# Summary of Risk Management Plan (RMP)

Fampyra® (Fampridine)

Biogen Switzerland AG

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# SUMMARY OF THE RISK MANAGEMENT PLAN (RMP) FOR FAMPYRA (FAMPRIDINE)

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of Fampyra is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation/ Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please not that the reference document which is valid and relevant for the effective and safe use of Fampyra in Switzerland is the "Arzneimittelinformation/ Information sur le medicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Biogen Switzerland AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Fampyra.

## Overview of disease epidemiology

Multiple sclerosis (MS) is a condition affecting the central nervous system. In MS, inflammation destroys the protective sheath around the nerves leading to symptoms such as muscle weakness, muscle stiffness, and difficulty walking. MS usually starts in people between 20 and 40 years of age and affects approximately twice as many women than men.

The total number of people having MS worldwide is estimated to be 2 to 2.5 million. It is estimated that in Europe 93 out of every 100,000 persons have MS. Of those, approximately 45% will have difficulty walking.

## Summary of treatment benefits

Fampyra is a medicine to improve walking in adults with walking difficulties due to MS. At present, there is no other medication approved for this indication.

Fampyra stops potassium from leaving the nerve cells damaged by MS, improving the signals passing down the nerve and allowing patients to walk better. Fampyra does not "cure" walking difficulties, but clinical studies show that in some patients, it can improve walking speed.

In previously conducted phase 3 clinical studies, excluding ENHANCE, that enrolled 916 patients who walk 2 to 10 times slower than a typical healthy person, about one-third of patients treated with the approved dose of Fampyra (10 mg BID) had a faster walking speed compared to patients treated with placebo, within a few weeks of starting Fampyra.

In the completed study 218MS305 (ENHANCE), 633 patients were analysed and it showed statistically significant improvements in patient-reported and quantitative outcome measures related to walking, balance, and function in daily life of patients with MS. These results confirm

that fampridine treatment results in clinically meaningful improvements in walking for patients with MS who have a pre-existing walking disability. This additional evidence of benefit is accompanied by an unchanged safety profile.

## Unknowns relating to treatment benefits

In studies conducted in EU and Canada, nearly all patients were Caucasian and aged between 18 and 64 years. Patients not Caucasian or younger than 18 or older than 65 years were not studied.

## Summary of safety concerns

### Important identified risks

| Risk | What is known | Preventability |
|---|---|---|
| Risk of fits (seizures) | Fits have been reported uncommonly (up to 1 in 100 people) in patients taking Fampyra. | Patients should not receive Fampyra<br>- If they are known to have seizures or have past history of seizures<br>- if they have kidney problems<br>- Caution is recommended when using Fampyra in patients who have any factors or are taking any medicines which affect their risk of seizure |
| Risk of serious allergic reactions (hypersensitivity reactions) | Serious allergic reactions have been reported uncommonly (up to 1 in 100 people) in patients taking Fampyra. | Patients with known allergy to Fampyra or any other ingredients of this medicine should not take Fampyra.<br>Patients who have allergic reactions to Fampyra should stop taking Fampyra and see their doctor immediately, and should not restart.<br>Special attention should be given to patients within the first week of Fampyra treatment and in patients who have a previous history of allergies to medicines. |
| Risk of Urinary tract infections (UTIs) | Very common reports of UTIs have been reported in patients taking Fampyra. | Drinking adequate amounts of liquids, frequently urinating to empty the bladder and good hygiene practices will all reduce the risk of a UTI. |

| Risk | What is known | Preventability |
|---|---|---|
| Risk of interaction with medicines that affect excretion through the kidneys ('OCT2 inhibitors') | Fampyra may interact with these medicines which may affect excretion of Fampyra and increase the amount of drug in the body | Fampyra should not be used at the same time as medicines known as OCT2 inhibitors, for example, cimetidine. |
| Risk of heart rhythm disorders | Common reports (affecting up to 1 in 10 people) of heartbeat that you can feel (palpitations) and uncommon reports (may affect up to 1 in 100 people) of fast heart rate (tachycardia) have been reported in patients taking Fampyra. Heart rhythm disorders have been reported at high doses of Fampyra. | Patients should inform their doctor or pharmacist if they feel aware of their heartbeats (palpitations).<br>Fampyra should be administered with caution to patients with symptoms of heart rhythm disorder as there is limited safety information available in these patients.<br>Patients should not take more than the recommended dose of Fampyra. |

## Important potential risks

| Risk | What is known (Including reason why it is considered a potential risk) |
|---|---|
| Potential risk of interaction with medicines that are called 'OCT2 substrates' | Special attention should be given if Fampyra is used at the same time as any medicine that may affect how the kidneys eliminate medicines for example, metformin, carvedilol and propranolol. |
| Potential risk of interactions with medicines that are known to lower the seizure threshold (and thus increase the risk for seizures) | If Fampyra is used at the same time as medicines that may increase the risk of seizure themselves, the risk of seizures with Fampyra may be increased. |

## Missing information

| Risk | What is known |
|---|---|
| Limited information on children and teenagers | Children and teenagers were not included in the studies. However, the number of people with MS in this age group is small. It is also unlikely that many children and teenagers with MS patients in this age group will have severe enough walking difficulties to need treatment with Fampyra. |
| Limited information on patients aged >65 years | Most patients included in the studies were less than 65 years old. As the kidney function tends to get worse with age and Fampyra is removed from the body by the kidneys, it is recommended that the kidney function is checked in elderly patients before and during treatment with Fampyra. |
| Limited information on use in women who are pregnant | There is no study information on female MS patients who received Fampyra during pregnancy. Use of Fampyra during pregnancy is not recommended. |
| Limited information in patients with kidney problems | The experience of the Fampyra use in patients with kidney problems is small. Patients with kidney problems may be at greater risk for seizures. Therefore, Fampyra should not be used in patients with kidney problems. |
| Unknown if there could be an | It is not known if Fampyra may interact with medicines used to treat epilepsy |

| Risk | What is known |
|---|---|
| interaction with medicines used to treat epilepsy which have an effect on sodium-potassium current | although there are published studies to suggest that this is unlikely. |
| Limited information on long-term use of Fampyra | There is still limited information on the long-term use of Fampyra. |

## Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) that provides physicians, pharmacists, and other health care professionals with details on how to use the medicine and the risks and recommendations for minimizing them. An abbreviated version of this in a lay language is also provided for use by patients in the form of the the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

There are no additional risk minimization measures.

## Planned post authorisation development plan

| Study/activity (including study number) | Objectives | Safety concerns/ efficacy issue addressed | Status | Planned date for submission of (interim and) final results |
|---|---|---|---|---|
| Post authorisation safety study 218MS401 (LIBERATE) Fampridine Observational Study (Category 3) | To collect additional safety data and to characterise the utilisation patterns of fampridine in clinical practice | Incidence rate of seizures and other AEs of interest, utilisation patterns of fampridine. | Study ongoing. | Final study report submission planned for Q4 2019 |
| Study RD7.5 D-ER012010 | To evaluate the effect of a dose lower than 10 mg BID in subjects with renal impairment | Use of fampridine in patients with renal impairment | Completed | Final report submitted. |
| Preclinical study on rat granulosa cells | To identify the concentration of $IC_{50}$ of progesterone secretion in cultured rat granulosa cells. | To address potential concern that fampridine may have an effect on steroidogenesis in humans | Completed | Final report submitted in June 2013 |

| Study/activity (including study number) | Objectives | Safety concerns/ efficacy issue addressed | Status | Planned date for submission of (interim and) final results |
|---|---|---|---|---|
| Clinical trial<br>Phase 2 exploratory study (218MS205 [MOBILE])<br>(Category 2) | To assess the effect of treatment with fampridine (BIIB041) 10 mg BID on walking ability and balance in subjects with MS | Data from this study will also be used to assess safety of fampridine in an unselected population, including those with cardiovascular diseases. | Completed | Final study report submitted with annual renewal January 2014 |
| Clinical trial<br>Phase 4 market access study<br>218MS403 (ENABLE)<br>(Category 4) | To assess the effect of long-term fampridine (BIIB041) 10 mg BID on quality of life as reported by subjects with MS in an open-label, multicentre study | To assess the effect of long-term treatment with fampridine on quality of life | Completed | Final study report submitted with annual renewal January 2014 |
| 218MS301 Canadian Extension Study | To evaluate the safety and tolerability of oral fampridine in an open-label extension study among Canadian subjects with MS who participated in Acorda extension trials (n=36) | To assess the long-term safety and tolerability of oral fampridine in Canadian subjects with MS | Completed | Final study report submitted with annual renewal January 2014 |
| Post Authorisation Safety Study on Adherence to Renal Testing Recommendation in the Fampyra EU SmPC (Routine Risk Minimization Measure) Among Fampyra-treated Patients with Multiple Sclerosis (MS) in Europe (Retrospective observational post authorisation safety cohort studies) | To provide information about the frequency of renal testing and the distribution of the renal function test values in order to understand the degree of adherence to the risk minimisation measures for the product | To assess the effectiveness of the risk minimisation measure of renal function evaluation recommendation in the Fampyra SmPC | Completed | Final study report submitted with PSUR no.7 |

| Study/activity (including study number) | Objectives | Safety concerns/ efficacy issue addressed | Status | Planned date for submission of (interim and) final results |
|---|---|---|---|---|
| Clinical trial<br>Phase 3 long-term confirmatory Study (218MS305 [ENHANCE])<br>(Category 2) | To investigate a broader primary endpoint clinically meaningful in terms of walking ability and to further evaluate the early identification of responders in order to guide further treatment | To assess the safety and tolerability of fampridine 10 mg BID over a 24-week treatment period. | Completed | Final report submitted Q4 2016 |
| Clinical trial<br>DER-401 | To evaluate the safety and efficacy of 2 doses of oral fampridine tablets (5 mg and 10 mg BID) in patients with MS in a multicentre, randomized, double-blind, placebo-controlled, parallel-group study | To evaluate the efficacy of 2 doses of fampridine (5 mg and 10 mg BID) at the approximate time of peak plasma concentration, in patients with MS. | Completed | Submitted December 2012. |
| Clinical trial<br>AMP-MS-1008 | To evaluate the effects of fampridine withdrawal on gait and balance parameters in subjects with MS in an open-label, proof of concept study | To determine changes in overall gait as well as in multiple gait and balance parameters after withdrawal of fampridine in subjects who were considered responders to treatment (defined as an improvement on the T25FW between an off-drug and on-drug evaluation prior to entry into the study). | Completed | Submitted on 18 January 2013 |

**Studies which are a condition of the marketing authorization**

Phase 2 study 218MS205 (MOBILE) and Phase 3 long term confirmatory Study 218MS305 (ENHANCE) were required under the conditions of the marketing authorisation.

# Summary of changes to the Risk Management Plan over time

## Major changes to the Risk Management Plan over time

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| 5.0 | March 2011 | | Other significant updates are:<br>The MAH proposed the commitment to conduct a preclinical seizure threshold study fulfilled.<br>The nonclinical safety specification has been re-written to improve the flow of the section as well as the terminology typically used by the MAH.<br>The RMP has been updated with the results of a study using a lower dose (7.5 mg) of Fampyra in patients with renal impairment.<br>The section of the RMP about Potential for Misuse for Illegal Purposes has been updated with the results from two nonclinical studies (CMT-011-001 and MPI 1471-006). |
| 5.1 | August 2012 | Important identified risk of "hypersensitivity" added | RMP part of a Type II variation (EMEA/H/C/002097/II/0010) |
| 5.2 | December 2012 | Important identified risk of "hypersensitivity" was changed to "serious hypersensitivity reactions" | RMP part of a Type II variation (EMEA/H/C/002097/II/0010)<br>Other significant updates are:<br>Deadline to submit the full study report of the Steroidogenesis study (Q2 2013) has been updated<br>Post-Authorisation Experience section updated with FDA MedWatch Safety communication about the risk of seizures in patients with MS<br>Acorda DER-401 study<br>Comments from the assessment of RMP v5.1 |
| 6.0 | October 2012 | Important identified risk of "hypersensitivity" added | Other significant updates are:<br>Comments from the assessment of RMP v5.0 |
| 7.0 | March 2013 | UTI changed from "Important missing information" to "important identified risk" | Other significant updates are:<br>RMP transferred to a new template according to GVP Module V – Risk management systems<br>Comments from the assessment of RMP v6.0 |
| 8.0 | September 2013 | Interactions with (medicinal) products that may lower the seizure | Other significant updates are:<br>Comments from assessment of RMP v7.0 |

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| | | threshold have been moved from important missing information to important potential risk.<br>Lack of efficacy has been added as important missing information.<br>The important potential risk of Effect on steroidogenesis was removed following the completion of nonclinical study in cultured rat granulosa cells, which demonstrated that inhibition of progesterone secretion would not be expected to occur in MS patients taking Fampridine.<br>Exposure during lactation has been removed as important missing information as not considered an important safety concern.<br>Important missing information of 'potential interactions with renally secreted drugs' has been removed as overlap with interactions with OCT 2 inhibitors (important identified risk) and OCT2 substrates (important potential risk). | |
| 9.0 | March 2014 | | Other significant updates are:<br>The RMP has been updated with the results of Phase 2 study MOBILE and Phase 4 study ENABLE.<br>Exposure data have been updated.<br>AEs data have been updated.<br>Comments from assessment of RMP v8.0 |
| 10.0 | March 2015 | | Other significant updates are:<br>The RMP has been updated with follow up forms of the targeted questions on cardiac arrhythmias, renal function evaluation and assessment of response to fampridine therapy for post marketing reports.<br>The results of the post authorisation safety studies, the CPRD study and the German MS study have been included.<br>Exposure data have been updated.<br>Comments from assessment of RMP v9.0 and PSUR no.6 |
| 10.1 | August 2015 | | Other significant updates are:<br>Comments from assessment of RMP v.10.0 - the RMP has been updated with a |

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| | | | targeted pregnancy follow-up questionnaire (Annex 7f – Fampyra Pregnancy Queries).<br>The 218MS401 Fampridine Pregnancy Exposure Registry and related information has been removed.<br>Biogen 218MS304 (MOTION) study included.<br>Table VI.1.2 Table of ongoing and planned additional pharmacovigilance studies/ activities in the Pharmacovigilance Plan is now the same as Table III.5.1. |
| 10.2 | September 2015 | | Other significant updates are:<br>The targeted pregnancy follow-up questionnaire was updated according to PRAC updated assessment report comments. |
| 11.0 | October 2016 | Updated information on completed study ENHANCE<br>Removed Lack of efficacy from the missing information section based on ENHANCE data<br>Removed obsolete information from the RMP | Results from Study 218MS305 (ENHANCE) included.<br>Due date for 218MS304 (MOTION) CSR amended from Q2 2016 to Q3 2017.<br>Due date for 218MS401 (LIBERATE) final study report amended from Q1 2018 to Q3 2021. |
| 11.1 | February 2017 | None | Summary of risk minimisation activity table updated, QPPV details updated |
| 12.0 | July 2017 | Removed study 218MS304 (MOTION - Japan) from the RMP as per new GVP guidelines<br>Updated details and milestones for proposed early termination of 218 MS401 (LIBERATE) study<br>Moved Important potential risk of cardiovascular disorders to important identified risk | Study 218MS304 (MOTION) is a Multicenter, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of Oral Prolonged-Release Fampridine in Japanese Subjects with Multiple Sclerosis Followed by an Open-Label Safety Extension.<br>Due date for 218MS401 (LIBERATE) final study report amended from Q3 2021 to Q4 2019. |
| 12.1 | July 2017 | Reinstated Cardiovascular disorders under the Important potential risk | The request to move from potential to identified, was made during the ongoing PSUR assessment procedure. It is not yet final. |

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| 13.0 | December 2017 | Cardiovascular disorders risk renamed to Cardiac arrhythmias, and upgraded to important identified risk.<br>Updated clinical trial and post-marketing exposure data.<br>Removed the commitment to submit annual progress reports for Study 218MS401 (LIBERATE) | Based on the final PSUR 09 assessment report<br>Updated clinical trial and post-marketing exposure data.<br><br>Given that the study is being closed early and the planned CSR submission is in Q4 2019, the EMA Rapporteurs have agreed that no annual progress report is needed in 2018. |

CPRD = Clinical Practice Research Datalink; FDA = Food and Drug Administration; MAH = marketing authorisation holder; OCT2 = organic cation transporter 2; PRAC = Pharmacovigilance Risk Assessment Committee; REMS = Risk Evaluation and Mitigation Strategies; RMP = risk management plan.