Public Assessment Report
Scientific discussion

Eletriptan Bluefish 20 mg and 40 mg Film-Coated Tablets

Eletriptan Hydrobromide

ES/H/0422/001-002/DC

Applicant: Chanelle Medical

This module reflects the scientific discussion for the approval of **Eletriptan Bluefish 20 mg and 40 mg film-coated tablets**. The procedure was finalised on July 2017.

INTRODUCTION

This decentralised procedure concerns a generic application of eletriptan hydrobromide, under Eletriptan Bluefish 20 mg and 40 mg film-coated tablets trade name, claiming essential similarity with the innovator product Relpax film-coated tablets (Pfizer Italia S.r.l.), which has been authorised in the EU since January 2000.

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

With Spain as the Reference Member State in this Decentralized Procedure, Chanelle Medical is applying for the Marketing Authorisations for Eletriptan 20 mg and 40 mg film-coated tablets in DK, FR, IE, IT and SE.

Eletriptan is indicated for the acute treatment of migraine with or without aura. Eletriptan is a potent and selective agonist at the vascular 5-HT_{1B} and neuronal 5-HT_{1D} receptors. Eletriptan also exhibits high affinity for the 5-HT_{1F} receptor, which may contribute to its anti-migraine mechanism of action. Eletriptan has modest affinity for the human recombinant 5-HT_{1A}, 5-HT_{2B}, 5-HT_{1E}, and 5-HT_{7} receptors. Eletriptan is also effective in the treatment of associated symptoms of migraine such as vomiting, nausea, photophobia, and phonophobia. Eletriptan has been shown to be effective in the treatment of recurrent migraine headache. Eletriptan is effective in migraine with or without aura and in menstrual associated migraine. If taken during the aura phase, eletriptan has not been demonstrated to prevent migraine headache and, therefore, eletriptan should only be taken during the headache phase of migraine.

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for **Eletriptan Bluefish 20 mg and 40 mg film-coated tablets** for Chanelle Medical.

I. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

Drug substance

Eletriptan hydrobromide is not described in the Ph.Eur. The drug substance data is provided in the form of an Active Substance Master File. Letter of access as well as the applicant parts is included in the dossier.

The synthesis is generally described in sufficient details. Potential impurities along with their control have been adequately discussed.

The proposed limits for related substances are in line with ICH thresholds and are considered acceptable. The remaining specification is appropriate to guarantee a sufficient quality of the active ingredient and the limits are justified. Description of the analytical methods are acceptable as well as their validation. A summary of batch analysis data is given and CoAs provided. All data are within the specified limits.

Stability studies have been conducted with the drug substance. No significant changes in any parameters were observed. The proposed retest period is justified.

Drug Product

Eletriptan 20 mg film coated tablets: The product is presented as an orange, round, convex shaped, film coated tablet. The tablet is plain on one side and embossed with “20” on the other, approximately 6 mm in diameter.

Eletriptan 40 mg film coated tablets: The product is presented as an orange, round, convex shaped, film coated tablet. The tablet is plain on one side and embossed with "40" on the other, approximately 8 mm in diameter.

The product composition is adequately described.

The development of the product has been described, the choice of excipients is justified and their functions explained. The selection of the dissolution procedure conditions can be considered adequate as Ph. Eur. requirements for immediate release solid oral dosage form. In addition, the specifications for dissolution to be used for quality control of the product are justified.

The manufacturing process and in-process controls correspond to the actual standards of pharmaceutical technology and are suitable to guarantee an appropriate quality of the process. Critical parameters of the manufacturing process are justified. Batch size is clearly stated.

Excipients are properly described.

The drug products release specification is according to regulatory requirements. The description and validation of the analytical methods are considered satisfactory. Batch analysis data is provided.

The information on the reference standards are presented.

The container closure system is acceptable. The primary container is Opaque PVC/PCTFE/Aluminium blister pack.

The proposed shelf-life of 30 months with no special storage conditions for the drug product is considered acceptable.

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 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)

The Applicant justified the lack of an ERA based on Eletriptan 20 mg and 40 mg Film-coated Tablets is intended to substitute the reference medicinal product and thus, it does not suppose an increase in the environmental exposure of eletriptan and on the environmental impact of other triptans, which have similar receptor-binding profiles to eletriptan.

Taking into account Eletriptan 20 and 40 mg film-coated tablet is a generic product and there is no concerns about the ERA of other previously authorized medicinal product containing eletriptan as active ingredient, including generics, Eletriptan 20 and 40 mg film-coated tablet is not expected to pose a risk to the environment.

II.3 Clinical aspects

Introduction

Eletriptan hydrobromide is a well-known drug 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 of test and reference products has been demonstrated for 40 mg strength. These data can be extrapolated to the additional strength (i.e., 20 mg) since all the requirements described in section 4.1.6 of the Bioequivalence Guideline are fulfilled.

Bioequivalence

To support the application, the Applicant has submitted a bioequivalence study in order to demonstrate the bioequivalence of Eletriptan 20 mg and 40 mg film-coated tablets (Chanelle Medical) with the reference product Relpax® 40 mg film-coated tablets (Pfizer Italia S.r.l.).

This study was proposed to be conducted as a two-stage, single centre, open-label, randomized, single-dose study with a two-way crossover design to compare the bioavailability of eletriptan between test and reference product in healthy male adult subjects under fasting conditions.

In the two-stage design the study flow was as follows:

- Interim analysis: evaluate bioequivalence at stage 1 using α-level of 0.0294 rendering a 94.12% confidence interval: if bioequivalence is met, no additional group will be enrolled and the study will be judged to have passed.
- Interim power analysis: if bioequivalence is not demonstrated in the interim analysis, power at stage 1 with α-level at 0.0294 will be evaluated. If power< 80%, then an additional group will be enrolled in stage 2. If power ~80%, then no additional group will be enrolled and the study will be stopped as the study failed to show bioequivalence.

Although, a two-stage study was proposed to be performed, the second stage was not conducted in accordance with the protocol since the bioequivalence was demonstrated in the first stage.

As the application concerns an immediate release film-coated tablet formulation and the eletriptan PK parameters are shown to be linear (please refer to Relpax SmPC) over the recommended dose range (20-80 mg) and according to the innovator SmPC eletriptan should be swallowed whole with water, a single dose study under fasting conditions with the highest strength is considered acceptable to demonstrate bioequivalence with the reference product.

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 have been inspected by Regulatory Authorities of the European Union without critical findings.

Design

The study was a two-stage, single oral dose, randomised, open label, two treatment, two period, two sequence, cross-over bioequivalence study in healthy, male, adult, human subjects under fasting conditions comparing equal doses of the test and reference products with a washout period of 4 days.

The wash-out period of 4 days is considered adequate since the drug has a half-life of approximately 4 hours and this wash-out exceeds 5 elimination half-lives and no pre-dose levels were detected.

Considering the elimination half-life of eletriptan, the sampling schedule and the sampling time period of 24 hours seems long enough to estimate PK parameters.

Considering the expected time to peak concentration (1.5 hours), sampling is reasonably frequent over the first 3 hours and should be sufficient to allow an accurate measurement of t_{max} and C_{max}.

Test product: Eletriptan 40 mg Film-Coated Tablets manufactured by Kemwell Biopharma Pvt. Ltd., India. Batch number: ELB15001A. Batch size: 18,600 tablets. Expiry date (Retest day): February 2016. Assay (content): 101.0% of label claim.

Reference product: Relpax 40 mg film-coated tablets manufactured by Pfizer Italy S.r.l. from the Italian market. Batch number: D10358237. Expiry date (re-test day): August 2016. Assay (content): 100.4 % of label claim.

The medication was administered as a single dose by oral route with 240 ml of water. The subjects had been fasting since 10 hours before dosing and until 4 hours after dose administration.

No water or fluids were permitted from 1 hour before study drugs administration until 1 hour after the dose, no fluid intake was allowed apart from the 240 ml of water used for the administration of the study drug. Following 1 hour, the subjects were allowed to drink water as desired.

The test and reference product are adequate for a generic application. Reference product was obtained from the Italian market. The product was administered in accordance with the Relpax SmPC in fasting condition.

A total of 28 subjects were dosed; subject No. 13 withdrew for personal reasons after study drug administration in study period I but before study drug administration in study period II and the 27 subjects who completed the study 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 linear trapezoidal rule. The methods used in this study for the pharmacokinetic calculations are considered acceptable.

Statistical analysis

Statistical analysis was performed by using WinNonlin Linear Mixed Effects Modeling V5.2.

Analyses of variance were performed on the logarithmically transformed pharmacokinetic parameters AUC_{0-t} and C_{rmax}.

In the analysis after stage l (i.e., interim analysis), the analysis of variance model included sequence, period and drug formulation as fixed factors and subjects nested within sequence as random effects, employing 2.94% level of significance (i.e., α).

The 94.12% CIs of the Geometric Mean Ratio (GMR) (test/Reference) for both primary PK parameters C_{max} and AUC_{0-t} were evaluated against the bioequivalence acceptance range of 80.00-125.00%.

Bioequivalence (BE) of the test product and the reference product is concluded if the 94.12% CIs of the GMR of both primary PK parameters fall within the BE acceptance range.

As described in the Guideline on the investigation of bioequivalence, it is acceptable to use a two-stage approach when attempting to demonstrate bioequivalence. In this approach, the Type

I error has been preserved and the stopping criteria has been defined in the protocol prior to the study. The analysis of the first stage was treated as an interim analysis and was conducted at adjusted significance level using 94.12% confidence intervals.

The two-stage design employed it is not considered correct in the European Union because it is based on simulation but it is acceptable because bioequivalence was shown in the interim analysis.

The results are summarized in the table below.

PK Parameter	94.12% Confidence Intervals			
	Point estimate%	Lowe limit %	Upper Limit %	Intra-subject CV%
C_{max}	94.55%	84.14%	103.77%	17.39%
AUC_{0-t}	104.34%	98.53%	110.49%	10.65%

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference product with respect to the extent and rate of absorption/exposure as the 94.12% confidence intervals for the ln-transformed AUC_{0-t} and C_{max} are within the acceptance range of 80-125%.

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

Efficacy and safety of the active substance eletriptan hydrobromide 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 product.

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. In addition, the request for a biowaiver for the lower strengths (i.e., 20 mg) applied for is accepted.

Agreement between Member States was reached during the procedure. The decentralised procedure was finalised with a positive outcome in July 2017.