LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Fampridine STADA
(fampridine)

SE/H/2001/01/DC

This module reflects the scientific discussion for the approval of Fampridine STADA. The procedure was finalised on 2022-03-02. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Fampridine STADA, 10 mg, prolonged-release tablet.

The active substance is fampridine. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Fampridine STADA, 10 mg, prolonged-release tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Stada Arzneimittel AG, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, CZ, DE, DK, ES, FI, FR, IS, LU, SI as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Fampyra, 10 mg, prolonged-release tablets authorised in the Community since 2011, from Germany with Biogen Netherlands B.V. as marketing authorisation holder.

The reference product used in the bioequivalence studies is Fampyra, 10 mg, prolonged-release tablets with Biogen Netherlands B.V. as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of fampridine are well known. As fampridine is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Fampridine STADA is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Fampridine STADA from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted four bioequivalence studies comparing Fampridine with the reference product Fampyra.

Pharmacokinetic properties of the active substance
Absorption: Absolute bioavailability of fampridine prolonged-release tablets has not been assessed, but relative bioavailability (as compared to an aqueous oral solution) is 95 %.

When fampridine tablets are taken with food, the reduction in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) of fampridine is approximately 2-7 % (10 mg dose). The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. However, C_{max} increases by 15-23 %. Since there is a clear relationship between C_{max} and dose related adverse reactions, it is recommended to take fampridine without food.

Linearity: The pharmacokinetics of fampridine is linear.

Elimination: The terminal half-life is 6 hours.

Study 0017-18 (Single-dose, fasted)
Methods
This was a single-dose, two-way crossover study conducted in 24 healthy volunteers, comparing Fampridine, 10 mg, prolonged-release tablets with Fampyra, 10 mg, prolonged-release tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 36 hours post-dose. Plasma concentrations of fampridine were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The study was conducted between 2018-08-22 and 2018-10-10.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for fampridine, n=21.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**331.36 ± 79.23**	**336.08 ± 79.15**	**28.41 ± 5.07**	**3.00 (1.00-5.00)**
Reference	**324.42 ± 92.26**	**329.34 ± 91.00**	**26.50 ± 4.41**	**3.50 (2.00-8.00)**
***Ratio (90% CI)**	**102.2 (96.07-108.77)**	**102.0 (95.96-108.47)**	**106.4 (102.19-110.81)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the 90 % confidence interval for the ratio of the test and reference products fell within the tightened acceptance range of 90.00-111.11 %.

Study 0018-18 (Single-dose, fed)

Methods

This was a single-dose, two-way crossover study conducted in 30 healthy volunteers, comparing Fampridine, 10 mg, prolonged-release tablets with Fampyra, 10 mg, prolonged-release tablets under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 36 hours post-dose. Plasma concentrations of fampridine were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The study was conducted between 2018-08-22 and 2018-10-16.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for fampridine, n=28.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**347.52 ± 68.87**	**352.55 ± 66.49**	**33.28 ± 5.82**	**5.25 (1.50-6.00)**
Reference	**340.25 ± 70.27**	**347.05 ± 66.85**	**33.59 ± 4.72**	**5.25 (1.50-6.00)**
***Ratio (90% CI)**	**102.2 (98.63-105.96)**	**101.6 (98.37-104.93)**	**98.4 (94.12-102.95)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the 90 % confidence interval for the ratio of the test and reference products fell within the tightened acceptance range of 90.00-111.11 %.

Study 0720-18 (Multiple-dose, fasted)

Methods

This was a multiple-dose, two-way crossover study conducted in 45 healthy volunteers, comparing Fampridine, 10 mg, prolonged-release tablets with Fampyra, 10 mg, prolonged-release tablets under fasting conditions. The subjects were administered 11 doses in each study period. For each dose, one

tablet of 10 mg of either test or reference product was administered together with 240 ml of water. From Day 01 to Day 05, the subjects received morning and evening dose and for Day 06, the subjects received a morning dose. All the subsequent doses were administered at an interval of 12 hours with reference to the previous dose. Blood samples for concentration analysis were collected pre-dose and up to 12 hours post-dose. Plasma concentrations of fampridine were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for $C_{\tau,ss}$, $C_{max,ss}$ and $AUC_{0-\tau,ss}$. The study was conducted between 2019-04-11 and 2019-05-26.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 3 below.

Table 3. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD, tmax median, range) for fampridine, n=40.

Treatment	$AUC_{0-\tau,ss}$ ng*h/ml	$C_{max,ss}$ ng/ml	$C_{\tau,ss}$ ng/ml	$t_{max,ss}$ h
Test	**290.69 ± 66.68**	**37.33 ± 7.62**	**11.69 ± 4.94**	**2.52 (0.33-5.00)**
Reference	**299.02 ± 67.28**	**37.09 ± 7.10**	**13.47 ± 5.30**	**2.67 (0.67-4.35)**
***Ratio (90% CI)**	**97.1 (94.28-100.01)**	**100.3 (97.07-103.74)**	**86.1 (79.84-92.87)**	**-**

$AUC_{0-\tau}$	area under the plasma concentration-time curve during one dosing interval
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
t_{max}	time for maximum plasma concentration

**calculated based on ln-transformed data*

For $AUC_{0-\tau,ss}$ and $C_{max,ss}$ the 90 % confidence interval for the ratio of the test and reference products fell within the acceptance range of 80.00-125.00 %. However, $C_{\tau,ss}$ was unable to meet the bioequivalence criteria as the lower CI% fell outside the conventional acceptance range of 80.00-125.00 % as well as the tightened acceptance range.

Study 20-VIN-0478 (Multiple-dose, fasted)
This study was conducted during clock-stop, as requested by RMS.

Methods
This was a multiple-dose, two-way crossover study conducted in 64 healthy volunteers, comparing Fampridine, 10 mg, prolonged-release tablets with Fampyra, 10 mg, prolonged-release tablets under fasting conditions. The subjects were administered 11 doses in each study period. For each dose, one tablet of 10 mg of either test or reference product was administered together with 240 ml of water. From Day 01 to Day 05, the subjects received morning and evening dose and for Day 06, the subjects received a morning dose. All the subsequent doses were administered at an interval of 12 hours with reference to the previous dose. Blood samples for concentration analysis were collected pre-dose and up to 12 hours post-dose. Plasma concentrations of fampridine were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for $C_{\tau,ss}$, $C_{max,ss}$ and $AUC_{0-\tau,ss}$. The study was conducted between 2021-06-12 and 2021-07-21.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 4 below.

Table 4. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD, tmax median, range) for fampridine, n=59.

Treatment	$AUC_{0-\tau,ss}$ ng*h/ml	$C_{max,ss}$ ng/ml	$C_{\tau,ss}$ ng/ml	$t_{max,ss}$ h
Test	**258.791 ± 52.7719**	**30.923 ± 5.9172**	**11.656 ± 4.0381**	**2.667 (1.00-5.50)**
Reference	**275.017 ± 61.3997**	**33.028 ± 6.7216**	**12.484 ± 4.5865**	**2.667 (1.00-5.00)**
***Ratio (90% CI)**	**94.15 (91.65-96.71)**	**93.49 (90.71-96.37)**	**94.06 (87.94-100.61)**	**-**

$AUC_{0-\tau}$	area under the plasma concentration-time curve during one dosing interval
$C_{max,ss}$	maximum plasma concentration at steady state
$C_{\tau,ss}$	minimum plasma concentration at steady state at the end of dosing interval
$t_{max,ss}$	time for maximum plasma concentration at steady state

**calculated based on ln-transformed data*

For $AUC_{0-\tau,ss}$, $C_{max,ss}$ and $C_{\tau,ss}$ the 90 % confidence interval for the ratio of the test and reference products fell within the acceptance range of 80.00-125.00 %.

Discussion and overall conclusion

The bioequivalence studies and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) and the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1). The bioanalytical methods were adequately validated.

Even though acceptance criteria of 90.00-111.11 % was used in studies 0017-18 and 0018-18, the conventional acceptance range of 80.00-125.00 % can be accepted.

According to the Bioequivalence Guideline, if for a particular formulation at a particular strength multiple studies have been performed some of which demonstrate bioequivalence and some of which do not, the body of evidence must be considered as a whole. The existence of a study which demonstrates bioequivalence does not mean that those which do not can be ignored.

In this case, study 20-VIN-0478 showed bioequivalence while study 0720-18 did not. The applicant has shown that outcome of study 0720-18 was significantly impacted by the presence of an outlier. In study 20-VIN-0478, more subjects were included and was thus less sensitive for an outlier. Hence, bioequivalence can be concluded between test and reference product at steady state in fasting conditions.

Based on the submitted bioequivalence studies, Fampridine is considered bioequivalent with Fampyra.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 STADA.

Safety specification

The MAH has submitted the version 1.2 RMP dated 2022-Jan-05 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.

The submitted Risk Management Plan, version 1.2 signed 2022-01-05 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet was 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 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

The quality of the generic product, Fampridine STADA, is found adequate. There are no objections to approval of Fampridine STADA, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is

acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Fampridine STADA, 10 mg, prolonged-release tablet was positively finalised on 2022-03-02.

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SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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