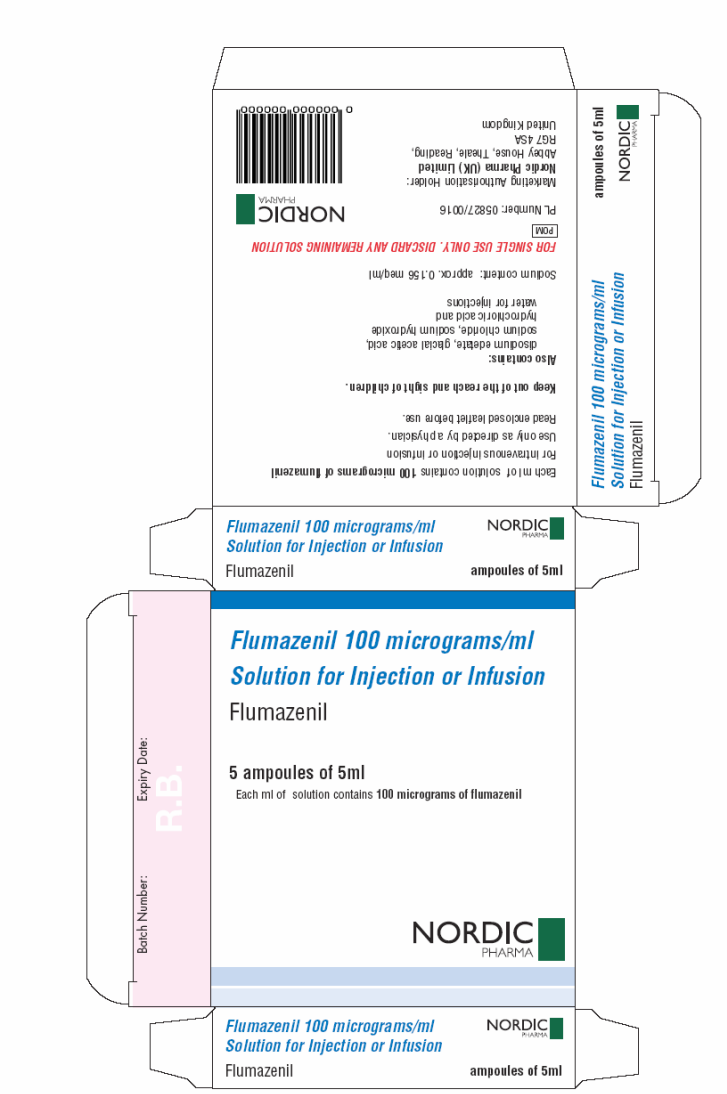
PL 05827/0016

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/01/2006

10 DATE OF REVISION OF THE TEXT

13/01/2006



Flumazenil 100 mcg/ml
Solution for Injection or Infusion
For I.V. use
(500 mcg Flumazenil/5 ml)
PL 05827/0016 B.N:
Nordic Pharma Exp

Label allows for wrap round facility based on 14mm diameter

BATCH/EXPIRY DETAILS WILL BE PRINTED/EMBOSSED ONTO THE CARTON AS SPECIFIED BY THE PRINTER/MANUFACTURER

PATIENT INFORMATION LEAFLET

Flumazenil 100micrograms/ml Solution for Injection or Infusion

Please read this leaflet carefully. If you have any questions or are not sure about anything, ask your doctor, dentist or pharmacist.

WHAT IS IN YOUR MEDICINE

Flumazenil 100micrograms/ml Solution for Injection or Infusion contains the active ingredient flumazenil. 1 ml of solution contains 0.1 mg (100 micrograms) of flumazenil. Each ampoule contains 0.5 mg (500 micrograms) of flumazenil in 5 ml solution.
Flumazenil reverses the effects of medicines known as benzodiazepines which are sometimes used to induce deep sleep. It is given by a slow, single or continuous injection into a vein. It works rapidly although the effects may wear off within a few hours and sleep may re-occur.
Flumazenil 100micrograms/ml Solution for Injection or Infusion also contains the inactive ingredients disodium edetate, glacial acetic acid, sodium chloride, sodium hydroxide, hydrochloric acid and water for injections.
This medicine is available in packs 5 ampoules .
The manufacturer is Reig Jofre S.A., C/Gran Capitan 10, Sant Joan Despi, 08970, Barcelona, Spain.
The marketing authorisation holder is Nordic Pharma UK Limited, Abbey House, 1650 Arlington Business Park, Theale, Reading, RG7 4SA, United Kingdom

ABOUT YOUR MEDICINE

Flumazenil is used for the complete or partial reversal of benzodiazepine sedation and general anaesthesia following certain diagnostic tests and operations. It is also used in intensive care patients who are on artificial ventilators. By reversing the effects of benzodiazepines, it raises the level of consciousness and allows the person to return to independent breathing.

BEFORE TAKING YOUR MEDICINE

If the following statements apply to you, flumazenil must not be given to you.

- If you are allergic to flumazenil, benzodiazepines (e.g. diazepam, midazolam, temazepam) or to any of the other ingredients of Flumazenil 100micrograms/ml Solution for Injection or Infusion.
- If you are epileptic and have been receiving benzodiazepine treatment for a long period of time.
- If you have been taking benzodiazepines and certain antidepressants (e.g. amitriptyline, imipramine, dothiepin hydrochloride) at the same time.
- If you are taking benzodiazepines to control a potentially life-threatening condition.

BEFORE STARTING TREATMENT, MAKE SURE YOUR DOCTOR KNOWS IF:

- You have a head injury
- You have a history of anxiety or are particularly anxious about the operation
- You suffer from coronary heart disease, epilepsy or severe liver disease.
- You are taking other medicines, including those not prescribed by your doctor. This is extremely important, as using more than one medicine at the same time can strengthen or weaken the effect of the medicines involved. It is especially important to tell your doctor if you are taking zopiclone (for insomnia) or antidepressants (e.g. amitriptyline, imipramine).

Flumazenil may affect your ability to drive or operate machinery. You should not drive or operate machinery or take part in any physically or mentally demanding activity for 24 hours after receiving this medicine.

Flumazenil 100micrograms/ml Solution for Injection or Infusion contains less than 1mmol (23mg) sodium per dose; it is therefore considered to be "sodium-free".

You must tell your doctor if you are pregnant, if you think you are pregnant or if you intend to become pregnant. Your doctor will then decide whether you should receive this medicine.

Flumazenil may pass into breast milk. If you are breast feeding this medicine should be avoided, except in an emergency. Your doctor will advise you.

Flumazenil 100micrograms/ml Solution for Injection or Infusion must not be used if the glass ampoule is damaged, or if the contents appear cloudy, or if there are any small particles in the solution.

HOW YOUR MEDICINE IS GIVEN

- Flumazenil 100micrograms/ml Solution for Injection or Infusion should only be given to you under the supervision of an experienced doctor.
- Your doctor will decide on a suitable dose for you. Doses vary and will depend on the procedure you have received and the level of sedation. Your bodyweight, age, general condition of health and your response to the drug will also influence the dose you receive.
- The starting dose is 200 micrograms given by slow injection into a vein over 15 seconds. If this does not achieve the level of consciousness required after 60 seconds, a further dose of 100 micrograms can be given. This dose can be repeated every 60 seconds as necessary until the correct level of consciousness is achieved, or until you have received a maximum total dose of 1 mg, or in intensive care situations, 2 mg. The usual dose is 300-600 micrograms.
  If you become drowsy again you may be given a slow, continuous injection (infusion) into a vein at a rate of 100-400 micrograms per hour until the correct level of consciousness is achieved.
  If after repeated doses there is no marked improvement in consciousness or independent breathing, your doctor will probably stop giving flumazenil and use another method to raise your level of consciousness.
- If you have been given a muscle relaxant before or during an operation, your doctor will not treat you with flumazenil until the effects of the muscle relaxant have completely worn off.
- If you have received treatment with benzodiaepines, flumazenil may give you withdrawal symptoms such as anxiety attacks, dizziness and sweating. The withdrawal symptoms may occur even if you stopped taking the benzodiazepines in the weeks before flumazenil was given. Your doctor may give you a slow injection of diazepam or midazolam (benzodiazepines) into a vein to reduce this.
- Flumazenil should only be given to children if it is considered appropriate by the doctor.
- If you are elderly or have a liver condition your dose of flumazenil will be adjusted with particular care.
- If you think you have been given too much flumazenil, you should feel no ill effect, however, it would be wise to contact your doctor, pharmacist or hospital as quickly as possible.

Flumazenil treatment ends when you become fully conscious. However, because the effects of flumazenil may wear off quickly and you may need repeat doses, you should remain under close medical supervision until all drowsiness has subsided.

AFTER TAKING YOUR MEDICINE

Flumazenil can occasionally cause nausea, vomiting and flushing. It may cause you to become agitated, anxious or fearful but this is generally if you are awakened too quickly. Intensive care patients may have increases in blood pressure and heart rate. These effects usually disappear quickly without any treatment.
Very rarely seizures may occur, particularly if you suffer from epilepsy or severe liver disease.
If you have received treatment with benzodiazepines you may experience withdrawal symptoms such as anxiety attacks, dizziness, sweating and palpitations even if you stopped taking the benzodiazepines in the weeks before flumazenil was given. Such symptoms may be treated by your doctor with a slow injection into the vein of diazepam or midazolam.
If you are concerned about these or any other unwanted effects talk to your doctor.

STORING YOUR MEDICINE

- This medicine does not require any special storage conditions
- Keep this medicine out of the reach and sight of children
- This medicine must not be used after the expiry date printed on the pack
- REMEMBER this medicine is for you. Only a doctor can prescribe it for you. Never give it to others. It may harm them even if their symptoms are the same as yours.

FURTHER INFORMATION:

You can get more information on Flumazenil 100micrograms/ml Solution for Injection or Infusion from your doctor, dentist or pharmacist.

DATE OF PREPARATION OF THIS LEAFLET

May 2005

NORDIC PHARMA