CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Midazolam Sandoz 1 mg/ml and 5 mg/ml, solution for injection or infusion Sandoz B.V., the Netherlands

midazolam (as 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/2461/001-002/DC
Registration number in the Netherlands: RVG 110832, 110837

19 March 2013

Pharmacotherapeutic group:	Benzodiazepine derivatives
ATC code:	N05CD08
Route of administration:	intravenous; intramuscular; rectal
Therapeutic indication:	conscious sedation, anaesthesia, sedation in intensive care units in adults and children
Prescription status:	prescription only
Date of authorisation in NL:	12 November 2012
Concerned Member States:	Decentralised procedure with CZ, HU, PL, SI.
Application type/legal basis:	Directive 2001/83/EC, Article 10(1), 10(3)

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 Sandoz 1 mg/ml and 5 mg/ml, solution for injection or infusion from Sandoz B.V. The date of authorisation was on 12 November 2012 in the Netherlands.

Midazolam is a short-acting sleep-inducing medicinal product that is indicated for:

In adults
- Conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia.
- Anaesthesia
  - Premedication before induction of anaesthesia
  - Induction of anaesthesia
  - As a sedative component in combined anaesthesia
- Sedation in intensive care units

In 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

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 system enables the active ingredient of 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 rapid metabolic transformation. Midazolam has a sedative and sleep-inducing effect of pronounced intensity. It also exerts an anxiolytic, an anticonvulsant and a muscle-relaxant effect.
After i.m. or i.v. administration anterograde amnesia of short duration occurs (the patient does not remember events that occurred during the maximal activity of the compound).

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

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC for the 5 mg/ml strength and article 10(3) for the 1 mg/ml strength, a hybrid application regarding a difference in strength from the originator.

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 Sandoz 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 products 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

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 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 both suppliers of 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.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and the CEPs. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches per manufacturer.

Stability of drug substance
The retest period is 5 years for both manufacturers, when stored under the stated conditions. 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 Sandoz 1 mg/ml contains as active substance 1 mg/ml of midazolam as midazolam hydrochloride, and is a clear, slightly yellow solution with pH 2.9 – 3.7 and osmolality of 280 – 330 mOsmol/kg.
Midazolam Sandoz 5 mg/ml contains as active substance 5 mg/ml of midazolam as midazolam hydrochloride, and is a clear, slightly yellow solution with pH 2.9 – 3.7 and osmolality of 280 – 330 mOsmol/kg.

The solution for injection or infusion is packed in colourless glass type I ampoules. The 1 mg/ml product is available in an ampoule containing 5 ml solution, and the 5 mg/ml solution in 1 ml, 3 ml and 10 ml ampoules.

The excipients are: sodium chloride, hydrochloric acid, water for injections and sodium hydroxide (for pH adjustment).

Pharmaceutical development
The drug product is the same type of aqueous solution and contains the same concentration of the same active substance and the same excipients as the originator. Therefore, from a chemical-pharmaceutical point of view the absence of a bioequivalence study is considered justified. Sterility is guaranteed by sterile filtration of the solution and autoclaving after filling. The autoclaving process is carried out under the Ph.Eur./DAB standard conditions, thus separate development investigations have not been undertaken. The MAH provided sufficient background information of the pH range of 2.9-3.7.
The choice of the packaging material is justified. The development of the product has been satisfactorily performed and explained.

Manufacturing process
The manufacturing process is a straightforward process including preparation of the bulk solution, filtration, filling into the ampoules and closing, and terminal sterilization in the ampoules. The batch formulae are in accordance with the corresponding product formulae. Batch validation data have been provided on at least 3 batches per strength. The validation data of all batches are considered satisfactory.

Control of excipients
All excipients including the protective gas nitrogen comply with the respective Ph. Eur. monographs. The data provided on the excipients used is considered to be sufficient.

Quality control of drug product
Drug product specifications are proposed on appearance of solution (colour, clarity/degree of opalescence), pH, osmolality, extractable volume, identification, HPLC related substances, particulate contamination, bacterial endotoxins and sterility. The specifications are considered adequate. The initially different requirements for the two strengths have been harmonized. Satisfactory validation data for the analytical methods have been provided.
Forced degradation studies have been performed, and the HPLC methods are considered stability indicating. All Ph. Eur. impurities can be detected. The potential degradation products are appropriately limited. Batch analysis results have been provided at least three batch of each strength.

Stability of drug product
1 mg/ml strength: 36 months stability data at 25°C/65% RH and 6 months at 40°C/75% RH for 3 production batches of 250 L are available. All results met the set requirements and no specific trends have been noted. Based on the available stability data the claimed shelf-life of 3 years could be granted.
5 mg/ml strength: 5 years normal stability data are available for the 5 mg/1 ml form, 18 months normal stability data for the 15 mg/3 ml form and 6 months data for the 50 mg/10 ml form. Based on the available stability data the claimed shelf-life of 5 years could be granted.
Photostability studies demonstrated that midazolam hydrochloride solution is light sensitive.
For both strengths no special temperature condition is required and as additional storage label “Store in the outer packaging in order to protect from light” is applicable.
Compatibility studies have been provided for diluting the 1 mg/ml and 5 mg/ml strengths with the infusion liquids of 0.9% NaCl, 5% & 10% dextrose, Ringer’s solution, and Hartmann’s solution. 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 °C 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

This product is a generic formulation of Dormicum solution for injection or infusion, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has

been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

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 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.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

Midazolam Sandoz 1 mg/ml and Midazolam Sandoz 5 mg/ml, solution for injection or infusion are parenteral aqueous 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 Sandoz 5 mg/ml is entirely the same as the originator. A biowaiver for the 1 mg/ml strength can also be granted as the excipients are basically the same as those of the 5 mg/ml strength. 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 products can be used instead of their reference product.

Risk management plan
Midazolam was first approved in 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 post authorisation 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

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted in another DCP. The SPC was updated to comply with the most recent QRD template. This is considered acceptable.

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 two rounds with 11 participants. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. During the first round one question did not score the required 81% score. However, during the second round all questions scored 81% or above. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Midazolam Sandoz 1 mg/ml and 5 mg/ml, solution for injection or infusion have a proven chemical-pharmaceutical quality and are generic/hybrid forms of Dormicum 5 mg/ml solution for injection or infusion. 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 has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

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 Midazolam Sandoz 1 mg/ml and 5 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 2 October 2012. Midazolam Sandoz 1 mg/ml and 5 mg/ml, solution for injection or infusion were authorised in the Netherlands on 12 November 2012.

The date for the first renewal will be: 2 October 2017.

There were no post-approval commitments 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
DAB	Deutsche Arzneibuch
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
$t_{½}$	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