CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Flumazenil B. Braun 0.1 mg/ml, solution for injection 0.5 mg/5 ml and 1.0 mg/10 ml
B. Braun Melsungen AG (Melsungen), Germany

flumazenil

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/915/01/MR
Registration number in the Netherlands: RVG 32038

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Pharmacotherapeutic group:	antidotes
ATC code:	V03AB25
Route of administration:	intravenous
Therapeutic indication:	the complete or partial reversal of the central sedative effects of benzodiazepines.
Prescription status:	prescription only
Date of authorisation in NL:	10 May 2005
Concerned Member States:	Mutual recognition procedure with AT, BE, DE, ES, FI, IE, IT, LU, NO, PL, PT, SE and UK.
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the concerned member states have granted a marketing authorisation for Flumazenil B. Braun 0.1 mg/ml, solution for injection 0.5 mg/5 ml and 1.0 mg/10 ml from B. Braun Melsungen AG (Melsungen), Germany. The date of authorisation was on 10 May 2005 in the Netherlands.

The product is indicated for the complete or partial reversal of the central sedative effects of benzodiazepines. It may therefore be used in anaesthesia and in the intensive care in the following situations:
In anaesthesia
- Termination of hypnosedative effects in general anaesthesia induced and/or maintained with benzodiazepines in hospitalized patients.
- Reversal of benzodiazepine sedation in short-term diagnostic and therapeutic procedures in ambulatory patients and hospitalized patients.

In intensive care situations
- For the specific reversal of the central effects of benzodiazepines, in order to restore spontaneous respiration.
- For diagnosis and treatment of intoxications or overdose with only or mainly benzodiazepines.

A comprehensive description of the indications and posology is given in the SPC.

Flumazenil, an imidazobenzodiazepine, is a benzodiazepine antagonist which, by competitive interaction, blocks the effects of substances acting via the benzodiazepine-receptor. Neutralisation of paradoxal reactions of benzodiazepines has been reported. According to experiments in animals, the effects of substances, which are not acting via the benzodiazepine-receptor (like barbiturates, GABA-mimetics and adenosine-receptor agonists), are not blocked by flumazenil. Non-benzodiazepine-agonists, like cyclopyrrolones (zopiclon) and triazolopyridazines, are blocked by flumazenil. The hypnosedative effects of benzodiazepines are blocked rapidly (within 30-60 seconds) after intravenous administration. Depending on the difference in elimination time between agonist and antagonist, the effect can recur after several hours. Flumazenil has possibly a slight agonistic, anticonvulsive effect. Flumazenil caused withdrawal, including convulsions in animals receiving long-term flumazenil treatment. Flumazenil is well tolerated, even in high doses.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Anexate, solution for injection 0.5 mg/5 ml and 1.0 mg/10 ml (NL License RVG 12857), which has been registered in the Netherlands by Roche Nederland B.V. since 1988. In addition, reference is made to Anexate authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Flumazenil B. Braun 0.1 mg/ml is a product for parenteral use, has the same type of (aqueous) solution and contains the same concentration of the active substance and same excipients as the reference product, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current products can be used instead of their reference product.

No new preclinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is flumazenil, a established active substance described in the European Pharmacopoeia (Ph.Eur.). Ph.Eur is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU. Flumazenil is a white or almost white crystalline powder. The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with additional specifications for residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitablity concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, and the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

The active substance is stable for 2 years when stored in amber glass container. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Medicinal Product

Composition
Flumazenil 0.1 mg/ml solution for injection contains as active substance flumazenil and is a clear colourless solution.

The solution for injection is packed in colourless glass ampoules (glass Type I) of 5 ml and 10 ml.

The excipients are: disodium edetate, glacial acetic acid, sodium chloride, sodium hydroxide for pH adjustment, water for injections.

The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs, except for the sodium hydroxide, which complies with in-house specifications.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The objective was to develop a product that would be essentially similar to the innovator product Anexate.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 4 pilot-scale batches and 6 full-scale batches batches in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification of the finished product includes tests for appearance, extractable volume, particulate matter, identification, pH, impurities, assay, bacterial endotoxins and sterility. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data 4 pilot-scale batches from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 4 batches in accordance with applicable European guidelines demonstrating the stability of the product over 36 months. On basis of the data submitted, a shelf life was granted of 3 years. The labelled storage conditions are: "Do not store above 25°C."

Chemical and physical in-use stability data have been provided demonstrating that the product remains stable for 24 hours following dilution at 25°C.

After first opening the medicinal product should be used immediately.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

This product is a generic formulation of Anexate, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of flumazenil released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Flumazenil is a well-known active substance with established efficacy and tolerability.

The SPC is in line with the SPC as approved for procedures NL/H/625-627 and NL/H/639 (Flumazenil Actavis 0,1 mg/ml, solution for injection) except for product names, marketing authorisation holder, marketing authorisation number and all chemical-pharmaceutical sections.

Flumazenil 0.1 mg/ml solution for injection is a parenteral formulation containing the same active substance in the same concentration as the currently authorized reference medicinal product. As Flumazenil 0.1 mg/ml solution for injection is a product for parenteral use, has the same type of (aqueous) solution and contains the same concentration of the active substance and same excipients as the reference product, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

Risk Management Plan
Flumazenil was first approved in 1987, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of flumazenil can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation, which are not

adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

Readability test

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 test consisted of one round with 20 participants, instead of two rounds with 10 participants. The questions covered the following are as sufficiently: traceability, comprehensibility. Applicability was not mentioned separately. The MAH has provided the raw data and an amended readability report in which the development of the questionnaire has been described, the results are presented in such way that traceability and comprehensibility/applicability have been separated.

It is however noted that:

- Good traceability for 9 out of the 15 questions was below 80% and in the report hardly any discussion is included how the traceability could be improved.
- The comprehensibility/applicability was acceptable for all questions except for one.
- In section 8 possible improvements are discussed (including improvement of the comprehensibility of the indications), but no amendments are introduced.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Flumazenil B. Braun 0.1 mg/ml, solution for injection 0.5 mg/5 ml and 1.0 mg/10 ml have a proven chemical-pharmaceutical quality and are a generic form of Anexate, solution for injection 0.5 mg/5 ml and 1.0 mg/10 ml. Anexate is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is in line with the SPC as approved for procedures NL/H/625-627 and NL/H/639 (Flumazenil Actavis 0,1 mg/ml, solution for injection). The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Flumazenil B. Braun 0.1 mg/ml, solution for injection 0.5 mg/5 ml and 1.0 mg/10 was authorised in the Netherlands on 10 May 2005.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The mutual recognition recognition procedure was finished on 21 December 2006. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Flumazenil B. Braun 0.1 mg/ml, solution for injection 0.5 mg/5 ml and 1.0 mg/10 with the reference product, and have therefore granted a marketing authorisation.

The PSUR submission cyclus is 3 years. The first PSUR will cover the period from December 2006 till December 2009.

The date for the first renewal will be 21 December 2011.

No post-approval commitments have been made during the procedure:

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Submission of a new or updated Ph.Eur. Certificate of Suitability for an active substance or starting/reagent/intermediate in the manufacturing process of the active substance. From a manufacturer currently approved.	NL/H/0915/ 001/IA/001	IA	10-4-2008	24-4-2008	Approved	N