CBG MEB

Public Assessment Report

Scientific discussion

Dalpam 2 mg, 5 mg and 10 mg tablets

(diazepam)

NL/H/3588/001-003/DC

Date: 6 April 2017

This module reflects the scientific discussion for the approval of Dalpam 2 mg, 5 mg and 10 mg, tablets. The procedure was finalised on 5 December 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Dalpam 2 mg, 5 mg and 10 mg tablets from Neogen Developments N.V.

The product is indicated for:
- anxiety
- adjunct in the control of skeletal muscle spasm, including spasticity caused by upper motor neuron disorders (such as cerebral palsy)
- alcohol withdrawal symptoms
- premedication before general anaesthesia or for sedation during minor surgical or investigative procedures

Benzodiazepines are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Valium 2 mg, 5 mg and 10 mg tablets which has been registered in the EEA by Roche since 1963. In the Netherlands, the registration of Valium was withdrawn since 2006. The EU reference product used in the bioequivalence study is Valium 10 mg tablets registered by NV Roche SA in Belgium.

The concerned member state (CMS) involved in this procedure was Croatia.

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

II. QUALITY ASPECTS

II.1 Introduction

The product is a white to almost white round, flat, tablet with a break line on one side:
- Dalpam 2 mg tablet has “2” marked on the other side.
- Dalpam 5 mg tablet has “5” marked on the other side.
- Dalpam 10 mg tablet has “10” marked on the other side.

The tablets are packed in Al/PVC blisters and HDPE tablet containers with white PE caps.

The excipients are lactose monohydrate, pregelatinised maize starch and magnesium stearate.

The tablets are not dose proportional, rather the amount of filler/diluent is adjusted based on the amount of active substance.

II.2 Drug Substance

The active substance is diazepam, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Diazepam is a white or almost white crystalline powder. It is very slightly soluble in water, soluble in ethanol. The drug substance is considered as highly soluble. It was found that three polymorphs are known for diazepam; polymorph I is used for this product.

Two CEP procedures are 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 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.

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. It meets the requirements of the monograph in the Ph.Eur. and CEPs, with an additional requirement for particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for two full scale batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The formulation was based on that of the innovator. Size/shape/dimensions of the products have been adequately discussed and are suitable for the intended (paediatric) population due to the presence of a score line. The products can be divided into equal doses. The choices of the packaging and manufacturing process are justified. Pharmaceutical development has been adequately performed.

A bioequivalence study has been performed with the 10 mg test product and the innovator product of the Belgian market. Supportive dissolution studies have been performed in three media, according to NfG on Investigation of Bioequivalence. The resulting dissolution profiles are considered similar.
The MAH proposed a biowaiver of strength for the 2 mg and 5 mg products. Overall, dissolution profiles are similar to the 10 mg product. In 0.1N HCl dissolution was more than 85% for all strengths within 15 minutes. In pH 4.5 and pH 6.8, f_2 values showed comparability of the dissolution profiles.

Manufacturing process
The manufacturing process consists of the following steps: weighing, pre-mixing, sieving, blending, compression and packaging. The manufacturing process has been adequately validated according to relevant European guidelines on three batches of the smallest production scale and on two batches of the production scale of the 2 mg strength. Process validation of the 5 mg and 10 mg strengths will be conducted post-approval and a protocol has been provided. This is accepted.

Control of excipients
The excipients comply with the Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, assay, degradation, loss on drying, dissolution, uniformity of dosage units and microbiological quality. The release and shelf-life limits are identical except for the limit in loss on drying. 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 from three smallest production scaled batches and two largest production scaled batches of 2 mg, two smallest production scale batches and one pilot scaled batch of the 5 mg and 10 mg products, from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided three smallest production scaled batches of 2 mg product, two smallest production scale batches and one pilot scaled batch of the 5 mg and 10 mg products, at 25°C/60% RH (up to 18 months), 30°C/75% RH (up to 18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline, as in

addition to the 30°C/75% RH the back-up condition 30°C/65% RH is used. The batches were stored in the proposed packaging. A decrease in resistance to crushing has been observed at accelerated conditions. Fluctuations in assay levels and specified impurity levels are also observed during long-term stability testing. A shelf-life period of 30 months is granted. No specific storage restriction is necessary. The results of photostability studies confirmed that the tablets are not sensitive to visible and UV light.

In use stability data has been provided demonstrating that the product remains stable for 100 days following first opening of the container. In addition, the MAH has shown that the product remains stable after thermal cycling for up to 21 days and after storage in open petri-dished for up to 6 months. As there is no difference in stability results of long-term, accelerated, in-use and open petri-dish storage, no in-use period has to be claimed in the SmPC.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Dalpam has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:
- The MAH has committed to undertake comparative dissolution profile testing on the first three production batches.
- The MAH has committed to perform in use stability study on all batches included in the stability program product at the end of shelf-life.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Dalpam 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 Valium 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

Diazepam 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence study

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Dalpam 10 mg tablets (Neogen Developments NV, Belgium) is compared with the pharmacokinetic profile of the reference product Valium 10 mg tablets (NV Roche SA, Belgium).

The choice of the reference product

The choice of the Belgian reference product in the bioequivalence study has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver for the 2 mg and 5 mg tablets based on the bioequivalence study with the highest strength of 10 mg can be granted as:

- the strengths have been manufactured by the same manufacturing process
- the compositions are qualitatively similar
- the amount of the active substance is less than 5% of the tablet core weight for all strengths
- the amount of filler has been changed to account for the change in amount of active substance and the amounts of other core excipients are the same
- dissolution tests at 0.1N HCl, pH 4.5 and 6.8, showed similar profiles for the three strengths of the test product according to guidance criteria
- the pharmacokinetics of diazepam can be considered dose linear in the dose range of 2-10 mg

Design

A single-dose, open-label, randomised, two-treatment, two-sequence, two-period, cross-over bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 18-38 years. Each subject received a single dose (10 mg) of one of the two diazepam formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 11 hours. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected before dosing and at 0.17, 0.33, 0.50, 0.75, 1.00, 1.25, 1.50, 2.00, 2.50, 3.00, 4.00, 6.00, 9.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the products.

The design of the study is acceptable. As diazepam can be taken regardless of food, a study under fasting conditions is acceptable. The half-life of diazepam is up to 48 hours. Plasma sampling until 72 hours after dosing is appropriate and a wash-out period of 14 days is sufficient.

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

One subject was excluded by the clinical investigator due to abnormal laboratory results (decreased haemoglobin, haematocrit and red blood cell count) before admission to period II. Therefore 27 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of diazepam under fasted conditions.

Treatment N=27	AUC_{0-t} ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	5651 ± 1946	339 ± 81.7	0.75 (0.33 – 3.0)	45 (18 – 99)
Reference	5666 ± 2025	348 ± 100	0.75 (0.33 – 2.5)	39 (18 – 85)
***Ratio (90% CI)**	1.00 (0.97 - 1.04)	0.98 (0.90 - 1.07)	--	--
CV (%)	1.01 (0.98 - 1.04)	0.97 (0.89 - 1.06)	--	--

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Dalpam is considered bioequivalent with Valium.

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 Dalpam.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Severe respiratory insufficiency • Additive CNS depressant effects when administered with alcohol or CNS depressants • Dependence and withdrawal symptoms • Anterograde amnesia • Psychiatric and paradoxical reactions
Important potential risks	• Use in pregnancy • Impaired fertility
Missing information	• Use in infants below the age of 6 months

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Valium. 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 test consisted of: a pilot test with four participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dalpam 2 mg, 5 mg and 10 mg tablets is a proven chemical-pharmaceutical quality and is a generic form of Valium tablets. Valium 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 Dalpam with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 December 2016.

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