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/1263/001/DC
**Registration number in the Netherlands:** RVG 101556
**30 November 2009**

**Pharmacotherapeutic group:** antidotes
**ATC code:** V03AB25
**Route of administration:** intravenous
**Therapeutic indication:** complete or partial reversal of the central sedative effects of benzodiazepines
**Prescription status:** prescription only
**Date of authorisation in NL:** 27 August 2009
**Concerned Member States:** Decentralised procedure with AT, DE, DK, EL, ES, FR, IE, IT, MT, PL, PT, RO, 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 member states have granted a marketing authorisation for Flumazenil 0.1 mg/ml PCH, solution for injection, from Pharmachemie B.V. The date of authorisation was on 27 August 2009 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 1-2 minutes) 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.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Anexate 0.5 mg/5 ml and 1.0 mg/10 ml solution for infusion (NL 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 0.1 mg/ml PCH is an aqueous solution for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No new pre-clinical 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, and no paediatric development programme has been submitted, as this is not required for a generic medicinal product.
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, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a white or almost white crystalline powder, very slightly soluble in water, freely soluble in methylene chloride and sparingly soluble in methanol.

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 suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or 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 European Pharmacopoeia, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Quality control of drug substance
The MAH has adopted the Ph.Eur. specifications/analytical methods and the additional specifications/analytical methods as included on the CEP. Additional limits for yeasts and moulds have been provided. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full-scale batches.

Stability
Stability data on the active substance have been provided as part of the CEP. The MAH applies a retest period of 1 year from the date of manufacturing, which is approvable.

* 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.

Medicinal Product

Composition
Flumazenil 0.1 mg/ml PCH is a clear, almost colourless solution, free from foreign matter.

The solution for infusion is packed in colourless glass type I ampoules, containing 5 ml or 10 ml.

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

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions are explained. Development studies are performed to determine the solubility of flumazenil, thermal stability, photostability, the microbiological and chemical stability of flumazenil solution for injection upon holding, and compatibility studies with excipients and primary packaging. All excipients comply with their Ph.Eur. specifications. No overage is used. Additionally, a comparison of composition and the physico-chemical parameters with the innovator product has been made. The results of this comparison indicate that the formulation and the physicochemical properties of the product flumazenil 0.1 mg/ml
solution for injection are essentially similar to the formulation and the physicochemical properties of the reference product Anexate. The choice of the packaging is justified. Type I glass ampoules will be packed in a cardboard box. The ampoules should be kept in the outer carton to prevent degradation from light and should not be freeze or refrigerated.

**Compatibility**
Flumazenil should only be diluted with sodium chloride 9 mg/ml (0.9 %) solution or glucose 50 mg/ml (5 %) solution. Compatibility between flumazenil and other solutions for injection has not been established. The MAH committed to carry out compatibility testing on the drug product with 0.45% NaCl + 2.5% glucose (in accordance with compatibility claimed for the NL innovator product), and to provide the results as soon as available.

**Manufacturing process**
The manufacturing process consists of dissolution and mixing steps, after which the solution is cooled. After cooling the pH is checked and if necessary the solution is adjusted. The solution is then filled up to the final volume with water for injection. Finally, the solution is filtered and aseptically filled into clean, sterile ampoules. The filled ampoules are terminally sterilized.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for two production-scale batches with two filling volumes per batch (5 ml and 10 ml). Since the manufacturing process is seen as a standard process, this is regarded to be sufficient. The shelf life specification for pH is between 3.5-4.5, osmolality of the solution is about 298 mOsmol/kg.
All batches complied with the specifications. Several commitments have been made regarding process validation, see page 6 of this report.

**Quality control of drug product**
The product specification includes tests for appearance, pH, identity, assay, impurities/degradation, identification and content of EDTA, extractable volume, subvisible particles, bacterial endotoxins and sterility. The release and end of shelf-life specifications are identical, except for the limitations for the impurities. The proposed limitations for impurities are acceptable. The analytical methods have been adequately described and validated. Batch analytical data have been provided on two commercial-size batches, demonstrating compliance with the release specifications.

**Stability tests on the finished product**
Stability data have been provided for two commercial-size batches of the finished product of each presentation, stored at 25°C/60 (18 months) and 40°C/75 (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in type I glass ampoules.
When stored under long term conditions, the appearance and colour of the solution do not change. The pH values and the assay values do not change significantly, but some variation is observed. The values for several impurities increase during the storage period, but remain within the specifications. When stored under accelerated conditions the same results are seen as under long term conditions. Based on the results of the stability study, a shelf life of 24 months could be granted. Photostability testing was performed on two batches of the finished product, one of each presentation. Appearance, colour, pH, assay and impurity profile of the product did not change, but EDTA content of the uncovered product decreased. The product is light sensitive and should therefore be protected from light. The MAH committed to provide the results of ongoing stability studies and results of one further stability batch, up to the projected shelf-life of 60 months, as soon as available.
Adequate compatibility results have been provided to justify an in-use shelf-life of 24 hours after dilution with 0.9% NaCl or 5% glucose solution.

**Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies**
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.
II.2 Non clinical aspects

This product is a generic formulation of Anexate solution for infusion, 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.

Flumazenil 0.1 mg/ml PCH, solution for injection is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Flumazenil 0.1 mg/ml PCH is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. 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 postauthorization 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. A total of 22 participants were recruited via online advertisement and/or local press. All participants were potential users. Candidates with working experience in pharmaceuticals, medicines, market research or media, and candidates who had participated in user tests before were excluded. The age of the participants (12 females, 10 males) ranged from 18-63 years. Minimum level of education was a general certificate of secondary education, the highest level an undergraduate degree. The test consisted of a pilot test with two participants, followed by 2 rounds with 10 participants each. A total number of 20 questions were asked. Sixteen questions specifically addressed the key safety messages of the leaflet in a randomized order; the other 4 questions were meant to obtain a general impression of the package leaflet, including aspects as design and lay-out. In both rounds the criteria for a successful test (when, for each question, 90% of all participants are able to find the information requested within the PIL, and 90% of all participants can show that they understand and can act upon it) were met. No weaknesses of the PL were identified from the 16 questions specifically addressing the key safety issues, despite the fact that a considerable number of participants considered the leaflet lengthy and the font size small. Therefore, no changes to the PIL were proposed. The results show that the leaflet is easy to read and understand. The package leaflet is in line with the current readability requirements.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Flumazenil 0.1 mg/ml PCH, solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Anexate 0.5 mg/5 ml and 1.0 mg/10 ml solution for infusion. 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, package leaflet and labelling are in the agreed templates and are in agreement with other flumazenil containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Flumazenil 0.1 mg/ml PCH with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 21 January 2009. Flumazenil 0.1 mg/ml PCH, solution for injection was authorised in the Netherlands on 27 August 2009.

A European harmonised birth date has been allocated (14 January 1987) and subsequently the first data lock point for flumazenil is May 2009. The first PSUR will cover the period from January 2009 to May 2009, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 31 January 2013.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product
- The MAH committed to verify the physicochemical stability of the bulk solution during the 72-hour period, in accordance with a revised process validation protocol.
- The MAH committed to complete the process validation program on a third full-scale batch and on the first three batches of all other proposed commercial batch sizes, and to provide the results.
- The MAH committed to provide all impurity results numerically on the certificates of analysis to be provided in the future.
- The MAH committed to validate the bioburden test method on the first three batches, and to provide the updated validation report as soon as available.
- The MAH committed to provide the results of ongoing stability studies and results of one further stability batch, up to the projected shelf-life of 60 months, as soon as available.
- The MAH committed to carry out compatibility testing on the drug product with 0.45% NaCl + 2.5% glucose (in accordance with compatibility claimed for the NL innovator product), and to provide the results as soon as available.
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\textsubscript{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
EDTA   ethylenediaminetetraacetic acid
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
PIL    Package Leaflet
PSUR   Periodic Safety Update Report
SD     Standard Deviation
SPC    Summary of Product Characteristics
\(t\textsubscript{1/2}\) Half-life
\(t\textsubscript{\text{max}}\) Time for maximum concentration
TSE    Transmissible Spongiform Encephalopathy
USP    Pharmacopoeia in the United States
### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addition of a site for batch release (not including batch control/testing)</td>
<td>NL/H/1263/001/IA/001</td>
<td>IA</td>
<td>7-9-2009</td>
<td>21-9-2009</td>
<td>Approval</td>
<td>N</td>
</tr>
</tbody>
</table>