COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fampridine SUN 10 mg prolonged-release tablets

(fampridine)

NL/H/5018/001/DC

Date: 1 June 2021

This module reflects the scientific discussion for the approval of Fampridine SUN 10 mg prolonged-release tablets. The procedure was finalised at 2-2-2021 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 Fampridine SUN 10 mg prolonged-release tablets, 10 mg, from Sun Pharmaceutical Industries Europe B.V.

The product is indicated for the improvement of walking in adult patients with multiple sclerosis with walking disability (EDSS 4-7).

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 Fampyra 10 mg prolonged-release tablets (NL RVG 106803) which has been centrally registered by Biogen Netherlands B.V since 20 July 2011 (original product) via procedure EMEA/H/C/002097 with MA holders Biogen Netherlands B.V. and has MA numbers EU/1/11/699/001-004).

The concerned member states (CMS) involved in this procedure were France, Germany, Spain and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Fampridine SUN is a white to off-white, round, biconvex, bevelled edge, film-coated tablet imprinted with “429” in black ink on one side and plain on the other side. Each prolonged-release tablet contains as active substance 10 mg of fampridine.

Fampridine SUN is supplied in blister packs.

The excipients are:

Tablet core:
Hypromellose
Povidone
Microcrystalline cellulose (E460)
Magnesium stearate

Film-coating:
Hypromellose
Talc (E553b)

Ethyl cellulose (E462)
Triacetin (E1518)
Titanium dioxide (E171)

Imprinting ink:
Shellac glaze (E904)
Iron oxide black (E172)
Propylene glycol (E1520)
Ammonium hydroxide (E527)

II.2 Drug Substance

The active substance is Fampridine a known active substance not described in the Ph. Eur. but described in the US Pharmacopoeia, as Dalfampridine. The active substance is a white crystalline powder, is soluble in water, and has no chiral centres. The manufacturing process gives a constant crystalline form.

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
After the formation of fampridine, the active substance is purified and micronized to obtain the final active substance. No class 1 organic solvents or heavy metal catalysts are used during the synthesis.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three production scale batches.

Stability of drug substance
Stability data on the active substance has been provided for four batches stored at 25˚C/60% RH for up to 24 months and three batches at 40˚C/75% RH for 6 months. Based on the data submitted, a retest period could be granted of 3 years when stored in tight, light resistant container at 20°C to 25°C, with excursions permitted between 15°C and 30°C. The post-approval commitment ensures that the long-term stability study will be continued till the proposed re-test period is achieved.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been extensively and adequately described, the choice of excipients is justified and their functions explained. The MAH has adequately described the formulation and manufacturing process development. A clear risk assessment has been made and the optimum formulation and commercial manufacturing process were chosen. The studies have been described with all relevant plots provided and clear conclusions were drawn. All elements of the control strategy have been implemented and control of excipients has been done as per development studies.

A bioequivalence study has been performed with a suitable batch of the test product versus the European Reference Product Fampyra 10 mg prolonged-release tablets. Supportive dissolution studies in three media (0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer 6.8 (also QC medium)) have been provided and show similarity (f2 values between 50 and 100). Alcohol-dose dumping has been studied using pH 6.8 Phosphate buffer with 0%, 5%, 10% and 20% (v/v) of alcohol. The drug release of the test product with different concentrations of alcohol are comparable with the drug release of the test product without alcohol and also with the European reference product at respective concentration of alcohol.

Manufacturing process

The manufacturing process consists of sifting, wet granulation, wet milling, drying, screening and dry milling, sifting and blending, compression, film-coating, tablet printing and packaging. The process is considered a non-standard process in view of the pharmaceutical form (prolonged-release tablets). Process validation data on the product has been presented for three commercial scale and one pilot scaled batches. The process has been adequately validated.

Control of excipients

The excipients comply with Ph. Eur. monograph requirements and the coating and printing materials comply with in-house specifications. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for description (visual appearance and dimensions), identification, identification of colorant, dissolution, uniformity of dosage units, water content, related substances, microbial limits and residual solvents. The release and shelf-life requirements are identical except for the limit for water content and limit for related substances. This is considered to be acceptable. The analytical methods have been adequately described and validated. Verification data of the microbial limit test as per Ph. Eur. has been provided. Batch analytical data from the proposed production site have been provided on three commercial scale batches, demonstrating compliance with the release specification.

A risk evaluation on the potential presence of nitrosamines has been provided and no risk has been identified.

Stability of drug product

Stability data on the product has been provided on one pilot scale and two commercial scale batches stored at 25°C/60% RH (1 x 12 months and 2 x 24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Al-Al blisters with built-in desiccant. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. Hence a storage restriction regarding protection from light is not necessary.

All results at accelerated and long-term conditions are within specification and no significant changes are observed at accelerated conditions. Unknown impurities increase to borderline results at 24 months. The proposed shelf-life period of 18 months with no specific storage restrictions is acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Fampridine SUN 10 mg prolonged-release tabletshas a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. A post approval commitment to ensure that the long-term stability study will be continued till the proposed re-test period is achieved was made by the MAH.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of fampridine are well known. As fampridine is a widely used, well-known active substance, the MAH has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since fampridine SUN 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Clinical efficacy and safety of fampridine are well known. As fampridine is a widely used, well-known active substance, the MAH has not provided additional studies, besides bioequivalence studies, and further studies are not required. Overview based on literature review is, thus, appropriate. The submitted clinical overview on the clinical pharmacology, efficacy and safety is adequate.

For this generic application, the MAH has submitted three bioequivalence studies which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies:

- Study I: single dose fasting study with the 10 mg tablet
- Study II: single dose fed study with the 10 mg tablet
- Study III: multiple dose study with the 10 mg tablet

In these studies the pharmacokinetic profile of the test product Fampridine SUN 10 mg prolonged-release tablets (Sun Pharmaceutical Industries Europe B.V.) is compared with the pharmacokinetic profile of the reference product Fampyra 10 mg prolonged-release tablets (Biogen Netherlands B.V.) under fasting, fed and steady state conditions.

The study design is considered adequate. A single dose study under fasting conditions and fed conditions and a multiple dose have been submitted, which is in accordance with the guidelines for prolonged release formulations.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the EU reference product Fampyra 10 mg prolonged-release tablets (Biogen Netherlands B.V.). The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in these studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

The design of the studies are considered to be acceptable.

Bioequivalence studies

Bioequivalence study I - single dose under fasting conditions

Design

The MAH has conducted a randomised, open-label, balanced, single-dose, two-treatment, two-sequence, two-period, two-way crossover bioequivalence study under fasting conditions. This study was performed in 56 healthy male subjects, aged 18-45 years. The tablet was orally administered with 240 ml of water after 10 hours of overnight fasting. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 12, 16, 20 and 24 hours after administration of the products.

Results

Of the 56 subjects 52 subjects were eligible for pharmacokinetic analysis. Reasons for exclusion were: 2 cases of adverse events, one case of a positive alcohol test and one case of failure to check-in at the testing facility.

Table 1. The pharmacokinetic variables of fampridine of the Test and Reference under fasting conditions (as mean ± s.d.; t_{max} as median (range)).

Treatment N=52	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Test	294 ± 56	315 ± 68	25 ± 4	3.5 (1.5 – 7.0)	5.2 ± 1.2
Reference	298 ± 58	318 ± 68	26 ± 4	3.5 (1.5 - 8.0)	5.2 ± 1.0
***Ratio (90% CI)**	0.99 (0.95 - 1.03)	0.99 (0.95 – 1.03)	0.95 (0.92 – 0.99)	--	--
CV (%)	12.2	13.0	10.6	--	--

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

Bioequivalence study II - single dose under fed conditions

Design

The MAH has conducted a randomised, open-label, balanced, single-dose, two-treatment, two-sequence, two-period, two-way crossover bioequivalence study under fed conditions. This study was performed in 36 healthy male subjects, aged 18-45 years. Fed conditions are as follows: after 10 hours of overnight fasting, the subjects received a high fat/high calory breakfast (bread, cheese, milk, eggs, chicken, potatoes and chutney) 30 minutes prior to the

administration of the study drug. After 30 minutes the tablet was orally administered with 240 ml of water. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 20 and 24 hours after administration of the products.

Results
Out of 36 subjects 30 subjects were eligible for pharmacokinetic analysis. Reasons for exclusion were: 3 cases of adverse events, one case of failure to check-in at the testing facility, one case of a positive drug abuse test and one case of a positive alcohol test.

Table 2. The pharmacokinetic variables of fampridine of the Test and Reference under fed conditions (as mean ± s.d.; t_{max} as median (range)).

Treatment N=30	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	308 ± 57	324 ± 66	30 ± 5	4.5 (2.0 – 5.5)	4.7 ± 1.2
Reference	310 ± 52	323 ± 57	32 ± 5	4.25 (2.0 - 5.0)	4.5 ± 0.8
***Ratio (90% CI)**	0.99 (0.96 - 1.02)	1.00 (0.97 – 1.02)	0.95 (0.92 – 1.00)	--	--
CV (%)	6.3	6.1	10.0	--	--

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

Bioequivalence study III - multiple dose
Design
The MAH has conducted a randomized, open-label, balanced, multiple -dose, two-treatment, two-sequence, two-period, two-way crossover bioequivalence study under fasting steady state conditions. Steady state conditions were as follows: after 8 hours of overnight fasting, the subjects administered the study drug twice daily (morning and evening) with 12 hours in between doses. On day 5 of the testing period, subjects will only receive one dose of the study drug. The study drug was administered with 240 ml of water. A wash-out period of seven days was kept between the two periods.

Blood samples were taken pre-dose at day 3, 4 and 5 and at day 5 at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, and 12 hours after administration of the products.

Results

Out of 60 subjects 56 subjects were eligible for pharmacokinetic analysis. Reasons for exclusion were: one case of an adverse event, one case of withdrawn consent, one case of a positive alcohol test and one protocol violation (tobacco).

Table 3. . The pharmacokinetic variables of fampridine of the Test and Reference at steady state (as mean ± s.d.; t_{max} as median (range)).

Treatment N=56	AUC_{0-t} (ng.h/ml)	C_{tau} (ng/ml)	$C_{max\ ss}$ (ng/ml)	C_{avg} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	287 ± 56	13.8 ± 4.2	34 ± 6	24 ± 5	2.5 (1.0 – 5.5)	$0.693/k_{el}$
Reference	301 ± 50	14.4 ± 3.6	35 ± 6	25 ± 4	2.5 (0.5 – 5.0)	$0.693/k_{el}$
***Ratio (90% CI)**	0.95 (0.92 – 0.98)	0.94 (0.88 – 1.01)	0.95 (0.92 – 0.99)	--	--	--
CV (%)	10.7	22.3	10.6	--	--	--

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{tau} plasma concentration fluctuation
$C_{max\ ss}$ maximum plasma concentration steady state
C_{avg} average plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation
CI confidence interval
K_{el} elimination rate constant

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$, C_{tau}, C_{max} and $C_{max\ ss}$ are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies fampridine SUN 10 mg prolonged-release tablets is bioequivalent with the reference product Fampyra SUN 10 mg prolonged-release 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 Fampridine SUN.

Table 4. Summary table of safety concerns as approved in RMP

Important identified risks	• Seizure • Serious hypersensitivity • UTIs • Interaction with OCT2 inhibitors • Cardiac arrhythmias
Important potential risks	• Interaction with OCT2 substrates • Interaction with drugs with potential to lower seizure threshold
Missing information	• Special population: • Pregnancy exposure • Elderly population aged > 65 years of age • Paediatric and adolescent patients • Patients with impaired renal function • Interaction with anti-epileptic agents affecting sodium-potassium current • Long-term safety

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 Fampyra SUN. No new clinical studies were conducted. The MAH demonstrated through three bioequivalence studies 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 language used for the purpose of user testing the PL was English. The test was completed by 20 participants, spread across 2 rounds. 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

Fampridine SUN 10 mg prolonged-release tablets has a proven chemical-pharmaceutical quality and is a generic form of Fampyra 10 mg prolonged-release tablets. Fampyra 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.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for fampridine SUN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 February 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