EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2020
EMA/CHMP/432671/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fampridine Accord

International non-proprietary name: fampridine

Procedure No. EMEA/H/C/005359/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

% Fluctuation	Percentage fluctuation during steady state
AE	Adverse Event
ANOVA	Analysis of variance
AP	Applicant's Part (or Open Part) of ASMF
ASMF	Active Substance Master File = Drug Master File
AUC_%Extrap_obs	Residual area in percentage
AUC0-∞	Area under the plasma concentration versus time curve from time zero to infinity
AUC0-t	Area under the plasma concentration versus time curve from time zero to the last measurable plasma concentration
$AUC_{\tau,ss}$	Area under the concentration versus time curve during a dosing interval at steady state computed using linear trapezoidal rule. (τ = Dosing interval)
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
BMI	Body Mass Index
$C_{av,ss}$	Average plasma concentration at steady state
CI	Confidence interval
C_{max}	Maximum measured plasma concentration
$C_{max,ss}$	Maximum measured plasma concentration at steady state
C_{pd}	Minimum observed concentration prior to dosing
CHMP	Committee for Medicinal Products for Human Use
$C_{\tau,ss}$	Concentration at the end of the dosing interval at steady state
EC	European Commission
EMA	European Medicines Agency
EU	European Union
FT-IR	Fourrier Transform Infrared Spectroscopy
GC	Gas Chromatography
ERA	Environmental Risk Assessment
GCP	Good Clinical Practices
GLM	General Linear Model
GLP	Good Laboratory Practices
h/Hr/Hrs	Hour(s)
HDPE	High-density polyethylene
HPLC	High Performance Liquid Chromatography
ICH	International Conference on Harmonization
IPC	In-process control
IR	Infrared
K2EDTA	Di Potassium Ethylene Diamine Tetraacetic Acid
KF	Karl Fisher
LC-MS/MS	Liquid Chromatography/ Tandem Mass Spectrometry
LDPE	Low-density polyethylene
LLOQ	Lower Limit of Quantification
Ln	Logarithmic value to the base 'e'
LOD	Limit of Detection
LOQ	(1) Limit of Quantification, (2) List of Questions
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MV	Method Validation

N	Number
ND	Not detected
ng / mL	Nanogram per milliliter
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NTI	Narrow Therapeutic Index
PDE	Permitted Daily Exposure
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
PI	Product Information
PPCP	Polypropylene co-polimer
PRAC	Pharmacovigilance Risk Assessment Committee
PSD	Particle size distribution
Rcf	Relative Centrifugal Force
RH	Relative Humidity
RMANOVA	Repeated Measures ANOVA
RMP	Risk Management Plan
RP	Restricted Part (or Closed Part) of ASMF
SAE	Serious Adverse Event
SAS	Statistical analysis system
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
T1/2	Terminal half-life
Tlag	The time prior to the first measurable (non-zero) concentration
Tmax	Time of the maximum measured plasma concentration
Tmax,ss	Time of the maximum measured plasma concentration during dosing interval at steady state
TOST	Two one-sided test
TTC	Threshold of toxicological concern
USP RS	United States Pharmacopoeia Reference Substance
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XRD	X-Ray Diffraction
λ z	First order rate constant associated with the terminal (log-linear) portion of the curve

1. Background information on the procedure

1.1. Submission of the dossier

The Applicant Accord Healthcare S.L.U. submitted on 29 July 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Fampridine Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'.

The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 April 2019.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The Applicant applied for the following indication:

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

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Fampyra instead of non-clinical and clinical unless justified otherwise

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Fampyra 10 mg prolonged-release tablet
- Marketing authorisation holder: Biogen Netherlands B.V.
- Date of authorisation: 20-07-2011
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/11/699/001-004

Medicinal product authorised in the Union/Member state where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Fampyra 10 mg prolonged-release tablet
- Marketing authorisation holder: Biogen Netherlands B.V.
- Date of authorisation: 20-07-2011
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/11/699/001-004

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Fampyra 10 mg prolonged-release tablet
- Marketing authorisation holder: Biogen Netherlands B.V.
- Date of authorisation: 20-07-2011
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation number(s): EU/1/11/699/003
- Bioavailability study number(s): 487-14, 488-14, 489-14

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the Applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The Applicant did not seek Scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Rajko Kenda

The application was received by the EMA on	29 July 2019
The procedure started on	15 August 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	4 November 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	18 November 2019
The CHMP agreed on the consolidated List of Questions to be sent to the Applicant during the meeting on	12 December 2019
The Applicant submitted the responses to the CHMP consolidated List of Questions on	30 March 2020
The Rapporteurs circulated the Joint Assessment Report on the Applicant's responses to the List of Questions to all CHMP members on	5 May 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 May 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the Applicant	28 May 2020

on	
The Applicant submitted the responses to the CHMP List of Outstanding Issues on	23 June 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	9 July 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Fampridine Accord on	23 July 2020

2. Scientific discussion

2.1. Introduction

The product Fampridine Accord 10 mg prolonged-release tablets has been developed as a generic equivalent to Fampyra, 10 mg prolonged-release tablets, Biogen Netherlands B.V. which was authorised in the Europe on 20 July 2011.

Fampridine is a potassium channel blocker. By blocking potassium channels, fampridine reduces the leakage of ionic current through these channels, thereby prolonging repolarization and thus enhancing action potential formation in demyelinated axons and neurological function. Presumably, by enhancing action potential formation, more impulses might be conducted in the central nervous system.

The proposed indication is: Fampridine Accord is indicated for the improvement of walking in adult patients with multiple sclerosis with walking disability (EDSS 4-7).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as prolonged release tablets containing 10 mg of fampridine as active substance.

Other ingredients are:

Tablet core: hypromellose (E464), silica, colloidal anhydrous (E551), cellulose microcrystalline (E460) and magnesium stearate (E572);

Film-coating: hypromellose (E464), titanium dioxide (E171), and macrogol (E1521);

The product is available in are packed in aluminium-aluminium perforated unit- dose blister packs, as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of active substance is 4-pyridinamine corresponding to the molecular formula $C_5H_6N_2$. It has a relative molecular mass of 94.11 and the following structure:

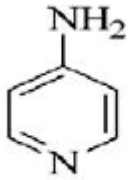


Figure 1: Active substance structure

The chemical structure of active substance was elucidated by a combination of infrared spectrum (FT-IR), ultraviolet spectrum, NMR spectrum (^1H and ^{13}C), mass spectrum, and elemental analysis. The solid state properties of the active substance were measured by XRD.

The active substance is a slightly hygroscopic white powder soluble in water, in methanol, in acetone, in tetrahydrofuran, in isopropanol, in acetonitrile, in N,N-dimethylformamide, in dimethylsulfoxide, and in alcohol.

Dalfampridine does not contain chiral centres hence no isomers are possible. Polymorphism has not been observed for the active substance. Currently only one crystal form has been found and described and it is appropriately controlled in the active substance specifications.

Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturer.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The active substance is synthesized in five main stages, with four stages consisting in chemical bond formation or cleavage followed by a crystallization and purification stage. One well defined starting material is proposed with acceptable specification and complying with ICH Q11. Carry-over of impurities from starting material to final active substance is well evaluated.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are satisfactory.

Potential related substances and their origin have been identified and limits for their control established in the active substance specification as per ICH Q3A and ICH M7.

The contents of all the solvents used in the synthesis is included in the active substance specification. Class I solvents, as possible impurities in solvents, are controlled in the specification.

Elemental analysis as per ICH Q3D was performed. No element is intentionally added in the manufacturing process. Results for all elements are below the 30 % of ICH limit. No further control of elemental impurities in the active substance is required.

Any individual unspecified impurity in fampridine is controlled at not more than 0.10%.

Satisfactory discussion on possible genotoxic impurities is included. Four potentially genotoxic impurities were identified. Three of the genotoxic impurities are routinely controlled with Threshold of toxicological concern (TTC) limit (75 ppm) in final active substance specification. The fourth genotoxic impurity is routinely controlled in Intermediate stage-IV.

A risk assessment for nitrosamine impurities has been performed for the active substance in line with "Information on nitrosamines for marketing authorisation holders. In the starting material synthesis, no solvents, with a possible source of secondary or tertiary amines, and no reagents that could be. nitrite source, like sodium nitrite, are used. In all the five stages of the manufacture of the active substance, no nitrite, secondary or tertiary amines are used. Therefore, it can be concluded that the formation of n-nitrosamine impurities is not likely in the active substance.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is primarily packed in transparent low-density polyethylene bag, placed in a polyethylene bag and outer triple laminated bag, in HDPE drum. The primary bag is tied with strip seal to make it airtight. The primary packaging materials comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification, includes tests for description (visual), identification (IR, HPLC, XRD), water (KF), sulfated ash (Ph. Eur.), related substance (HPLC), assay (HPLC), residual solvents (GC), appearance of solution (Ph. Eur.), density, particle size (Malvern mastersizer, sieve analysis), and microbial examination (Ph. Eur.).

The specification parameters are set according to ICH Q6A and for impurities in accordance with ICH Q3A and M7 guidelines. Test parameters also include residual solvents (as discussed above), identification of polymorph (by XRD) and particle size. Additional parameters for density and particle size distribution (by sieve), which are not part of the active substance specification in the ASMF, have been introduced to ensure manufacturability of the active substance in the finished product by direct compression.

The proposed limits have been tightened during the review and are acceptable.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data of 3 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* description, identification, water, related substances, assay and microbial limit test. The analytical methods used were the same as for release and were stability

indicating. All principal physical and chemical parameters were well within the limits during the accelerated and long-term storage conditions without showing any sign of degradation.

Results on stress conditions (acid degradation (5N HCl), alkali degradation (5N NaOH), oxidation degradation (H_2O_2), thermal degradation, UV and fluorescent light degradation, and humidity degradation (75% RH) were also provided on one batch. Extensive degradation is observed at oxidative conditions. In all other degradation conditions, no interference is observed between impurities and fampridine, peak purity values are acceptable and mass balance is achieved. Based on observed oxidative degradation the proposed storage in airtight container is acceptable.

Photostability testing following the ICH guideline Q1B was performed on one batch. All reported results for all tests were within the acceptable limits of the current specification. Therefore, the active substance does not need to be protected from light.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months when the active substance is stored at 25°C, with excursions permitted to 15°C-30°C, in the proposed airtight container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished medicinal product is a prolonged release tablet. The film-coated tablets are a white to off white, oval shaped, biconvex, bevel-edged, approximately 13.1 x 8.1 mm in dimensions, debossed with "FH6" on one side and plain on other side.

The aim of this product development was to formulate robust, physicochemical similar and stable generic formulation of the reference product Fampyra 10 mg prolonged-release tablets.

The active substance is slightly hygroscopic crystalline powder with no known polymorphs. It does not exhibit stereoisomerism.

As demonstrated by the pH solubility profile study, the active substance is Biopharmaceutics Classification System (BCS) class I, molecule have high solubility across the physiological pH range 1.2 to 6.8. Various physical and chemical properties of the active substances are affected by their particle size distribution and shape and biopharmaceutical behaviour. Therefore, the particle size is controlled in the specifications of the active substance with two independent tests and during the manufactured of the finished product.

A pre-formulation study was carried out with the same excipients used in the core of the reference product tablet, in the proportions expected to be used during formulation. These are common excipients for this type of pharmaceutical form, functioning as diluent, glidant and lubricants. A compatibility study of the active substance with different excipients was carried through binary mixtures of the active substance with the excipients, stored at 40°C/75% RH (open conditions) and 50°C (closed condition) in glass vials for 4 weeks. No interaction was observed with any of excipients during the study.

The final composition chosen for the tablet core is qualitative the same as the reference product; the excipient chose for the film coating is equivalent to the one of the refence product; for a comparison between the test and reference product, see Table 1.

Table 1: Composition of finished product

Excipients in test product	Excipients in reference product
Hypromellose	Hypromellose
Silica, colloidal anhydrous	Silica, colloidal anhydrous
Cellulose, microcrystalline	Cellulose, microcrystalline
Magnesium stearate	Magnesium stearate
Film coating material: Opadry 03B58900 white (Hypromellose, Titanium dioxide, Macrogol)	Film coating material: Hypromellose, Titanium dioxide (E-171), Polyethylene glycol 400

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

During the manufacturing method development, direct compression with directly compressible grade excipients was selected for manufacturing process. This decision was based on literature references, prior knowledge, low final active substance quantity (only 2.70% in core tablets) and poor flow properties of fampridine, as revealed in pre-formulation studies. Wet granulation with water was excluded due to presence of hypromellose as release controlling polymer and wet granulation with an organic solvent was also excluded because of environmental considerations. The concentration of the functional excipients (i.e. release controlling polymer, lubricant) was optimised for manufacturability in developmental trials. The dissolution profile of the active substance was not affected by different concentration and viscosity of the release controlling polymer, and different concentration of lubricant. During development optimisations in blending time, lubrication time and hardness were made. No critical process parameters were defined during process development. Blending time before lubricant addition and time of lubrication are presented as process parameters tested in order to assure blend uniformity before compression stage.

The product dissolution was evaluated across the physiological pH range 1.2 to 6.8 with 50 RPM/ paddle/900 ml. Complete release was observed in 0.1 N HCl and acetate buffer pH 4.5 for the finished product. In phosphate buffer pH 6.8 slightly slower active substance release was observed as compared with 0.1 N HCl and acetate buffer pH 4.5. Considering prolonged-release formulation design, pharmacokinetics and multimedia dissolution profiles of reference product, the following dissolution media and conditions were selected: pH=6.8 phosphate buffer, 900 ml, apparatus: paddle, and speed: 50 RPM. The discriminatory power of the dissolution method was demonstrated by a change in formulation of the finished product, namely reducing the hypromellose content per tablet from 253 to 148 mg/tablet and compensating the difference with an equivalent increase of the diluent (microcrystalline cellulose) which, as expected, showed faster release of the active substance.

Comparative dissolution profiles between the batches used in the BE study (generic and reference medicinal product) in 3 different media (0.1N HCl, acetate buffer pH 4.5, phosphate buffer pH 6.8) / paddle, 900 ml, 50 rpm were provided. Dissolution profile of test product BE batch with two other process validation batches) of test product to assess batch to batch consistency are also compared. It can be concluded that in-vitro dissolution profile is comparable in all the media as the similarity factor (f2) is more than 50.

A comparative in-vitro alcohol-induced dose-dumping dissolution study has been carried out at 0.1 N HCl on one batch of the proposed and the reference medicinal product, at the recommended alcohol concentrations (0, 5, 20, 40%) and at pH 6.8 phosphate buffer on one batch of the proposed medicinal product, at the recommended alcohol concentrations (0, 5, 10, 20%) to evaluate the impact and possible interaction of finished product in the presence of alcohol. As the f2 is more than 50 at all the

concentrations evaluate, it can be concluded that the generic product has similar dissolution profile to that of reference product in dissolution media with and without alcohol, hence there is no concern of dose dumping in the presence of alcohol.

A comparative in-vivo bioequivalence (BE) study have been performed between the proposed and reference medicinal product.

The primary packaging is aluminium -aluminium perforated unit- dose blister. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 5 main steps: sifting of raw materials, direct blending, lubrication, compression and final film-coating.

Blend homogeneity is critical for the quality of finished product due to low active substance content and is routinely tested as in-process control. The in-process controls are adequate for this type of manufacturing process.

Holding times of 30 days for granules (blend mixture) and core tablets and of 3 months for bulk film coated tablets are acceptable as supported by data. It is confirmed that the shelf-life is calculated in accordance with Note for Guidance on Start of Shelf-Life of the Finished Dosage Form (CPMP/QWP/072/96).

The manufacturing process is non-standard as the modified release preparation is considered a specialized pharmaceutical dosage form, according to the Annex II to note for guidance on process validation. Process validation has been carried out on three commercial size batches manufactured according to the commercial composition. All the validation parameters were within the defined acceptance criteria and found satisfactory. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), average weight of tablet, identification (HPLC, UV, titanium dioxide), water (KF), dissolution (UV), uniformity of dosage units (Ph. Eur.), related substances (HPLC), assay (HPLC), and microbial examination (Ph. Eur.).

Impurity profile of 3 batches of the proposed medicinal product manufactured by finished product manufacturer as per the final formula was compared with the impurity profile of reference medicinal product. The impurity profile was similar to the one of the reference product and no additional impurities have been observed.

The limits for impurities and water content have been tightened during the procedure and the limits for dissolution testing have also been revised to be within the ±10% of value of batch used in BE study at each time point.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities, using the component assessment approach (option 2b). The obtained measured concentration results show that the content of elemental impurities in the final product from all the potential sources (e.g. active substance, excipients, container closure system, manufacturing equipment) is below 30% of PDE (permitted daily exposure in line with

ICH Q3D). Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

Risk evaluation for the presence of nitrosamine impurities in the finished product has been carried out and no risk has been identified.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, water, dissolution, related substances, assay, and microbial examination. The analytical procedures used are stability indicating. The tests performed during stability study under the long term and accelerated conditions are complying with the specifications and well within the acceptance criteria.

Bulk stability studies were performed in one batch stored into PPCP container pack under long term conditions (25 ºC / 60% RH) for 12 months. The tests performed are complying with the specifications and well within the acceptance criteria. Based on satisfactory stability data on PPCP container, 12 months storage period is assigned for PPCP container. Tablets are to be repacked in to blisters within 12 months from the date of bulk packing into PPCP containers. The proposed storage condition is "Store below 25°C".

Results on forced degradation conditions (acid hydrolysis (5M methanolic HCl at 80°C for 72 hours), alkali hydrolysis (5M NaOH at 80°C for 72 hours), peroxide oxidation (H_2O_2 at room temperature for 72 hours), water hydrolysis stress study (at 80°C for 72 hours), thermal stress study (105°C for 72 hours), and UV stress study (for 72 hours) have been provided. Forced degradation study is carried out to identify the likely degradation products and to validate the stability indicating power of the analytical procedures by using forced degradation samples. Based on results, it is concluded that method for the determination of related substances of the finished product is stability indicating in nature.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results of conducted photo stability study reveal that the finished product is photo stable.

Thermal cycling study has been carried out to study the effect of transportation on stability of the finished product. The product was subjected to three cycles of two days at low temperature (-20 ±5 °C) followed by high temperature 50 ± 2°C / 75 ± 5% RH. Results are found well within acceptance criteria.

Based on available stability data, the proposed shelf-life of 36 months and without storage conditions as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics (PK) 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, PK and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment (ERA) studies were submitted. This was justified by the Applicant as the introduction of Fampridine Accord manufactured by Accord Healthcare S.L.U. is considered unlikely to result in any significant increase in the combined sales volumes for all fampridine containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

Upon request, the Applicant submitted a new updated non-clinical overview with more recent publications on pharmacology, PK and toxicology of fampridine in animal species and a critical evaluation of available information in the light of patient's safety. The CHMP is of the opinion that the Applicant has justified the absence of non-clinical studies based on the literature review and the claim that Fampridine Accord is a generic of the reference product Fampyra. The literature data presented in the dossier is considered acceptable and sufficient for the assessment of non-clinical aspects of Fampridine Accord in the applied indication.

Upon request and in line with the Questions and answers on Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), the Applicant was

requested to further justify the absence of possible significant increase of environmental exposure to the drug substances, providing concrete relevant data such the consumed quantities of Fampridine in kg/year. The justification for not providing new ERA studies is acceptable.

2.3.4. Conclusion on the non-clinical aspects

The CHMP considers the non-clinical aspects adequate to support this application.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for a prolonged-release tablet, containing Fampridine.

For this generic application, the Applicant has submitted three bioequivalence studies on 10 mg strength: one single dose study under fasting and one single dose study under fed conditions as well as one multiple dose study under fasted conditions in accordance with the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1) and Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

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 and 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 is required in case of drug significant accumulation.

In addition, according to the 'Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms' (EMA/CHMP/EWP/280/96 Rev1) 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. Please refer to section 2.2 Quality aspects.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

GCP

The Clinical trials were performed in accordance with Good Clinical Practices (GCP) as claimed by the Applicant.

The Applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Clinical studies

To support the application, the Applicant has submitted three bioequivalence studies in which the PK profile of the test product Fampridine Accord 10 mg prolonged-release tablets is compared with the PK profile of the reference product Fampyra 10 mg prolonged-release tablets (Biogen Idec Limited, UK):

- **Single dose study No. 487-14** under **fasting** conditions
- **Single dose study No. 488-14** under **fed** conditions

- **Multi dose study No. 489-14** under **fasting** conditions

Table 2: Tabular overview of clinical studies

Protocol Number	Study title
487-14	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of two products of Fampridine prolonged release tablets 10 mg in normal healthy, adult, human subjects under **fasting** condition.
488-14	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of two products of Fampridine prolonged release tablets 10 mg in normal healthy, adult, human subjects under **fed** condition.
489-14	An open label, balanced, randomized, two-treatment, two-period, two-sequence, multiple dose, two-way crossover, full replicate, bioequivalence study of two products of Fampridine prolonged release tablets 10 mg at steady state in healthy, adult, human subjects under **fasting** condition.

2.4.2. Pharmacokinetics

Methods

Study design

Study No. 487-14 - Single-dose fasting study

Study 487-14 was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single, oral dose, crossover, bioequivalence study of two products of Fampridine prolonged-release tablets 10 mg in normal, healthy, adult, human subjects under fasting conditions, with a screening period of 28 days prior to the dosing in Period-I and with a washout period of 5 days between the successive dosing days.

The duration of the clinical part of the study was about 8 days (11 hours prior to the dose administration in Period-I until the last PK sample in Period-II).

The subjects received one tablet of either test or reference products randomly with 240 mL of ambient temperature on the day of dosing as per the randomization schedule in each period of the study. Finished product was administered after at least 10.00 hours overnight fasting.

The study design employed (as a randomized fasting single dose cross-over design) is appropriate for the bioequivalence study according to the requirements stated in the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1). The absorption, distribution and elimination phases are all well characterized. The washout period of 5 days is considered adequate as Fampridine has an elimination half-life of 6 hours (about 4 hours in the actual study) and no pre-dose levels were detected.

The plasma concentrations of fampridine were determined in an analytical laboratory at the following times: 0.000 hour (pre-dose) and at 0.500, 1.000, 1.250, 1.500, 1.750, 2.000, 2.250, 2.500, 2.750,

3.000, 3.333, 3.667, 4.000, 4.333, 4.667, 5.000, 6.000, 8.000, 10.000, 12.000, 16.000, 20.000, 24.000 and 36.000 hours following drug administration. Considering the expected time to peak concentration (3 hours) and the elimination half-life, the sampling schedule and the sampling time period of 36 hours seems long enough to estimate PK parameters.

Study No. 488-14 - Single-dose fed study

Study 488-14 was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of two products of Fampridine prolonged-release tablets 10 mg in healthy, adult, human subjects under fed condition, with a screening period of 28 days prior to the dosing in Period-I and with a washout period of 7 days between the successive dosing days.

The duration of the clinical part of the study was about 10 days (11 hours prior to the dose administration in Period-I until the last PK sample in Period-II).

The study design employed (as a randomized fasting single dose cross-over design) is appropriate for the bioequivalence study according to the requirements stated in the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1). The absorption, distribution and elimination phases are all well characterized. The washout period of 7 days is considered adequate as fampridine has an elimination half-life of 6 hours (about 4 hours in the actual study) and no pre-dose levels were detected.

After an overnight fast of at least 10 hours, the subjects were served high fat high calorie vegetarian breakfast, which they consumed within 30 minutes. The composition of the meal has been described with regard to protein, carbohydrate and fat content and is in according to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98).

A single oral dose (10 mg) of either the test product or the reference product was administered to the subjects at 30 minutes after serving the breakfast with 240 mL of drinking water at ambient temperature. The investigational medicinal product administration was as per the randomization schedule and under open-label conditions.

The plasma concentrations of fampridine were determined in an analytical laboratory at the following times: 0.000 hour (pre-dose) and at 0.500, 1.000, 1.500, 2.000, 2.333, 2.667, 3.000, 3.250, 3.500, 3.750, 4.000, 4.250, 4.500, 4.750, 5.000, 5.333, 5.667, 6.000, 6.500, 7.000, 8.000, 10.000, 12.000, 16.000, 20.000, 24.000 and 36.000 hours following drug administration in each period.

Considering the expected time to peak concentration (about 5 hours) and the elimination half-life, the sampling schedule and the sampling time period of 36 hours seems long enough to estimate PK parameters.

Study No. 489-14 - Multiple-dose fasting study

Study 489-14 was an open label, balanced, randomized, two-treatment, two-period, two-sequence, multiple oral dose, fully replicate, crossover, bioequivalence study in healthy, adult, human subjects under fasting conditions, with a screening period of 28 days prior to the first dose administration in Period-I. All the subjects were administered the study drug in each period in each group. The order of receiving Test Product-T and Reference Product-R for each subject on day 05 and day 06 of both the periods of the study was determined according to a randomization schedule. A washout period of 9 days was maintained between the last dose of Period-I and the first dose of Period-II.

The duration of the clinical part of the study was about 56 days (11 hours before administration of the morning dose on Day 01 in Period-I of group-I until the 12 hours after the morning dose administration on Day 06 in Period-II of group-IV).

After an overnight fast of at least 08 hours for morning dose (Day 01 to Day 06) and after fast of at least 02 hours for evening dose (Day 01 to Day 05), a single oral dose (10 mg) of either the test or the reference product was administered with 240 mL of drinking water at ambient temperature as per the randomization schedule and under open-label conditions.

Single dose of the test or the reference product was administered orally to each subject twice daily from Day 01 to Day 05 at morning & evening and only once in the morning on Day 06 in each period.

The blood samples were collected prior to morning dose on each day (Day 01, 03, 04, 05 and 06) and prior to evening dose on Day 03 and 04 and on Day 05 and 06 at 0.333, 0.667, 1.000, 1.333, 1.667, 2.000, 2.333, 2.667, 3.000, 3.333, 3.667, 4.000, 4.500, 5.000, 6.000, 8.000, 10.000 and 12.000 hours post-dose administration in each period.

In line with the guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1), multiple-dose study is recommended for the prolonged release formulation when a drug has a tendency to accumulate after multiple dosing at the recommended dosing interval. The study has been performed under fasted conditions as per EMA guideline recommendation for a steady-state study if the SmPC states that the product should be taken in fasted state. The proposed fasting periods of 8 h before morning administration and 2 h before the evening administration are acceptable.

The study design employed (as a full replicate cross-over design with two consecutive administration of the same product after reaching steady-state) is adequate in relation to characterization of the PK of Fampridine after oral administration. Achievement of steady state is assessed by comparing at least 3 pre-dose morning concentrations for each formulation.

The washout period of 9 days is considered adequate as fampridine has an elimination half-life of 6 hours and no pre-dose levels before the first dose on period II were detected. Samples were collected for a dosing interval of 12 hours after the last dose, which is considered sufficient.

Test and reference products

The test and reference products used for all three studies (Study No. 487-14, Study No. 488-14 and Study No. 489-14) is as follows:

Test product (T):	**Fampridine prolonged-release tablets 10 mg**	
	Batch No.:	S03247
	Manufacturer:	Intas Pharmaceuticals Ltd., India
	Measured content (% of label claim):	97,7%
	Manufactured date:	03/2015
	Expiry date:	02/2017
	Release date:	12.05.2015 (according to certificate of analysis)
Reference product (R):	**FAMPYRA® prolonged-release tablets 10 mg**	
	Batch No.:	73375
	Manufacturer:	Alkermes Pharma Ireland Ltd., Monksland, Athlone, Co. Westmeath, Ireland.

MAH:	Biogen Idec Limited, Innovation House, 70 Norden Road, Maidenhead, Berkshire, SL6 4AY, United Kingdom.
Batch site (biobatch):	Not applicable
Measured content	
(% of label claim):	97,6%
Exp. Date:	08/2016

The reference and test products are acceptable. The member state where the reference product was purchased from is Germany.

Satisfactory certificates of analysis of the test and reference products bio-batch are presented. The difference in the assay between the test and reference product is less than 5%, which is acceptable. This difference was not taken into account in the PK or statistical analysis.

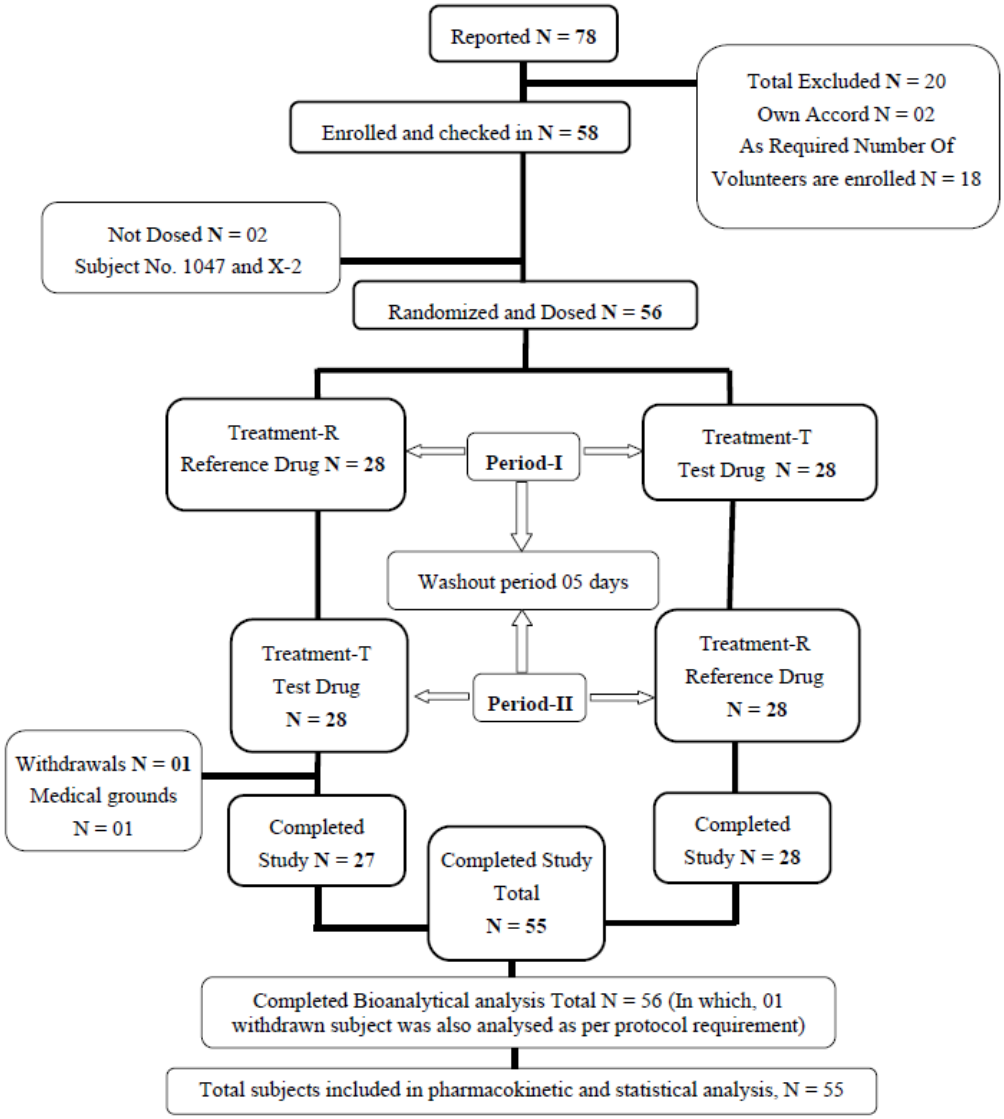
Size of the test product bio-batch of 200,000 tablets is acceptable.

According to the information provided in Module 3, the test product bio-batch formulation is identical to the formulation intended to be marketed.

Population(s) studied

Study No. 487-14 - Single-dose fasting study

Figure 2: Flow-chart Study No. 487-14



As per the protocol, 56 non-smoker, healthy, adult, volunteers of Asian ethnicity between 18 to 45 years of age (both inclusive), living in and around Ahmedabad city or western part of India, having a Body Mass Index (BMI) between 18.5 to 27 kg / m^2 (both inclusive) and with normal clinical and laboratory results, were enrolled for the study. No female volunteers were enrolled in the study. The population chosen is according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1). Inclusion and exclusion criteria are acceptable and performed according to the protocol requirements. All the subjects were dosed as per the randomization.

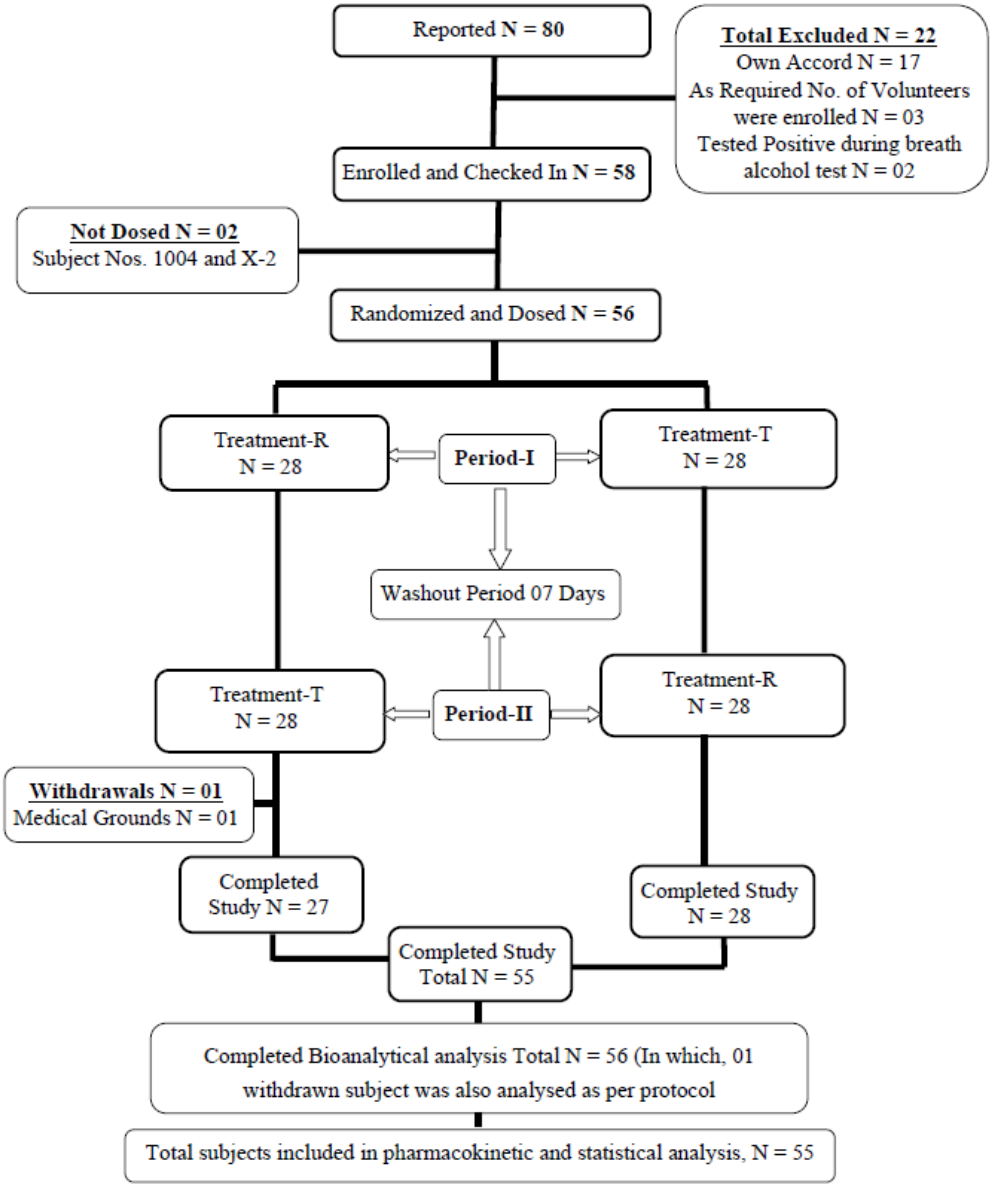
Out of these 58 subjects, 56 subjects were dosed in Period-I. Out of the dosed 56 subjects, 55 subjects completed the clinical phase of the study successfully. There was one post-dose withdrawal in the study, on medical grounds in Period-II. Upon request, the Applicant presented the Case Report/Record Form (CRF) to justify the withdrawal of this subject. The reason of the withdrawal is acceptable. There were no missing samples during the conduct of study. Plasma samples of all 56 subjects were analysed. In which, withdrawn subject was also analysed as per protocol requirement.

Total **55 subjects** were included in the **PK and statistical analysis**. The safety assessment includes information for all 56 subjects who were dosed at least once during this study.

There were no protocol deviations during the conduct of study. The blood sampling time deviations did not affect the PK analysis, which were based on real sampling times.

Study No. 488-14 - Single-dose fed study

Figure 3: Flow-chart Study No. 488-14



The study was conducted on Asian population. As per the protocol the 56 subjects (male) who participated in this study were non-smokers, healthy adult human volunteers between 18 to 45 years of age (both inclusive), having a BMI between 18.5 to 27 (both inclusive), calculated as weight in kg / height in m^2 with normal clinical and laboratory results. The population chosen is according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1). Inclusion and exclusion criteria are acceptable and performed according to the protocol requirements. All the subjects were dosed as per the randomization.

Out of the dosed 56 subjects, 55 subjects completed the clinical phase of the study successfully. There was one post-dose withdrawal during the conduct of the study, on medical grounds in Period-II. Upon request, the Applicant presented the CRF to justify the withdrawal of this subject. The reason of the withdrawal is acceptable. Plasma samples of all 56 subjects were analysed. In which, withdrawn subject was also analysed as per protocol requirement. There were no missing samples during the conduct of the study.

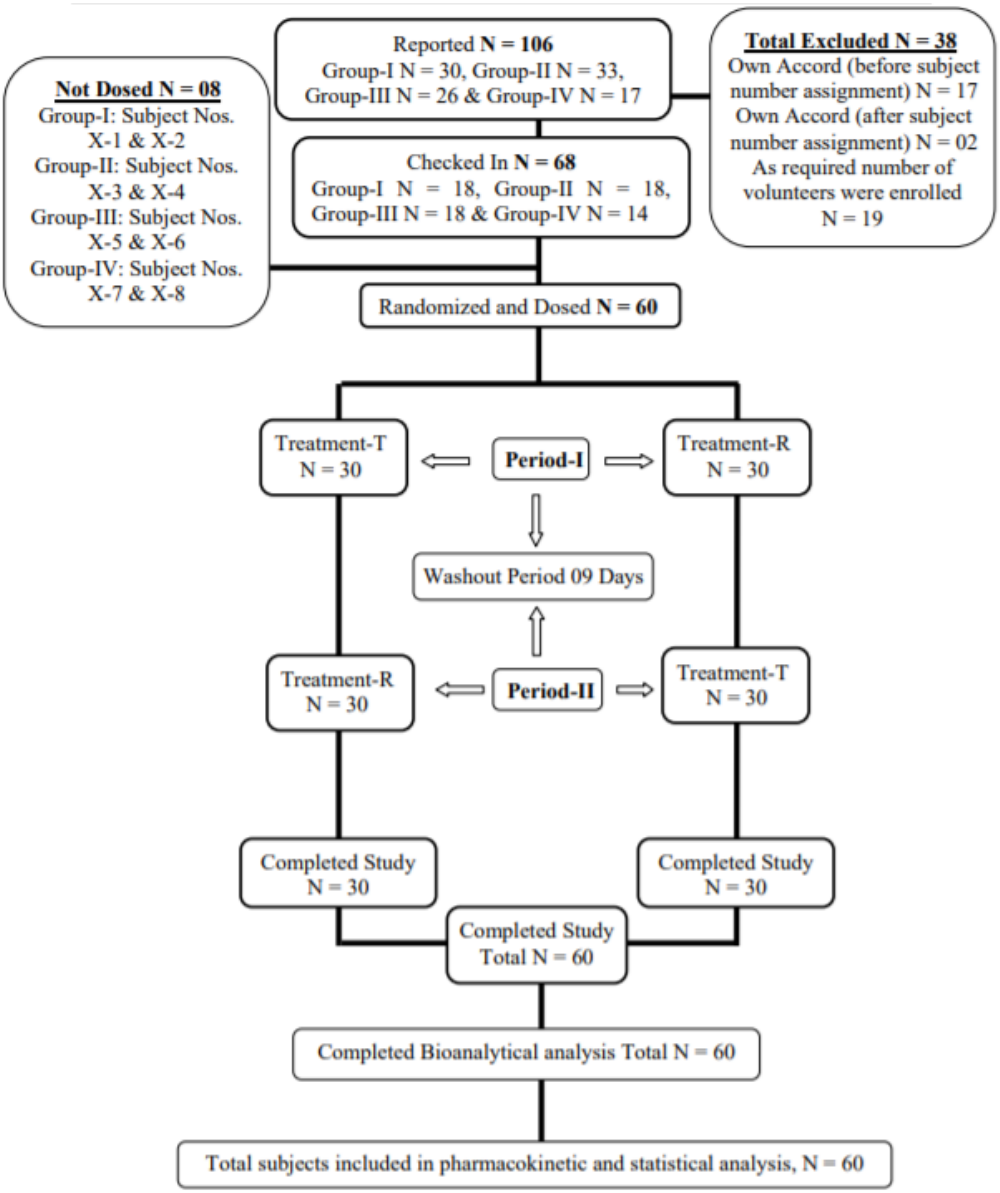
Total **55 subjects** were included in the **PK and statistical analysis**. The safety assessment includes information for all 56 subjects who were dosed at least once during this study.

Protocol deviations were associated mainly with scheduled blood sampling and concomitant medications. The blood sampling time deviations did not affect the PK analysis, which were based on actual sampling time points.

Four subjects took concomitant medication (ibuprofen, paracetamol and pheniramine maleate) to treat their adverse events (AEs). These drugs do not present interactions with the medication of the study. In addition, potentially interfering drugs have been investigated in the validation of the bioanalytical method including ibuprofen, paracetamol and pheniramine maleate without effect on the determination of fampridine.

Study No. 489-14 - Multiple-dose fasting study

Figure 4: Flow-chart Study No. 489-14



The study was conducted on Asian population. As per the protocol the **60 subjects** (male) who participated in this study were non-smokers, healthy adult human volunteers between 18 to 45 years of age (both inclusive), having BMI between 18.5 to 30 kg / m^2 (both inclusive), with normal clinical and laboratory results. The population chosen is according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1). Inclusion and exclusion criteria are acceptable and performed according to the protocol requirements. All the subjects were dosed as per the randomization.

Subjects were dosed in **four groups**.

Group-I

Dosed in Period-I: 05 April 2016 – 11 April 2016

Dosed in Period-II: 19 April 2016 – 25 April 2016

A total of 18 subjects were checked in for Period-I of the study.

On the day of check-in for Period-I, prior to check-in, one subject informed the study personnel that he did not want to continue his further participation in the study due to his personal reason. Hence, the subject discontinued from the study on his own accord. He was replaced with next available volunteer. Both the extra subjects were checked out of the facility as no more subjects discontinued / were withdrawn from the study prior to first dosing in Period-I. Hence, a total of 16 subjects were dosed in Period-I of the study and all the dosed subjects completed the clinical phase of the study successfully.

Group-II

Dosed in Period-I: 12 April 2016 – 18 April 2016

Dosed in Period-II: 26 April 2016 to 02 May 2016

A total of 18 subjects were checked in for Period-I of the study.

On the day of check-in for Period-I, prior to check-in, one subject informed the study personnel that he did not want to continue his further participation in the study due to his personal reason. Hence, the subject discontinued from the study on his own accord. He was replaced with next available volunteer. Both the extra subjects were checked out of the facility as no more subjects discontinued / were withdrawn from the study prior to first dosing in Period-I. Hence, a total of 16 subjects were dosed in Period-I of the study and all the dosed subjects completed the clinical phase of the study successfully.

Group-III

Dosed in Period-I: 10 May 2016 – 09 May 2016

Dosed in Period-II: 24 May 2016 to 23 May 2016

A total of 18 subjects were checked in for Period-I of the study. Two subjects were checked in for the study, in order to compensate for any dropouts prior to first dosing in Period-I. Both the extra subjects were checked out of the facility as none of the subjects discontinued / were withdrawn from the study prior to first dosing in Period-I. Hence, a total of 16 subjects were dosed in Period-I of the study and all the dosed subjects completed the clinical phase of the study successfully.

Group-IV

Dosed in Period-I: 11 May 2016 – 16 May 2016

Dosed in Period-II: 25 May 2016 to 30 May 2016

A total of 14 subjects were checked in for Period-I of the study. Two subjects were checked in for the study, in order to compensate for any dropouts prior to dosing in Period-I. Both the extra subjects were checked out of the facility as none of the subjects discontinued / were withdrawn from the study prior to first dosing in Period-I. Hence, a total of 12 subjects were dosed in Period-I of the study and all the dosed subjects completed the clinical phase of the study successfully.

In all the four groups, all the dosed 60 subjects completed the clinical phase of the study successfully.

Plasma samples of all the 60 subjects were analysed. Total **60 subjects** were included in the **PK and statistical analysis**.

Protocol deviations are listed and discussed, and none is considered by the investigator to have impact on the overall study outcome.

The blood sampling time deviations did not affect the PK analysis, which were based on actual sampling time points.

Two subjects took concomitant medication (ibuprofen and paracetamol) during the study to treat their AEs. These drugs do not present interactions with the medication of the study. In addition, potentially

interfering drugs have been investigated in the validation of the bioanalytical method including ibuprofen and paracetamol without effect on the determination of fampridine.

One subject took concomitant medication (Cefadroxyl) post-study since he had abnormal laboratory value (increase in white blood cell count).

Analytical methods

Study No. 487-14 - Single-dose fasting study

Pre-study and in-study validations were performed according to the requirements of the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/09). Statement on Good Laboratory Practices (GLP) compliance is provided.

Pre-study validation (method validation (MV) (I)-137-15, dated August 5, 2015)

The analytical method for the determination of Fampridine in K_2EDTA (Di Potassium Ethylene Diamine Tetraacetic Acid) human plasma over the calibration range of 0.202 to 40.251 pg/mL pg/mL was developed and validated at the Lambda Therapeutic Research Ltd., Ahmedabad, Gujarat, India.

Dalfampridine and Fampridine-d4 (ISTD) were extracted from plasma by liquid-liquid extraction method using extraction solvent. The plasma layer was flash-frozen, and the organic layer was transferred into pre-labelled tubes. The contents were then evaporated to dryness at about 40ºC (±2°C) temperature under nitrogen gas stream and reconstituted with mobile phase. The contents were then finally transferred into appropriate auto sampler vials for analysis.

The pre-study validation of the analytical method is satisfactory. The method met the acceptance criteria for all the validation parameters evaluated, demonstrating acceptable performance.

The long-term stability data of fampridine stored human plasma at -65°C ± 10°C was demonstrated for 51 days and for 369 days, respectively in K_2EDTA human plasma and it covers the 42 days maximum storage samples at -65°C ± 10°C.

The possible interference from co-administration of Cetirizine, Ibuprofen, Aspirin, Ranitidine, Diclofenac, Domperidone, Caffeine, Paracetamol and Nicotine was evaluated at the stage of bioanalytical method validation. The co-administered drugs did not show any significant interference at the retention time and transition of Fampridine and Fampridine-d4 (ISTD). It can be concluded that the quantification method is selective for the analysis of Fampridine in presence of above mentioned co administered drugs.

For the carry over investigation, representative chromatograms of extracted high sample, extracted blank plasma and extracted low sample are shown. In response to D120 list of questions (LoQ), the Applicant has provided results showing that the carry over in the blank samples following the high concentration standard is greater than 20% of the Lower Limit of Quantification (LLOQ) sample and 5% of the internal standard sample.

In response to the Rapporteur's request, the Applicant has investigated the extent of any interference caused by metabolites (3-hydroxy-4-aminopyridine and 3-hydroxy-4-aminopyridine sulphate) of the drug as well as evaluated the possibility of back-conversion of a metabolite (3-hydroxy-4-aminopyridine and 3-hydroxy-4-aminopyridine sulphate) into parent analyte by incurred sample reanalysis data.

In response to D120 LoQ regarding missing the Method validation plan for Main validation, Addendum I and Addendum II, the Applicant`s argumentation that there is no any need for a separate validation plan as the Standard Operating Procedure (SOP) method and the SOP method validation are already in place (Addendum I and Addendum II) and give a detailed insight regarding procedure to be followed at the time of conduct of Method validation, is considered acceptable.

In response to the D120 LoQ, the Applicant has provided SOP LTR.BA-05-00 and also version LTR.BA-05-03.

In-study validation (of Study No. 487-14 (Version 01), dated June 25, 2019

The plasma samples of subjects were analysed using a validated Liquid Chromatography/ Tandem Mass Spectrometry (LC-MS/MS) method for the estimation of Fampridine (Dalfampridine) in human plasma containing K_2EDTA as an anticoagulant, using 5-OH methyl tolterodine-d_{14} as an internal standard over the calibration range of 0.202 to 40.251 ng/mL at the Lambda Therapeutic Research Ltd., Ahmedabad, Gujarat, India.

Study samples total storage period: 42 days at -65±10°C C in K_2EDTA human plasma.

Calibration curve standards and quality control samples prepared during method validation No. MV (I)-137-15 were also used for project No. 487-14. Separately weighed stocks were used for the preparation of calibration curve standards and quality control samples.

The analyte and internal standard were extracted from plasma by liquid-liquid extraction method.

The calibration standards of the in-study validation are acceptable.

The quality control samples are representative of the study samples concentration.

The same instrument that was used for validation was used for samples analysis.

Certificates of analysis for reference and internal standard were included in the dossier.

The reasons for reanalysis of samples in each of the sample analysis are considered justified.

The incurred sample reanalysis confirmed the reproducibility of the method.

Twenty percent of the subject's chromatograms are presented.

According to Applicant, there was no protocol or SOP deviations during study sample analysis and during method validation.

In response to D120 LoQ, the Applicant has clarified concerns regarding analytical runs #29, #04, #15 and #25.

Study No. 488-14 - Single-dose fed study

Pre-study and in-study validations were performed according to the requirements of the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/09). Statement on GLP compliance is provided.

Pre-study validation (MV (I)-137-15, dated August 5, 2015)

Please refer to pre-study validation for previous bioequivalence study No. 487-14.

In-study validation (of Study No. 488-14 (Version 00), dated September 10, 2015

The plasma samples of subjects were analysed using a validated LC-MS/MS method for the estimation of Fampridine (Dalfampridine) in human plasma containing K_2EDTA as an anticoagulant, using 5-OH methyl tolterodine-d_{14} as an internal standard over the calibration range of 0.202 to 40.251 ng/mL at the Lambda Therapeutic Research Ltd., Ahmedabad, Gujarat, India.

Study samples total storage period: 43 days at -65±10°C C in K_2EDTA human plasma

Long-term storage stability was demonstrated: 51 days at -65±10°C C in K_2EDTA human plasma (validation report - addendum-I)

Calibration curve standards and quality control samples prepared during method validation No. MV (I)-137-15 were also used for project No. 488-14. Separately weighed stocks were used for the preparation of calibration curve standards and quality control samples.

The analyte and internal standard were extracted from plasma by liquid-liquid extraction method.

The calibration standards of the in-study validation were acceptable.

The quality control samples are representative of the study samples concentration.

The same instrument that was used for validation was used for samples analysis.

Certificates of analysis for reference and internal standard were included in the dossier.

The reasons for reanalysis of samples in each of the sample analysis are considered justified.

The incurred sample reanalysis confirmed the reproducibility of the method.

Twenty percent of the subject's chromatograms are presented.

According to Applicant, there was no protocol or significant SOP deviations during study sample analysis.

Study No. 489-14 - Multiple-dose fasting study

Pre-study and in-study validations were performed according to the requirements of the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/09). Statement on GLP compliance is provided.

Pre-study validation (MV (I)-137-15, dated August 5, 2015)

Please refer to pre-study validation for previous bioequivalence study No. 487-14.

In-study validation (of Study No. 489-14 (Version 00), dated August 19, 2016

The plasma samples of subjects were analysed using a validated LC-MS/MS method for the estimation of Fampridine (Dalfampridine) in human plasma containing K_2EDTA as an anticoagulant, using 5-OH methyl tolterodine-d_{14} as an internal standard over the calibration range of 0.203 to 40.122 ng/mL at the Lambda Therapeutic Research Ltd., Ahmedabad, Gujarat, India.

The analyte and internal standard were extracted from plasma by liquid-liquid extraction method.

Study samples total storage period: 81 days at -65±10°C C in K_2EDTA human plasma

Long-term storage stability was demonstrated: 369 days at -65±10°C C in K_2EDTA human plasma (validation report - addendum-II)

The calibration standards of the in-study validation were acceptable.

The quality control samples are representative of the study samples concentration.

The same instrument that was used for validation was used for samples analysis.

Certificates of analysis for reference and internal standard were included in the dossier.

The reasons for reanalysis of samples in each of the sample analysis are considered justified.

The incurred sample reanalysis confirmed the reproducibility of the method.

Twenty percent of the subject's chromatograms are presented in this report.

According to Applicant, there was no protocol or SOP deviations during study sample analysis.

Pharmacokinetic variables

Study No. 487-14 - Single-dose fasting study

The PK parameters for Fampridine were calculated from the plasma concentration vs. time profile by non-compartmental model using WinNonlin Professional Software Version 5.3 (Pharsight Corporation, USA).

Primary PK parameters were C_{max} (Maximum measured plasma concentration), AUC_{0-t} (Area under the plasma concentration versus time curve from time zero to the last measurable plasma concentration) and $AUC_{0-\infty}$ (Area under the plasma concentration versus time curve from time zero to infinity)

Secondary PK parameters were T_{max} (time of the maximum measured plasma concentration), λ_z (first order rate constant associated with the terminal log-linear portion of the curve), T_{lag} (time prior to the first measurable (non-zero) concentration), $t_{1/2}$ (terminal half-life) and AUC_% Extrap_obs (residual area in percentage).
PK software and method for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ estimation are considered acceptable.

Actual time of blood collection was considered for PK calculations.

The selected primary PK variables are appropriate for a single dose bioequivalence study.

Study No.488-14 - Single-dose fed study

Same as above.

Study No. 489-14 - Multiple-dose fasting study

The PK parameters for Fampridine were calculated from the plasma concentration vs. time profile by non-compartmental model using Phoenix® WinNonlin® Version 6.4 (Certara L.P.) for Fampridine.

Actual time points of the sample collection are used for the calculation of PK parameters.

Day 01, 03, 04, and 05 in each period:

Primary PK parameters: C_{pd} (minimum observed concentration prior to dosing)

Day 05 (After morning dose of day 05) and Day 06 (After morning dose of day 06) in each period:

Primary PK parameters: $C_{max,ss}$ (maximum measured plasma concentration at steady state) $C_{\tau,ss}$ (Concentration at the end of the dosing interval at steady state), $AUC_{\tau,ss}$ (Area under the concentration versus time curve during a dosing interval at steady state computed by trapezoidal rule. (Dosing interval, τ = 12 hour)).

Secondary PK parameters: $T_{max,ss}$ (time of the maximum measured plasma concentration at steady state), %Fluctuation (percentage fluctuation during steady state) and $C_{av,ss}$ (average plasma concentration at steady state)

PK software and method for ($C_{max,ss}$, $C_{\tau,ss}$ and $AUC_{\tau,ss}$) estimation are considered acceptable.

The selected primary PK ($C_{max,ss}$, $C_{\tau,ss}$ and $AUC_{\tau,ss}$) variables are appropriate for a multiple dose bioequivalence study according to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms.

Statistical methods

Study No. 487-14 - Single-dose fasting study

Statistical comparison of the PK parameters of the two formulations was carried out by Lambda Therapeutic Research Ltd. using statistical software package PROC GLM of SAS® Version 9.3 (SAS Institute Inc., USA).

Analysis of variance (ANOVA) model included Sequence, Formulation, Subject (Sequence) and Period as fixed effects. Each analysis of variance was to be included calculation of least-squares means, the difference between adjusted formulation means and the standard error associated with the difference.

An F-test was performed to determine the statistical significance of the effects involved in the model at a significance level of 5%.

The power of the study to detect 20% difference between test and reference formulations was calculated and reported for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Fampridine.

Ratio of geometric least squares means of test and reference formulations was calculated and reported for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Fampridine.

All concentration values below the LLOQ are set to zero for the PK and statistical calculations.

ANOVA, power and ratio analysis for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are calculated and reported for Fampridine.

Using two-one sided tests for bioequivalence, 90% confidence intervals (CI) for the ratio of the geometric least-squares means between drug formulations are calculated for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Fampridine.

The two formulations were classified as bioequivalent if the standard 90% CI of the PK parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) with log transformation were within the 90.00-111.11% range. The tightened acceptance range of 90.00-111.11% for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ was pre-specified in the study protocol as required for drugs with narrow therapeutic index (NTI). According to the Fampyra European Public Assessment Report, fampridine has a NTI.

The statistical software and method are considered acceptable.

Study No. 488-14 - Single-dose fed study

Statistical comparison of the PK parameters of the two formulations was carried out by Lambda Therapeutic Research Ltd. using statistical software package PROC GLM of SAS® Version 9.3 (SAS Institute Inc., USA).

The terms used in the ANOVA model were Sequence, Formulation, Subject (Sequence) and Period as fixed effects. Each analysis of variance was to be included calculation of least-squares means, the difference between adjusted formulation means and the standard error associated with the difference.

An F-test was performed to determine the statistical significance of the effects involved in the model at a significance level of 5% (alpha = 0.05).

The power of the study to detect 10% difference between test and reference formulations was calculated and reported for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Fampridine.

Ratio of geometric least squares means of test and reference formulations was calculated and reported for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Fampridine.

Intra-subject variability was to be calculated and reported for ln-transformed PK parameters C_{max},

AUC_{0-t} and $AUC_{0-\infty}$ for Fampridine.

Using two-one sided tests for bioequivalence, 90% CI for the ratio of the geometric least-squares means between drug formulations are calculated for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Fampridine.

The two formulations were classified as bioequivalent if the standard 90% CI of the PK parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) with log transformation were within the 90.00-111.11% range. The tightened acceptance range of 90.00-111.11% for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ was pre-specified in the study protocol as required for drugs with NTI.

The statistical software and method are considered acceptable.

Study No. 489-14 - Multiple-dose fasting study

Statistical comparison of the PK parameters of the two formulations was carried out by Lambda Therapeutic Research Ltd. using PROC GLM of SAS® Version 9.3 (SAS Institute Inc., USA).

C_{pd} on Days 1, 3, 4 and 5 are reported for Fampridine.

The ln-transformed PK parameters $C_{max,ss}$, $C_{\tau,ss}$ and $AUC_{\tau,ss}$ from all the groups were subjected to for Fampridine.

ANOVA model included Group, Sequence, Sequence*Group, Subject (Sequence*Group), Formulation and Period (Group) effects.

In response to D120 LoQ, the Applicant has submitted results of the exploratory analysis with the requested factors: Group, Sequence, Sequence*Group, Subject (Sequence*Group), Formulation, Group*Formulation and Period (Group). Group*Formulation effect are found to be statistically insignificant for ln-transformed PK parameters Cmax,ss (p-value: 0.6880), $C_{\tau,ss}$ (p-value: 0.5814) and AUCτ,ss (p-value: 0.8994) for Fampridine.

Repeated measure Analysis of Variance (RMANOVA) was performed on ln-transformed PK parameter C_{pd} (last three pre-dose concentrations for Day 03 to 05) for Fampridine.

An F-test was performed to determine the statistical significance of the effects involved in the model at a significance level of 5% (alpha = 0.05).

The power of the study to detect 20% difference between the test and reference formulations was calculated and reported for ln-transformed PK parameters $C_{max,ss}$, $C_{\tau,ss}$ and $AUC_{\tau,ss}$ of Fampridine.

Ratio of geometric least squares means of test and reference formulations was calculated and reported for ln-transformed PK parameters $C_{max,ss}$, $C_{\tau,ss}$ and $AUC_{\tau,ss}$ for Fampridine.

Intra-subject variability and standard deviation of reference product was calculated and reported for ln-transformed PK parameters $C_{max,ss}$, $C_{\tau,ss}$ and $AUC_{\tau,ss}$ for Fampridine.

Data of reference product from two consecutive administrations (day 05 and day 06) was used for the calculation of intra subject variability of reference product.

RMANOVA is performed on ln-transformed PK parameter C_{pd} (last three pre-dose concentrations on day 3, 4 and 5) for Fampridine.

ANOVA, power and ratio analysis for ln-transformed PK parameters $C_{max,ss}$, $C_{\tau,ss}$ and AUCτ,ss are calculated and reported for Fampridine.

Using two-one sided tests for bioequivalence, 90% CI for the ratio of the geometric least-squares means between drug formulations are calculated for ln-transformed PK parameters $C_{max,ss}$, $C_{\tau,ss}$ and AUCτ,ss for Fampridine.

The two formulations were classified as bioequivalent if the standard 90% CI of the PK parameters ($C_{max,ss}$, $C_{\tau,ss}$ and $AUC_{\tau,ss}$) with log transformation were within the 90.00-111.00% range. The tightened acceptance range of 90.00-111.00% for $C_{max,ss}$, $C_{\tau,ss}$ and $AUC_{\tau,ss}$ was pre-specified in the study protocol as required for drugs with NTI.

The statistical software and method are considered acceptable.

Results

Study No. 487-14 - Single-dose fasting study

Total **55 subjects** were included in the **PK** and **statistical analysis**.

Table 3: Descriptive statistics (arithmetic mean ± SD) of PK parameters for Fampridine (non-transformed values) (N=55)

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	3.017 (1.500 - 6.000)	3.333 (1.267 - 5.000)
C_{max} (ng/mL)	25.645 ± 4.9356	26.684 ± 5.7355
AUC_{0-t} (ng.h/mL)	298.279 ± 71.8631	302.138 ± 79.6557
$AUC_{0-\infty}$ (ng.h/mL)	302.990 ± 71.3099	306.059 ± 79.6153
λ_z (1/h)	0.159 ± 0.0171	0.165 ± 0.0164
$t_{½}$ (h)	4.421 ± 0.4937	4.230 ± 0.4308
AUC_%Extrap_obs (%)	1.685 ± 1.4507	1.371 ± 1.1649
T_{lag} (h)*	0.000 (0.000 - 0.000)	0.000 (0.000 - 0.000)

*Tmax and Tlag are represented in median (min-max) value.

Table 4: Relative Bioavailability Results for Fampridine (ln-transformed values) (N = 55)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	25.242	26.137	96.6	92.93 - 100.36	12.1	99.7
$lnAUC_{0-t}$	289.736	291.344	99.4	95.52 - 103.54	12.7	99.5
$lnAUC_{0-\infty}$	294.722	295.417	99.8	95.95 - 103.73	12.3	99.6

Table 5: ANOVA (p-values)

Parameters	ANOVA (p-value)			
	Formulation	Sequence	Period	Subject (Seq)
lnC_{max}	0.1355	0.0201	0.0106	<0.0001
$lnAUC_{0-t}$	0.8191	0.0529	0.0173	<0.0001
$lnAUC_{0-\infty}$	0.9199	0.0393	0.0182	<0.0001

Note: p-value is statistically significant if it is < 0.05.

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference with respect to the extent and rate of absorption/exposure as the 90% CI for the ln-transformed C_{max}, $AUC_{0-\infty}$ and AUC_{0-t} are within the acceptance range of 90.00 – 111.11%.

T_{max} was not observed in any of the subjects in the first sample time point. No pre-dose concentration has been detected.

The LLOQ of 0.202 pg /mL was sensitive enough to detect levels of 5% of the minimum C_{max} (0.859 pg /mL is 5% of the minimum C_{max} =17.188 pg /mL) to exclude the possibility of a relevant carry-over effect.

A significant subject (sequence) effect has been detected for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The Applicant addressed this issue and concluded that a subject (sequence) effect is frequently caused by inter-individual variations. This explanation is endorsed.

A significant sequence effect has been detected for $AUC_{0-\infty}$ and C_{max}. The Applicant addressed this issue and concluded that this sequence effect is just statistically significant and can be ignored as the study was a single dose study conducted in healthy volunteers, not comparing an endogenous substance, had an adequate washout and used appropriate design and analysis and meets bioequivalence criteria successfully. This explanation is endorsed.

In addition, a significant period effect has been detected for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. The Applicant addressed this issue and concluded that this period effect is just statistically significant and can be ignored as clinical conditions were kept identical in both the period of the study, and there were no pre-dose concentrations observed, and the decision of equivalence is based on the 90% CI by Schuirmann two one-sided test (TOST) approach which is within the acceptance criteria i.e. 90.00% to 111.11%. This explanation is endorsed.

The extrapolated AUC is not higher than 20% for any single subject.

No subject received concomitant medication during this study. One subject received medication after he withdrawn from the study.

Study No. 488-14 - Single-dose fed study

Total 55 subjects were included in **the PK and statistical analysis**.

Table 6: Descriptive statistics (arithmetic mean ± SD) of PK parameters for Fampridine (non-transformed values) (N=55)

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	5.333 (2.667 - 6.500)	5.333 (2.667 - 5.700)
C_{max} (ng/mL)	30.860 ± 4.6347	30.692 ± 4.9857
AUC_{0-t} (ng.h/mL)	316.218 ± 58.0006	311.351 ± 57.2285
$AUC_{0-\infty}$ (ng.h/mL)	319.306 ± 57.6170	314.732 ± 56.7443
λ_z (1/h)	0.159 ± 0.0142	0.159 ± 0.0127
$t_{½}$ (h)	4.393 ± 0.4065	4.388 ± 0.3619
AUC_%Extrap_obs (%)	1.033 ± 0.8292	1.148 ± 0.9384
T_{lag} (h)*	0.000 (0.000 - 0.517)	0.000 (0.000 - 0.500)

*Tmax and Tlag are represented in median (min-max) value.

Table 7: Relative Bioavailability Results for Fampridine (ln-transformed values) (N = 55)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	30.516	30.269	100.8	98.54 - 103.14	7.2	100.0
$lnAUC_{0-t}$	310.982	305.950	101.6	100.08 - 103.24	4.9	100.0
$lnAUC_{0-\infty}$	314.233	309.522	101.5	100.03 - 103.03	4.6	100.0

Table 8: ANOVA (p-values)

Parameters	ANOVA (p-value)			
	Formulation	Sequence	Period	Subject (Seq)
lnC_{max}	0.5534	0.5874	0.0009	<0.0001
$lnAUC_{0-t}$	0.0847	0.1057	<0.0001	<0.0001
$lnAUC_{0-\infty}$	0.0929	0.0935	<0.0001	<0.0001

Note: p-value is statistically significant if it is < 0.05.

Based on the statistical analysis submitted by the Applicant, the test product is equivalent to the reference with respect to the extent and rate of absorption/exposure as the 90% CI for the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are within the acceptance range of 90.00 – 111.11%.

The C_{max} at fed conditions was higher compared to the fasting conditions which is in good agreement with the reported changes for C_{max} in the literature.

T_{max} was not observed in any of the subjects in the first sample time point. No pre-dose concentration has been detected.

The LLOQ of 0.202 pg /mL was sensitive enough to detect levels of 5% of the minimum C_{max} (1.043 pg /mL is 5% of the minimum C_{max} =20.864 pg /mL) to exclude the possibility of a relevant carry-over effect.

A significant subject (sequence) effect has been detected for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. The Applicant addressed this issue and concluded that a subject (sequence) effect is frequently caused by inter-individual variations. This explanation is endorsed.

A significant period effect has been detected for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. The Applicant addressed this issue and concluded that this period effect is just statistically significant and can be ignored as clinical conditions were kept identical in both the period of the study, and there were no pre-dose concentrations observed, and the decision of equivalence is based on the 90% CI by Schuirmann TOST approach which is within the acceptance criteria i.e. 90.00% to 111.11%. This explanation is endorsed.

The extrapolated AUC is not higher than 20% for any single subject.

Study No. 489-14 - Multiple-dose fasting study

Total **60 subjects** were included in the **PK** and **statistical analysis**.

Table 9: Descriptive statistics (arithmetic mean ± SD) of PK parameters in steady-state for Fampridine (non-transformed values) (N=120 Observations)

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T (N = 120 Observations)	Reference Product-R (N = 120 Observations)
$T_{max,ss}$ (h)*	2.333 (0.667 - 5.000)	2.333 (0.667 - 5.000)
$C_{max,ss}$ (ng/mL)	33.880 ± 5.6277	33.985 ± 6.8213
$C_{\tau,ss}$ (ng/mL)	12.854 ± 4.8662	13.029 ± 4.7779
$AUC_{\tau,ss}$ (ng.h/mL)	274.561 ± 54.1428	277.261 ± 57.6838
$C_{av,ss}$ (ng/mL)	22.880 ± 4.5119	23.105 ± 4.8070
Fluctuation (%)	98.840 ± 27.6415	97.104 ± 26.3176

*T_{max} is represented in median (min-max) value.

Table 10: Relative Bioavailability Results for Fampridine (ln-transformed values) (N = 120 Observations)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Power (%)
	Test Product-T (N = 120 Observations)	Reference Product-R (N = 120 Observations)	Ratio (T/R) %		
$lnC_{max,ss}$	33.533	33.474	100.2	98.16 - 102.23	100.0
$lnC_{\tau,ss}$	12.005	12.280	97.8	92.83 - 102.96	95.2
$lnAUC_{\tau,ss}$	270.403	272.849	99.1	97.09 - 101.16	100.0

Table 11: Intra-subject Coefficient of Variation and within-subject standard deviation of reference product (S_{WR}) for Fampridine (N = 120 Observations)

Dependent	$lnC_{max,ss}$	$lnC_{\tau,ss}$	$lnAUC_{\tau,ss}$
Intra-subject CV of Reference Product-R (%)	11.0	20.5	8.7
Within-subject standard deviation of Reference Product-R (S_{WR})	0.1100	0.2030	0.0873

Table 12: ANOVA (p-values) for Study No. 489-14

Parameters	ANOVA (p-value)					
	Group	Sequence	Seq*Group	Formulation	Period (Group)	Subject (Seq* Group)
$lnC_{max,ss}$	<0.0001	<0.0001	0.0288	0.8861	0.0371	<0.0001
$lnC_{\tau,ss}$	0.0207	<0.0001	<0.0001	0.4704	0.0479	<0.0001
$lnAUC_{\tau,ss}$	<0.0001	<0.0001	<0.0001	0.4688	0.0055	<0.0001

Note: p-value is statistically significant if it is < 0.05.

The Applicant tested the achievement of steady state by measuring morning and evening C_{pd} over days 3, 4 and 5 and subsequent performing RMANOVA tests including the terms DAY and DAY*Formulation.

The effect of DAY was significant for the morning doses (p-value: 0.0024) and not for the evening doses (p-value: 0.2315). The Applicant assumed the achievement of steady state based on the effect of the interaction DAY*Formulation, which was neither significant for morning doses (p-value: 0.7629) nor for evening doses (p-value: 0.1689). In response to D120 LoQ, the Applicant has adequately justified the inclusion of Formulation as a fixed effect instead of performing separate ANOVA tests for each product as well as the use of the interaction term DAY*Formulation for the assumption that the steady state was achieved.

Based on the statistical analysis submitted by the Applicant, the test product is equivalent to the reference with respect to the extent and rate of absorption/exposure as the 90% CI for the ln-transformed $C_{max,ss}$, $C_{\tau,ss}$ and $AUC_{\tau,ss}$ were within the acceptance range of 90.00-111.00%.

The LLOQ of 0.202 pg /mL was sensitive enough to detect levels of 5% of the minimum C_{max} (1.1274 pg /mL is 5% of the minimum C_{max}=22.549 pg /mL) to exclude the possibility of a relevant carry-over effect.

A significant sequence effect (i.e. p-value < 0.05) has been detected for $C_{max,ss}$, $C_{\tau,ss}$ and $AUC_{\tau,ss}$. The Applicant addressed this issue and concluded that this sequence effect is just statistically significant and can be ignored as the study was a multiple dose study conducted in healthy volunteers, not comparing an endogenous substance, had an adequate washout and used appropriate design and analysis and meets bioequivalence criteria successfully. This explanation is endorsed.

Group, Sequence, Sequence*Group, Subject (Sequence*Group), Period (Group) effects were found to be statistically significant (i.e. p-value < 0.05) for ln-transformed PK parameters $C_{max,ss}$, $C_{\tau,ss}$ and $AUC_{\tau,ss}$ for Fampridine. The Applicant addressed this issue and concluded that these significant effects can be ignored considering the analysis approach adopted for fully replicate study design. This explanation is endorsed.

In response to D120 LoQ, the Applicant submitted results of the exploratory analysis with the requested factors: Group, Sequence, Sequence*Group, Subject (Sequence*Group), Formulation, Group*Formulation and Period (Group) effects. Group*Formulation effect were found to be not statistically significant for ln-transformed PK parameters Cmax,ss (i.e. p-value: 0.6880), $C_{\tau,ss}$ (i.e. p-value: 0.5814) and $AUC_{\tau,ss}$ (i.e. p-value: 0.8994) for Fampridine.

All other ANOVA effects were found to be not statistically significant (i.e. p-value >0.05) ln-transformed PK parameters $C_{max,ss}$, $C_{\tau,ss}$ and $AUC_{\tau,ss}$ for Fampridine.

There were one missing sample of reference product on Day-6 (reported as non-reportable) for one subject during the conduct of the study. This subject was not excluded from the PK and statistical analysis, which is in accordance with the protocol and thus acceptable.

Safety data

Study No. 487-14 - Single-dose fasting study

During the study 1 AE was reported in Period-II of the study after administration of Test Product. One subject had complaint of loose stools (2 to 3 episodes). The AE was sudden at onset, intermittent in occurrence and mild in severity. The relationship to the study drug was judged by the investigator as unlikely for the AE. The subject was withdrawn from the study on medical grounds. His AE was resolved.

There were no serious (SAE) or significant AEs during the conduct of the study. Data from this study demonstrated that the test and the reference products were well tolerated by healthy subjects, as a single dose administration.

Study No. 488-14 - Single-dose fed study

During the study 8 AEs were reported by 7 subjects. 2 AEs were reported in Period-I, 3 AEs were reported in Period-II and 3 AEs were reported during post-study safety assessment. Two subjects in the test group reported a total of 2 AEs and 5 subjects in the reference group reported a total of 6 AEs. All the AEs were classified as mild in nature. All of the AE resolved with medications. The causality assessment was judged as possible for 4 AEs and as unlikely for 4 AEs.

Out of the total reported eight 8 AEs, one AE was significant. One subject was withdrawn from the study on medical grounds due to upper respiratory tract infection. The subject was treated appropriately and was followed up until resolution. The causality assessment was judged as possible for the AE.

The post-study safety assessments included haematology and biochemistry (except random glucose, sodium, potassium and chloride). The laboratory reports were reviewed by a clinician and were found to

be clinically acceptable (including all the out of reference range reports) for all the subjects except for 2 subjects. Clinically significant abnormalities were observed for one subject (increase in white blood cell count) and for the second subject (increase in white blood cell and eosinophil count). Both subjects were followed up until resolution of their AEs.

There were no serious AEs during the conduct of the study. Data from this study demonstrated that the test and the reference products were well tolerated by healthy subjects, as a single dose administration. Although the safety profile of both products was not comparable, no difference in the safety profile can be anticipated.

Study No. 489-14 - Multiple-dose fasting study

During the study 6 AE) were reported by 5 subjects. 3 AEs were reported in Period-I, 2 AEs were reported in Period-II and 1 AE was reported during post-study safety assessment of the study.

2 AEs were reported in two subjects after administration of Reference Product and 4 AEs were reported in three subjects after administration of Test Product.

All the AEs were mild in nature. The subjects were followed up until resolution of their AEs.

The causality assessment was judged as possible for 2 AEs and as unlikely for 4 AEs.

There were no clinically significant findings in the vital signs assessment, electrocardiogram recordings or the laboratory tests in any of the subjects in the study except for one subject, who had abnormal laboratory value (increase in white blood cell count) during post-study safety assessment. AE was recorded and the subject was followed up until AE resolution.

There were no SAE or significant AEs during the conduct of the study. Data from this study demonstrated that the test and the reference products were well tolerated by healthy subjects, as a multiple dose administration. Although the safety profiles of both products were not comparable, no difference in the safety profile can be anticipated.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

Essential similarity is claimed to Fampyra 10 mg prolonged-release tablets, Biogen Netherlands B.V., The Netherlands, approved via centralised procedure on 20-07-2011 (EMEA/H/C/002097).

Fampridine is a well-known active substance with established efficacy and tolerability. A clinical overview 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 clinical data.

To support this application, the Applicant submitted three bioequivalence studies performed in 2015 and 2016. The Applicant conducted bioequivalence studies in which the PK profile of the test product Fampridine Accord 10 mg prolonged-release tablets is compared with the PK profile of the reference product Fampyra 10 mg prolonged-release tablets (Biogen Netherlands B.V.). One single dose study under fasted conditions, one single dose study under fed conditions and one multiple dose study under

fasted conditions were conducted. The choice of the reference product in the bioequivalence study has been justified. The analytical method has been adequately validated. All other concerns identified in the bioanalytical and validation reports were resolved.

According to the Applicant, competent authorities/EU inspectors have inspected the study site Lambda Therapeutic Research Ltd. In response to D120 LoQ, the Applicant has submitted inspection outcome of BfArM performed in 2014. In response to D120 LoQ, the Applicant has submitted monitoring of the clinical phase for all studies.

The first **study (487-14)** was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single, oral dose, cross-over bioequivalence study of two products of Fampridine prolonged-release tablets 10 mg carried out under fasted conditions in 56 healthy male subjects, with a screening period of 28 days prior to the dosing in period-I and with a washout period of 5 days between the successive dosing days. The design of the bioequivalence study is adequate in relation to characterization of the PK of Fampridine after oral administration. The absorption, distribution and elimination phases are all well characterized. The washout period of 5 days is considered adequate as Fampridine has an elimination half-life of 6 hours (about 4 hours in the actual study) and no pre-dose levels were detected. Out of the dosed 56 subjects, 55 subjects completed the clinical phase of the study successfully and were included in the PK and statistical analysis. One subject was withdrawn from the study on medical grounds in Period-II. Upon request, the Applicant justify the withdrawal and explanation is considered acceptable.

The statistics and PK variables are adequately described. The results of the study conclude bioequivalence with the chosen reference product with respect to the extent and rate of absorption/exposure as the 90% CI for the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within the acceptance range of 90.00-111.11% as corresponds for a drug with NTI

The second **study (488-14)** was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single, oral dose, cross-over bioequivalence study of two products of Fampridine prolonged-release tablets 10 mg carried out under fed conditions in 56 healthy male subjects, with a screening period of 28 days prior to the dosing in period-I. After an overnight fast of at least 10 hours and within 30 minutes after serving a high-fat, high calorie breakfast the subjects were administered a single 10 mg dose of the study medication with 240 ml of drinking water. The total caloric content was 937.66 kcal. There were 2 dosing periods, separated by a washout period of 7 days. The design of the bioequivalence study is adequate in relation to characterization of the PK of Fampridine after oral administration. The absorption, distribution and elimination phases are all well characterized. The washout period of 7 days is considered adequate as Fampridine has an elimination half-life of 6 hours and no pre-dose levels were detected. Out of the dosed 56 subjects, 55 subjects completed the clinical phase of the study successfully and were included in the PK and statistical analysis. One subject was withdrawn from the study on medical grounds in period-II. Upon request, the Applicant justify the withdrawal and explanation is considered acceptable.

The statistics and PK variables are adequately described. The results of the study conclude bioequivalence with the chosen reference product with respect to the extent and rate of absorption/exposure as the 90% CI for the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within the acceptance range of 90.00-111.11%.

The third **study (489-14)** was an open label, balanced, randomized, two-treatment, two-period, two-sequence, multiple oral dose, fully replicate, crossover, bioequivalence study of two products of Fampridine prolonged-release tablets 10 mg carried out under fasted conditions in 60 healthy male subjects, with a screening period of 28 days prior to the dosing in period-I. Subjects were dosed in four groups. The order of receiving Test Product-T and Reference Product-R for each subject on day 05 and day 06 of both the periods of the study was determined according to a randomization schedule.

The full replicate design with two consecutive administration of the same product after reaching steady-state is adequate in relation to characterization of the PK of Fampridine after oral administration. The washout period of 9 days is considered adequate as Fampridine has an elimination half-life of 6 hours and no pre-dose levels were detected. In all the four groups, all the dosed 60 subjects completed the clinical phase of the study successfully and were included in the PK and statistical analysis.

The Applicant tested the achievement of steady state by measuring morning and evening C_{pd} over days 3, 4 and 5 and subsequent performing RMANOVA tests including the terms DAY and DAY*Formulation. The effect of DAY was significant for the morning doses. The Applicant assumed the achievement of steady state based on the effect of the interaction DAY*Formulation, which was not significant. In response to D120 LoQ, the Applicant has adequately justified the inclusion of Formulation as a fixed effect instead of performing separate ANOVA tests for each product as well as the use of the interaction term DAY*Formulation for the assumption that the steady state was achieved.

In response to D120 LoQ, the Applicant has submitted results of the exploratory analysis with the requested factors: Group, Sequence, Sequence*Group, Subject (Sequence*Group), Formulation, Group*Formulation and Period (Group) effects. Group*Formulation effect are found to be statistically not significant for ln-transformed PK parameters Cmax,ss (p-value: 0.6880), $C_{\tau,ss}$ (p-value: 0.5814) and AUC$_{\tau}$,ss (p-value: 0.8994) for Fampridine.

The results of the study conclude bioequivalence with the chosen reference product with respect to the extent and rate of absorption/exposure as the 90% CI for the ln-transformed $C_{max,ss}$, $C_{\tau,ss}$ and AUC$_{\tau}$,ss were within the acceptance range of 90.00-111.00%.

In addition, 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.

There are no major objections for approval from the clinical point of view.

2.4.6. Conclusions on clinical aspects

A clinical overview is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional clinical data.

Based on the results of the presented bioequivalence studies, Fampridine Accord 10 mg prolonged-release tablets could be considered bioequivalent with Fampyra 10 mg prolonged-release tablets.

The treatment was well tolerated by the subjects enrolled in the study. Fampridine Accord 10 mg prolonged-release tablets, and Fampyra 10 mg prolonged-release tablets have similar safety profiles.

2.5. Risk management plan

Safety concerns

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

Pharmacovigilance plan

The PRAC and CHMP agreed that routine pharmacovigilance activities, including collection and reporting of adverse reactions, and signal detection are considered sufficient to monitor the safety of the medicinal product in the licensed indication. No additional pharmacovigilance activities are deemed necessary.

Risk minimisation measures

The PRAC and CHMP agreed that routine risk minimisation measures are considered sufficient. The safety information in the PI is aligned with the originator product.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the Applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Fampyra. The bridging report submitted by the Applicant has been found acceptable.

3. Benefit-risk balance

The chemical-pharmaceutical documentation in relation to Fampridine and finished product are generally of sufficient quality in view of the present European regulatory requirements.

This application concerns a generic version of Fampridine 10 mg prolonged-release tablets. The reference product Fampyra is indicated for the 'improvement of walking in adult patients with multiple sclerosis with walking disability (EDSS 4-7)'. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and updated upon request and considered sufficient. From a clinical perspective, this application does not contain new data on the PK and pharmacodynamics as well as the efficacy and safety of the active

substance; the Applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis in which the PK profile of the test product Fampridine Accord 10 mg prolonged-release tablets is compared with the PK profile of the reference product Fampyra 10 mg prolonged-release tablets (Biogen Netherlands B.V.). The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. One single dose study under fasted conditions, one single dose study under fed conditions and one multiple dose study under fasted conditions were conducted.

Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. PK and statistical methods applied were adequate.

The test formulation of Fampridine Accord met the protocol-defined criteria for bioequivalence when compared with Fampyra. The point estimates and their 90% CI for the parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of 90.00 to 111.11%. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Fampridine Accord is favourable in the following indication:

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

The CHMP therefore recommends the granting of the marketing authorisation, subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

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 European Medicines Agency;
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.