

**FLUMAZENIL 100 MICROGRAMS/ML SOLUTION FOR  
INJECTION OR INFUSION**

**PL 24610/0004**

**UKPAR**

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## **FLUMAZENIL 100 MICROGRAMS/ML SOLUTION FOR INJECTION OR INFUSION**

**PL 24610/0004**

### **LAY SUMMARY**

The MHRA today granted Bowmed Limited a Marketing Authorisation (licence) for the medicinal product Flumazenil 100micrograms/ml Solution for Injection or Infusion (PL 24610/0004).

This is a prescription-only medicine (POM) for the complete or partial reversal of the central sedative effects of benzodiazepines. It 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.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Flumzenil 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**

**PL 24610/0004**

**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 100micrograms/ml Solution for Injection or Infusion to Bowmed Limited on 22<sup>nd</sup> August 2007. The product is a prescription-only medicine.

This 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 500micrograms/5ml ampoule (Roche Products Limited, UK). The reference product has been authorised in the UK since March 1988 and so the 10-year period of data exclusivity has expired.

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**

### **DRUG SUBSTANCE**

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 based on the European Pharmacopoeia has been provided.

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

All potential known impurities have been identified and characterised.

Active flumazenil is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

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

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 2 years when stored in type I amber glass ampoules.

### **DRUG PRODUCT**

#### **Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely EDTA, water for injections, sodium chloride, sodium hydroxide, and glacial acetic acid. All excipients used comply with their respective European Pharmacopoeial monograph, with the exception of EDTA which complies with the USP.

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.

#### **Impurity profiles**

Impurity profiles for the drug product were found to be similar to that of the reference product.

#### **Manufacture**

A description and flow-chart of the manufacturing method have been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

**Finished product specification**

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container Closure System**

Product is packaged in Type I clear glass ampoules. Specifications and Certificates of Analysis for all packaging used have been provided. This is satisfactory. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in sizes of 5ml or 10ml ampoules.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years when stored below 30°C has been set, which is satisfactory.

**Conclusion**

It is recommended that Marketing Authorisation is granted for this application.

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

## **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 is 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 application of this type.

### **EFFICACY**

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

The SPC, PIL and labelling are satisfactory and consistent with that for 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 benefit/risk balance is considered to be positive.

**FLUMAZENIL 100 MICROGRAMS/ML SOLUTION FOR  
INJECTION OR INFUSION****PL 24610/0004****STEPS TAKEN FOR ASSESSMENT**

1	The MHRA received the marketing authorisation application on 27 <sup>th</sup> October 2005
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 15 <sup>th</sup> November 2005
3	Following assessment of the application the MHRA requested further information relating to the quality dossiers on 21 <sup>st</sup> September 2006
4	The applicant responded to the MHRA's requests, providing further information on 8 <sup>th</sup> March 2007
5	The applications were determined on 22 <sup>nd</sup> August 2007

**SUMMARY OF PRODUCT CHARACTERISTICS****1 1 NAME OF THE MEDICINAL PRODUCT**

Flumazenil 100 micrograms/ml, Solution for injection or infusion

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each 5ml ampoule contains 500 micrograms of flumazenil.

Each 10ml ampoule contains 1mg of flumazenil

For a full list of excipients, see 6.1.

**3 PHARMACEUTICAL FORM**

Solution for injection or infusion.

A clear, colourless or slightly yellow solution.

**4 CLINICAL PARTICULARS****4.1 THERAPEUTIC INDICATIONS**

Flumazenil Injection is indicated for the complete or partial reversal of the central sedative effects of benzodiazepines. It 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**

Flumazenil Injection is for slow intravenous injection or infusion. It should only be administered under the supervision of an experienced physician.

Flumazenil Injection 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 employed. The rate of infusion should be individually adjusted to achieve the desired level of arousal.

The individually titrated, slow injections or infusions of Flumazenil Injection 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 over 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 Flumazenil Injection, a non-benzodiazepine aetiology must be assumed.

**Elderly**

No specific data are available on the use of Flumazenil Injection 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.

### Children

There are insufficient data to make dosage recommendations for Flumazenil Injection 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

Flumazenil Injection is contraindicated in patients with known hypersensitivity to flumazenil, benzodiazepines or any of the excipients.

Flumazenil Injection 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 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 Injection should not be used to reverse benzodiazepine effects.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In view of the short duration of action of Flumazenil Injection and the possible need for repeat doses, the patient should remain under close observation until all possible central benzodiazepine effects have subsided.

The use of Flumazenil Injection is not recommended in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Although Flumazenil Injection 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 Injection 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 Injection in such patients may trigger these withdrawal symptoms, even in patients who stopped taking the benzodiazepine in the weeks preceding Flumazenil Injection 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 Injection 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 Injection 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 Injection is not recommended either as a treatment for benzodiazepine dependence or for the management of protracted benzodiazepine abstinence syndromes.

#### **4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**

Flumazenil Injection 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 Flumazenil Injection. However, Flumazenil Injection 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 Flumazenil Injection in cases of intentional overdose 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 Flumazenil Injection and vice versa.

#### **4.6 PREGNANCY AND LACTATION**

Like other benzodiazepine compounds, Flumazenil Injection 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 but animal studies have shown no teratogenic potential. The established medical principle of only administering drugs in early pregnancy when considered absolutely necessary should therefore be observed.

Emergency use of Flumazenil Injection during lactation is not contraindicated.

#### **4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

Patients who have received Flumazenil Injection 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 Injection 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, particularly 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 Injection usually subside rapidly without the need for special treatment.

Excessive and/or rapidly injected doses of Flumazenil Injection 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 Injection administration (depending on the half-life of the benzodiazepine used). Such symptoms may be treated by slow intravenous injection of diazepam or midazolam (see section 4.2 Posology and method of administration). There is also a possibility of mild and transient withdrawal reactions occurring even after a short period of administration of benzodiazepines.

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

Hypersensitivity reactions (including anaphylaxis) have occurred very rarely.

**4.9 OVERDOSE**

Even when given intravenously at doses of 100mg, no symptoms of overdosage attributable to Flumazenil Injection have been observed.

**5 PHARMACOLOGICAL PROPERTIES****5.1 PHARMACODYNAMIC PROPERTIES**

*Pharmacotherapeutic group:* Antidotes

*ATC code:* V03AB25

Flumazenil Injection, 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 Flumazenil Injection 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 100mg).

***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.

***Metabolism***

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.

***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 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**

EDTA

Glacial Acetic Acid  
Sodium Chloride  
Sodium Hydroxide  
Water for Injections

**6.2 INCOMPATIBILITIES**

None stated.

**6.3 SHELF LIFE**

Unopened: 3 years.

The product should be used immediately after opening.

**6.4 SPECIAL PRECAUTIONS FOR STORAGE**

Store below 30°C

**6.5 NATURE AND CONTENTS OF CONTAINER**

Clear glass 5ml and 10ml ampoules. Cartons of 5 ampoules.

**6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**

Flumazenil injection solution may be diluted with Sodium Chloride Intravenous Infusion BP or Dextrose 5% Intravenous Infusion BP. Chemical and physical stability has been demonstrated for 24 hours at room temperature.

Flumazenil infusion should be administered within 3 hours of preparation.

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

For single use only. Discard any unused contents.

**7 MARKETING AUTHORISATION HOLDER**

Bowmed Limited

113 Promenade

Cheltenham GL50 1NW

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 24610/0004

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

22/08/2007

**10 DATE OF REVISION OF THE TEXT**

22/08/2007

## PATIENT INFORMATION LEAFLET

## Flumazenil 100 micrograms/ml Solution for Injection and infusion

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do NOT pass it on to others. It may harm them even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or your pharmacist.

**In this leaflet:**

1. What Flumazenil Injection is and what it is used for.
2. Before you are given Flumazenil Injection
3. How Flumazenil Injection is given
4. Possible side effects
5. Storing Flumazenil Injection
6. Further information

**1. WHAT FLUMAZENIL INJECTION IS AND WHAT IT IS USED FOR**

Your doctor has decided to give you Flumazenil Injection because it reverses the effects of medicines called benzodiazepines (such as diazepam, midazolam, temazepam), which are sometimes used to cause deep sleep. Flumazenil Injection is used:

- to reverse the sleepiness you experience from a general anaesthetic after some diagnostic tests and operations.
- in intensive care patients who are on artificial ventilators. By reversing the effects of benzodiazepines, it allows the person to begin breathing without the help of ventilators.

Flumazenil is a solution given by a slow, single injection or slow continuous injection (infusion) into a vein. It works rapidly although the effects may wear off within a few hours and you may fall asleep again.

**2. BEFORE YOU ARE GIVEN FLUMAZENIL INJECTION**

You should not be given Flumazenil Injection if:

- You are allergic or have had any reactions to flumazenil or benzodiazepines.
- You are allergic or have had any reactions to any of the other ingredients in the injection (these are listed in Section 6, Further information).
- You suffer from epilepsy (fits/convulsions) and have been taking benzodiazepines for a long time.
- You have been taking benzodiazepines and certain antidepressants (such as amitriptyline, imipramine, dothiepin hydrochloride) at the same time.
- You are taking benzodiazepines to control a possibly life threatening condition (such as very severe epilepsy or raised pressure in the brain).

If you are unsure about any of these, ask your doctor.

**Before you are given Flumazenil Injection you should tell your doctor if:**

- You have a head injury.
- You suffer from or have in the past suffered from anxiety, or are very anxious about your operation.
- You suffer from heart disease, epilepsy (fits/convulsions) or severe liver disease.

**Taking other medicines**

Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines. This includes any that you may have bought without a prescription. This is extremely important because some medicines can strengthen or weaken the effect of others.

It is especially important to tell your doctor if you are taking zopiclone (to help you sleep) or antidepressants.

**Pregnancy and breast-feeding**

You **MUST TELL** your doctor if:

- you are pregnant, you think you are pregnant or you are likely to become pregnant. Your doctor will decide if you should be given this medicine.
- you are breast-feeding. Small amounts of this medicine may pass into breast milk. The medicine should be avoided except in an emergency. Your doctor will advise.

**Driving and using machines**

You should not drive or operate machinery or do physical or mental work for 24 hours after receiving this medicine. Ask your doctor if you are unsure.

**3. HOW FLUMAZENIL INJECTION IS GIVEN**

Flumazenil Injection will be given only under the supervision of an experienced doctor.

- Flumazenil is given by slow injection through a vein into the bloodstream over 15 seconds.
- Your dose will depend on the operation or procedure you have received and the level of sedation. This dose can be repeated every 60 seconds until the correct level of consciousness is reached.

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[Laetus code]



- If you become drowsy again, you may be given a slow, continuous injection (infusion) into a vein until the correct level of consciousness is reached.
- The treatment ends when you become fully awake.
- 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 gone.

**Adults and the elderly:**

Flumazenil Injection is suitable for adults including the elderly. Your doctor will calculate the dose of Flumazenil Injection and how long you will need to be treated.

**Adolescents and Children:**

Flumazenil may be used in adolescents and children if the doctor considers it essential.

**4. POSSIBLE SIDE EFFECTS**

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

All medicines can cause allergic reactions although serious allergic reactions are very rare. Any hives (slightly raised, itchy, skin patches that are paler or redder than the surrounding skin), sudden swelling of the hands, feet, ankles, or swelling of the face, lips, mouth or throat, which may cause difficulty swallowing or breathing, should be reported to a doctor immediately.

- Flumazenil can occasionally cause nausea (feeling sick), vomiting (being sick) and a feeling of warmth or flushing.
- Flumazenil 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, flumazenil can cause seizures (fits), particularly if you suffer from epilepsy or severe liver disease.

**INFORMATION FOR THE HEALTHCARE PROFESSIONAL**

The following information is intended for medical or healthcare professionals only.

**Instructions for use and handling:**

Flumazenil 100micrograms/ml may be diluted with Sodium Chloride Intravenous Infusion BP or Dextrose 5% Intravenous Infusion BP.

Chemical and physical stability has been demonstrated for 24 hours at room temperature.

Flumazenil 100micrograms/ml should be administered within 3 hours of preparation.

**Withdrawal symptoms**

If you have received treatment with benzodiazepines you may experience withdrawal symptoms such as anxiety attacks, dizziness, sweating and a rapid heart rate even if you stopped taking the benzodiazepines in the weeks before flumazenil was given. Your doctor may treat such symptoms with a slow injection into the vein of medicines known as diazepam or midazolam.

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

**5. HOW TO STORE FLUMAZENIL INJECTION**

Keep out of the reach and sight of children.

Do not use Flumazenil Injection after the expiry date which is printed on the label and carton.

Your medicine should be stored below 30°C. Your doctor, pharmacist or nurse will know how to store Flumazenil Injection properly.

**6. FURTHER INFORMATION****What Flumazenil Injection contains**

- The active ingredient is flumazenil
- The other ingredients are ethylenediamine tetraacetic acid, glacial acetic acid, sodium chloride, sodium hydroxide and water for injection.

**What Flumazenil Injection looks like and contents of the pack:**

Flumazenil Injection is available in 5ml and 10ml ampoules. The 5 ml ampoule contains 500 micrograms of flumazenil, and the 10ml ampoule contains 1mg of flumazenil.

**Marketing Authorisation Holder:**

Bowmed Limited, 113 Promenade, Cheltenham, UK.

**Manufacturer:**

Combino Pharm S.L., C/ Fructos Gelabert 6-8, 08970 Sant Joan Despi - Barcelona, Spain.

Date of leaflet preparation: November 2006

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

For single use only. Discard any unused contents.

**Storing Flumazenil Injection:**

Store below 30°C.

The product should be used immediately after opening.

Date of leaflet preparation: November 2006

**Flumazenil**  
100 micrograms/ml  
Solution for injection or  
infusion

**500 micrograms/  
5ml**

For intravenous use.  
PL 24610/0004  
Bowmed Limited. **POM**

Batch:  
EXP:

**Flumazenil**  
100 micrograms/ml  
Solution for injection or  
infusion

**1mg / 10ml**

For intravenous use.  
PL 24610/0004  
Bowmed Limited. **POM**

Batch:  
EXP:

**Flumazenil**  
100 micrograms/ml  
Solution for injection or  
infusion

**500 micrograms/5ml**

For intravenous use.  
PL 24610/0004  
Bowmed Limited. [POM]

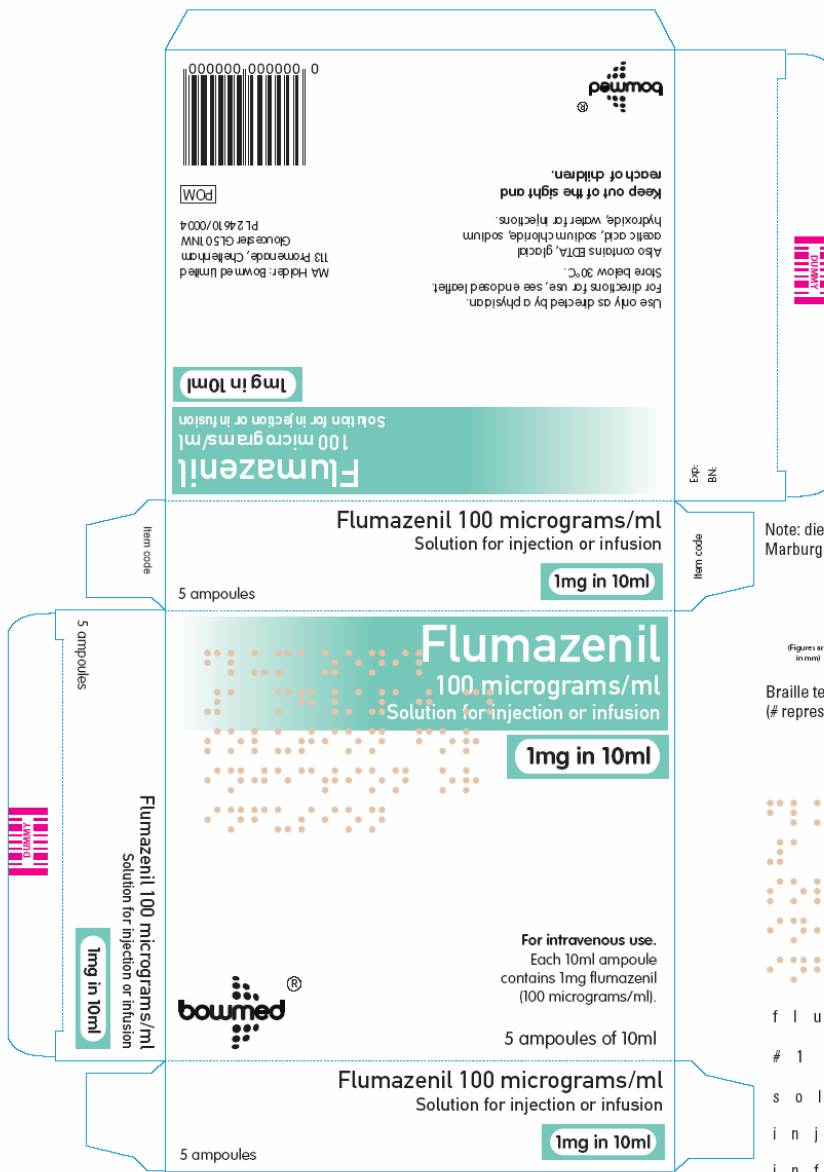
Batch:  
EXP:

**Flumazenil**  
100 micrograms/ml  
Solution for injection or  
infusion

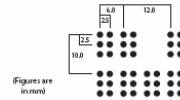
**1mg / 10ml**

For intravenous use.  
PL 24610/0004  
Bowmed Limited. [POM]

Batch:  
EXP:



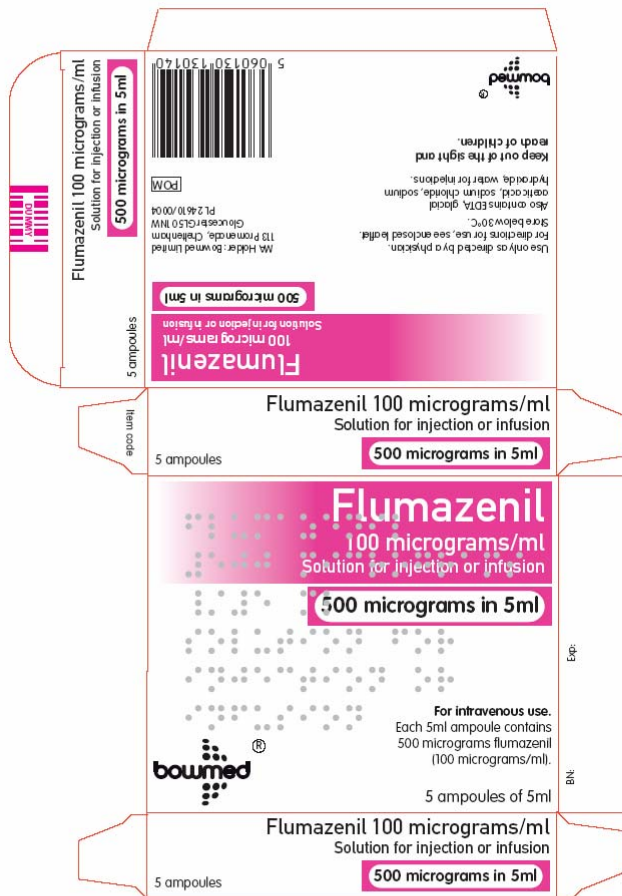
Note: dies comply with Marburg Medium cell dimensions:



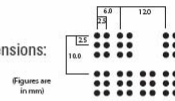
Braille text reads as follows (# represents "number sign"):

flumazenil  
 # 1 m g / # 1 0 m l  
 s o l u t i o n f o r  
 i n j e c t i o n o r  
 i n f u s i o n

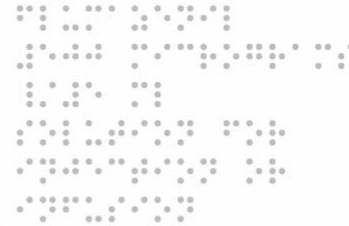
BATCH/EXPIRY DETAILS WILL BE PRINTED/EMBOSSSED IN THE AREA SHOWN



Note: dies comply with Marburg Medium cell dimensions:



Braille text reads as follows (# represents "number sign"):



flumazenil  
 # 5 0 0 micrograms  
 / # 5 ml  
 solution for  
 injection or  
 infusion

BATCH/EXPIRY DETAILS WILL BE PRINTED/EMBOSSED IN THE AREA SHOWN