

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Midazolam Accord 1 mg/mL, solution for injection or infusion
Midazolam Accord 5 mg/mL, solution for injection or infusion
Accord Healthcare Ltd, United Kingdom**

midazolam hydrochloride

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/1077/001-002/DC
Registration number in the Netherlands: RVG 100470, 100485**

22 December 2009

Pharmacotherapeutic group:	Benzodiazepine derivatives
ATC code:	N05CD08
Route of administration:	intravenous; intramuscular
Therapeutic indication:	conscious sedation, anaesthesia, sedation in intensive care units in adults and children
Prescription status:	prescription only
Date of authorisation in NL:	8 June 2009
Concerned Member States:	Decentralised procedure with AT, BE, CY, CZ, DE, DK, EE, EL, ES, FI, HU, IE, IT, LV, MT, NO, PL, PT, SE, SI, SK, 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 Midazolam Accord 1 mg/mL and Midazolam Accord 5 mg/mL, solution for injection or infusion, from Accord Healthcare Ltd. The date of authorisation was on 8 June 2009 in the Netherlands.

The product is indicated for:

In both adults and children

- Conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia.
- Anaesthesia
 - Premedication before induction of anaesthesia
- Sedation in intensive care units

In adults only

- Anaesthesia
 - Induction of anaesthesia
 - As a sedative component in combined anaesthesia

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

Midazolam is a derivative of the imidazobenzodiazepine group. The free base is a lipophilic substance with low solubility in water.

The basic nitrogen in position 2 of the imidazobenzodiazepine ring enables the active ingredient in midazolam to form water-soluble salts with acids. These produce a stable and well tolerated solution for injection or infusion.

The pharmacological effect of midazolam is characterised by short duration because of a rapid metabolic transformation over a short time. Midazolam has a potent sedative and sleep-inducing effect. Furthermore, it has the effect of relieving anxiety and convulsions and of relaxing muscles.

After intramuscular or intravenous administration, anterograde amnesia of short duration occurs; (the patient does not remember events occurring at the time of the substance's maximal activity).

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Dormicum 5 mg/ml solution for injection (NL RVG 10064) which has been registered in the Netherlands by Roche Nederland B.V. since 1984. In addition, reference is made to Dormicum 1 mg/ml and 5 mg/ml authorisations in the individual member states (reference product). Dormicum solution for injection is available on the European market in both 1 mg/ml and 5 mg/ml concentrations.

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 Midazolam Accord 1 mg/mL and 5 mg/mL are products for parenteral use, these are exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of their 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 application.

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 these product types 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 midazolam hydrochloride, an established active substance, described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a white or yellowish crystalline powder, practically insoluble in water, freely soluble in acetone and in ethanol and 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.

Quality control of drug substance

The active substance specification is in accordance with the Ph.Eur. The MAH has set additional requirements for related substances and residual solvents. The drug substance specifications are in line with the CEP. The MAH has included batch analysis results of three batches, demonstrating compliance with the specifications.

Stability of drug substance

In accordance with the CEP, the re-test period for the drug substance is two years if stored in triple polyethylene bag placed in a polyethylene container. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** 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

Midazolam Accord 1 mg/mL contains as active substance 1 mg/ml of midazolam as midazolam hydrochloride, and is a clear, colorless to pale yellow solution with a pH in the range of 2.9-3.7 and 170 mOsm/kg to 230 mOsm/kg osmolality.

Midazolam Accord 5 mg/mL contains as active substance 5 mg/ml of midazolam as midazolam hydrochloride, and is a clear, colorless to pale yellow solution with a pH in the range of 2.9 - 3.7 and 270 mOsm/kg to 330 mOsm/kg osmolality.

The 1 mg/ml solution for injection or infusion is packed in 5 ml type I clear white snap off and blue band ampoules.

The 5 mg/ml solution for injection or infusion is packed in 1 ml, 3 ml and 10 ml type I clear white snap off ampoules with yellow, blue and red band, respectively.

For both strengths the excipients are: sodium chloride, concentrated hydrochloric acid (for pH-adjustment), 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.

Pharmaceutical development

All components of the drug product are simple and commonly used. The following aspects were studied in the pharmaceutical development: the stability of midazolam in solution, thermal stability, the stability of midazolam towards the lower and higher extreme of the pH range, the stability of midazolam Injection upon holding, compatibility with process steam components, photostability and stability in the presence of dissolved oxygen. The choice of the packaging material is justified. The development of the product has been satisfactorily performed and explained.

Manufacturing process

The manufacture of Midazolam Accord 1 mg/mL and 5 mg/mL is performed by dissolving the ingredient of sodium chloride in the solvent water for injections. Midazolam is added with constant stirring. Hydrochloric acid solution is added and stirred and the pH is checked and if necessary adjusted with sodium hydroxide or hydrochloric acid, with continuous stirring. The bulk solution is adjusted to 100% volume with water for injections. The bulk is then filtered and the solution is aseptically filled into clean, sterile ampoules. An inert gas (nitrogen) is used to displace oxygen from the solution during processing to reduce the possibility of oxidative changes in the formulation. The filled ampoules are steam sterilized. Three batches for each formulation (1 mg/ml; 5ml and 5 mg/ml; 1, 3 and 10 ml) were included in the process validation. All batches complied with the specifications. Given the relative simplicity of the manufacturing process, it has been sufficiently validated. No overages are used.

Quality control of drug product

The product specification includes tests for appearance, identification, acidity, extractable volume, subvisible particles, sterility, assay of midazolam, bacterial endotoxins and related substances. The release requirements are acceptable. The analytical methods have been adequately described and validated. Three pilot scale batches were included in the process validation. All batches complied with the specifications. The release and shelf-life specifications are identical with the exception of the specification for the related substances.

Compatibility

The innovator product claims compatibility with Normal Saline, Glucose 5% and 10 % in water, Fructose intravenous infusion (Levulose 5%), Potassium Chloride, Sodium Chloride, Calcium Chloride intravenous infusion (Ringer's solution) and Compound Sodium Lactate intravenous infusion (Hartmann's solution). Midazolam's compatibility with these infusion fluids was studied. After dilution, the solution was observed for signs of discoloration, precipitation or particulate matter for a period of 24 hours at room temperature. The compatibility of midazolam with the commonly used diluents has been satisfactorily established in the compatibility studies.

Stability tests on the finished product

Batch analyses results for 3 pilot scale batches for each formulation (1 mg/ml; 5ml and 5 mg/ml; 1, 3 and 10 ml) have been submitted in the stability study. The same analytical methods were used as described for the product specification. For none of the batches tested, a significant change is observed at both long term and accelerated conditions. The results of the continued studies, at least up to the proposed storage period are awaited. The MAH committed to provide stability results of three full-scale batches of 1 mg/ml (5 ml) and 5 mg/ml (1 ml, 3 ml and 10 ml). On the basis of the currently available data, a shelf-life of 24 months was granted.. Midazolam in solution was found to degrade highly in the presence of light. Therefore the labelled storage conditions are *Store in the original package in order to protect from light*.

Chemical and physical in-use stability of the dilutions has been demonstrated for 24 hours at room temperature (15 – 25°C) or for 3 days at +2 to +8 °C.

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

These products are generic formulations of Dormicum solution for injection, 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

These products are 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 midazolam 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

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

Midazolam Accord 1 mg/mL and Midazolam Accord 5 mg/mL, solution for injection or infusion are parenteral formulations and therefore fulfil 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 Midazolam Accord 1 mg/mL and Midazolam Accord 5 mg/mL 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. Dormicum is available on the market in 1 mg/ml and 5 mg/ml concentration with filling volumes of 5 ml (1 mg/ml) and 1 ml, 3 ml and 10 ml (5 mg/ml). The current products can be used instead of their reference product.

Pharmacovigilance system

The MEB has been assured that the system of pharmacovigilance will be in place and functioning before the product is marketed. The MAH has made some post-approval commitments regarding pharmacovigilance; these can be found in the list of commitments on page 7 of this report.

Risk management plan

Midazolam was first approved in September 1982, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of midazolam 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. 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

SPC

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the innovator product Dormicum 5 mg/ml (FR/H/0232/001-002).

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 test consisting of two rounds was carried out with 20 participants. As a result of the first round no changes to either the leaflet or the questionnaire were deemed necessary. This was also the case after the second round of testing. After two rounds of user testing, 99.2% of the subjects were able to locate the requested information and to answer correctly. The lay-out of the leaflet was scored acceptable for 70% of the lay-out items with the exception of type and

size of fonts used. As a result, no changes were deemed necessary to the content of the patient information leaflet of Midazolam Accord 1 and 5 mg/ml.

Overall, it can be concluded that there were sufficient questions about the critical sections. In the test it was easy to determine which results are linked to which conclusions. The conclusions are clear, concise and have been clearly presented. Furthermore, the following areas have been sufficiently covered: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Midazolam Accord 1 mg/mL and Midazolam Accord 5 mg/mL, solution for injection or infusion have a proven chemical-pharmaceutical quality and are generic forms of Dormicum solution for injection. Dormicum 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 committed to have the pharmacovigilance system in place and functioning before the product is placed on the market.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other midazolam 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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Midazolam Accord 1 mg/mL and 5 mg/mL with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 5 December 2008. Midazolam Accord 1 mg/mL and Midazolam Accord 5 mg/mL were authorised in the Netherlands on 8 June 2009.

A European harmonised birth date has been allocated (10 September 1982) and subsequently the first data lock point for midazolam is September 2009. The first PSUR will cover the period from December 2008 to September 2009, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 1 June 2010.

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

Quality - Medicinal product

- The MAH committed to provide stability results of three full-scale batches of 1 mg/ml (5 ml) and 5 mg/ml (1 ml, 3 ml and 10 ml).

Pharmacovigilance system

- The MAH committed to document the SOP 'Interaction between safety issues and product defects' and those SOPs which are in preparation, before the products are placed on the market, in the Pharmacovigilance system.
- The MAH committed to have a validated database in place before the product is placed on the market.
- The MAH committed to take appropriate measures to ensure that master copies of pharmacovigilance source documents are sufficiently protected and will be in place before the products are placed on the market.
- The MAH committed to take appropriate measures to ensure that the quality management system will be in place before the products are placed on the market.

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
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _{1/2}	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