Summary of Risk Management Plan (RMP)

Skyclarys™ (Omaveloxolon)

Biogen Switzerland AG

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Summary of the Risk Management Plan (RMP) for Skyclarys™ (Omaveloxolon)

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 Skyclarys™ 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 note that the reference document which is valid and relevant for the effective and safe use of Skyclarys™ in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (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 Skyclarys™.

Summary of the Risk Management Plan for Skyclarys

This is a summary of the RMP for Skyclarys. The RMP details important risks of Skyclarys, how these risks can be minimized, and how more information will be obtained about Skyclarys's risks and uncertainties (missing information).

Skyclarys's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Skyclarys should be used.

This summary of the RMP for Skyclarys should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which are part of the European public assessment report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Skyclarys's RMP.

I. The Medicine and What It Is Used For

Skyclarys is authorized for the treatment of FA in adults and adolescents aged 16 years and older It contains omaveloxolone as the active substance and it is given orally.

Further information about the evaluation of Skyclarys's benefits can be found in Skyclarys's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Skyclarys, together with measures to minimize such risks and the proposed studies for learning more about Skyclarys's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about undesirable effects is collected continuously and regularly analyzed, including Periodic safety update report (PSUR) assessment, so that immediate action can be taken, as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Skyclarys is not yet available, it is listed under "missing information" below.

II.A. List of Important Risks and Missing Information

Important risks of Skyclarys are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Skyclarys. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term safety of the medicine).

List of Important Risks and Missing Information

List of important risks and missing information	
Important identified risks	None
Important potential risks	Drug-induced liver injury Congestive heart failure
Missing information	Use in pregnancy Long-term safety

II.B. Summary of Important Risks

Important potential risk: Drug-induced liver injury	
Evidence for linking the risk to the medicine	Among patients treated with Skyclarys in the randomized, double-blind, placebo-controlled study, adverse reactions of aminotransferase elevations included: ALT increased in 37.3% of patients, AST increased in 21.6% of patients, and GGT increased in 5.9% of patients. One patient (2%) was discontinued for aminotransferase elevation >8× the ULN, as prespecified in the study protocol. The incidence of elevations of ALT or AST above 5x and 3x the ULN was 16% and 31%, respectively, in

	patients treated with Skyclarys. Laboratory evaluations identified 69% of patients with aminotransferase elevations that were less than 3× the ULN. These were generally transient and reversible, with maximal values occurring within the first 12 weeks of treatment. Mean values generally decreased towards baseline levels with continued treatment or after interruption in therapy.
Risk factors and risk groups	Patients with pre-existing hepatobiliary disease, acute viral infections affecting the liver, and patients taking concomitant medications known to be associated with transaminase elevations are at risk for development of transaminase elevation.
Risk minimisation measures	Routine risk minimization measures: SmPC section 4.4. PIL section 2 and 4. SmPC section 4.4: ALT, AST, and bilirubin should be monitored prior to initiation of omaveloxolone monthly during the first 3 months of treatment, and periodically thereafter as clinically indicated. If ALT or AST increases to > 5 × the ULN, omaveloxolone should be immediately discontinued and liver function tests should be repeated as soon as possible. (See SmPC section 4.4). PIL section 2: If you have problems with your liver, your doctor may decide to change the dose or not start treatment with Skyclarys. Your doctor will decide on whether to discontinue Skyclarys if liver problems develop. PIL section 4: Based on your blood tests, your doctor may tell you that you have high liver enzymes. Your doctor will decide on treatment and whether Skyclarys should be continued. Restricted medical prescription Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: An observational, multinational, post-marketing registry of omaveloxolone-treated patients with Friedreich's ataxia

Important potential risk: Congestive heart failure	
Evidence for linking the risk to the medicine	Congestive heart failure has not been reported in patients with FA treated with omaveloxolone. In a randomized study in patients with type 2 diabetes associated with Stage 4 CKD, adjudicated heart failure events were reported in 96/1088 patients (8.8%) randomized to a structural analog of omaveloxolone with a similar mechanism of action, vs 55/1097 patients (5.0%) randomized to placebo. The excess in heart failure events

	occurred within the first 4 weeks after beginning treatment and were often preceded by evidence of sodium retention and fluid overload. Elevated baseline BNP levels (>200 pg/mL) and pre-existing heart failure were identified as the risk factors contributing to the excess in observed heart failure events. This phenomenon occurred specifically in the setting of type 2 diabetes mellitus and Stage 4 CKD with a structural analog of omaveloxolone.
Risk factors and risk groups	Patients with type 2 diabetes mellitus and Stage 4 CKD with high baseline BNP levels and history of symptomatic congestive heart failure are at a potential risk for the development of congestive heart failure with omaveloxolone use.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4. PIL sections 2 and 4 SmPC section 4.4: Patients should be advised of the signs and symptoms of congestive heart failure associated with fluid overload, such as sudden weight gain (≥1.4 kg in one day or ≥2.3 kg in one week), peripheral oedema, and shortness of breath. If signs and symptoms of fluid overload develop, BNP (or NT proBNP) should be monitored and managed according to standard clinical guidance. Treatment with Skyclarys should be interrupted during fluid overload management. If fluid overload cannot be appropriately managed, treatment with Skyclarys should be discontinued. Per clinical judgment, more frequent monitoring of patients with a recent hospitalization for fluid overload due to underlying cardiomyopathy, diabetic stage IV CKD, or other etiologies is strongly recommended. PIL section 2: Your doctor will also test for BNP (B-type natriuretic peptide, a blood test for heart problems) before you start taking Skyclarys. Contact your doctor immediately if you have sudden weight gain, swelling of legs, ankles, or feet, or shortness of breath, which may be signs or symptoms of heart problems while taking Skyclarys. Your doctor will decide on treatment and whether Skyclarys should be continued. PIL section 4: Based on your blood tests, your doctor may tell you that you have increased BNP (a marker for heart problems). Your doctor will decide on treatment and whether Skyclarys should be continued. Restricted medical prescription Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: An observational, multinational, post-marketing registry of omaveloxolone-treated patients with Friedreich's ataxia

Missing information: Use in pregnancy	
Risk minimisation measures	Routine risk minimization measures: SmPC section 4.6. PIL section 2 SmPC section 4.6: Skyclarys should not be used during pregnancy or in women of childbearing potential not using contraception. Patients should use effective contraception prior to starting treatment with Skyclarys, during treatment, and for 28 days following discontinuation of treatment. Skyclarys may decrease the efficacy of hormonal contraceptives (see section 4.5). Advise patients to avoid concomitant use with combined hormonal contraceptives (eg, pill, patch, ring). Counsel females using hormonal contraceptives to use an alternative contraceptive method (eg, non-hormonal intrauterine system) or additional non-hormonal contraceptive (eg, condoms) during concomitant use and for 28 days after discontinuation of Skyclarys. Skyclarys should not be used while breast-feeding. PIL section 2: You should not take Skyclarys if you are pregnant, think you may be pregnant, or are planning to have a baby. Tell your doctor immediately if you become pregnant while you are being treated with Skyclarys. Using Skyclarys can reduce the effectiveness of hormonal birth control. You should use a different method of birth control, such as a non-hormonal IUD (intrauterine device) or barrier contraceptives such as condoms. A reliable method of birth control should be used during Skyclarys treatment and for 28 days after stopping treatment with Skyclarys. Talk to your doctor about the most suitable birth control for you. Do not breast-feed your baby while you are being treated with Skyclarys. Restricted medical prescription Additional risk minimization measures: None

Missing information: Long-term safety	
Risk minimisation measures	Routine risk minimization measures: None Additional risk minimization measures: None

Additional pharmacovigilance activities	Additional pharmacovigilance activities: An observational, multinational, post-marketing registry of omaveloxolone-treated patients with Friedreich's ataxia

II.C. Post-Authorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

There are no current studies which are conditions of the marketing authorization or specific obligation of Skyclarys.

II.C.2. Other Studies in Post-Authorization Development Plan

Reata is proposing an observational, multinational, post-marketing registry of omaveloxolone-treated patients with FA for 5 years which will provide longitudinal safety data after commercial launch. Reata will work in close collaboration with the Friedreich's Ataxia Research Alliance (FARA) to use the data collection infrastructure set up for the Clinical Outcome Measures in FA-Global Clinical Consortium (FA-GCC) natural history studies. The safety registry will evaluate the long-term safety of omaveloxolone in patients with FA in the real-world setting and to further characterize the safety concerns of the important potential risks of DILI and CHF. The study will also capture reasons and timing of omaveloxolone treatment interruptions, discontinuations, and drug overdose. The protocol will be established and submitted for review to the health authority for feedback prior to the initiation of the registry. The registry is proposed to include subjects on commercial omaveloxolone. This will provide long-term data. Proposed size of the registry is 300 total subjects prescribed omaveloxolone. The safety data will be communicated to the health authority on a yearly basis.