Public Assessment Report

Scientific discussion

Midazolam Orpha 15 mg, film-coated tablets
(midazolam maleate)

NL/H/2815/001/DC

Date: 9 July 2014

This module reflects the scientific discussion for the approval of Midazolam Orpha 15 mg, film-coated tablets. The procedure was finalised on 28 February 2014. For information on changes after this date please refer to the module 'Update'.

This report includes a summary, on pages 9-11.
I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Midazolam Orpha 15 mg, film-coated tablets from Orpha-Devel Handelsund Vertriebs GmbH.

The product is indicated for short-term treatment of insomnia. Benzodiazepines should only be used if the condition is severe and disabling or in case the patient has extreme distress as a result of the disorder. Midazolam is indicated in adults.

A comprehensive description of the indication and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Dormicum 15 mg film-coated tablets (NL License RVG 10539) which has been registered in the Netherlands by Roche B.V. since 27 November 1985.

The concerned member states (CMS) involved in this procedure were Austria, Denmark, Finland, Germany, Norway, Sweden and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Midazolam Orpha 15 mg is a blue, round tablet with a breaking score on one-side. The tablet can be divided into equal doses. One tablet of Midazolam Orpha contains midazolam maleate, equivalent to 15 mg midazolam.

The tablets are packed in PVC/PVDC Aluminium blisters.

The excipients are:

- Core of tablet - lactose monohydrate, microcrystalline cellulose, pregelatinised starch, magnesium stearate, talc
- Film coating – hypromellose, macrogol 400, titanium dioxide (E171), indigo carmine (E132).

II.2 Drug Substance

The active substance is midazolam maleate, an established drug substance, not described in the European Pharmacopoeia (Ph.Eur.). A Ph.Eur. monograph is however available for midazolam. The drug substance is a white to yellowish, crystalline powder, which is freely soluble in methanol and in 0.1M HCl, slightly soluble in water and sparingly soluble in ethanol. The drug substance shows polymorphism, where two polymorphic forms exist. Form I can be considered a metastable form which changes over time into Form II.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process of midazolam maleate consists of seven steps. No class 1 solvents or heavy metal catalysts are used. The drug substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.
Quality control of drug substance
The drug substance specification has been established in-house. The drug substance specification is based on the Ph.Eur. monograph for midazolam with some additional requirements. This specification is appropriate. Batch analytical data demonstrating compliance with the drug substance specification have been provided for four commercial-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for ten commercial-scale batches stored at 25°C/60%RH (up to 60 months) and four batches stored at 40°C/75%RH (up to 6 months). No significant changes or trends were observed under both storage conditions. The proposed re-test period of 24 months is acceptable. Based on the results of a photostability study the storage condition is ‘store protected from light’.

II.3 Medicinal Product

Pharmaceutical development
The primary goal of the development was to formulate a product essentially similar to Dormicum 15 mg tablets. A bioequivalence study has been performed with the 15 mg test product versus this reference product. The composition of the tablets used in the bioequivalence study is identical to the proposed commercial composition. Comparative dissolution data between the same two batches at pH 1.2, 4.5, 6.8 and in water confirmed similarity between the test and reference batches used in the bioequivalence study.

The particle size requirement was sufficiently justified. A study on the influence of particle size of the drug substance on dissolution of the drug product has been included. With regard to dividing the tablet into equal doses, conformance with the Ph.Eur. test on subdivision of tablets was demonstrated.

Manufacturing process
The components of the tablet core are mixed after which the mixture is compressed into tablets and film coated. The film-coated tablets are packed into their commercial packages. The manufacturing process is seen as a standard process and has been satisfactorily described. The process has been adequately validated on four full-scale batches.

Control of excipients
The excipients comply with the Ph.Eur. and the specifications are acceptable. For the Opadry mixture acceptable in-house specifications are applied.

Quality control of drug product
The product specification includes tests for appearance, identification, uniformity of dosage units (at release only), average weight (at release only), subdivision of tablets (at end-of-shelf-life only), dissolution, assay, related substances, and microbiological quality. The specification is acceptable. Batch analysis data have been provided for four full-scale batches, demonstrating compliance with the drug product specification.

Stability of drug product
Stability data have been provided for 3 full-scale batches packaged in PVC/PVDC-Aluminium blisters. The drug product has been stored at 25°C/60% RH (up to 24 months for 1 batch and 18 for 2 batches) and 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions are in line with ICH requirements. At all storage conditions an increase in impurities is seen leading to out-of-specification results after 6 months storage at accelerated conditions. Results for assay are variable at all three storage conditions, but show no clear trend. No trends or changes were seen in any of the other parameters. It was demonstrated that the drug product does not degrade under exposure to light according to the ICH Q1B guideline. Thus the product is photostable. A shelf life of 24 months is justified. The granted storage condition is ‘Do not store above 30°C’, based on the available stability data and in accordance with the Guideline on Declaration of Storage Conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
No materials of human or animal origin are used in the manufacture of Midazolam maleate tablets, except for lactose. Lactose monohydrate complies with the Note for Guidance EMEA/410/01 rev.2., so a theoretical risk of transmitting TSE can be excluded.
II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Midazolam Orpha 15 mg, film-coated tablets has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Midazolam Orpha is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Dormicum 15 mg film-coated tablets, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

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.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Midazolam Orpha 15 mg (Orpha Devel Handels-und Vertriebs GmbH, AT) is compared with the pharmacokinetic profile of the reference product Dormicum 15 mg film-coated tablets (Roche Nederland B.V., NL).

The choice of the reference product in the bioequivalence study has been justified by comparison of compositions of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasting conditions in 82 healthy male subjects, aged 18-55 years. The study was designed to be performed in two stages: a first stage with 12 participants and a second stage with 70 subjects. An interim analysis was performed after stage 1 whether to conclude bioequivalence between the test and the reference products or to calculate the number of subjects needed for stage 2 to provide at least 80% power. Bioequivalence was not demonstrated at the interim analysis as the power of the $C_{max}$ was below 80%. Therefore the sample size was recalculated and the study proceeded to stage 2 with 70 more subjects.
Each subject received a single dose (15 mg) of one of the 2 midazolam formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. Each trial stage had at least 2 days wash-out between the two treatment periods.

Blood samples were collected 30 minutes pre-dose and at 10 min, 20 min, 30 min, 45 min, 1 h, 1 h 15 min, 1 h 30 min, 1 h 45 min, 2 h, 2 h 15 min, 2 h 30 min, 3 h, 4 h, 6 h, 8 h, 12 h after administration of the products.

Midazolam can be taken with or without food. A study in the fasting condition is therefore agreed as this is more sensitive to detect differences between the test and reference product. The use of a predefined adaptive sequential design (two-stage approach) is acceptable and was performed according to required standards. The overall type I error and the stopping criteria were clearly defined prior to the study. The use of 94.12% confidence intervals with a power of at least 80% for both the analysis of stage 1 and the combined data from stage 1 and stage 2 is agreed.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

All subjects (n=82) completed the study and were included in the pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_max (median, range)) of midazolam under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} µg.h/ml</th>
<th>AUC_{0-∞} µg.h/ml</th>
<th>C_max µg/ml</th>
<th>t_max h</th>
<th>t_{1/2} h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>241 ± 85</td>
<td>264 ± 103</td>
<td>114 ± 85</td>
<td>0.5</td>
<td>--</td>
</tr>
<tr>
<td>Reference</td>
<td>243 ± 87</td>
<td>264 ± 106</td>
<td>103 ± 54</td>
<td>0.5</td>
<td>--</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>0.99 (0.94 – 1.04)</td>
<td>1.00 (0.95 – 1.05)</td>
<td>1.07 (0.94 – 1.22)</td>
<td>--</td>
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</tr>
<tr>
<td>CV (%)</td>
<td>--</td>
<td>--</td>
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</table>

\*ln-transformed values

Conclusion on bioequivalence study

The confidence intervals for AUC_{0-t}, AUC_{0-∞} and C_max are within the calculated and proposed 94.12% confidence interval of the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Midazolam Orpha 15 mg is considered bioequivalent with Dormicum 15 mg film-coated tablets.

Seventeen (17) subjects reported 17 adverse events (AE): 6 with reference drug and 11 subjects with test drug periods (13.41% of all 82 volunteers). All of the AEs were evaluated as related to study medication except one. All AEs in the 16 subjects were represented by a mild or moderate decrease of systolic and diastolic blood pressure (BP). The trend of diminished BP is explained with the sleepiness condition that was observed in the subjects and this decrease of BP has been accompanied by sinus rhythm physiological bradycardia in parallel with the decrease in the BP. These side events are well-known and no new safety signals were identified.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).
IV.3 Risk Management Plan

The MAH 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 Midazolam Orpha.

Summary table of safety concerns as approved in RMP

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Important potential risks</th>
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<tbody>
<tr>
<td>• Respiratory depression</td>
<td>• Sleep walking and associated behaviour (e.g. sleepdriving, sleep eating)</td>
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<tr>
<td>• Anterograde amnesia</td>
<td>• Abuse and diversion</td>
</tr>
<tr>
<td>• Psychiatric and paradoxical reactions</td>
<td>• Falls and fractures (mostly elderly)</td>
</tr>
<tr>
<td>• Impaired ability to drive and operate machinery and accidents</td>
<td>• Interaction with alcohol</td>
</tr>
<tr>
<td>• Tolerance and dependence</td>
<td>• Interaction with CNS depressing medicinal products</td>
</tr>
<tr>
<td>• Withdrawal symptoms/ insomnia</td>
<td>• Interaction with moderate to severe CYP3A4 inhibitors or inducers</td>
</tr>
</tbody>
</table>

| Important missing information                                                              |                                                                                           |
| • Use in patients with myasthenia gravis                                                  | • Use in patients with severe respiratory depression or sleep apnoea syndrome              |
| • Use in patients with a history of drug or alcohol abuse                                  | • Use in patients with a history of drug or alcohol abuse                                  |
| • Use in pregnancy and during lactation                                                   | • Use in patients with severe hepatic function                                             |

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Dormicum. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 PL was English. The test consisted of two rounds with 10 participants each. A diagnostic and scoring readability testing was performed to test traceability and comprehensibility. 17 questions were asked relating to the content of the PL and 4 questions to its structure. Questions were asked about several key messages of the leaflet. Additionally the participants were asked to give their personal opinion of the final PIL. No modifications have been made in between testing rounds.

In both rounds the results showed that the information to answer each question was traced 100% of the time and each participant showed that he or she understood the information by answering the questions correctly 100% of the time. With regard to the difficulty in tracing the information, the results show that the information is either straightforward or basic. Participants indicated that the leaflet is too long with too much information. Also participant indicated that the font size is too small. However, as the leaflet contains all key messages and follows the principles of the Readability guideline, this is accepted. No revision of the leaflet has been made.
VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Midazolam Orpha 15 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Dormicum 15 mg film-coated. Dormicum is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 Orpha 15 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 28 February 2014.

There were no post-approval commitments made during the procedure.
## 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>
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Summary Public Assessment Report

Generics

Midazolam Orpha 15 mg, film-coated tablets
midazolam

NL/H/2815/001/DC

Date: 9 July 2014
Summary Public Assessment Report

Generics

Midazolam Orpha 15 mg, film-coated tablets

Active substance: midazolam

This is a summary of the public assessment report (PAR) for Midazolam Orpha 15 mg, film-coated tablets. It explains how this medicine 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 Midazolam Orpha.

For practical information about using this medicine, patients should read the package leaflet or contact their doctor or pharmacist.

What is Midazolam Orpha 15 mg and what is it used for?
Midazolam Orpha 15 mg is a 'generic medicine'. This means that it is similar to a 'reference medicine' already authorised in the European Union (EU) called Dormicu15 mg, film-coated tablets.

This medicine is prescribed for the short-term treatment of adults with sleep disturbances. Midazolam Orpha is only prescribed if the disturbance is serious and physical and/or mental functioning is impaired, or if a patient suffers seriously from the consequences of these sleep disturbances.

How is this medicine used?
The medicine can only be obtained with a prescription. The usual dosage is 15 mg per day. The doctor may however decide that a lower dose should be used. In any case a maximum dosage of 15 mg must not be exceeded.
This medicine should be taken for as short a period of time as possible and in the lowest possible dosage. Treatment does not generally last longer than 2 weeks. Only a doctor can decide whether the treatment may last longer.
This medicine must be taken right before going to sleep, next to or in the bed, without chewing it and with a glass of water. It can be taken at any moment of the day, provided one can be sure of at least seven to eight hours of undisturbed sleep.

How does this medicine work?
Midazolam belongs to a group of medicinal products known under the name benzodiazepines. It is a medicinal product which affects the signals that transfer information through nerve cells in the brain and which is used to treat sleep disturbances. It cause sleepiness, muscle relaxation and has a calming effect. Thus it helps one fall asleep. The reason for the sleep disturbances is, however, not solved.

How has this medicine been studied?
Because Midazolam Orpha 15 mg is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Dormicum. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of this medicine?
Because Midazolam Orpha 15 mg is a generic medicine and is bioequivalent to the reference medicine Dormicu 15 mg, its benefits and risks are taken as being the same as the reference medicine.

Why is this medicine approved?
It was concluded that, in accordance with EU requirements, this medicine has been shown to have comparable quality and to be bioequivalent to Dormicum. Therefore, the view was that, as for Dormicum, the benefit outweighs the identified risks.

What measures are being taken to ensure the safe and effective use of this medicine?
A risk management plan has been developed to ensure that this medicine 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 Midazolam Orpha 15 mg, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about this medicine**
In the Netherlands, the marketing authorisation for Midazolam Orpha 15 mg, film-coated tablets was granted on 7 May 2014.

The full PAR for this medicine can be found on the website [http://mri.medagencies.org/Human](http://mri.medagencies.org/Human). For more information about treatment with Midazolam Orpha 15 mg, read the package leaflet ([http://mri.medagencies.org/download/NL_H_2815_001_FinalPL.pdf](http://mri.medagencies.org/download/NL_H_2815_001_FinalPL.pdf)) or contact your doctor or pharmacist.

This summary was last updated in July 2014.