Summary of Risk Management Plan (RMP)

Qalsody™ (tofersen)

Biogen Switzerland AG

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Summary of the Risk Management Plan (RMP) for Qalsody™ (tofersen)

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 minimise them.

The RMP summary of Qalsody™ 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 Qalsody™ 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 Qalsody™.

Summary of Risk Management Plan for Qalsody (tofersen)

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

Qalsody's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Qalsody should be used.

This summary of the RMP for Qalsody 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 is part of the European Public Assessment Report (EPAR).

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

I. The medicine and what it is used for

Qalsody is authorised for the treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene (see the SmPC for the full indication). It contains tofersen as the active substance, and it is given solution for intrathecal injection (one vial contains 100 mg tofersen).

Further information about the evaluation of Qalsody's benefits can be found in Qalsody's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

Measures to minimise 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 authorised 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 (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute ***routine risk minimisation*** measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including 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 Qalsody is not yet available, it is listed under "missing information" below.

II.A List of important risks and missing information

Important risks of Qalsody are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Qalsody. 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 (e.g., on the long-term use of the medicine):

List of important risks and missing information	
Important identified risks	• Myelitis and/or radiculitis • Increased intracranial pressure and/or papilloedema
Important potential risks	• None
Missing information	• None

II.B Summary of important risks

This section presents a summary of important identified risks, important potential risks and missing information.

Important Identified Risk(s)	
Myelitis and/or radiculitis	
Evidence for linking the risk to the medicine	Events consistent with inflammation in the central nervous system, including myelitis and radiculitis, have occurred in participants receiving tofersen in clinical trials. Whilst the mechanisms of these inflammatory events and the relationship between the laboratory abnormalities and these events are not well understood, myelitis in the general population is an uncommon clinical diagnosis. Therefore, the occurrence of these events in a relatively small population in the study is unusual and a possible causal relationship with tofersen cannot be excluded.
Risk factors and risk groups	There are no known risk factors for the development of myelitis and/or radiculitis in tofersen-treated participants.

Important Identified Risk(s)	
Risk minimisation measures	***Routine risk minimisation measures:*** • SmPC Sections 4.4 and 4.8. • PIL Sections 2 and 4. • Legal status: Prescription only medicine ***Additional risk minimisation measures:*** • None
Additional pharmacovigilance activities	***Additional pharmacovigilance activities***: • Study 233AS102 • Study 233AS401 See Section II.C of this summary for an overview of the post-authorisation development plan.
Increased intracranial pressure and/or papilloedema	
Evidence for linking the risk to the medicine	Reports of increased intracranial pressure and/or papilloedema have been observed in participants receiving treatment with tofersen, but not in the placebo group. The hypothetical mechanism is related to CNS inflammation. There is a temporal relationship with tofersen. Untreated, chronic papilloedema can lead to progressive visual field loss in the form of visual field defects, nerve fiber bundle defects, and even blindness.
Risk factors and risk groups	All of the increased intracranial pressure and/or papilloedema events occurred in participants receiving 100 mg tofersen. None of them were from lower dosage cohorts. There were no patient-level risk factors that have been identified.
Risk minimisation measures	***Routine risk minimisation measures:*** • SmPC Sections 4.4 and 4.8 • PIL Sections 2 and 4 • Legal status: Prescription only medicine ***Additional risk minimisation measures:*** • None
Additional pharmacovigilance activities	***Additional pharmacovigilance activities***: • Study 233AS102 • Study 233AS401 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Potential Risk(s)
None

Missing Information
None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are specific obligations in the context of a marketing authorisation under exceptional circumstances:

233AS102: An Extension Study to Assess the Long-Term Safety, Tolerability, Pharmacokinetics, and Effect on Disease Progression of BIIB067 Administered to Previously Treated Adults with Amyotrophic Lateral Sclerosis Caused by Superoxide Dismutase 1 Mutation

Purpose of the study: This study is an extension of Study 233AS101. The extension study will allow collection of PK and PD data during dose interruption and resumption, providing information on the dynamic behavior of the system. This information will supplement PK and PD data collected in Study 233AS101 for the purpose of creating models of the exposure-response relationship. These models will be used to simulate and assess the PD profiles under various dosing regimens and will inform the dose levels and frequencies to be tested in future studies. The primary objective of the study is to evaluate the long-term safety and tolerability of BIIB067 in participants with SOD1-ALS. The secondary objective is to evaluate the PK, PD, biomarker effects, and efficacy of BIIB067 administered to participants with ALS and confirmed SOD1 mutation.

233AS401: An observational registry-based study to evaluate the long-term safety of tofersen in patients with SOD1-ALS.

Purpose of the study: The primary objectives of this study will be to describe demographic and clinical characteristics of SOD1-ALS patients at baseline and stratified by tofersen treatment status and estimate the incidence of SAEs among all participants and stratified by tofersen treatment status, including serious neurologic events previously reported in clinical trial participants (e.g., myelitis, radiculitis, aseptic meningitis, increased intracranial pressure and/or papilloedema).

233AS303 (ATLAS): A phase 3 randomized, placebo-controlled study in clinically presymptomatic adults with a confirmed SOD1 mutation.

Purpose of the study: This study is to investigate if initiation of tofersen in presymptomatic SOD1-ALS patients can delay or prevent emergence of clinically manifest ALS.

Integrated Analysis of Variant-Specific Survival

Purpose of the study: Descriptive analyses of disease duration (survival) by SOD1 variant-type in tofersen-treated (Studies 101/102; disease registries vs. untreated patients (disease registries, natural history datasets/literature)

Combined data from:

- Study 101 (A, B, C)
- Study 102
- Disease registries (ALS/MND-NHC and Precision-ALS)
- Natural history datasets/literature

II.C.2 Other studies in post-authorisation development plan

None.