

# Public Assessment Report

## Scientific discussion

**Diazepam Bluefish 5 mg Tablets**

**Diazepam**

**Registration number in Spain: xxx**

**ES/H/0378/001/DC**

**Applicant: Bluefish Pharmaceuticals AB**

This module reflects the scientific discussion for the approval of **Diazepam Bluefish 5 mg tablets**. The procedure was finalised on January 2016. For information on changes after this date please refer to the module 'Update'.



## **INTRODUCTION**

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This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Valium® 5 mg tablets (Daiichi Sankyo España S.A). Valium® tablets has been registered in Europe since 1963.

The legal basis of the application is Article 10(1) of Directive 2001/83/EC.

The Concerned Member State involved in this procedure is PT.

The efficacy and security of diazepam has been demonstrated in several studies conducted with the reference product as well as with its use experience after placed in the market. Diazepam Bluefish 5 mg tablets are submitted under an abridged application and no studies regarding pharmacology, pharmacokinetic, security and efficacy has been carried out besides the bioequivalence studies against the reference product.

The product is indicated for the treatment of:

### Anxiety

Benzodiazepines are only indicated for the treatment of a severe disorder, disabling or subjecting the patient to extreme stress.

Oral use of Diazepam Bluefish is indicated for symptomatic suppression of anxiety, agitation and psychological stress caused by psychoneurotic states and transient situational disorders.

### Alcohol withdrawal

In patients with alcohol withdrawal, it may be useful for the symptomatic relief of acute agitation, tremor and hallucinations.

### Musculoskeletal pain

It is a useful coadjuvant for the relief of musculoskeletal pain due to spasms or local pathology (inflammation of muscles or joints, trauma, etc.). It can also be used to combat spasticity caused by spinal and supraspinal interneuron diseases, such as cerebral palsy and paraplegia, as well as athetosis and syndrome of generalized rigidity.

### Anticonvulsant therapy

Diazepam Bluefish orally can be used as coadjuvant treatment of seizure disorders but it has not been proven useful as a single treatment. In these cases, the physician should periodically evaluate the usefulness of the drug for the individual patient.

A comprehensive description of the product information is given in the SmPC.

## **RECOMMENDATION**

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for Diazepam Bluefish 5 mg tablets for Bluefish Pharmaceuticals AB.



## **I. SCIENTIFIC OVERVIEW AND DISCUSSION**

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### **II-1 Quality aspects**

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#### DRUG SUBSTANCE

Diazepam is a known active substance described in Ph.Eur. A Ph. Eur. There are two suppliers of active substance, in both cases a Certificate of Suitability has been submitted to support the quality of the active ingredient.

Both CEPs include re-test period.

#### DRUG PRODUCT

##### Description of the product

The drug product is an uncoated, immediate release tablet containing 5 mg of diazepam as drug substance. Tablet is white to almost white round, flat, with 050 on one side and scored on the other side.

The qualitative composition of the tablets is as follows:

- Diazepam
- Lactose monohydrate
- Starch pregelatinised
- Magnesium stearate

Diazepam tablets are packed in Al/PVC blisters and white HPDE bottles.

##### Pharmaceutical development

The pharmaceutical development has been properly described.

The function of the excipients has been discussed. The dissolution method is recommended by USP Diazepam tablets and the discriminatory power of the method has been demonstrated.

##### Manufacture of the product and process controls

The manufacturing process is described in detail, and taking into account that the content of active substance is very low (2.38%), and the manufacturing process is a direct compression, validation data has been provided with industrial batches.

##### Excipients

The information provided is adequate. The analytical procedures used to control the excipients are performed according to the European Pharmacopoeia monographs.

##### Product specification

Specifications proposed are adequate. The limits proposed for the different parameters have been adequately justified.

All analytical methods have been correctly validated following the ICH Q2 (R1) Guideline.



### Container closure system

Diazepam tablets are packed in:

- blisters which comprise of aluminium foil heat seal to a clear PVC foil
- white HDPE bottles

The components of the container closure system comply with the requirements of Commission Regulation (EU) No 10/2011.

### Stability

Stability studies have been performed following the ICH guidelines. The stability data support the proposed shelf-life and storage conditions.

## **II-2 Non-clinical aspects**

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A non-clinical overview on the pharmacology, pharmacokinetics and toxicology of the active substance has been provided, which is based on up-to-date and adequate scientific literature. The submitted application concerns film coated tablets with the active substances in the same form as the reference product.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate and the Member States agreed that no further non-clinical studies are required.

### **Environmental Risk Assessment (ERA)**

No ERA was submitted. The following justification for the absence of environmental assessment was provided by the Applicant: "This product is intended to substitute other identical products on the market. Therefore, the approval of this product does not result in an increase of the total quantity of diazepam and metabolites released into the environment. It does not contain any component which results in additional hazard to the environment during storage, distribution, use and disposal."

In accordance with the Guideline on the Environmental Risk Assessment for medicinal products for human use (CPMP/SWP/4447/00), the absence of this Environmental Risk Assessment is therefore justified.

## **II.3 Clinical aspects**

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### **Introduction**

Diazepam is well-known drugs with established efficacy and safety.

No new clinical efficacy or safety studies were conducted, which is acceptable for this abridged application. A clinical overview has been provided, which is based on scientific literature. 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.

### **Biowaiver**



The bioequivalence between test and reference products has been demonstrated for the 10 mg strength (please refer to the section of results). These data can be extrapolated to the other strength since all the requirements described in section 4.1.6 of the Bioequivalence Guideline are fulfilled.

### **Bioequivalence**

The Applicant has submitted the bioequivalence study DIAZ472: ða randomized, two-period, two-treatment, two-sequence, single dose, open label, crossover bioequivalence study of Diazepam 10 mg tablets of (SC SANTA SA, Romania) versus Valium® 10 mg tablets of (NV Roche SA, Belgium) in healthy subjects under fasting conditions to demonstrate bioequivalence with the reference product according to the requirements of the EMA Guideline on the investigation of bioequivalence.

The clinical part of the study was performed from May 11<sup>th</sup>, 2014 to June 06<sup>th</sup>, 2014.  
The analytical part was conducted from June 21<sup>st</sup>, 2014 to July 08<sup>th</sup>, 2014.

The Clinical part of the study was performed at Arab Pharmaceutical Industry Consulting/Pharmaceutical Research Unit (APIC/PRU), 19, Yajooz Street, Al-jubaiha.  
The analytical portion was conducted at Arab Pharmaceutical Industry Consulting/Pharmaceutical Research Unit/ Yajooz Street, Al-jubaiha-building 19 P.O Box 1084 Sweileh 11910, Jordan.

The trial has been conducted in compliance with GCP requirements. Monitoring reports have been submitted. QA statement of audits assuring compliance to GCP was issued by Head-QA. The clinical, the analytical, the pharmacokinetic and the statistical sites were inspected by Regulatory Authorities of the European Union without critical findings.

#### *Design*

This was an open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study in healthy, adult, human subjects under fasting

This approach is acceptable as the application concerns an oral immediate release formulation (tablets). In addition, no specific recommendation about concomitant food intake was mentioned in the SmPC of the reference product even if a food effect has been reported with a moderate fat meal showing a delayed absorption, an average decrease in  $C_{max}$  of 20% in addition to a 27% decrease in AUC. Therefore, a single dose study under fasting conditions is considered acceptable.

The wash-out period of 14 days (more than five times the half-lives) is considered adequate since the drug has a half-life of approximately 48 hours and no pre-dose level was detected.

The sampling time point up to 72.00 hours is considered acceptable since according to the Guideline on the investigation of bioequivalence  $AUC_{0-72h}$  may be used as an alternative to  $AUC_{0-t}$  for comparison of extent of exposure as the absorption phase has been covered by 72 h for immediate release formulations.

The sampling is reasonably frequent over the first 2 hours and should be sufficient to allow an accurate measurement of  $t_{max}$ .

Test product: Diazepam 10 mg tablets manufactured by SC SANTA SA, Romania. Batch number: DIA10\_P001. Batch size: 100,000 tablets. Proposed batch size: 250,000-1,000,000 tablets. Manufacturing date: November 06<sup>th</sup>, 2013. Expiry date: November 2015. Assay (content): 98.6% of label claim.



Reference product: Valium® 10 mg tablets manufactured by Roche SA, Spain (please see assessor's comment). Batch number: E0046E5. Expiry date: April 2018. Assay (content): 99.7 % for of label claim.

All batches were tested before expiry date and a similar content of active substance is shown. Therefore, content correction is not necessary.

All subjects received the same dose of study medication on day 1 in the morning between 08:00 and 08:27 of the two periods in the fasting state orally, with 240 mL of water in sitting position.

In the present study, thirty-two (32) subjects were enrolled and twenty-eight were randomised to a treatment sequence in the study, in accordance with the protocol. In all, 27 subjects completed the clinical phase of the study and were used in the pharmacokinetic and statistical analysis.

The study population is considered acceptable with regards to demographic characteristics. The inclusion and exclusion criteria are considered to be acceptable.

#### *Analytical methods*

The analytical method has been adequately validated before the conduct of the study and during the analysis of the subject samples. Therefore, the analytical method is considered acceptable for analysis of the plasma samples.

#### *Pharmacokinetic data analysis*

Pharmacokinetic parameters were calculated using a non-compartmental method with acceptable software. AUC was calculated by the trapezoidal rule. The methods used in this study for the pharmacokinetic calculations are considered acceptable

#### *Statistical analysis*

The methods used in this study for the statistical evaluation are considered acceptable. ANOVA was performed on log-transformed pharmacokinetic parameters  $C_{max}$  and  $AUC_{0-t}$  were considered as the primary pharmacokinetic parameters. The analysis of variance model included the following factors: sequence, subjects nested within sequence, period and treatment.

Based on the log-transformed parameters, the 90% confidence intervals of the relative mean plasma for  $AUC_{0-t}$  and  $C_{max}$  of the test to reference products should be between 80-125% to conclude bioequivalence.

#### *Results*

The 90% confidence intervals mean treatment T/R ratios are shown in the following table:

Bioequivalence evaluation of diazepam:

Parameter	Ratio % (Test/Reference)	90% Confidence Interval
Ln ( $AUC_{0-t}$ )	100.29	96.87-103.85
Ln ( $C_{max}$ )	98.30	90.44-106.85

The 90% confidence intervals calculated for  $AUC_{0-t}$  and  $C_{max}$  are within the bioequivalence acceptance range of 0.80 to 1.25 and therefore bioequivalence has been proven. No clinically significant differences were observed between the median  $t_{max}$  of test and reference products.



### **Risk Management Plan**

A risk management plan in accordance with the requirements of Directive 2001/83/EC as amended has been submitted.

No additional risk minimization activities were required beyond those included in the product information.

### **Discussion on the clinical aspects**

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference product.

Efficacy and safety of the active substance diazepam is well documented for the reference medicinal product. The design of the submitted bioequivalence study is adequate and the results allow us to conclude bioequivalence with the reference.

### **III OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

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

The SmPC, PIL and labelling are considered satisfactory and consistent with the information for the reference medicinal product. The user testing of the Package Information Leaflet has been tested in accordance with Article 59(3) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

The benefit/risk balance was considered to be positive.

Agreement between Member States was reached during the procedure. The decentralised procedure was finalised with a positive outcome in June 2016.