Public Assessment Report
Scientific discussion

Paxiflas 37.5 mg/325 mg Orodispersible Tablets (Tramadol hydrochloride / Paracetamol)

Registration number in Spain: xxx

EU-procedure number: ES/H/0331/001/DC

Applicant: Laboratorios Gebro Pharma, S.A.

This module reflects the scientific discussion for the approval of **Paxiflas 37.5 mg/325 mg Orodispersible Tablets**. The procedure was finalised on February 2016. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Zaldiar® 37.5 mg/325 mg film-coated tablets by Laboratories Grunenthal, registered in the EU since May 04th, 2002.

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

The Concerned Member States involved in this procedure is PT.

The product is indicated for the symptomatic treatment of moderate to severe pain. Tramadol/Paracetamol is positioned as a step II analgesic by the WHO and should be utilised accordingly as indicated by the physician.

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 **Paxiflas 37.5 mg/325 mg Orodispersible Tablets** for Laboratorios Gebro Pharma S.A.

II. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

ACTIVE SUBSTANCES

Tramadol Hydrochloride is an active substance described in Ph. Eur. A Ph. Eur. Certificate of Suitability has been submitted to support the quality of the active ingredient. The CEP include re-test period.

Paracetamol is an active substance described in Ph. Eur. A Ph. Eur. Certificate of Suitability has been submitted to support the quality of the active ingredient. The CEP does not include re-test period but stability data have been included in the dossier to support the proposed re-test period.

FINISHED PRODUCT

Description of the product

Tramadol Hydrochloride 37.5 mg and Paracetamol 325 mg Orodispersible Tablets are white, round, tablets with central concave depression on both the surfaces having mint odour

The qualitative composition of the tablets is as follows:

- Tramadol HCl
- Paracetamol

- Aspartame (E951)
- Crospovidone
- Ethylcellulose N7
- Magnesium Stearate
- Mannitol (Pearlitol 25C)
- Mannitol Powder (Pearlitol 50C)
- Mannitol granular (Pearlitol 400 DC)
- Povidone K30
- Silica, Colloidal Anhydrous
- Flavour Peppermint

The drug product is packed into Alu-Alu Blister.

The pharmaceutical development has been adequately described.
Excipients are commonly used in pharmaceutical industry and they are of Ph. Eur. quality except peppermint flavour that presents in-house specifications. The function of each excipient in the drug product is described and compatibility study has been performed.

Manufacture of the product and process controls
The manufacturing process is sufficiently described and the process controls are appropriate, considering the nature of the product and the manufacturing method.
The commercial batch size is defined.
The dossier includes sufficient validation data to guarantee that the manufacturing process is controlled and to ensure batch to batch reproducibility and compliance with product specifications.

Excipients
The information provided is adequate. The specifications for the different excipients are justified by their official adoption in the relevant Ph. Eur. monograph or by an in-house monograph (for the non-compendial excipient).

Product specification
The specifications proposed for the tablets are adequate. The limits proposed for the different parameters have been adequately justified.
The analytical methods have been properly described and validated.

Container closure system
Tramadol Hydrochloride 37.5 mg and Paracetamol 325 mg Orodispersible Tablets are packed into Alu-Alu Blister. Then these Alu-Alu blisters are packed into cartons.
The components of the container closure system comply with the specifications established in the applicable Ph. Eur. monographs.

Stability of the product
The 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

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 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 medicinal product has the same quantitative and qualitative composition in active substances and a similar pharmaceutical form to the reference product. The introduction on the market of this medicinal product will not mean an increased exposure to the environment, since the generic medicinal product is intended to substitute the reference medicinal product as well as other generic products in the market.
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

Introduction

Tramadol hydrochloride and Paracetamol are a 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

Not applicable. The Applicant only applies for the 37.5 mg/325 mg strength and this strenght is tested *in vivo*.

Bioequivalence

The Applicant has submitted a bioequivalence study (study code: ARL/13/448) 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 conducted from 25/09/2014 to 12/10/2014.
The bioanalytical part of the study was conducted from 16/10/2014 to 05/11/2014.
The trial has been conducted in compliance with GCP requirements. Monitoring reports have been submitted. QA statement of audits assuring compliance to GCP were issued by Head-QA.
The Clinical, the Analytical and the PK and Statistical sites were inspected in 2012 by Regulatory Authorities of the European Unionwithout critical findings.

Design

The submitted study was a randomized, balanced open-label, three treatment, three period, three sequence, single oral dose, crossover, bioequivalence study in normal, healthy human subjects under fasting condition with a washout period of 7 days for period I and II and 8 days for period II and III.

The application concerns an oral immediate release formulation (orodispersible tablets) and as indicated in the SmPC of the reference product: "tramadol/paracetamol may be administered independently of meal times"; therefore a 3x3 cross-over single dose study under fasting conditions is considered acceptable to demonstrate bioequivalence. The ODT was compared with (A) and without (B) concomitant water intake with the reference product with concomitant intake of 240 mL of water (C).

The wash-out period and the sampling schedule are considered acceptable for an adequate characterisation of the systemic exposure of a drug with such a half-life and Tmax.

The reference product is adequate with regards to expiry date, content and it was obtained from German market.
All batches were tested before expiry date and a similar content of active substance is shown. Therefore, content correction is not necessary.

In the present study, a total of 37 subjects completed all the clinical phase of the study.

The study population is considered acceptable with regards to demographic characteristics.
The inclusion and exclusion criteria and the subject withdrawals and drop-outs 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.
Values for the T_{max} parameter were analysed by a non-parametric approach (Wilcoxon Signed-Rank Test).

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 (+) Tramadol

Table of Geometric Means and 90% Confidence Interval for (+) Tramadol
Test A vs. Reference C

Parameter	Ratio (Test/Reference)	90% Confidence Interval
Ln (AUC_{0-t})	107.02	104.42-109.68
Ln (C_{max})	102.88	97.92-108.09
Ln ($AUC_{0-Đ}$)	107.00	104.35-109.72

Table of Geometric Means and 90% Confidence Interval for (+) Tramadol
Test B vs. Reference C

Parameter	Ratio (Test/Reference)	90% Confidence Interval
Ln (AUC_{0-t})	105.6624	103.12-108.27
Ln (C_{max})	102.0306	97.15-107.15
Ln ($AUC_{0-Đ}$)	105.5169	102.93-108.17

Bioequivalence evaluation of (-) Tramadol

Table of Geometric Means and 90% Confidence Interval for (-) Tramadol
Test A vs. Reference C

Parameter	Ratio (Test/Reference)	90% Confidence Interval
Ln (AUC_{0-t})	107.08	104.31-109.93
Ln (C_{max})	103.05	98.03- 108.33
Ln ($AUC_{0-Đ}$)	107.01	104.16-109.94

Table of Geometric Means and 90% Confidence Interval for (-) Tramadol
Test B vs. Reference C

Parameter	Ratio (Test/Reference)	90% Confidence Interval
Ln (AUC_{0-t})	105.38	102.68-108.16
Ln (C_{max})	101.73	96.82-106.90
Ln ($AUC_{0-Đ}$)	105.14	102.37-107.99

Bioequivalence evaluation of Paracetamol

Table of Geometric Means and 90% Confidence Interval for Paracetamol
Test A vs. Reference C

Parameter	Ratio (Test/Reference)	90% Confidence Interval
Ln (AUC_{0-t})	101.32	99.35-103.33
Ln (C_{max})	91.56	84.57- 99.14
Ln ($AUC_{0-Đ}$)	101.35	99.39-103.34

Table of Geometric Means and 90% Confidence Interval for Paracetamol
Test B vs. Reference C

Parameter	Ratio (Test/Reference)	90% Confidence Interval
Ln ($AUC_{0-t)}$	103.27	101.28-105.30
Ln (C_{max})	93.69	86.59-101.37
Ln ($AUC_{0-Ð}$)	103.11	101.14-105.13

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 ï 1.25 and therefore bioequivelence has been proven. No clinically significant differences were observed between the median Tmax 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 substances tramadol hydrochloride and paracetamol are 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 February 2016.