COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fampridine Intas 10 mg prolonged-release tablets

(fampridine)

NL/H/4942/001/DC

Date: 19 October 2020

This module reflects the scientific discussion for the approval of Fampridine Intas 10 mg prolonged-release tablets. The procedure was finalised at 25 August 2020. 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 Intas 10 mg prolonged-release tablets, from Intas Third Party Sales 2005, S.L.

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 which has been registered in the EEA by Biogen Netherlands B.V. since 20 July 2011 through a centralised procedure (EU/1/11/699).

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

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

II. QUALITY ASPECTS

II.1 Introduction

Fampridine Intas is a white to off white, oval shaped, biconvex, bevel-edged, film coated prolonged-release tablet, debossed with “FH6” on one side and plain on the other side. Each prolonged-release tablet contains 10 mg of fampridine.

The prolonged-release tablets are packed in Aluminium/aluminium blister packs.

The excipients are:
Tablet core – hypromellose, microcrystalline cellulose, colloidal anhydrous silica, and magnesium stearate
Film-coat - hypromellose (E464), titanium dioxide (E171) and macrogol 400 (E1521)

II.2 Drug Substance

The active substance is fampridine, an established active substance not described in the European Pharmacopoeia (Ph.Eur.) but is included in the United States Pharmacopeia (USP), as dalfampridine (fampridine). Fampridine is a white powder and slightly hygroscopic. It is

soluble in water, methanol, acetone, tetrahydrofuran, isopropanol, acetonitrile, N,N-dimethylformamide, dimethyl sulfoxide and ethanol. It does not contain any chiral carbon atoms; therefore it does not exhibit stereo activity. Fampridine does not exhibit polymorphism. Currently only one crystal form has been found and described.

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 synthesis of fampridine consist of five stages. The manufacturing process is adequately described. In-process controls and specifications of intermediates are provided. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. Fampridine is not described in Ph. Eur., therefore specification parameters are set according to ICH guidelines. In the drug substance specification from drug product manufacturer are additional parameters for density and particle size distribution which are not part of drug substance specification in the ASMF. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scale batches.

Stability of drug substance

Stability data on the active substance have been provided for three production scale batches stored at 25°C/60%RH (60 months) and 40°C/75%RH (6 months). All provided accelerated and long-term stability data are within specification limits and no obvious trends or significant changes were observed. Based on the data submitted, a retest period could be granted of 36 months when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The aim of this product development was to formulate a robust, physicochemical similar and stable generic formulation of fampridine in line with reference product Fampyra.

The drug substance is a BCS Class I compound (high solubility and high permeability) and solubility pH independent. Dissolution of final product has been evaluated in pH covering the physiological range from 1 to 6.8, showing no effect of pH on dissolution.
Dissolution data on biobatches of test and reference product used in the bioequivalence study are submitted. Similarity of dissolution profiles is established with 12 individual values per time point in three different media (0.1N HCl, acetate buffer pH 4.5, phosphate buffer pH 6.8). Overall, the pharmaceutical development has been adequately described.

Manufacturing process

The manufacturing process consists of sieving raw materials, direct blending, lubrication, compression and final film-coating and has been validated according to relevant European guidelines. Process validation data on the product have been presented for three commercial scale batches in accordance with the relevant European guidelines.

Control of excipients

The specifications of the excipients are according to the respective Ph.Eur. monograph except for coating material which is tested as per in-house specification. These 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, average weight, identification, water content, dissolution, uniformity of dosage units, related substances, assay and microbial examination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three submission batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three commercial scale batches stored at 25°C/60% RH (up to 36 months) and 40°C/75% RH (up to 6 months). Photostability study was conducted on one batch of the drug product according to ICH Q1B. Based on the results it can be concluded that the drug product is photostable. On basis of the data submitted, a shelf life was granted of 3 years. No specific storage conditions need to be included in the SmPC or on the label.

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 Intas has 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 Fampridine Intas 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 Fampyra 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

Fampridine 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 three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Fampridine Intas 10 mg prolonged-release tablets (Intas Third Party Sales 2005, S.L., Spain) is compared with the pharmacokinetic profile of the reference product Fampyra 10 mg prolonged-release tablets (Biogen Netherlands B.V., Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of with the EU reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies

For this generic application, three bioequivalence studies (single dose under fasting and fed conditions and multiple dose study) have been submitted, which are discussed below. This approach is considered acceptable since fampridine is formulated in a prolonged release unit tablet formulation and the application concerns a product that should be taken without regard to food. In addition, according to the Guideline on the pharmacokinetic and clinical evaluation of prolonged release dosage forms, at least a single dose in fasting and fed conditions as well as a multiple dose study in fasting conditions are required in case of drug significant accumulation. Furthermore, according to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms, for oral formulations, *in vitro* studies to investigate the release in alcoholic solutions to confirm that there is no higher risk of dose-dumping is case of concomitant intake with alcohol has been performed.

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.

Bioequivalence study I – single dose under fasting conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 56 healthy male subjects, aged 18-45 years. Each subject received a single dose (10 mg) of one of the 2 fampridine 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 5 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.3, 3.7, 4, 4.3, 4.7, 5, 6, 8, 10, 12, 16, 20, 24 and 36 hours after administration of the products.

Results

One subject was withdrawn from the study on medical grounds. Therefore, a total of 55 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=55	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)

Test	298 ± 72	303 ± 71	25.6 ± 4.9	3.0 (1.5-6.0)	4.4 ± 0.5
Reference	302 ± 80	306 ± 80	26.7 ± 5.7	3.3 (1.3-5.0)	4.2 ± 0.4
***Ratio (90% CI)**	0.99 (0.96 – 1.04)	1.00 (0.96 – 1.04)	0.97 (0.93 – 1.00)	--	--
CV (%)	12.7	12.3	12.1	--	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Bioequivalence study II – single dose under fed conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 56 healthy male subjects, aged 18-45 years. Each subject received a single dose (10 mg) of one of the 2 fampridine formulations. The tablet was orally administered with 240 ml water 30 minutes after serving of breakfast. 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, 2.3, 2.7, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.3, 5.7, 6, 6.5, 7, 8, 10, 12, 16, 20, 24 and 36 hours after administration of the products.

Results

One subject was withdrawn from the study on medical grounds. Therefore, a total of 55 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of fampridine under fed conditions.

Treatment N=55	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	316 ± 58	319 ± 58	30.6 ± 4.6	5.3 (2.7-6.5)	4.4 ± 0.4
Reference	311 ± 57	315 ± 57	30.7 ± 5.0	5.3 (2.7-5.7)	4.4 ± 0.4
***Ratio (90% CI)**	1.02 (1.00 – 1.03)	1.02 (1.00 – 1.03)	1.01 (0.99 – 1.03)	--	--
CV (%)	4.9	4.6	7.2	--	--

$AUC_{0-\infty}$	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

**ln-transformed values*

Bioequivalence study III – multiple dose under fasting conditions

Design

A multiple dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 60 healthy male subjects, aged 18-45 years. Each subject received a single dose of one of the 2 fampridine formulations. All the subjects were administered the study drug (10 mg) in each period in each group. The order of receiving the test product and reference product for each subject on day 5 and day 6 of both the periods of the study was determined according to a randomisation schedule. The duration of the clinical part of the study was about 56 days. After an overnight fast of at least 8 hours for morning dose (Day 1 to Day 6) and after fast of at least 2 hours for evening dose (Day 1 to Day 5), a single oral dose (10 mg) of either the test or the reference product was administered with 240 ml of drinking water.

Blood samples were collected prior to morning dose on day 1, 3, 4, 5 and 6 and prior to evening dose on day 3 and 4. The blood samples were collected on day 6 at 0.3, 0.667, 1, 1.3, 1.7, 2, 2.3, 2.7, 3, 3.3, 3.7, 4, 4.5, 5, 6, 8, 10 and 12 hours post-dose administration in each period.

Results

All 60 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of fampridine in steady-state under fasted conditions.

Treatment N=55	**$AUC_{0-\tau}$** ng/ml/h	**$C_{max,ss}$** ng/ml	**$C_{\tau,ss}$** ng/ml	**$C_{av,ss}$** ng/ml	**$t_{max,ss}$** h	**Fluctuation (%)**
Test	275 ± 54	33.9 ± 5.6	12.9 ± 4.9	22.9 ± 4.5	2.3 (0.7-5.0)	99 ± 28
Reference	277 ± 58	34.0 ± 6.8	13.0 ± 4.8	23.1 ± 4.8	2.3 (0.7-5.0)	97 ± 26
***Ratio (90% CI)**	0.99 (0.97 – 1.01)	1.00 (0.98 – 1.02)	0.98 (0.93 – 1.03)	--	--	--
CV (%)	8.7	11.0	20.5	--	--	--

$A_{UC0-\tau}$	Area under the plasma concentration curve during a dosage interval at steady state
$C_{max,ss}$	Maximum plasma concentration at steady state
$C_{min,ss}$	Minimum plasma concentration at steady state
$t_{max,ss}$	Time until $C_{max,ss}$ is reached
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies

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

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

Important identified risks	None
Important potential risks	None
Missing information	None

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. No new clinical studies were conducted. The MAH demonstrated through 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Fampyra (EMEA/H/C/002097) and Solifenacin succinate 5 mg/10 mg film-coated tablets (DK/H/2339/001 002. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Fampridine Intas 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.

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 Fampridine Intas with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 August 2020.

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