COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Diazepam Stada 2 mg, 5 mg and 10 mg tablets (diazepam)

NL/H/5247/001-003/DC

Date: 16 November 2021

This module reflects the scientific discussion for the approval of Diazepam Stada 2 mg, 5 mg and 10 mg tablets. The procedure was finalised at 18 August 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
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 Diazepam Stada 2 mg, 5 mg and 10 mg tablets, from Kappler Pharma Consult GmbH.

The products are indicated in adults for:

- Symptomatic treatment of anxiety: Benzodiazepines are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.
- Symptomatic treatment of Alcohol Withdrawal syndrome.

And indicated in adults and children over 6 years old for:

- Symptomatic treatment of skeletal muscle spasm (inflammation of muscles or joints, trauma), including spasticity caused by upper motor neuron disorders (such as cerebral palsy, paraplegia as well as athetosis and stiff-person syndrome).

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. In the Netherlands, the registration of Valium was withdrawn since 2006.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 states (CMS) involved in this procedure were Belgium, Czech Republic (5 mg and 10 mg strength only), Italy, Luxembourg, and Poland.

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

II. QUALITY ASPECTS

II.1 Introduction

Diazepam Stada are white to almost white round, flat tablets, with “2”, “5” or “10” on one side and a break line on the other side and contain as active substance 2 mg, 5 mg, or 10 mg of diazepam. The tablets can be divided into equal doses.

The tablets are packed in Al/PVC blisters or white HDPE bottles with PE screw cap. Blisters together with patient information leaflet are placed in a carton with imprinted label text. Bottles either have booklet label leaflet or together with patient information leaflet are placed in a carton with imprinted label text.

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

II.2 Drug Substance

The active substance is diazepam, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is very slightly soluble in water and soluble in ethanol (96%). It is a white to almost white crystalline powder. The polymorphic form has been investigated and Form I is produced.

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 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 and meets the requirements of the monograph in the Ph.Eur. and CEP. Batch analytical data demonstrating compliance with this specification have been provided for four full scale batches.

Stability of drug substance
The active substance is stable for 60 months when stored in double LDPE bags (outer black) placed in a HDPE container. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The formulation was based on that of the innovator, except for the use of colourants (none in this formulation but present in innovator). Diazepam tablets have a break line on one side and during the development stage the dosage uniformity within the tablet halves was studied. The samples were subjected to a breakability test and comply with mass uniformity requirements of European Pharmacopoeia. The MAH sufficiently justified that the shape and size of the tablets (halved tablets) is suitable for paediatric use

and that lactose, widely used in dairy products and used in infant feed formulas, is also suitable for the use in children. A bioequivalence study has been performed with a suitable test product (10 mg, commercial manufacturing process, commercial formulation) and the innovator product of the Belgian market. Supportive dissolution studies have been performed in three media, according to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The discriminative nature of the quality control dissolution method has been adequately shown. The resulting dissolution profiles are considered similar. The MAH has requested a biowaiver of strength for the 2 mg and 5 mg products, which will be discussed in section IV. The choices of the packaging and manufacturing process are justified. The pharmaceutical development of the product has been adequately performed for the adult population.

Manufacturing process

The manufacturing process consists of the following steps: weighing, pre-mixing, sieving, blending, compression and packaging. The process has been described in sufficient detail. The studies performed during manufacturing process development have been taken into account in the setting of in-process controls and finished product specifications. As the product is stored in bulk, the MAH has stated compliance to the Note for Guidance on the Start of Shelf-life of finished products. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches of the minimum production scale of the 2 mg strength and three batches at the maximum production scale. Process validation of the 5 mg and 10 mg strengths will be conducted post-approval and a protocol has been provided.

Control of excipients

The excipients comply with the Ph.Eur. monographs. The MAH discussed the functionality-related characteristics of pregelatinised starch (binder) and magnesium stearate (lubricant), and no requirements additional to Ph. Eur. are needed. The MAH remarked that for lactose monohydrate, due to its high content in the final product (approximately 80%), the specification on particle size distribution is applied. The excipients are not novel. These specifications are acceptable.

Microbiological attributes

The development batches were tested for microbial limits as per Ph. Eur. monograph. The tablets show compliance to the proposed limits. The test for microbiological quality has been included in the finished product specification as per the Ph. Eur. 5.1.4. Skip-testing is acceptable based on the provided results.

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 (room temperature and spectrum), assay, degradation, loss on drying, dissolution, uniformity of dosage units, related substances and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

The dissolution specification of Q=85% in 15 min is in line with the *Reflection Paper on the dissolution specification for generic solid oral immediate release products with systemic action* (EMA/CHMP/CVMP/QWP/ 336031/2017).

Based on EMA guidance a risk evaluation has been performed for the presence of nitrosamines in the active substance and in the finished product including the drug product packaging. The assessment considers the formation of nitrosamines as outlined in the guidance through all steps of the involved processes. The MAH has deemed there is no risk for nitrosamines with respect to the main conditions for nitrosamine formation, generally in view of the discussion provided this is agreed upon. Forced degradation studies have been performed, although tables with clear percentages decrease (HPLC assay) and increase (HPLC degradation products) per stress condition have not been provided. However, the chromatograms provided sufficiently demonstrate that the HPLC method for related substances is stability indicating and the specificity acceptance criteria have been met.

The analytical methods have been adequately described. Satisfactory validation data for the analytical methods have been provided. Batch analytical data on 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 from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three smallest production scaled batches of the 2 mg product, and for two smallest production scale batches and one pilot scaled batch of the 5 mg and 10 mg products. The batches were stored at 25°C/60% RH (up to 48 and 60 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Alu/PVC blisters and HDPE bottles with polyethylene caps. The results of the stability studies (long-term and accelerated) are within specifications.

Fluctuations in assay levels and impurity levels are also observed during long-term stability testing. For the 2 mg tablets some results for related substances were out-of-spec, therefore the shelf-life claim for the 2 mg tablets in blister is limited to three years. Stability data have been provided demonstrating that the products remain stable for 100 days (in-use shelf life) following first opening of the container. In addition, the MAH has shown that the products remain stable after thermal cycling (freezing or refrigerating, followed by long-term or accelerated ICH conditions) for up to 21 days and after storage in open petri-dished for up to six 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.

Based on the submitted data, the claimed shelf-life and storage conditions are:

- 2 mg tablets: three years (Al/PVC blisters)
- 5 mg tablets: five years (Al/PVC blisters and white HDPE bottles with PE screw cap)
- 10 mg tablets: five years (Al/PVC blisters and white HDPE bottles with PE screw cap)

The photostability studies were performed in accordance with *Note for Guidance on the Photostability Testing of New Active Substances and Medicinal Products* (CPMP/ICH/279/95). The results confirmed that the tablets are not sensitive to visible and UV light. These medicinal products do not require any special storage conditions.

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 Diazepam Stada have 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 Diazepam Stada are 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

These products are generic formulations of the innovator products Valium which were withdrawn in 2006. Reference is made to the preclinical data obtained with the innovator products. 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

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Diazepam Stada 10 mg tablets (Kappler Pharma Consult GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Valium 10 mg tablets (Roche Nederland B.V., Belgium).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the test and reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver for the 2 and 5 mg tablets based on the bioequivalence study with the highest strength of 10 mg is granted as the following criteria of the *Guideline on the investigation of Bioequivalence* are met:

- 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;
- adequate dissolution tests 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.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover 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 pre-dose 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.

Diazepam may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of diazepam. Therefore, a food interaction study is not deemed necessary.

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, decreased haematocrit and decreased red blood cells) before admission to period II, so he did not take the reference product. 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_{0-72}** (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)	-	-

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study, Diazepam Stada 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 Diazepam Stada.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient.

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 10 mg product is similar to the pharmacokinetic profile of the respective reference product strength. A biowaiver has been granted for the lower 2 mg and 5 mg product strengths. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference products.

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: a pilot test, followed by two rounds with ten 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 package leaflet of medicinal products for human use*.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Diazepam Stada 2 mg, 5 mg and 10 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Valium 2 mg, 5 mg and 10 mg tablets. Valium are well-known medicinal products 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 Diazepam Stada with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 August 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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