

Public Assessment Report

Scientific discussion

Diazepam BBS (diazepam)

Asp no: 2017-1445, 2017-1446, 2017-1447

This module reflects the scientific discussion for the approval of Diazepam BBS. The procedure was finalised on 2018-10-12. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

The application for Diazepam BBS, 2 mg, 5 mg and 10 mg, tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, BBS Consult ApS applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Valium, 2 mg, 5 mg and 10 mg, tablet, authorised in Denmark and Belgium since 1963 and 1964, with Roche as marketing authorisation holder.

The reference product used in the bioequivalence study is Valium, 10 mg, tablet from Belgium with Roche as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Diazepam, 10 mg, tablet with the reference product Valium, 10 mg, tablet.

Pharmacokinetic properties of the active substance

Absorption: Diazepam has an oral bioavailability of 100%. Following an oral dose of 5 mg maximal plasma concentrations occur at approximately ½-1 hour.

The pharmacokinetics of diazepam is affected by food; however there are no restrictions with respect to food in the SmPC of the originator.

Linearity: The pharmacokinetics of diazepam is linear.

Elimination: The plasma decline of diazepam is biphasic after oral administration with a rapid distribution phase followed by a prolonged terminal phase. A terminal half-life of 20-70 hours has been reported.

Study DIAZ472

Methods:

This was a single-dose, two-way crossover study conducted in 28 healthy volunteers (27 completed), comparing Diazepam, 10 mg, tablet with Valium, 10 mg, tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72.00 hours post-dose. Plasma concentrations of diazepam were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-72h} and C_{max}. The study was conducted in 2014.

Results:

The results from the pharmacokinetic and statistical analysis are presented in

Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, $t_{\max}$ median, range) for diazepam, n=27.

Treatment	AUC_{0-72h} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	5650.60 $\pm$ 1946.24	338.78 $\pm$ 81.65	0.75 (0.33 - 3.00)
Reference	5666.34 $\pm$ 2024.82	347.78 $\pm$ 100.03	0.75 (0.33 - 2.50)
*Ratio (90% CI)	100.29 (96.87 - 103.85)	98.30 (90.44 - 106.85)	-
AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-72h} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strengths of 2 mg and 5 mg.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Absence of studies with the additional strengths of 2 mg and 5 mg is acceptable, as all conditions for biowaiver for additional strengths, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of diazepam is linear between 2 mg and 10 mg.

Based on the submitted bioequivalence study, Diazepam, 10 mg, tablets are bioequivalent with Valium, 10 mg, tablets.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

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 Diazepam BBS.

Safety specification

The MAH has submitted the updated version 1.2 RMP dated 05.09.2018 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	• Tolerance and dependence • Concomitant use with opioids
Important potential risks	None
Missing information	None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, version 1.2 RMP dated 05.09.2018, is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the MPA;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Diazepam Pilum 5 mg tablets (DK national procedure, Dnr: 111:2011/78389), Kaliumklorid Orifarm 750 mg prolonged release tablets (DK/H/2347/00) and Prednisolon Alternova tablets (Variation no. (Dnr): 2121:2012/37638). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Diazepam BBS, is found adequate. There are no objections to approval of Diazepam BBS, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Diazepam BBS, 2 mg, 5 mg and 10 mg, tablet was approved in the national procedure on 2018-10-12.

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/non approval	Summary/Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)