Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Flumazenil 0.1 mg/ml solution for injection / infusion

(flumazenil)

Procedure No: UK/H/6055/001/DC

UK Licence No: PL 41947/0017

ELC GROUP s.r.o

LAY SUMMARY
Flumazenil 0.1 mg/ml solution for injection / infusion (flumazenil)

This is a summary of the Public Assessment Report (PAR) for Flumazenil 0.1 mg/ml solution for injection / infusion (UK/H/6055/001/DC; PL 41947/0017). It explains how Flumazenil 0.1 mg/ml solution for injection / infusion was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Flumazenil 0.1 mg/ml solution for injection / infusion.

For practical information about using Flumazenil 0.1 mg/ml solution for injection / infusion, patients should read the package leaflet or contact their doctor or pharmacist.

What is Flumazenil 0.1 mg/ml solution for injection / infusion and what is it used for?
Flumazenil 0.1 mg/ml solution for injection / infusion is a generic medicine. This means that Flumazenil 0.1 mg/ml solution for injection / infusion is similar to a 'reference medicine' already authorised in the European Union (EU) called Anexate® 500 micrograms/5 mL solution for injection or infusion (Roche Products Limited).

Flumazenil reverses the effects of the 'benzodiazepine' medicine. It is used to:

- Wake patients up after an operation or medical test.
- Help patients to breathe for themselves and wake up if they have been on a ventilator in intensive care.

Flumazenil 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.

How is Flumazenil 0.1 mg/ml solution for injection / infusion used?
Flumazenil 0.1 mg/ml solution for injection / infusion is given by a health professional by slow injection into the vein.

The dose of Flumazenil varies from one patient to another. This depends on the age, weight, how well a patient's liver and kidneys are working and what a patient need the medicine for.

This medicinal product can only be obtained with a prescription from a doctor.

For further information on how Flumazenil 0.1 mg/ml solution for injection / infusion is used, please see the Summary of Product Characteristics or the package leaflet available on the MHRA website.

How does Flumazenil 0.1 mg/ml solution for injection / infusion work?
Flumazenil 0.1 mg/ml solution for injection / infusion contains the active ingredient flumazenil. It works by waking patients up after they have been made sleepy by a medicine called a 'benzodiazepine'.

How has Flumazenil 0.1 mg/ml solution for injection / infusion been studied?
As this product is a solution for injection / infusion, the applicant has not performed any bioequvalence studies. No additional studies were needed as Flumazenil 0.1 mg/ml solution for injection / infusion is a generic medicine that is given intravenously as an aqueous intravenous solution and contains the same active substance and content as the reference medicine, Anexate® 500 micrograms/5 mL solution for injection or infusion.

What are the benefits and risks of Flumazenil 0.1 mg/ml solution for injection / infusion?

As Flumazenil 0.1 mg/ml solution for injection / infusion is a generic medicine and is comparable to the reference medicine, Anexate® 500 micrograms/5 mL solution for injection or infusion, its benefits and risks are taken as being the same as those of Anexate® 500 micrograms/5 mL solution for injection or infusion.

Why is Flumazenil 0.1 mg/ml solution for injection / infusion approved?
No new or unexpected safety concerns arose from this application. It was, therefore, concluded that the benefits of Flumazenil 0.1 mg/ml solution for injection / infusion outweigh the risks; and the grant of a Marketing Authorisation was recommended.

What measures are being taken to ensure the safe and effective use of Flumazenil 0.1 mg/ml solution for injection / infusion?
A risk management plan has been developed to ensure that Flumazenil 0.1 mg/ml solution for injection / infusion is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Flumazenil 0.1 mg/ml solution for injection / infusion, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Flumazenil 0.1 mg/ml solution for injection / infusion
Romania and the UK agreed to grant a Marketing Authorisation for Flumazenil 0.1 mg/ml solution for injection / infusion (UK/H/6055/001/DC; PL 41947/0017) on 04 May 2016. A Marketing Authorisation was granted in the UK on 26 May 2016.

The full PAR for Flumazenil 0.1 mg/ml solution for injection / infusion follows this summary. For more information about treatment with Flumazenil 0.1 mg/ml solution for injection / infusion, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in June 2016.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member State (CMS) considered that the application for Flumazenil 0.1 mg/ml solution for injection / infusion (UK/H/6055/001/DC; PL 41947/0017), is approvable.

Flumazenil 0.1 mg/ml solution for injection / infusion is a prescription only medicine (POM), 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.

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

This application was submitted according to Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The applicant has cross-referred to Anexate® 500 micrograms/5 mL solution for injection or infusion, authorised to Roche Products Limited (PL 00031/0228) on 29 March 1988.

With the UK as the RMS in this Decentralised Procedure (UK/H/6055/001/DC), ELC GROUP s.r.o applied for the Marketing Authorisation for Flumazenil 0.1 mg/ml solution for injection / infusion Romania.

Flumazenil, 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 and may then reappear gradually within a few hours, depending on the half-life and dose ratio of the agonist and antagonist.

No new non-clinical or clinical studies were conducted, which is acceptable given that this is a generic application of an originator product that has been in clinical use for over 10 years. A bioequivalence study was not necessary to support this application for a parenteral product administered as an aqueous intravenous solution containing the same active substance as the reference product.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

Both Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 210 – 04 May 2016.). After a subsequent national phase, the UK granted a Marketing Authorisation (PL 41947/0017) for this product on 26 May 2016.

II QUALITY ASPECTS

II.1 Introduction

This product is a solution for injection / infusion. Each 5 ml or 10 ml ampoule contains 0.5 milligrams or 1 milligram respectively of flumazenil, as an active ingredient. The excipients present are disodium edetate, glacial acetic acid, sodium chloride, sodium hydroxide (for pH adjustment) and Water for Injections.

All excipients used comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for these excipients.

The finished product is packaged in 5 ml and 10 ml one point-cut glass ampoules.

The pack sizes are as follows:

Pack of 5 one point-cut glass ampoules of 5 ml.
Pack of 10 one point-cut glass ampoules of 5ml.
Pack of 5 one point-cut glass ampoules of 10 ml.
Pack of 10 one point-cut glass ampoules of 10ml.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

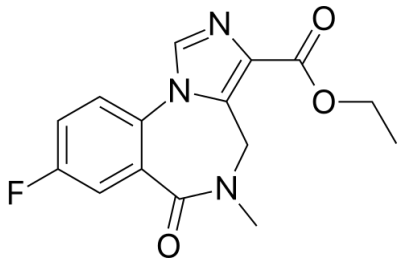
II.2 Drug Substance

Flumazenil

INN: **Flumazenil**

Chemical name(s): Ethyl 8-fluoro-5-methyl-6-oxo-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate

Structure:



Molecular formula: $C_{15}H_{14}FN_3O_3$
Molecular weight: 303.3 g/mol
Appearance: White or almost white crystalline powder.

Flumazenil is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, flumazenil, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the pharmaceutical development programme was to obtain stable solution for

injection/infusion containing flumazenil that could be considered as a generic medicinal product of Anexate® 500 micrograms/5 mL solution for injection or infusion (Roche Products Limited).

Satisfactory pharmaceutical development data have been submitted in support of the application.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated using the full scale commercial batch sizes and have shown satisfactory results.

Finished Product Specification
The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the product
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 3 years with no special storage conditions is set. This is satisfactory.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS
III.1 Introduction
No new non-clinical data have been supplied with this application and none are required for applications of this type. The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

III.2 Pharmacology
No new data have been submitted and none are required for applications of this type.

III.3 Pharmacokinetics
No new data have been submitted and none are required for applications of this type.

III.4 Toxicology
No new data have been submitted and none are required for applications of this type.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since the proposed product is intended for a generic substitution, its use will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this product from a non-clinical point of view.

IV CLINICAL ASPECTS
IV.1 Introduction
Flumazenil 0.1 mg/ml solution for injection / infusion is administered as an aqueous intravenous solution and contains the same active ingredient in the same concentration and pharmaceutical form using the same route of administration as the reference product. It also contains the same excipients as the reference product. As the product is indicated for intravenous administration and in accordance with the Note for Guidance on the investigation of bioavailability and bioequivalence

(CPMP/EWP/QWP/1401/98 Rev.1/Corr**), bioequivalence can be concluded without the need for further studies. No bioequivalence studies have been submitted and none are required.

IV.2 Pharmacokinetics

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

IV.3 Pharmacodynamics

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

IV.4 Clinical efficacy

No new efficacy data have been submitted and none are required for this application.

IV.5 Clinical safety

No new safety data have been submitted and none are required for this application.

IV.6 Risk Management Plan (RMP)

The Marketing Authorisation Holder has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Flumazenil 0.1 mg/ml solution for injection / infusion.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Important identified risks		
Safety concern	**Summary of routine risk minimisation measures**	**Summary of additional risk minimisation measures**
Hypersensitivity	In section 4.3 "Contraindications", it is noticed that Flumazenil is contra-indicated in patients with hypersensitivity to the active substance, benzodiazepines or any of the excipients. Listed in section 4.8 "Undesirable effects": Hypersensitivity reactions (such as anaphylactic reaction) with a rare frequency. Restricted medical prescription	Not applicable
Use in patient with hepatic impairment	In section 4.2 "Posology and method of administration" it is stated that since flumazenil is primarily metabolised in the liver, careful titration of dosage is recommended in patients with impaired hepatic function. In section 4.4 "Special warnings and precautions for use" it is stated that elimination may be delayed in patients with hepatic impairment. 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. Listed in section 4.8 "Undesirable effects »: Seizures (unknown frequency): 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. In section 5.2 "Pharmacokinetic properties" it is stated that Flumazenil is extensively metabolised in the liver. : In patients with impaired liver function, the elimination half-life of flumazenil is longer and the total body clearance lower than in healthy subjects. Restricted medical prescription	Not applicable
Convulsions in patients with epilepsy treated with long-term	It is stated in section 4.3 "Contraindications" that Flumazenil is contra-indicated in patients who have been administered benzodiazepines for the treatment of a potentially life- threatening condition (e.g. [….] or	Not applicable

Important identified risks		
Safety concern	**Summary of routine risk minimisation measures**	**Summary of additional risk minimisation measures**
benzodiazepines	status epilepticus). In section 4.4 "Special warnings and precautions for use" it is stated that 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. Listed in section 4.8 "Undesirable effects": seizures with an unknown frequency, 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. Section 4.9 "Overdose" explains that in cases of mixed-drug overdose, particularly with cyclic antidepressants, toxic effects (such as convulsions) may emerge with the reversal of benzodiazepine effects by flumazenil. Restricted medical prescription	
Increased intracranial pressure	Firstly, it is stated in section 4.3 "Contraindications" that Flumazenil is contra-indicated in patients who have been administered benzodiazepines for the treatment of a potentially life- threatening condition (e.g. increased intracranial pressure or [….]). In section 4.4 "Special warnings and precautions for use" it is stated that 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. A transient increased blood pressure (on awakening), unspecified, is reported in section 4.8 "Undesirable effects". Restricted medical prescription	Not applicable
Toxic effects (cardiac arrhythmia and	In section 4.3 "Contraindications" it is reported that in mixed intoxications with benzodiazepines and tricyclic and/or tetracyclic antidepressants, the toxicity of the antidepressants can be masked by protective	Not applicable

Important identified risks		
Safety concern	**Summary of routine risk minimisation measures**	**Summary of additional risk minimisation measures**
convulsion) in case of intoxication with benzodiazepines and cyclic antidepressants	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. In section 4.4 "Special warnings and precautions for use", it is stated that 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. In section 4.5 "Interaction with other medicinal products and other forms of interactions", it is stated that Flumazenil antagonises the central effects of benzodiazepines by competitive interaction at the receptor. The effects of non-benzodiazepine agonists that act via the benzodiazepine receptor, such as zopiclone, triazolpyridazine and others, are also blocked by flumazenil. Interactions with other centrally acting substances have not been observed. The pharmacokinetics of benzodiazepines 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.particular caution is necessary when using Flumazenil 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. Section 4.9 "Overdose" states that 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. Restricted medical prescription	
Residual and re-occurrence of benzodiazepine	In section 4.4 "Special warnings and precautions for use" it is stated that patients who have received flumazenil for the reversal of Benzodiazepine effects	Not applicable

Important identified risks		
Safety concern	**Summary of routine risk minimisation measures**	**Summary of additional risk minimisation measures**
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. In section 4.7 "Effects on ability to drive and use machines", it is specified that 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. Restricted medical prescription	
Precipitation of benzodiazepine withdrawal symptoms	In section 4.2 "Posology and method of administration" it is explained that the individually titrated, slow injections or infusions of Flumazenil 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 (Valium) or midazolam (Hypnovel) should be given by slow intravenous injection. In section 4.4 "Special warnings and precautions for use", it is stated that 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. 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. Listed in section 4.8 "Undesirable effects" with	Not applicable

Important identified risks		
Safety concern	**Summary of routine risk minimisation measures**	**Summary of additional risk minimisation measures**
	unknown frequency as: 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. Restricted medical prescription	

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended.

V USER CONSULTATION

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet (PIL) was English.

The package leaflet meets the criteria for readability, as set out in the *guideline on the readability of the label and package leaflet of medicinal products for human use.*

VI OVERALL CONCLUSION, BENEFIT-RISK ASSESSMENT AND RECOMMENDATION

QUALITY

The important quality characteristics of Flumazenil 0.1 mg/ml solution for injection / 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.

NON-CLINICAL

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

CLINICAL

In accordance with the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), bioequivalence studies were not conducted and none are required for this type of product.

No new or unexpected safety concerns arose from this application.

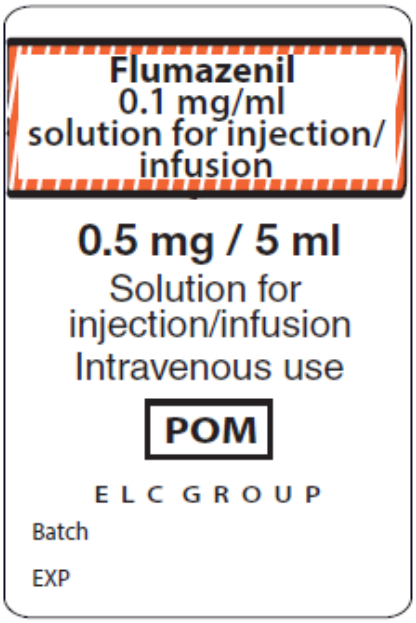
The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

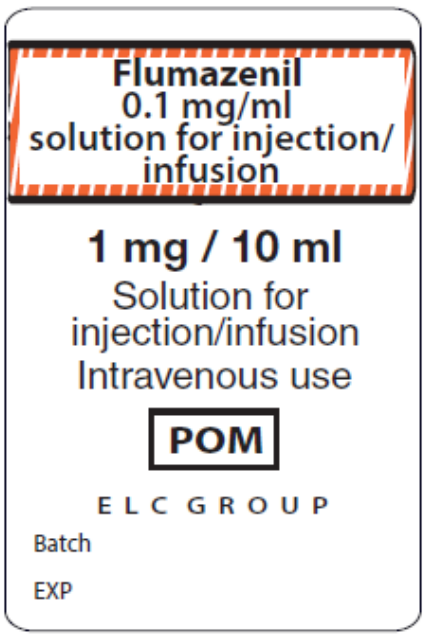
BENEFIT-RISK ASSESSMENT

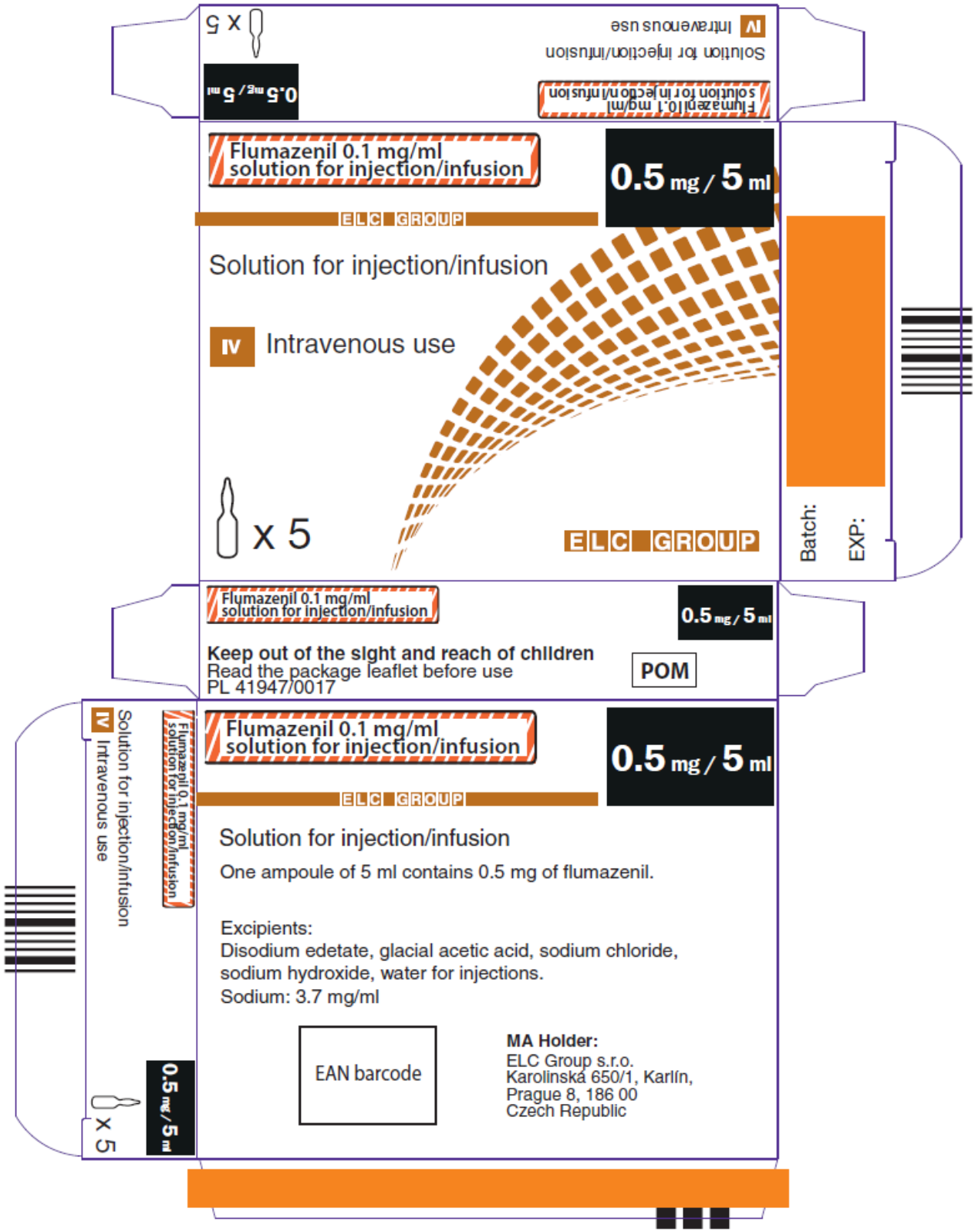
The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with flumazenil is considered to have demonstrated the therapeutic value of the compound. The proposed product is also considered bioequivalent to the reference product. The benefit risk is, therefore, considered to be positive.

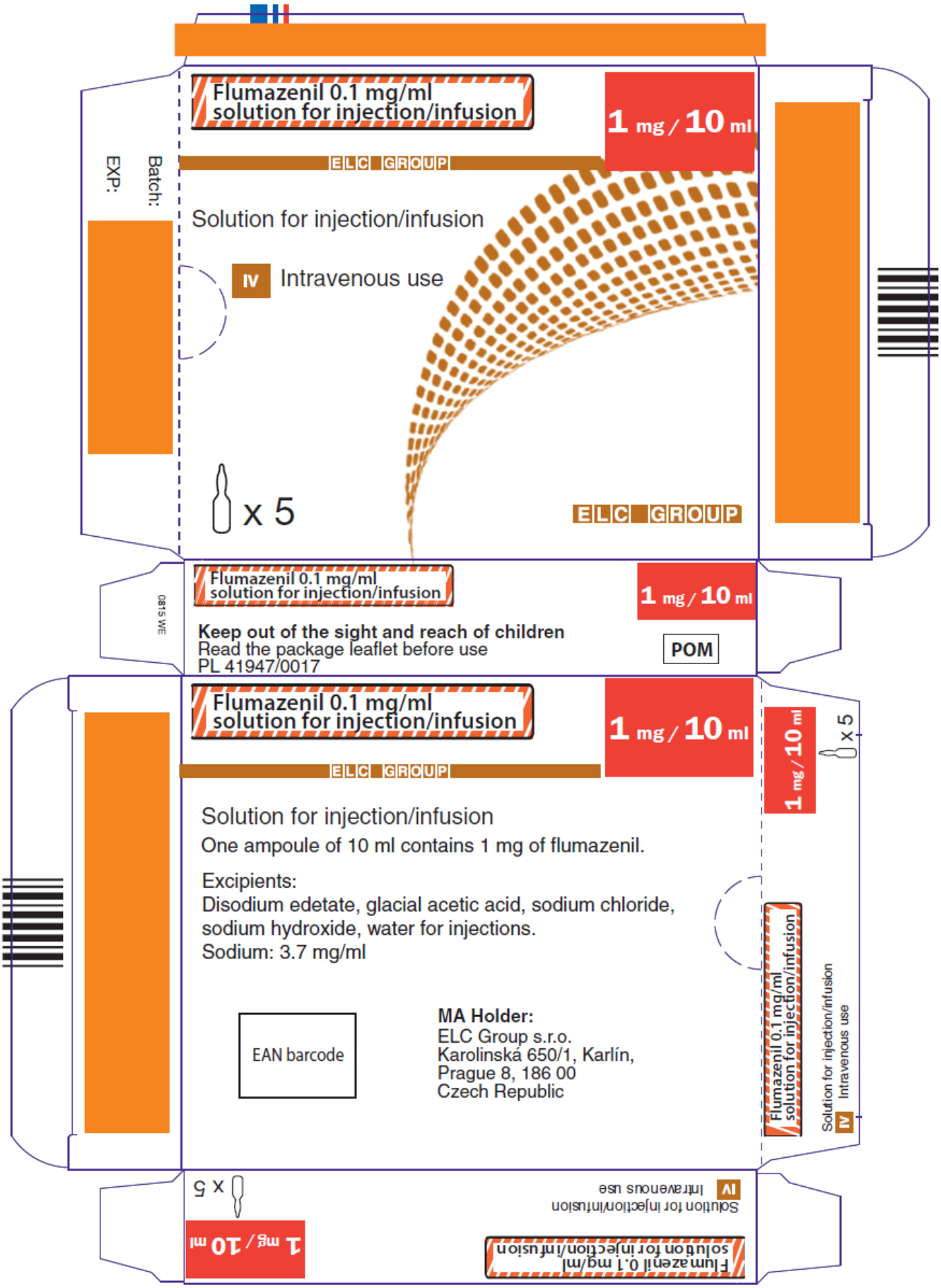
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

The approved text labelling for Flumazenil 0.1 mg/ml solution for injection / infusion is presented below:






Flumazenil 0.1 mg/ml solution for injection/infusion
0.5 mg / 5 ml
ELC GROUP
Solution for injection/infusion
IV Intravenous use
x 5
Batch:
EXP:
Keep out of the sight and reach of children
Read the package leaflet before use
PL 41947/0017
POM
One ampoule of 5 ml contains 0.5 mg of flumazenil.
Excipients:
Disodium edetate, glacial acetic acid, sodium chloride, sodium hydroxide, water for injections.
Sodium: 3.7 mg/ml
EAN barcode
MA Holder:
ELC Group s.r.o.
Karolinská 650/1, Karlín,
Prague 8, 186 00
Czech Republic


Flumazenil 0.1 mg/ml
solution for injection/infusion
1 mg / 10 ml
ELC GROUP
Solution for injection/infusion
IV Intravenous use
Batch:
EXP:
x 5
ELC GROUP
Flumazenil 0.1 mg/ml
solution for injection/infusion
1 mg / 10 ml
Keep out of the sight and reach of children
Read the package leaflet before use
PL 41947/0017
POM
0815 WE
Flumazenil 0.1 mg/ml
solution for injection/infusion
1 mg / 10 ml
ELC GROUP
Solution for injection/infusion
One ampoule of 10 ml contains 1 mg of flumazenil.
Excipients:
Disodium edetate, glacial acetic acid, sodium chloride,
sodium hydroxide, water for injections.
Sodium: 3.7 mg/ml
EAN barcode
MA Holder:
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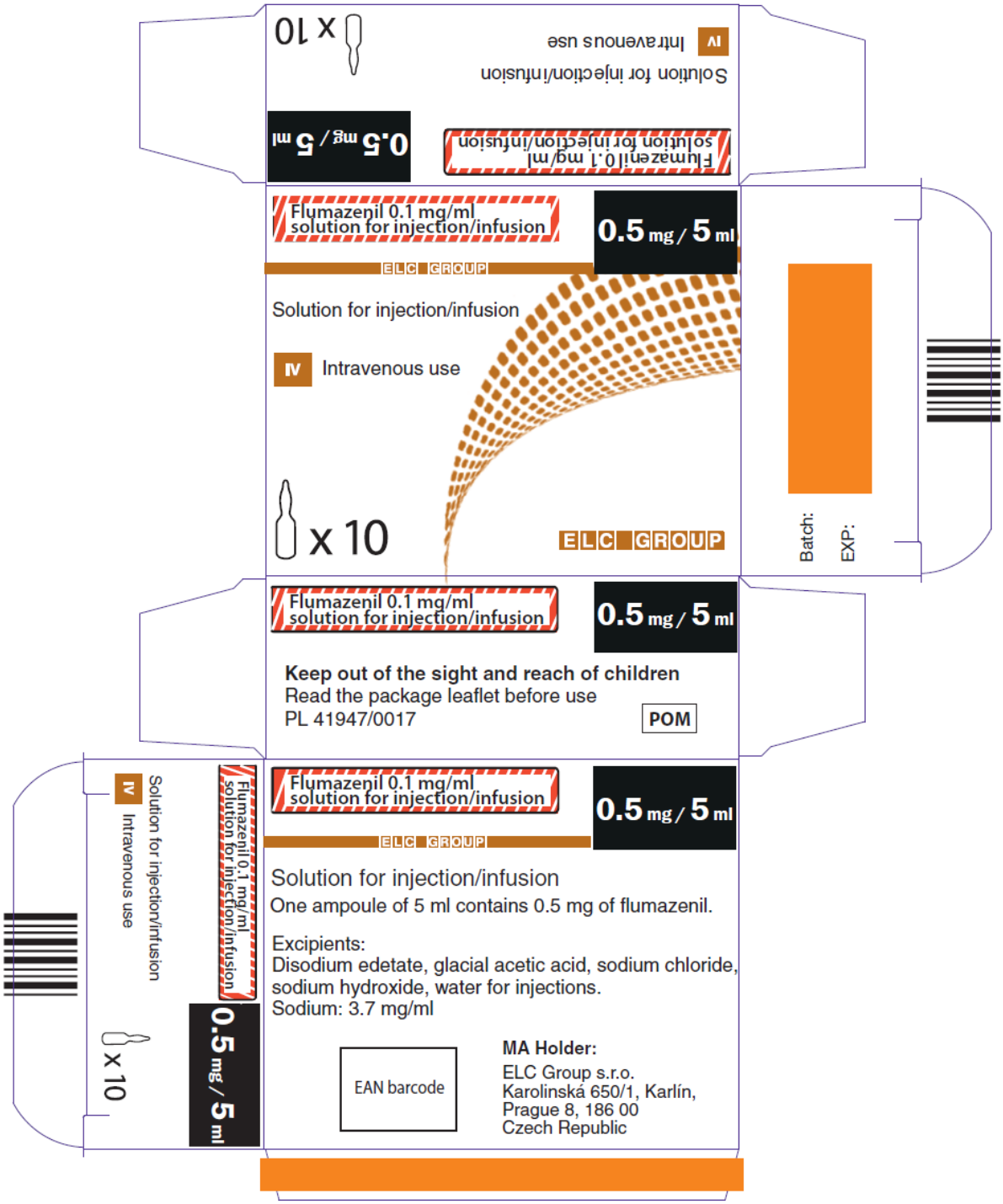
IV Intravenous use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0.5 mg / 5 ml
ELC GROUP
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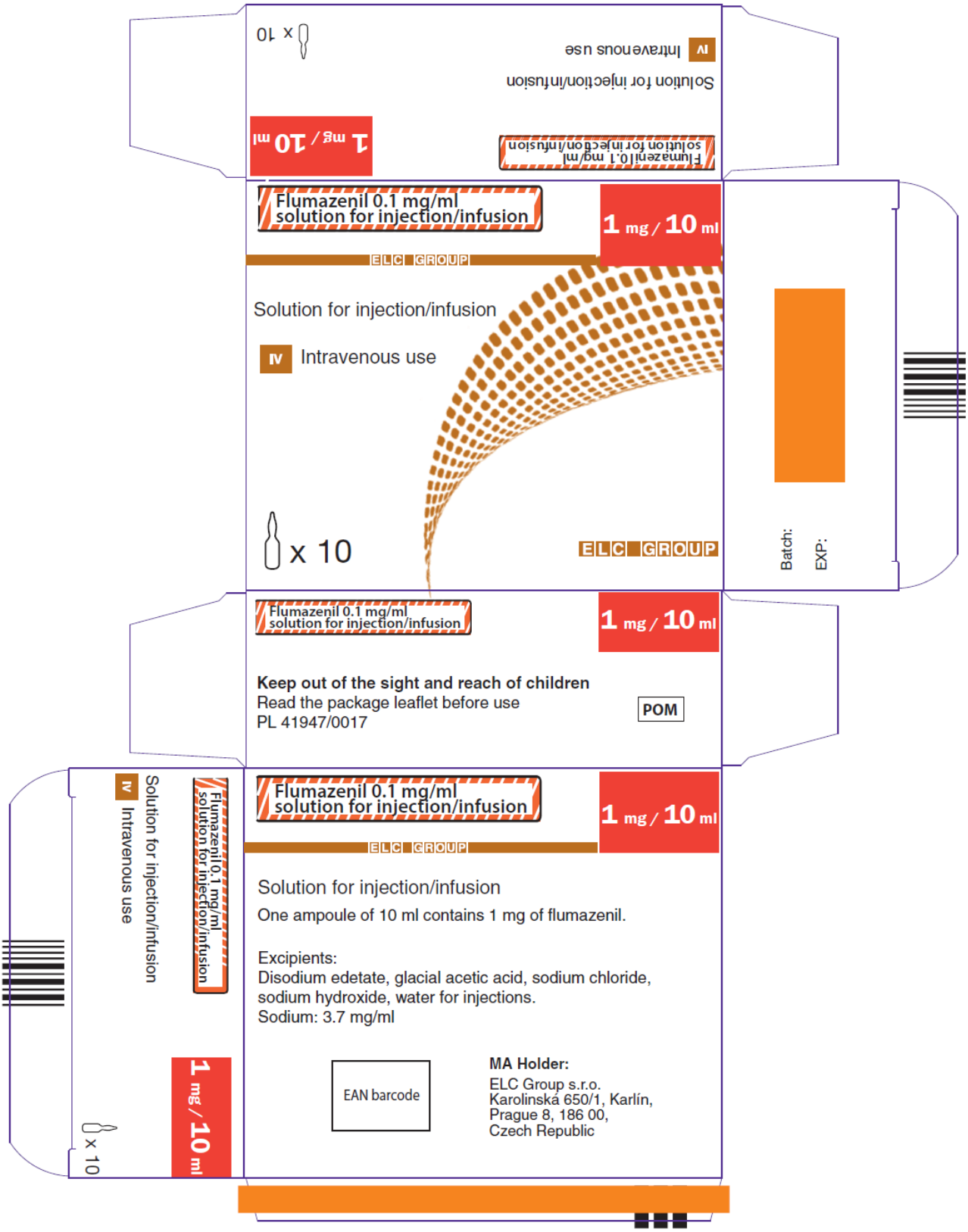
Flumazenil 0.1 mg/ml solution for injection/infusion
1 mg / 10 ml
ELC GROUP
Solution for injection/infusion
IV Intravenous use
x 10
Batch:
EXP:
Keep out of the sight and reach of children
Read the package leaflet before use
PL 41947/0017
POM
Solution for injection/infusion
One ampoule of 10 ml contains 1 mg of flumazenil.
Excipients:
Disodium edetate, glacial acetic acid, sodium chloride, sodium hydroxide, water for injections.
Sodium: 3.7 mg/ml
EAN barcode
MA Holder:
ELC Group s.r.o.
Karolinská 650/1, Karlín,
Prague 8, 186 00,
Czech Republic

Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)