CBG MEB

Public Assessment Report

Scientific discussion

Eletriptan Biogaran 20 mg and 40 mg film-coated tablets

(eletriptan hydrobromide)

NL/H/3116/001-002/DC

Date: 11 January 2016

This module reflects the scientific discussion for the approval of Eletriptan Biogaran 20 mg and 40 mg film-coated tablets. The procedure was finalised on 11 February 2015. 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 Eletriptan Biogaran 20 mg and 40 mg film-coated tablets from Biogaran.

The product is indicated in adults for the acute treatment of the headache phase of migraine attacks, with or without aura.

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 Relpax 20 mg and 40 mg film-coated tablets (NL License RVG 26578-26579) which has been registered in the Netherlands by Pfizer B.V. since 28 June 2001.

The concerned member states (CMS) involved in this procedure were France and Italy.

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

II. QUALITY ASPECTS

II.1 Introduction

Eletriptan Biogaran 20 mg is an orange, biconvex, round film-coated tablet with immediate release, engraved “20” on one face and plain on the other face with a diameter of 6 mm. The tablet contains 24.24 mg of eletriptan hydrobromide (equivalent to 20.0 mg of eletriptan).
Eletriptan Biogaran 40 mg is an orange, biconvex, round film-coated tablet with immediate release, engraved “40” on one face and plain on the other face with a diameter of 8 mm. The tablet contains 48.48 mg of eletriptan hydrobromide (equivalent to 40.0 mg of eletriptan)

The film-coated tablets are packed in PVC-ACLAR/Aluminium foil blisters.

The excipients are:
Core tablet - microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate
Film-coating - Opadry II orange 85F230075: polyvinyl alcohol partially hydrolyzed, titanium dioxide PEG 3350, talc, sunset yellow FCF aluminium lake.

The two tablet strengths are dose-proportional.

II.2 Drug Substance

The active substance is eletriptan hydrobromide, an established active substance, not described in any pharmacopoeia. The active substance is very slightly soluble in water and 0.1N HCl, practically insoluble in 0.1N NaOH and soluble in methanol. The molecule contains a chiral centre and the active substance is the R-enantiomer. Eletriptan hydrobromide is known to exist in three crystalline forms and in an amorphous form. Form β is used.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The drug substance is manufactured in 7 steps. The applied in-process controls and controls on all subsequent intermediates are considered sufficient. The process is described in sufficient detail.

Quality control of drug substance
An adequate specification is applied on eletriptan hydrobromide. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches of drug substance.

Stability of drug substance
Three batches have been stored for 18 months at 25°C/60% RH and 6 months at 40°C/75% RH. All stability results meet the set specifications. All parameters remained within the specifications. Supportive data were provided on three batches from a different manufacturing site, stored for 36 months at 25°C/60% RH and 6 months at 40°C/75% RH. No change in assay and total related substances were observed, hence, eletriptan hydrobromide is a stable molecule. Based on the provided data the claimed re-test period of 30 months can be accepted, without specific storage temperature.

II.3 Medicinal Product

Pharmaceutical development
The description of the formulation development is adequate. The starting point was the composition of the innovator product. Attention was paid to the concentration of croscarmellose, the exact nature (grade) of the main component microcrystalline cellulose grade, the loss of active substance due to vacuum conditions during compression, and further optimisation during compression. At the end of the development the dissolution profiles of the innovator product were approximated by the proposed product. Both test and reference bio-batches show dissolution results > 85% after 15 min in all three pH media supporting the view that the dissolution profiles of both products are comparable.
The product is indicated in adults for the acute treatment of the headache phase of migraine attacks, should release the drug substance as soon as possible in order to treat the migraine attack. For this reason and to be as close as possible to the dissolution profile of the bio-batch, the dissolution specification is NLT 85% (i.e. Q 80%) after 15 min in HCl pH 1.2.
A bioequivalence study was performed with the higher strength. From a chemical-pharmaceutical point of view the conditions for a biowaiver for the 20 mg strength are fulfilled.

Manufacturing process
A direct compression process was selected. The manufacturing steps have been adequately described including the involved in-process controls. The blending, lubrication and tableting steps are considered critical. The manufacturing process has been validated on 3 batches of both strengths. In general satisfactory process validation data have been provided. The dissolution results at 15 min were 90% or more.

Control of excipients
The excipients comply with pharmacopoeial requirements with additional requirements for microcrystalline cellulose (particle size distribution and bulk density) and lactose monohydrate (particle size distribution). The specifications are acceptable.

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 description, identification of eletriptan and titanium dioxide, assay, related substances, average mass, uniformity of dosage unit, water content, disintegration, dissolution and microbial limit. Batch analysis results are provided for the three validation batches for each strength. All results met the set requirements.

Stability of drug product
The three validation batches per strength have been put on stability and stored for 12 months at 25°C/60% RH, 12 months at 30°C/65% RH and 6 months at 40°C/75% RH. During these storage times no significant trends have been observed. Eletriptan is not sensitive to light.
Based on the available stability data the claimed shelf-life of 24 months without specific storage temperature can be accepted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Regarding the excipients of human or animal origin, it is stated for lactose that the used lactose is derived from milk collected from healthy cows, and for magnesium stearate that the used magnesium stearate is obtained from vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Eletriptan Biogaran 20 mg and 40 mg film-coated tablets 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 Eletriptan Biogaran is 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

This product is a generic formulation of Relpax, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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

Eletriptan 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Eletriptan Biogaran 40 mg (Biogaran, France) is compared with the pharmacokinetic profile of the reference product Relpax 40 mg film-coated tablets (Pfizer Holding France, France).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
A biowaiver is applied for the 20 mg strength based on the argumentations of kinetics linearity of eletriptan over the normal dose range (20-80 mg) and the proportional compositions among the strengths (20 and 40 mg). The coating suspensions are also proportional to the strengths.

Comparative dissolution has been demonstrated between strengths. Therefore, the conclusion of the bioequivalence study with the 40 mg strength can be extrapolated to the lower strength of 20 mg.

Bioequivalence studies

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy subjects (18 males/22 females), aged 29±6 years. Each subject received a single dose (40 mg) of one of the 2 eletriptan formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 10, 12, 16 and 24 hours after administration of the products.

The study design is acceptable. For an immediate release tablet which can be taken with or without food, a single dose study under fasting conditions using the highest strength is considered appropriate. Taking into account the expected time to peak concentration (1-2 hours) and the elimination half-life of eletriptan (about 4 hours), the sampling schedule and the sampling time period of 24 hours are adequate. Frequent sampling schedule at the first 3 hours is considered adequate, as t_{max} of eletriptan is 1-2 hrs. The wash-out period of 7 days is considered to be adequate.

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
A total of 38 subjects completed the clinical phase and were considered in the statistical analysis.
One subject withdrew consent from the study before dosing of period II for personal reasons (related to clinical events) and received one single oral dose of the test in period I. Another subject was withdrawn before dosing of period II due to a positive amphetamines test and received one single oral dose of the reference in period I. Both of them were excluded from pharmacokinetic and statistical analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of eletriptan under fasted conditions.

Treatment N=38	**AUC_{0-24}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	655±377	678±394	97.7±51.6	1.25 (0.5-5.0)	--
Reference	649±389	675±410	88.7±45.6	1.37 (0.5-5.0)	--
***Ratio (90% CI)**	1.02 (0.96-1.07)	--	1.09 (1.01-1.17)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-24} area under the plasma concentration-time curve from time zero to 24 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-24}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Eletriptan Biogaran 40 mg is considered bioequivalent with Relpax 40 mg film-coated tablets.

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 Eletriptan Biogaran.

Summary of safety concerns	
Important identified risks	- Myocardial ischaemia/infarction, - Cerebrovascular accident, - Serotonin syndrome, - Allergic reactions (including angioedema), - Medication overuse headache (MOH), - Concomittant use of SSRIs/SNRIs, - Concomitant use of ergotamine-containing or ergot-type medication.
Important potential risks	None
Missing information	- Use in the elderly (over 65 years of age), - Use in adolescents (12-17 years of age), - Use in children (6-11 years of age), - Use during pregnancy.

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Relpax. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

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 study consisted of two rounds, carried out with 10 participants per round. The participants were potential eletriptan users. A list of 15 questions was created to cover the most important parts of the PL with a focus on safety.
Before the first round started several improvements to the PL were made regarding lay out and QRD.

As required by the success criteria, at least 16 of the 20 participants (80%) were able to find and understand the information to each question asked in the first and the second round. As a result, no changes were deemed necessary to the patient information leaflet after the first and the second round.

Overall, it can be concluded that the readability test itself and the evaluation report are of an acceptable quality. There were sufficient questions about the critical sections. In the test it was easy to determine which results are linked to which conclusions. The conclusions are clear, concise and clearly presented. Furthermore, the following areas have been sufficiently covered: traceability, comprehensibility and applicability. The results show that the package leaflet 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

Eletriptan Biogaran 20 mg and 40 mg have a proven chemical-pharmaceutical quality and are generic forms of Relpax 20 mg and 40 mg film-coated tablets. Relpax is a well-known medicinal product 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 Eletriptan Biogaran with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 February 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached