24 March 2022
EMA/216122/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Amifampridine SERB

International non-proprietary name: amifampridine

Procedure No. EMEA/H/C/005839/0000

Note

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

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List of abbreviations

BCS	Biopharmaceutics Classification System
CFU	Colony Forming Units
DSC	Differential Scanning Calorimetry
FT-IR	Fourier Transform Infrared Spectroscopy
GC	Gas Chromatography
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
KF	Karl Fischer titration
LEMS	Lambert-Eaton myasthenic syndrome
NMR	Nuclear Magnetic Resonance
Ph. Eur.	European Pharmacopoeia
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
SmPC	Summary of Product Characteristics
USP	United States Pharmacopoeia
UV	Ultraviolet
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The Applicant SERB SA submitted on 29 April 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Amifampridine SERB, 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 29 January 2021.

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 on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The Applicant applied for the following indication Symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults.

1.2. Legal basis, dossier content

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 and complete quality data

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Firdapse, 10 mg, tablets
- Marketing authorisation holder: Serb SA
- Date of authorisation: 23.12.2009
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/09/601/001

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

- Product name, strength, pharmaceutical form: Firdapse, 10 mg, tablets
- Marketing authorisation holder: Serb SA
- Date of authorisation: 23.12.2009
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/09/601/001

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:

Not applicable as this application is submitted as a duplicate version of the reference medicinal product Firdapse 10 mg tablets, under the generic legal basis.

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Scientific advice

The Applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and appointed by the CHMP were: Nevenka Trsinar Brodt

The application was received by the EMA on	29 April 2021
The procedure started on	20 May 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	9 August 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	23 August 2021
The CHMP agreed on the consolidated List of Questions to be sent to the Applicant during the meeting on	16 September 2021
The Applicant submitted the responses to the CHMP consolidated List of Questions on	25 November 2021
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the Applicant's responses to the List of Questions to all CHMP members on	29 December 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 January 2022
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the Applicant on	27 January 2022
The Applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	22 February 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all	09 March 2022

CHMP and PRAC members on	
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 Amifampridine SERB on	24 March 2022

2. Scientific discussion

2.1. Introduction

This application for a marketing authorisation of Amifampridine SERB 10 mg tablets, concerns a generic application according to Article 10(1) of Directive 2001/83/EC of the centrally authorised medicinal product Firdapse 10 mg tablets. This is the 1st generic application of the reference product Firdapse.

SERB S.A. is the Applicant of this generic marketing authorisation application and the marketing authorisation holder of the reference medicinal product. Therefore, this application is also a duplicate MA under the scope of Article 82(1) of Regulation (EC) No 726/2004. The request for a duplicate MA on the ground of public health reasons was submitted to the European Commission (EC) on 21 January 2021 and was granted on 19 March 2021.

The Applicant has applied for the same indication as the originator:

- Amifampridine SERB is indicated for symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults.

To support this application, the Applicant has justified exemption of a bioequivalence study for Amifampridine SERB 10 mg tablets as the proposed generic medicinal product is a duplicate of the reference medicinal product Firdapse 10 mg tablets. Amifampridine SERB 10 mg tablets are manufactured using the same qualitative and quantitative composition in active substance and excipients, the same pharmaceutical form and are manufactured at the same manufacturing sites and to the same quality standards as the reference medicinal product.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as tablets containing 10 mg of amifampridine. The product contains the amifampridine phosphate salt.

Other ingredients are: microcrystalline cellulose, anhydrous colloidal silica and calcium stearate.

The product is available in perforated unit dose blisters composed of thermoformed aluminium-PVC/PVDC laminate sheets as described in section 6.5 of the SmPC.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of the active substance amifampridine phosphate is pyridine-3,4-diamine, phosphate salt corresponding to the molecular formula $C_5H_{10}N_3O_4P$ ($C_5H_7N_3$ x H_3PO_4). It has a relative molecular mass of 207.1 g/mol and the following structure:

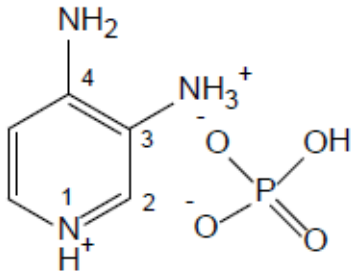

Figure 1: active substance structure

The chemical structure of amifampridine phosphate was elucidated by a combination of spectroscopic methods (^{1}H- and ^{13}C-NMR, FT-IR, UV spectroscopy), thermal analysis (Differential Scanning Calorimetry (DSC) and Thermal Gravimetric Analysis) and qualitative phosphate analysis. The solid-state properties of the active substance were measured by X-ray powder diffraction.

The active substance is a white crystalline powder. Amifampridine phosphate is soluble in water and slightly soluble in organic solvents such as dimethyl sulfoxide, glacial acetic acid and methanol.

Amifampridine phosphate has a non - chiral molecular structure.

Polymorphism has not been observed for the active substance.

2.2.2.2. Manufacture, characterisation and process controls

Amifampridine phosphate is synthesized in four main steps using a well-defined starting material with acceptable specifications. The active substance is manufactured by one manufacturing site, with additional sites involved for testing.

The manufacturing process has been described in sufficient detail and the overall control strategy and the risk mitigation measures are adequate to control the process and ensure active substance of intended and consistent quality. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Critical process parameters have been identified and proven acceptable ranges were established for those process parameters. Intermediates are isolated after each step and are subject to release testing prior to use in the next step.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on the Chemistry of Active Substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Potential genotoxic impurities were addressed; The starting material and intermediates are considered structural alerts for possible genotoxicity and are all controlled as identified impurities in the active substance specification.

Information in relation to residual solvents has been provided. Residual solvents are sufficiently controlled. Benzene, a possible contaminant in the solvents used, is adequately controlled.

Changes introduced during the development of the manufacturing process have been described in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is comparable to that produced by the proposed commercial process.

The primary packaging material complies with EC directive EC 10/2011 as amended.

2.2.2.3. Specification

The active substance specification includes tests for identity (FT-IR and identification of phosphates acc. Ph. Eur.), pH (Ph. Eur.), crystal polymorph (XRPD), appearance (visual), clarity and colour of solution (visual), solubility in water (visual), water content (KF), assay (HPLC), impurities (HPLC, 3 methods), residual solvent Ethanol (GC), palladium (ICP-MS), total aerobic count (Ph. Eur.) and yeasts and mould (Ph. Eur.).

Limits for impurities have been set below the qualification threshold according to ICH Q3A and in line with the threshold of toxicological concern according to ICH M7.

The analytical methods proposed are suitable to control the quality of the active substance and non-compendial methods have been appropriately validated in accordance with ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (10 production scale batches) of the active substance has been provided. The results are within the specifications and consistent from batch to batch.

2.2.2.4. Stability

Stability data from six production-scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for marketing for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 12 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: pH, appearance, clarity and colour of solution, loss on drying, assay and related substances. The microbiological quality (total aerobic count, yeast and mould (fungi)) will be tested at 48 months. The analytical methods used were the same as for release and were found stability indicating. All tested parameters were within the specifications and no trends or significant changes were observed.

Photostability testing following ICH guideline Q1B was performed on three batches.

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 24 months and storage conditions in the proposed container.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and pharmaceutical development

The finished product is presented as tablets containing 10 mg of amifampridine.

Amifampridine SERB is a generic of the reference medicinal product Firdapse, the Applicant's own product. Amifampridine SERB is pharmaceutically identical to the reference product. It is manufactured using the same qualitative and quantitative composition in active ingredient and excipients and has the

same pharmaceutical form. The generic medicinal product is manufactured by the same manufacturing sites and to the same quality standards as the reference medicinal product.

The formulation development is described in sufficient detail. The chosen formulation has been qualified by the use of the reference product.

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.

A bioequivalence study for Amifampridine SERB tablets was not conducted. The justification that the product is identical to the reference product in every aspect apart from the trade name (composition, pharmaceutical formulation, strength, manufacturing process, testing) was accepted. Dissolution results and dissolution profiles in accordance with the principles of the Guideline on investigation of bioequivalence have been provided. The development of the dissolution method was based on empirical knowledge. A discussion on the discriminatory power of the dissolution method has been provided. As the active substance is BCS class III with very high solubility over the physiological pH range and with rapid dissolution, the method is considered to be adequate without further justification.

There is only one known crystal form of amifampridine phosphate and therefore further discussion on polymorph control was not required. As amifampridine phosphate is freely soluble in water, a possible influence of the active substance particle size on bioavailability and dissolution performance can be excluded.

A discussion on the optimisation of manufacturing process and the critical process parameters has been presented and was found acceptable.

The primary packaging is perforated unit dose blisters (thermoformed aluminium-PVC/PVDC laminate sheets). 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.

2.2.3.2. Manufacture of the product and process controls

The manufacturing process consists of six main steps: weighing, sieving, mixing, lubrication, compression and packaging. A dry blending process and direct compression is used. The process is considered to be a standard manufacturing process.

Satisfactory information on storage and packaging material of the bulk tablets has been provided.

The critical steps of the manufacturing process have been appropriately identified (mixing, compression and packaging) and the critical steps are adequately controlled.

The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. The manufacturing process has been validated on three consecutive production scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.2.3.3. Product specifications

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form. They include identity (2 tests acc. Ph. Eur.), appearance (visual), subdivision of tablets (Ph. Eur.), disintegration (Ph. Eur.), dissolution (Ph. Eur.), content uniformity (Ph. Eur.), assay (spectrophotometric), microbiological quality (Ph. Eur.).

In line with the control strategy of the reference product, related substances are controlled in the active substance specification and formation of related substance through degradation is controlled in the shelf-life specification.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. In the risk assessment all potential sources have been considered (active substance, excipients, manufacturing equipment, container closure system). Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) Nº 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020). Based on the information provided the risk of presence of nitrosamine impurities in the finished product is negligible and therefore, no specific control measures are deemed necessary.

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 assay and impurities testing has been presented.

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

2.2.3.4. Stability of the product

Stability data from commercial batches of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH), for up to 12 months under intermediate conditions (30 ºC / 75 % 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 appearance, subdivision of tablets, resistance to crushing/hardness (Ph. Eur.), mean mass (Ph. Eur.), assay, related substances (HPLC) and microbiological quality.

During the stability studies a decrease of hardness was observed at all storage conditions. However, all results were within the specification limits. No other trends were observed.

In addition, three batches of finished product were exposed to light in accordance with the ICH Guideline on Photostability Testing of New Drug Substances and Products. The tablets are photosensitive, however the primary package protects the tablets from light exposure.

Based on available stability data, the proposed shelf-life of 3 years with the special precaution for storage "Store in the original package in order to protect from light." as stated in the SmPC (section 6.3 and 6.4) are acceptable.

2.2.3.5. 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. Amifampridine SERB is a generic of the reference medicinal product Firdapse, the Applicant's own product. Amifampridine SERB is pharmaceutically identical to the reference product having the same qualitative and quantitative composition in active ingredient and excipients and has the same pharmaceutical form. The generic medicinal product is manufactured by the same manufacturing sites using the same process and to the same quality standards as the reference medicinal product. On this basis it was considered acceptable that a bioequivalence study for Amifampridine SERB tablets was not conducted since the product is identical to the reference product in every aspect apart from the trade name.

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.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. 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 studies were submitted. This was justified by the Applicant as the introduction of Amifampridine SERB manufactured by SERB SA is considered unlikely to result in any significant increase in the combined sales volumes for all amifampridine containing products and the exposure of the environment to the active substance. Thus, the environmental risk assessment is expected to be similar.

2.3.3. Discussion on non-clinical aspects

The product Amifampridine SERB 10 mg tablets is a generic product and a duplicate of the reference medicinal product Firdapse 10 mg tablets, SERB S.A.

The Applicant has not provided additional studies and further studies are not required. This is acceptable since amifampridine is well-known active substance clinically used in humans for more than 10 years. The presented pharmacology, pharmacokinetics, and toxicology data are in line with the requirements for generic products. The review of the presented literature data did not provide any additional information relative to the nonclinical safety profile of amifampridine. It can be concluded that the safety of amifampridine remains unchanged.

The non-clinical aspects of the SmPC are in line with the SmPC of the reference medicinal product (Firdapse SmPC, 2020). As a precaution, the following statement has been added to section 6.6 of the SmPC:

Any unused product or waste material should be disposed of in accordance with local requirements. The wording in SmPC is considered acceptable.

Based on the presented environmental risk assessment data of Firdapse and the extreme rarity of the disease and low prevalence of LEMS in Europe (i.e., 1:100,000 inhabitants), it can be concluded that an increase in environmental exposure of amifampridine is not expected after the introduction of a generic, but rather the product already available on the market will be replaced and in those member states where the introduction of a generic may increase market access, shall have a negligible impact on the environment as consumption of amifampridine remains similar since the first introduction to the market. No additional studies need to be performed. Thus, the justification provided by the Applicant for the omission of the environmental risk assessment is considered acceptable and it is in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00).

2.3.4. Conclusion on the non-clinical aspects

There are no objections to approval of Amifampridine SERB 10 mg tablets from a non-clinical point of view.

2.4. Clinical aspects

The proposed generic product Amifampridine SERB is a duplicate of the reference medicinal product Firdapse, is manufactured using the same qualitative and quantitative composition in active substance and excipients, the same pharmaceutical form, and both are manufactured at the same manufacturing sites. Therefore, new clinical studies are neither required nor submitted. This product is identical in all aspects apart from the name to the reference product Firdapse 10 mg tablets with the active substance amifampridine phosphate, which is the Applicant's own product approved in the European Union EU since 23 December 2009 (Marketing authorisation number EU/1/09/601/001) under the centralised procedure for the symptomatic treatment of LEMS in adults.

Since the initial marketing authorisation under exceptional circumstances was granted for Firdapse (amifampridine phosphate tablets) on 23 December 2009, post-approval clinical commitments as Specific Obligations (SOBs) relating to the safety and efficacy of Firdapse were conducted during annual re-assessments, some of which led to SmPC updates to reflect the available clinical information. On 18 September 2020, the CHMP adopted the 10th annual re-assessment report (EMEA/H/C/001032/S/0066) on efficacy and safety of Firdapse in LEMS with a new SOB and approved by the EC on 18 November 2020. On 23 March 2021, the MAH applied for 11th annual re-assessment of the marketing authorisation under exceptional circumstances on efficacy and safety of Firdapse in LEMS (EMEA/H/C/001032/S/0071) and CHMP adopted a positive opinion recommending the granting of a marketing authorisation on 22 July 2021. The review of the postmarketing data along with the scientific published literature concerning efficacy and safety of the product in patients with LEMS confirmed its positive benefit-risk balance in the

approved indication(s).

The clinical overview is adequate and covers the pharmacology, efficacy, and safety of the product.

As this is a generic abridged application and a duplicate of the reference product marketing authorisation, no bioequivalence study with the reference medicinal product Firdapse 10 mg tablets has been carried out. The clinical data in support of the Amifampridine SERB 10 mg tablets application are identical to the up-to-date clinical data of the Firdapse 10 mg tablets, which has been assessed and approved (including all post-marketing procedures stated above). The present application is based on published data available since the initial marketing authorisation of Firdapse 10 mg tablets that support the SmPC.

Relevant for the assessment is the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1).

LEMS is an ultra-rare disease in which patients have muscle weakness because of a failure of the nerves to transmit electrical impulses to the muscles with a worldwide prevalence estimated between 1/250 000 and 1/333 300 (Orphanet Database). Firdapse was designated an orphan medicinal product on 18 December 2002 and was withdrawn from the Community Register of designated orphan medicinal products in December 2019 at the end of the 10-year period of market exclusivity.

Amifampridine blocks voltage-dependent potassium channels, thereby prolonging pre-synaptic cell membrane depolarisation. Prolonging the action potential enhances the transport of calcium into the nerve ending. The resulting increase in intra-cellular calcium concentrations facilitates exocytosis of acetylcholine-containing vesicles, which in turn enhances neuromuscular transmission. It improves muscle strength and resting compound muscle action potential amplitudes with an overall weighted mean difference of 1.69 mV (95% CI 0.60 to 2.77).

The pharmacodynamic profile of amifampridine has been studied for a range of doses. A prospective, placebo-controlled, randomised study in 26 patients with LEMS reported clinical efficacy for amifampridine at the standard recommended maximum dose of 60 mg/day (Sanders et al 2000). Two further studies in a total of 57 patients with LEMS have reported data from higher doses of amifampridine. McEvoy et al 1989 reported data from a short-term study in 12 patients with LEMS, which demonstrated that administration of amifampridine at doses up to 100 mg/day for a period of 3 days was effective in treating the autonomic and motor symptoms of LEMS. Sanders et al 1998 presented data on efficacy and safety of amifampridine treatment at doses up to 100 mg/day in 45 patients with LEMS who were treated for an average of 31 months. Therefore, in exceptional circumstances higher doses up to a maximum of 80 mg/day may be of benefit when given with the appropriate safety monitoring. It is recommended that dose titration from 60 mg/day to 80 mg/day is performed in 5 mg increments every 7 days. Upward dose titration should be discontinued if any adverse reaction or ECG abnormality is observed.

The effect of a single dose of 30 mg or 60 mg of amifampridine phosphate was used to evaluate the pharmacokinetic-QTc relationship of amifampridine concentration on cardiac repolarization exposure in healthy volunteers. This evaluation was conducted in a Phase 1, double-blind, randomized, crossover study to define the ECG effects of amifampridine phosphate at these doses compared to placebo and moxifloxacin (a positive control) in healthy men and women who are slow acetylators (n=52). There was no effect of amifampridine phosphate on heart rate, atrioventricular conduction or cardiac depolarization as measured by the heart rate, PR and QRS interval durations. No subjects developed new clinically relevant ECG morphological changes following administration of amifampridine phosphate. No effect was observed of amifampridine phosphate on cardiac repolarization as assessed using the QTc interval.

2.4.1. Discussion on clinical aspects

This application is an identical (duplicate) version of the reference medicinal product Firdapse 10 mg tablets under the generic legal basis. The Applicant is also the marketing authorisation holder for the reference product Firdapse 10 mg tablets.

According to the justification submitted by the Applicant, Amifampridine SERB 10 mg tablets has the same qualitative and quantitative composition in active substance and excipients, the same pharmaceutical form and are manufactured by the same process and on the same manufacturing sites as the reference medicinal product Firdapse 10 mg tablets. Therefore, the proposed product is considered bioequivalent to the reference product according to the Guideline of Investigation of Bioequivalence as they are pharmaceutically equivalent, and their bioavailability is univocally the same. This justifies that the product is exempt from bioequivalence studies and no further data are required for clinical studies. The Applicant's justification for non-submission of bioequivalence study is thus considered acceptable.

The efficacy and safety of the active substance amifampridine is well documented for the reference medicinal product Firdapse 10 mg tablets. The Applicant has provided bibliographical data to address this section. The available efficacy and safety data are appropriately reflected in the SmPC.

A positive benefit/risk ratio comparable to the reference medicinal product Firdapse 10 mg tablets can be concluded.

2.4.2. Conclusions on clinical aspects

There are no objections to approval of Amifampridine SERB 10 mg tablets from a clinical point of view.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 1: Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Seizures Food-drug interaction
Important potential risks	Movement disorders Cardiac toxicity including QTc prolongation. Peripheral vascular disorders/Raynaud's phenomenon Respiratory disorders including bronchospasm. Hepatotoxicity Serious gastrointestinal conditions Risk of nerve sheath tumour development (Schwannoma in rats)
Missing information	Limited information on use in patients with renal impairment Lack of information on use in patients with hepatic disease Lack of information on use during pregnancy and lactation Lack of information on potential drug-drug interactions (DDI) (including QTc prolonging drugs, seizure threshold reducing drugs, atropinic and cholinergic drugs, and depolarizing and nondepolarizing muscle relaxants) Lack of photosafety data

2.5.2. Pharmacovigilance plan

Routine pharmacovigilance activities are considered adequate to monitor the safety of the medicinal product.

Some additional pharmacovigilance activities are ongoing/completed with the originator products. However, those will not be requested or obligations for this generic application.

2.5.3. Risk minimisation measures

In line with the reference product, the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication

The safety information in the PI is aligned to the reference medicinal product.

Routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product. No additional are deemed necessary.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.1 is acceptable

2.6. Pharmacovigilance

2.6.1. 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.

2.6.2. 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

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the Applicant and has been found acceptable for the following reasons:

- The proposed MAH of Amifampridine SERB is the same as the MAH of reference product Firdapse (EMEA/H/C/001032), the Package leaflet will be identical to that of the reference product with regards to the content (apart from the product name) and layout. Therefore, the User Testing performed for Firdapse that has been reviewed in the original MAA is relevant for the current initial MAA

3. Benefit-risk balance

This application is an identical (duplicate) version of the reference medicinal product Firdapse 10 mg tablets under the generic legal basis. The reference product Firdapse 10 mg tablets is indicated for symptomatic treatment of LEMS in adults.

No nonclinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient.

From a clinical perspective, this application does not contain new data on the pharmacokinetics 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 is considered sufficient.

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

The originator product was authorised under exceptional circumstances, with the specific obligation of submitting yearly updates on any new information concerning efficacy and safety of the product in patients with LEMS. The CHMP agreed that this specific obligation should not be imposed on this application.

4. Recommendations

Outcome

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

Symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults

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 marketing authorisation holder (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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.