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Public Assessment Report

Name of the Product:

Fampridine Rontis 10 mg prolonged-release tablets

(fampridine)

Procedure number: HU/H/0642/001/DC

Marketing authorisation holder: Rontis Hellas Medical and Pharmaceutical Products S.A.

Date: 20 Dec 2020

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UPGRADE: STEPS TAKEN AFTER THE INITIAL PROCEDURE WITH AN INFLUENCE ON THE PUBLIC ASSESSMENT REPORT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Fampridine Rontis 10 mg prolonged-release tablets. The holder of the marketing authorisation is Rontis Hellas Medical and Pharmaceutical Products S.A.

The active substance is fampridine.

– Fampridine Rontis 10 mg prolonged-release tablets: Each prolonged-release tablet contains 10 mg of fampridine.

The other ingredients are:
- tablet core: hypromellose, microcrystalline cellulose, silica, colloidal anhydrous, magnesium stearate;
- film-coating: hydroxypropyl cellulose (E463), hypromellose (E464), talc (E553b), titanium dioxide (E171).

The appearance of the tablets is:
– The 10 mg prolonged-release tablets are off-white, film coated, oval biconvex 13.2 x 8.2 mm tablet with flat edge.

The prolonged-release tablets are available in packs in blisters.

Fampridine Rontis 10 mg prolonged-release tablets (further on: Fampridine Rontis) is a medicine used to improve walking in adults (18 years and over) with Multiple Sclerosis (MS) related walking disability. In multiple sclerosis, inflammation destroys the protective sheath around the nerves leading to muscle weakness, muscle stiffness and difficulty walking.

Fampridine Rontis contains the active substance fampridine, which belongs to a group of medicines called potassium channel blockers. They work by stopping potassium leaving the nerve cells, which have been damaged by MS. This medicine is thought to work by letting signals pass down the nerve more normally, which allows you to walk better.

What patients need to know before taking Fampridine Rontis

Patients must not take Fampridine Rontis if they
- are allergic to fampridine or any of the other ingredients of this medicine
- have a seizure or have ever had a seizure (also referred to as a fit or convulsion)
- have kidney problems
- are taking a medicine called cimetidine
- are taking any other medicine containing fampridine. This may increase their risk of serious side effects

Warnings and precautions

Patients must talk to their doctor or pharmacist before taking Fampridine Rontis if they
- feel aware of their heartbeat (*palpitations*)
- are prone to infections
- should use a walking aid, such as a cane, as needed
- feel dizzy or unsteady because of this medicine, this may result in an increased risk of falls
- have any factors or are taking any medicine which affects their risk of fits (*seizure*).

Patients must tell their doctor before they take Fampridine Rontis if any of these apply to them.

Children and adolescents

Fampridine Rontis should not be given to children or adolescents under the age of 18 years.

Elderly

Before starting treatment and during treatment doctor may check that patients' kidneys are working properly.

Other medicines and Fampridine Rontis

Those who are taking, have recently taken or might take any other medicines must consult their doctor or pharmacist. Patients must not take Fampridine Rontis if they are taking any other medicine containing fampridine.

Other medicines that affect the kidneys
Patients' doctor should be especially careful if fampridine is given at the same time as any medicine, which may affect how their kidneys eliminate medicines for example carvedilol, propanolol and metformin.

Fampridine Rontis with food and drink

Fampridine Rontis should be taken without food, on an empty stomach.

Pregnancy and breast-feeding

Patients must ask their doctor for advice before taking this medicine if they are pregnant, think they may be pregnant or are planning to have a baby. Fampridine Rontis is not recommended during pregnancy. Their doctor will consider the benefit of patients being treated Fampridine Rontis against the risk to their baby.
Patients should not breast-feed whilst taking this medicine.

Driving and using machines

Fampridine Rontis may have an effect on people's ability to drive or use machines, it can cause

dizziness. Patients must make sure they are not affected before they start driving or use machinery.

How to take Fampridine Rontis

The recommended dose is one tablet in the morning and one tablet in the evening (12 hours apart). More than two tablets should not be taken in a day. Between each tablet 12 hours must be left. The tablets should not be taken more often than every 12 hours.

Each tablet whole need to be swallowed with a drink of water. The tablet should not be divided, crushed, dissolves, sucked or chewed. This may increase patient's risk of side effects.

If the given Fampridine Rontis is supplied in bottles, the bottle will also contain a desiccant. The desiccant should be left in the bottle and must not be swallowed.

What to do if more Fampridine Rontis was taken that it should have been?

The doctor must be contacted immediately if too many tablets are taken. Patients should take the Fampridine Rontis box with themself if they go to see the doctor.The most likely effect in case of overdose is sweating, minor shaking (tremor), confusion, memory loss (amnesia) and fits (seizure). Other effects, which are not listed here, may be also noticed.

What to do if taking Fampridine Rontis was forgotten?

It is important not to take two tablets at once to make up for a missed dose. 12 hours between each tablet must always be left.

The doctor or the pharmacist may be asked, if any further questions on the use of this medicine are raised.

Possible side effects

Like all medicines, Fampridine Rontis can cause side effects, although not everybody gets them.

Patients must stop taking Fampridine Rontis and tell their doctor immediately, if they have a seizure.

Patients must stop taking Fampridine Rontis and see a doctor immediately, if experiencing one or more of the following allergic (hypersensitivity) symptoms: swollen face, mouth, lips, throat or tongue, reddening or itching of the skin, chest tightness and breathing problems.

Side effects are listed below by frequency:

Very Common side effects

May affect more than 1 in 10 people:

- Urinary tract infection

Common side effects

May affect up to 1 in 10 people:
- Feeling unsteady
- Dizziness
- Headache
- Feeling weak and tired
- Difficulty sleeping
- Anxiety
- Minor shaking (tremor)
- Numbness or tingling of skin
- Sore throat
- Common cold (nasopharyngitis)
- Flu (influenza)
- Difficulty breathing (shortness of breath)
- Feeling sick (nausea)
- Being sick (vomiting)
- Constipation
- Upset stomach
- Back pain
- Heartbeat that you can feel (palpitations)

Uncommon side effects

May affect up to 1 in 100 people
- Fits (seizure)
- Allergic reaction (hypersensitivity)
- Worsening of nerve pain in the face (trigeminal neuralgia)
- Fast heart rate (tachycardia)

How to store Roxampex?

This medicine does not require any special temperature storage conditions. It should be stored in the original package in order to protect from light and kept out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Fampridine Rontis 10 mg prolonged-release tablets. The procedure was finalised at 29 June 2020. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member state, CMS: Malta) concerned the generic versions of fampridine prolonged-release tablets.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for **Fampridin Rontis 10 mg prolonged-release tablets.**

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC (generic application). Therefore except for showing bioequivalence the application contained no new clinical or preclinical data, other than supporting literature where necessary.
The originator product is Fampyra 10 mg prolonged-release tablets marketed by Biogen Netherlands B.V. The first marketing authorisation for fampridine was granted on July 20th, 2011 via the centralized procedure for Fampyra.

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

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

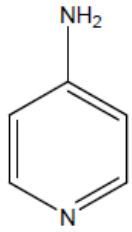
The chemical-pharmaceutical assessment report concerns the application for Marketing Authorisation via the Decentralised Procedure (DCP) for products Fampridine Rontis 10 mg prolonged-release tablets according to Article 10(1) of consolidated Directive 2001/83/EC (i.e. a generic application).
The products have been developed by Rontis Hellas Medical and Pharmaceutical Products S.A., Greece.

The reference product is Fampyra® prolonged-release tablets (containing 10 mg fampridine as active ingredient) which was the original product of Biogen Netherlands B.V., the Netherlands.

II.2 Drug substances

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: fampridine
Synonym: dalfampridine
Chemical name: 4-Aminopyridine
Structure:



Fampridine is soluble in water, methanol, acetone, tetrahydrofuran, isopropanol, acetonitrile, N,N-dimethylformamide, dimethylsulfoxide and alcohol, and soluble at pHs between 2.0 and 8.0. Fampridine does not contain a chiral centre and does not exhibit polymorphism.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the active pharmaceutical ingredient (API) is adequate.

Evidence of the structure has been confirmed by elemental analysis, UV, IR, mass, 1H NMR and 13C NMR spectrometry and XRD studies.
The impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

Fampridine is not official in the Ph.Eur. Therefore, an in-house specification has been set for the active substance. The presented specification is in accordance with the Ph.Eur. general monograph on Substances for Pharmaceutical Use and the ICH Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.
The substance complies with the requirements of the EMA guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period and storage conditions is acceptable.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim was to develop prolonged-release tablets containing fampridine as drug substance in 10 mg doses bioequivalent and pharmaceutically equivalent to the reference medicinal product the reference product Fampyra from Biogen.
A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.
As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance and composition was obtained.
Fampridine Rontis 10 mg prolonged-release tablet is an off-white, oval biconvex 13.2 x 8.2 mm film-coated tablet with flat edge.
The excipients used in the finished product are hypromellose 2208, microcrystalline cellulose, magnesium stearate, colloidal anhydrous silica; the film coating consists of hydroxypropylcellulose, hypromellose, titanium dioxide, and talc.
All excipients used comply with their respective European Pharmacopoeia monograph. Compliance of the product with the general monograph of the European Pharmacopoeia on the Products with the risk of TSE has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph.Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is OPA/Al/PVC//Al blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 2 years with no special storage conditions is approved.

The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From chemical-pharmaceutical points of view the product is approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of fampridine are well known. As fampridine is a widely used, well-known active substance, no further studies are required and the applicant provides none. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to the active ingredient, fampridine.

Overview based on literature review is appropriate.

III.2 Pharmacology

The drug product Fampridin Rontis 10 mg prolonged-release tablets contains the active substance fampridine, which a potassium channel-blocking agent that has been shown to restore conduction in focally demyelinated axons. 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.

Fampridine improves the symptoms of multiple sclerosis (MS) but does not influence the course of the disease itself. It improves conduction of action potentials in demyelinated nerve fibres and increases release of neurotransmitters in synapses and at neuromuscular junctions.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the Applicant. The pharmacokinetics of fampridine is well known and extensively described in the product information of the originator and published literature.

Like other aminopyridines, fampridine is rapidly absorbed from the gastrointestinal tract into circulation. Following oral administration of a single dose of fampridine at doses of no more than 2 mg/kg, the pharmacokinetic parameters of fampridine were similar across rat and dog, and were generally also similar to those observed in humans. Fampridine was rapidly absorbed with peak systemic exposure occurring within 1.5 hours.
No accumulation of fampridine, as demonstrated by the lack of increase in peak and total systemic exposure values (<2-fold), was observed following repeated dose administration of fampridine at multiple doses for multiple days in CD-1 mice, Sprague-Dawley rats, New Zealand White rabbits, Beagle dogs and humans. Thus, accumulation in plasma after repeated administration was not anticipated. The effect of food was only examined in dogs. Although the observed effect was small, the Cmax and AUC values were lower in fed versus fasted dogs. The compound is readily metabolised in the liver and metabolites are excreted in urine. In rat, approximately 36% of the parent drug was removed by hepatic first-pass metabolism.

Fampridine was metabolized primarily by hydroxylation, followed by sulphate conjugation. Although these metabolites were identified in all species, more extensive metabolism was determined in rats and dogs than in humans.
Fampridine mediated CYP-dependent drug-drug interactions taking place through inhibition or induction of CYP activity in humans appeared to be unlikely. Of three drugs commonly used by patients with multiple sclerosis (amitriptyline, baclofen and caffeine), only baclofen showed a significant interaction with fampridine in rats. This attenuated elimination of fampridine seen in baclofen-treated rats seemed to be irrelevant for human therapy, since it could not be substantiated by clinical data.
About 90% of the administered dose, following i.v. or oral administration, excreted in the urine. In rats and dogs, as compared with humans, the clearance rate was higher and the t1/2 was shorter; otherwise, the basic pharmacokinetic parameters of fampridine were similar between species. Elimination of fampridine was in a similar range between rats and dogs with a plasma t1/2 of 1-2 h, but was slightly prolonged in humans. The predominant route of elimination of radioactivity in rat and dog following oral administration was via urine with a negligible contribution eliminated in faeces (<2%).

III.4 Toxicology

Published information on toxicological studies with fampridine were the basis for the evaluation.
No new toxicity studies were submitted by the Applicant for the product, which is acceptable for this type of application.
In acute oral toxicity at the doses administered to dogs (up to a total dose of 5 mg/kg orally, divided into 4 equal doses) failed to cause mortality or clinical signs. Repeated dose toxicity in rats and dogs reported with NOAEL/LOAELs for the studies are 0.5/5 mg/rat and 10/20 mg/dog. Fampridine was studied in oral repeat dose toxicity studies in several animal species.

Adverse responses to orally administered fampridine were rapid in onset, most often occurring within the first 2 hours post-dose. Clinical signs evident after large single doses or repeated lower doses were similar in all species studied and included tremors, convulsions, ataxia, dyspnoea, dilated pupils, prostration, abnormal vocalization, increased respiration, and excess salivation. Gait abnormalities and hyper-excitability were also observed. These clinical signs were not unexpected and represent exaggerated pharmacology of fampridine. In addition, single cases of fatal urinary tract obstructions were observed in rats. The clinical relevance of these findings remains to be elucidated, but a causal relationship with fampridine treatment cannot be excluded.
In reproduction toxicity studies in rats and rabbits, decreased weight and viability of foetuses and offspring were observed at maternally toxic doses (9 mg/kg/day). However, no increased risk for malformations or adverse effects on fertility was noted. Studies for genotoxicity did not find any genetic toxic potential. Further, two-year dietary carcinogenicity studies of fampridine in mice and rats did not reveal carcinogenic potential.

Thus, preclinical data of fampridine reveals no special hazard for humans based on conclusive availability of toxicology data. It is concluded that fampridine can be safely used in humans according to the conditions specified in the SmPC.

III.5 Ecotoxicology/environmental risk assessment

Phase I refined environmental risk assessment was carried out for the generic product developed for oral administration, Fampridine 10 mg prolonged-release tablets.
According to the relevant guideline (EMEA/CHMP/SWP/4447/00 corr 2) the Applicant has refined Fpen by using IMS data of the five top European markets and has re-calculated the respective PECsurfacewater. The re-calculated concentration is below the limit value (0.01 μg/L) of the relevant guideline for all the considered markets, so there is no need for Phase II environmental fate and effects analysis.

Based on the refined ERA the prescribe use of the generic medicinal product, Fampridine 10 mg prolonged-release tablets does not indicate any potential environmental risk.

III.6 Discussion on the non-clinical aspects

Pharmacodynamics, pharmacokinetics and toxicology of fampridine are well-known. As Fampridine 10 mg prolonged-release tablets is a generic product there is no need for further excessive non-clinical studies. The non-clinical part of the application is thus acceptable.

From non-clinical points of view the product is approvable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Except for showing bioequivalence no new non-clinical pharmacokinetic studies were conducted by the Applicant as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended.

The application contains an adequate review of published clinical data.

IV.2 Pharmacokinetics

Absorption:
Orally administered fampridine is rapidly and completely absorbed from the gastrointestinal tract. Fampridine has a narrow therapeutic index. Absolute bioavailability of fampridine has not been assessed, but relative bioavailability (as compared to an aqueous oral solution) is 95%. The fampridine prolonged-release tablet has a delay in the absorption of fampridine manifested by slower rise to a lower peak concentration, without any effect on the extent of absorption.

When fampridine tablets are taken with food, the reduction in the area under the plasma concentration- time curve (AUC0-∞) of fampridine is approximately 2-7% (10 mg dose). The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. However, Cmax increases by 15-23%. Since there is a clear relationship between Cmax and dose related adverse reactions, it is recommended to take [Product name] without food (see section 4.2).

Distribution
Fampridine is a lipid-soluble medicinal product which readily crosses the blood-brain barrier. Fampridine is largely unbound to plasma proteins (bound fraction varied between 3-7% in human plasma). Fampridine has a volume of distribution of approximately 2.6 L/kg.
Fampridine is not a substrate for P-glycoprotein.

Biotransformation:
Fampridine is metabolised in humans by oxidation to 3-hydroxy-4-aminopyridine and further conjugated to the 3-hydroxy-4-aminopyridine sulfate. No pharmacological activity was found for the fampridine metabolites against selected potassium channels in vitro.

The 3-hydroxylation of fampridine to 3-hydroxy-4-aminopyridine by human liver microsomes appeared to be catalyzed by Cytochrome P450 2E1 (CYP2E1).

There was evidence of direct inhibition of CYP2E1 by fampridine at 30 μM (approximately 12% inhibition) which is approximately 100 times the average plasma fampridine concentration measured for the 10 mg tablet.

Treatment of cultured human hepatocytes with fampridine had little or no effect on induction of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2E1 or CYP3A4/5 enzyme activities.

Elimination:
The major route of elimination for fampridine is renal excretion, with approximately 90% of the dose recovered in urine as parent medicinal product within 24 hours. Renal clearance (CLR 370 mL/min) is substantially greater than glomerular filtration rate due to combined glomerular filtration and active excretion by the renal OCT2 transporter. Faecal excretion accounts for less than 1% of the administered dose.

Fampridine is characterized by linear (dose-proportional) pharmacokinetics with a terminal elimination half-life of approximately 6 hours. The maximum plasma concentration (Cmax) and, to a smaller extent, area under the plasma concentration-time curve (AUC) increase proportionately with dose.

There is no evidence of clinically relevant accumulation of fampridine taken at the recommended dose in patients with full renal function. In patients with renal impairment, accumulation occurs relative to the degree of impairment.

Pharmacokinetics in special patient groups

Elderly

Clinical studies of fampridine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients. Fampridine is primarily excreted unchanged by the kidneys, and with creatinine clearance known to decrease with age, monitoring of renal function in older patients should be considered (see section 4.2).

Paediatric Population

No data are available.

Patients with renal impairment:

Fampridine is eliminated primarily by the kidneys as unchanged medicinal product and therefore renal function should be checked in patients where renal function might be compromised. Patients with mild renal impairment can be expected to have approximately 1.7 to 1.9 times the fampridine concentrations achieved by patients with normal renal function. [Product name] must not be administered to patients with mild, moderate and severe renal impairment (see section 4.3).

Bioequivalence

To support the application, it was submitted as report two pivotal and one pilot single-dose bioequivalence studies with the strength of 10 mg prolonged-release tablets and one multiple dose bioequivalence study with the strength of 10 mg prolonged-release tablets.

Bioequivalence study No. 18-VIN-0714

Title of the study:
"A randomized, open-label, balanced, Single-Dose, Two-Treatment, Two-Sequence, Two-Period, Two-Way crossover oral bioequivalence study of Fampridine 10 mg prolonged-release tablets of Rontis Hellas S.A., Greece and Fampyra (Fampridine) 10 mg prolonged-release tablets of Biogen Idec Ltd., UK in healthy adult human subjects under fasting conditions."

Design of this investigation was a randomized, open-label, balanced, Single-Dose, Two-Treatment, Two-Sequence, Two-Period, Two-Way crossover oral bioequivalence study of Fampridine 10 mg prolonged-release tablets of Rontis Hellas S.A., Greece and Fampyra (Fampridine) 10 mg prolonged-release tablets of Biogen Idec Ltd., UK in healthy adult human subjects under fasting conditions. A washout period of seven days was kept between each consecutive dosing period.

Number of subjects:

– randomized and dosed: 24
– completed the study: 21
– included in the final statistical analysis: 21

Analytical method:
Objective of the bioanalytical phase of study was to estimate the Dalfampridine in K_3EDTA human plasma using Solid Phase Extraction with LC-ESI-MS/MS.

Results:

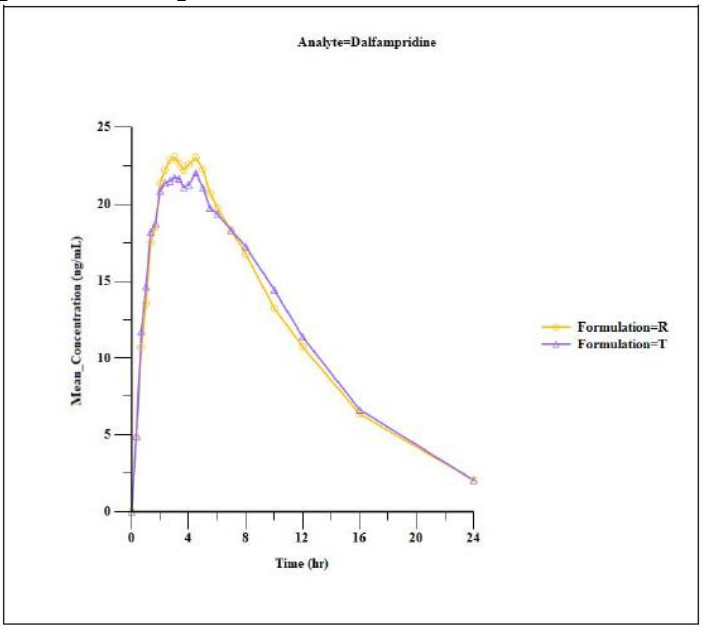
Here, after administration of single dose of Fampridine 10 mg prolonged release tablets, the geometric mean of partial $AUC_{0-\tau}$ does not cover more than 90 % of geometric mean AUC_{0-inf} for both test and reference products, hence, conditional primary parameters (AUC_{0-6} and AUC_{6-t}) were not considered as a primary pharmacokinetic parameter for assessing bioequivalence as per the protocol.

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range)

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h
Test	275.214 ± 47.1975	290.620 ± 52.6838	23.973 ± 3.6148	3.000 (1.33 - 5.00))
Reference	272.198 ± 49.3167	288.304 ± 56.0195	25.568 ± 3.7313	3.000 (1.33 - 5.00)
***Ratio (90% CI)**	101.41 (97.30% - 105.69%)	-	94.28 (89.29% - 99.56%)	-
AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.				

AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

Linear plot of mean plasma concentration vs. time for Fampridine



There was no statistical significant sequence or formulation effect found for ln-transformed $C_{max,}$ $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$, and no statistical significant period effect was found for $LnAUC_{0\text{-}t}$ and $LnAUC_{0\text{-}inf}$. The significant period effect found for LnC_{max} was not clinically relevant.

The Test to Reference ratio of geometric LSmeans and corresponding 90% confidence interval for the C_{max} and $AUC_{0\text{-}T}$ of fampridine (Dalfampridine) under fasting conditions were all within the acceptance range of 80.00 to 125.00%.

Safety:

The test and reference products were well tolerated by the subjects. Total six adverse events were reported during study. Out of them, three adverse events were reported after administration of test product and three adverse events were reported after administration of reference product. No serious adverse event occurred during the conduct of the study.

According to Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms "(AUC(0-τ) after the first dose covers less than 90% of mean AUC(0-∞)) a multiple dose study is required". According to the results of study 18-VIN-0714, the geometric mean of partial $AUC_{0\text{-}\tau}$ does not cover more than 90 % of geometric mean $AUC_{0\text{-}inf}$ for both test and reference products, thus a multiple dose study is required. This is the rational for study 19-VIN-015.

Bioequivalence study No. 19-VIN-011

Title of the study:
"A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single dose, crossover oral bioequivalence study of Fampridine 10 mg Prolonged-release tablets of Rontis Hellas S.A., Greece and Fampyra (Fampridine) 10 mg Prolonged-release tablets of Biogen Idec Ltd., UK in healthy adult human subjects under fed conditions."

Design of this investigation was a randomized, open-label, balanced, two-treatment, two-period, two-sequence, single dose, crossover oral bioequivalence study of Fampridine 10 mg Prolonged-release tablets of Rontis Hellas S.A., Greece and Fampyra (Fampridine) 10 mg Prolonged-release tablets of Biogen Idec Ltd., UK in healthy adult human subjects under fed conditions. A washout period of five days was kept between each consecutive dosing period.

Number of subjects:

– randomized and dosed: 24 (+02 extra*)
– completed the study: 23
– included in the final statistical analysis: 22

Analytical method:
Objective of the bioanalytical phase of study was to estimate the Dalfampridine in K_3EDTA human plasma using Solid Phase Extraction with LC-ESI-MS/MS.

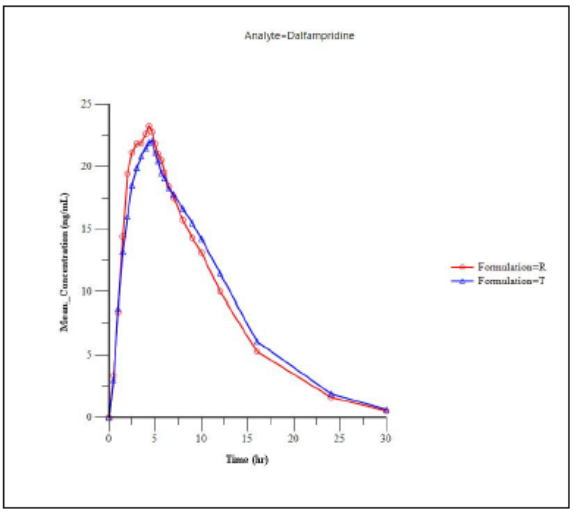
Results:

The geometric mean of partial $AUC_{0-\tau}$ does not cover more than 90 % of geometric mean $AUC_{0-\infty}$ for both test and reference products. Hence conditional primary parameters (Early partial AUC_{0-6} and terminal partial AUC_{6-t}) were not determined and considered as a primary pharmacokinetic parameter.

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range)

Treatment	**AUC_{0-t}** **ng/ml/h**	**$AUC_{0-\infty}$** **ng/ml/h**	**C_{max}** **ng/ml**	**t_{max}** **h**
Test	263.787 ± 35.8561	269.087 ± 37.0498	23.781 ± 2.5761	4.330 (3.00 - 9.00)
Reference	255.540 ± 32.0215	260.524 ± 33.0593	24.264 ± 2.7196	4.165 (1.50 - 8.00)
***Ratio (90% CI)**	103.02 (99.92 -106.21%)	103.07 (99.99 - 106.23%)	98.05 (92.80 -103.59%)	-

Linear plot of mean concentration vs. time for Fampridine



There was no statistical significant effect found for ln-transformed C_{max}, AUC_{0-t} and AUC_{0-inf}.

The Test to Reference ratio of geometric LSmeans and corresponding 90% confidence interval for the C_{max} $AUC_{0-\infty}$ and AUC_{0-T} of fampridine (Dalfampridine) under fed conditions were all within the acceptance range of 80.00 to 125.00%.

Safety:

The test and reference products were well tolerated by the subjects. One adverse event was reported during the study after administration of reference product. The adverse event was not life threatening and did not require subject`s hospitalization. No serious adverse event or clinically significant adverse event occurred during conduct of the study.

Bioequivalence study No. 19-VIN-015

Title of the study:
"A randomized, open-label, balanced, Multiple -Dose, Two-Treatment, Two-Sequence, Two-Period, Two-Way crossover oral bioequivalence study of Fampridine 10 mg prolonged-release tablets of Rontis Hellas S.A., Greece and Fampyra (Fampridine) 10 mg prolonged-release tablets of Biogen Idec Ltd., UK in healthy adult human subjects under fasting steady state conditions."

Design of this investigation was a randomized, open-label, balanced, Multiple -Dose, Two-Treatment, Two-Sequence, Two-Period, Two-Way crossover oral bioequivalence study of Fampridine 10 mg prolonged-release tablets of Rontis Hellas S.A., Greece and Fampyra (Fampridine) 10 mg prolonged-release tablets of Biogen Idec Ltd., UK in healthy adult human subjects under fasting steady state conditions. A washout period of six days was kept between each consecutive dosing period.

Number of subjects:

– randomized and dosed: 30
– completed the study: 28
– included in the final statistical analysis of $AUC_{0-\tau,ss}$, $C_{max,ss}$ and $C_{\tau,ss}$: 27

Analytical method:
Objective of the bioanalytical phase of study was to estimate the Dalfampridine in K_3EDTA human plasma using Solid Phase Extraction with LC-ESI-MS/MS.

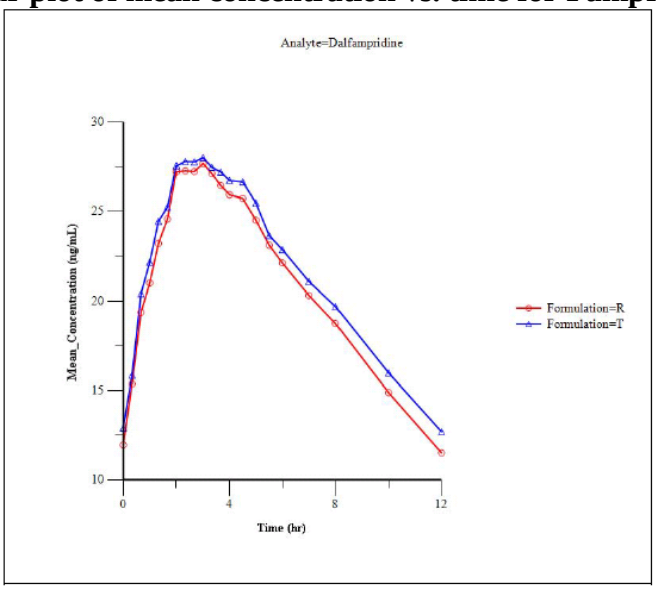
Results:

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range)

Treatment	**$AUC_{0-tau,ss}$** **ng/ml/h**	**$AUC_{0-\infty}$** **ng/ml/h**	**$C_{max,ss}$** **ng/ml**	**$C_{tau,ss}$** **ng/ml**
Test	254.890 ± 51.4613	1613.837 ± 334.5363	29.561 ± 5.9074	12.693 ± 3.1522
Reference	244.567 ± 47.4991	1642.044 ± 348.2787	29.630 ± 5.1888	11.508 ± 3.4167
***Ratio (90% CI)**	104.11 (99.45 - 108.99%)	-	99.27 (94.55 - 104.23%)	110.95 (102.39-120.23%)

Achievement of steady state was demonstrated.

Linear plot of mean concentration vs. time for Fampridine



There was no statistical significant sequence or period effect found for ln-transformed $C_{max,ss}$, $AUC_{0-\tau,ss}$ and $C_{\tau,ss}$, and no statistical significant formulation effect was found for ln-transformed $C_{max,ss}$ and $AUC_{0-\tau,ss}$. The significant formulation effect found for $LnC_{\tau,ss}$ was not clinically relevant.

The Test to Reference ratio of geometric LSmeans and corresponding 90% confidence interval for the $C_{max,ss}$ and $AUC_{0-\tau,ss}$ of fampridine (Dalfampridine) under fed conditions were all within the acceptance range of 80.00 to 125.00%.

Safety

The test and reference products were well tolerated by the subjects. A total of eight adverse events were reported during study. Out of them, three adverse events were reported after administration of test product and five adverse events were reported after administration of reference product. No serious adverse event or clinically significant adverse event occurred during conduct of the study.

Conclusion

Based on the submitted bioequivalence studies Fampridine 10 mg prolonged-release tablet of Rontis Hellas S.A., Greece is considered bioequivalent with Fampyra (Fampridine) 10 mg prolonged-release tablet of Biogen Idec Ltd., UK.

In PK studies, no new safety concern was emerged and the safety profile of the test and reference product was comparable.

IV.3 Pharmacodynamics

There were no clinical pharmacology studies performed to evaluate the pharmacodynamics of **Fampridine 10 mg prolonged-release tablets** and none are required for applications of this type.

The principal mechanism of action of fampridine is a dose-dependent block of fast, voltage-gated K+ channels (A current) in excitable membranes and in no excitable cells such as B cells or T lymphocytes.
It acts by blocking voltage-gated potassium channels, prolonging action potentials and thereby increasing neurotransmitter release at the neuromuscular junction. The mechanism of voltage-gated potassium channel (Kv) current blockade by fampridine is complicated and depends on such factors as the frequency of stimulation and the kinetic state of the channel. The current gating processes of activation, deactivation, and inactivation are all known to play a role in modulating fampridine block. For instance, in certain Kv channels, 4- AP can exhibit resting block or frequency-dependent block.
In a healthy subject without myelin deficiencies, the blockade of fast, voltage-gated potassium channels plays a minimal role in action potential conduction because the channels are covered by layers of myelin sheath. However, when myelin is destroyed, as is the case in MS, the potassium channels become exposed, shunting local circuit currents and creating impairments in the generation and conduction of action potentials. Demyelination also exposes slow potassium channels, further interrupting normal hyperpolarisation and blunting repetitive impulse release from the presynaptic terminal. Fampridine belongs to the family of mono-amino and di-amino pyridine derivatives. The drug is broadly classified as a potassium-channel blocker, with a primary mechanism of action described as dose-dependent blockade of slowly inactivating or non-inactivating voltage-gated potassium channels. Fampridine has been found to more readily enter open than closed channels, showing a preference for the cytoplasmic or intracellular side of the membrane. The drug may remain trapped in closed channels, possibly extending its duration of action. Evidence suggests that a secondary effect of fampridine is to increase neurotransmitter release by allowing larger than normal calcium influx at presynaptic terminals, which enhances neuronal communication.

IV.4 Clinical efficacy

No new efficacy or safety data have been submitted and none are required. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of fampridine.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of fampridine.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The Company has submitted a signed Summary of the PharOS' Pharmacovigilance System dated on (04.09.2018). In the amendment of it there is a signed technical agreement for pharmacovigilance services between PharOS and Rontis Hellas SA. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant GVP module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

IV.6.2.1 Summary of safety concerns

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

IV.6.2.2 Pharmacovigilance Plan

Routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Rontis's products containing fampridine.
No additional activities are needed.
Targeted questionnaires are in place for the originator's product (Fampyra; Biogen Netherlands B.V.) as part of routine pharmacovigilance for events of Seizure, Serious hypersensitivity, Urinary tract infection, Cardiac arrhythmias, Pregnancy exposure and Patients with impaired renal function so the same is requested from the MAHs of generics.

IV.6.2.3 Risk Minimisation Measures

Routine risk minimisation measures (i.e. wording in SmPC, PL and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to Rontis's products containing fampridine.
No additional activities are requested. For any further information on risk minimisation, please refer to the product information.

IV.6.3 PSUR

The requirements for submission of periodic safety update reports for these medicinal products 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.

IV.7 Discussion on the clinical aspects

The application concerns a generic product.
Fampridine 10 mg prolonged-release tablets is indicated for the improvement of walking in adult patients with multiple sclerosis with walking disability (EDSS 4-7).

To support the application, the Applicant has adequately demonstrated bioequivalence between **Fampridine 10 mg prolonged-release tablets** and Fampyra 10 mg prolonged-release tablets.

There were no objections against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present application concerns Fampridin Rontis 10 mg prolonged-release tablets, the generic version of fampridine. The applicant and the future holder of authorisation is Rontis Hellas Medical and Pharmaceutical Products S.A., Greece.

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

The application for this generic product contains an adequate review of published nonclinical and clinical data. Moreover, to support the application it was submitted as report two pivotal and one pilot single-dose bioequivalence studies with the strength of 10 mg prolonged-release tablets and one multiple dose bioequivalence study with the strength of 10 mg prolonged-release tablets.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted the marketing authorisation for Fampridin Rontis 10 mg prolonged-release tablets from Rontis Hellas Medical and Pharmaceutical Products S.A.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and user consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
IA B.I.b).1.d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	HU/H/0642/001/IA/001	no	11. 11. 2020	11. 12. 2020	approval	no