Risk Management Plan (RMP) Summary

for

Givlaari® (Givosiran)

Givlaari, 189mg/ml, Injektionslösung

Zl-Nr. 67895

Alnylam Switzerland GmbH

Document version: 1.0

Document date: May 2021

Based on EU RMP version 1.0 (data lock point: 31 January 2019)

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 Givlaari® 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 that is valid and relevant for the effective and safe use of Givlaari® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Alnylam Switzerland GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Givlaari®.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AHP	Acute hepatic porphyria
AIP	Acute intermittent porphyria
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESRD	End-stage renal disease
EU	European Union
OLE	Open-label extension
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TBILI	Total bilirubin
ULN	Upper limit of normal

SUMMARY OF THE RISK MANAGEMENT PLAN FOR GIVLAARI

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

Givlaari's Information for Health Care Professionals and its Information for Patients give essential information to healthcare professionals and patients on how Givlaari should be used. They can be found at www.swissmedicinfo.ch.

This summary of the RMP for Givlaari 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 safety concerns or changes to the current ones will be included in updates of Givlaari's RMP.

I. The medicine and what it is used for

Givlaari is authorized for treatment of Acute Hepatic Porphyria (AHP) in adult and adolescent patients. It contains givosiran as the active substance and it is given by injection under the skin (subcutaneous injection).

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

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Givlaari, together with measures to minimize such risks and the proposed studies for learning more about Givlaari'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 Summary of Product Characteristics (SmPC) addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The medicine's legal status; the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including in the Periodic Safety Update Report 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 Givlaari is not yet available, it is listed under "missing information" below.

There are no *additional risk minimization* measures for Givlaari in Switzerland at this time.

II.A List of Important Risks and Missing Information

Important risks of Givlaari are risks that need special risk management activities to further investigate or minimize 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 Givlaari. 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 longer-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	• Hepatic Effects • Renal Effects • Pancreatitis
Missing information	• Longer-term safety (>3 years) • Use in patients with moderate or severe hepatic impairment • Use in patients with end-stage renal disease or on dialysis • Use in pregnant or lactating women and effects on pregnancy outcomes • Carcinogenicity

II.B Summary of Important Risks and Missing Information

Important Identified Risks: None	
Important Potential Risk: Hepatic (Liver) Effects	
Evidence for linking the risk to the medicine	In toxicity studies in animals, minor and reversible changes in the liver and minimal-to-mild elevations in liver enzymes (transaminases) were seen at high doses. In clinical studies, transaminase elevations were observed more frequently in the givosiran group compared to placebo. These mostly occurred in the first 3 to 5 months of treatment with the majority resolving during continued dosing. Due to pre-defined stopping rules in the protocol, one patient with ALT>8xULN discontinued treatment, and one patient with ALT>5xULN interrupted treatment and restarted givosiran at a lower dose of 1.25 mg/kg once monthly. There have been no reports of transaminase (ALT and AST) >3×ULN concurrent with total bilirubin>2×ULN on givosiran, and no cases of hepatitis or Hy's law.

Important Identified Risks: None	
Important Potential Risk: Hepatic (Liver) Effects	
Risk factors and risk groups	AHP is associated with liver disease, including transaminase elevations, fibrosis, cirrhosis and primary liver cancer. Iron overload from chronic hemin administration is also a risk factor for hepatic effects.[a,b,c]
Risk minimization measures	Routine risk communication: • The effect of givosiran on serum transaminases are described in the Special warnings and precautions for use Section 4.4 and Undesirable effects (Section 4.8) of the SmPC and in Section 2 and Section 4 of the Package Leaflet. Routine risk minimization activities recommending specific clinical measures to address the risk: • Liver function tests should be monitored prior to initiating treatment, monthly for the first 6 months, and as clinically indicated thereafter as described in Special warnings and precautions for use Section 4.4 of the SmPC • Interruption or discontinuation should be considered for clinically relevant transaminase elevations as per Special warnings and precautions for use Section 4.4 of the SmPC • In patients with clinically relevant transaminase elevations who have dose interruption and subsequent improvement in transaminase levels, dose resumption at 1.25 mg/kg once monthly could be considered as described in Posology and method of administration (Section 4.2) of the SmPC. • There are limited data on efficacy and safety of the lower dose, particularly in patients who previously experienced transaminase elevations. There are no data on sequentially increasing the 1.25 mg/kg dose to the 2.5 mg/kg dose after dose interruption for transaminase elevations (see section 4.8), as per Special warnings and precautions for use (Section 4.4) of the SmPC. Other routine risk minimization measures beyond the Product Information: • Legal status: Prescription-only medication
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Hepatic effects will be monitored and further characterized in the ongoing OLE studies (ALN-AS1-002 and ALN-AS1-003), and the Company Sponsored AHP Registry.

References: [a]Schmitt C, Lenglet H, Yu A, Delaby C, Benecke A, Lefebvre T, et al. Recurrent attacks of acute hepatic porphyria: major role of the chronic inflammatory response in the liver. J Intern Med. 2018 Jul;284(1):78-91.
[b]Stewart MF. Review of hepatocellular cancer, hypertension and renal impairment as late complications of acute porphyria and recommendations for patient follow-up. J Clin Pathol. 2012 Nov;65(11):976-80.
[c]Willandt B, Langendonk JG, Biermann K, Meersseman W, D'Heygere F, George C, et al. Liver Fibrosis Associated with Iron Accumulation Due to Long-Term Heme-Arginate Treatment in AIP: A Case Series. 2015:77-81.

Important Potential Risk: Renal (Kidney) Effects	
Evidence for linking the risk to the medicine	In givosiran clinical studies, renal (kidney) adverse events, including worsening chronic kidney disease were observed more frequently in the givosiran group compared to placebo. Mild increases in serum creatinine and decrease in eGFR have also been observed with givosiran treatment, which resolved or stabilized with ongoing dosing. It is possible that these changes may correlate with changes in blood pressure observed with givosiran treatment. Therefore, the overall impact of givosiran treatment on renal function has not been fully characterized.
Risk factors and risk groups	Hypertension (high blood pressure) is a major risk factor associated with impaired renal function. Chronic kidney disease and hypertension are reported to occur in >50% of symptomatic AIP patients.[a]
Risk minimization measures	Routine risk communication: • The effect of givosiran on renal function is described in the Special warnings and precautions for use Section 4.4 and Undesirable effects (Section 4.8) of the SmPC and in Section 2 and Section 4 of the Package Leaflet. Routine risk minimization activities recommending specific clinical measures to address the risk: • Progression of renal impairment has been observed in some patients with pre-existing renal disease. Careful monitoring of renal function during treatment is required in such cases, as described in the Special warnings and precautions for use (Section 4.4) of the SmPC Other routine risk minimization measures beyond the Product Information: • Legal status: Prescription-only medication
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Reports related to renal function will be monitored and further characterized in the ongoing OLE studies (ALN-AS1-002 and ALN-AS1-003) and the Company Sponsored AHP Registry.

References: [a] Pallet N, Mami I, Schmitt C, Karim Z,Francois A. High prevalence of and potential mechanisms for chronic kidney disease in patients with acute intermittent porphyria. Kidney International. 2015;88:386-95.

Important Potential Risk: Pancreatitis	
Evidence for linking the risk to the medicine	Across the givosiran clinical program, two cases of pancreatitis have been reported in givosiran-treated patients, both considered unlikely related to givosiran due to the presence of gallbladder sludge or gallstones. Elevations in lipase and amylase were observed in both givosiran and placebo treatment groups, with a higher-grade severity observed more frequently in the placebo group than in the givosiran group.

Important Potential Risk: Pancreatitis	
	Pancreatic dysfunction has been reported in patients with AHP including elevations in amylase or lipase, acute and chronic pancreatitis, and a higher frequency of gallstones.[a,b,c] The potential role of givosiran treatment in pancreatitis has not been established.
Risk factors and risk groups	Gallstones and gallbladder disease are major risk factors for the development of pancreatitis. Gallstones and pancreatitis may be increased in the AHP population.[a,b,c]
Risk minimization measures	Routine risk communication: • Not Applicable Routine risk minimization activities recommending specific clinical measures to address the risk: • Not Applicable Other routine risk minimization measures beyond the Product Information: • Legal status: Prescription-only medication
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Reports indicative of pancreatitis will be monitored and further characterized in the ongoing open label extension studies (ALN-AS1-002 and ALN-AS1-003) and the Company Sponsored AHP Registry.

References: [a] Bonkovsky HL, Maddukuri VC, Yazici C, Anderson KE, Bissell DM, Bloomer JR, et al. Acute porphyrias in the USA: features of 108 subjects from porphyrias consortium. Am J Med. 2014 Dec;127(12):1233-41.
[b] Corden MH, Frediani J, Xu F, Liu QY, Chen SE, Bissell DM, et al. An 18-Year-Old With Acute-on-Chronic Abdominal Pain. Pediatrics. 2018 May;141(5).
[c] Stinton LM, Myers RP,Shaffer EA. Epidemiology of gallstones. Gastroenterol Clin North Am. 2010 Jun;39(2):157-69, vii.

Missing Information: Longer-Term Safety (>3 Years)	
Risk minimization measures	Routine risk communication: • A summary of the safety profile of givosiran in the clinical development program is provided in the Undesirable effects (Section 4.8) of the SmPC.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Long-term safety will be evaluated as part of the ongoing OLE Study ALN-AS1-002, in addition to the Company Sponsored AHP Registry.

Missing Information: Use in Patients with Moderate or Severe Hepatic Impairment	
Risk minimization measures	Routine risk communication: • Information on the absence of data in patients with moderate and severe hepatic impairment is included in the Posology and method of administration section 4.2 and Pharmacokinetic properties Section 5.2 of the SmPC.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Use in patients with moderate or severe hepatic impairment will be evaluated as part of the Company Sponsored AHP Registry.

Missing Information: Use in Patients with ESRD or on Dialysis	
Risk minimization measures	Routine risk communication: • Information on the absence of data in patients with ESRD and patients on dialysis is included in the Posology and method of administration section 4.2 and Pharmacokinetic properties Section 5.2 of the SmPC.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Use in patients with ESRD or on dialysis will be evaluated as part of the Company Sponsored AHP Registry.

Missing Information: Use in Pregnant or Lactating Women and Effects on Pregnancy Outcomes	
Risk minimization measures	Routine risk communication: • Information on the limited clinical data in pregnant women and no clinical data in lactating women is included in the Fertility, pregnancy and lactation (Section 4.6) of the SmPC, with a cross-reference to nonclinical data on embryo-fetal development, lactation, and fertility in the Preclinical safety data (Section 5.3) sections of the SmPC. Routine risk minimization activities recommending specific clinical measures to address the risk: • Advice is provided to evaluate the benefits and risks of treatment with givosiran during pregnancy and breastfeeding for the mother and infant, and the mother's clinical need for givosiran in the Fertility, pregnancy and lactation (Section 4.6) of the SmPC and section 2 of the Package Leaflet.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Use in pregnancy or lactation and effects on pregnancy outcome will be evaluated as part of the Company Sponsored AHP Registry.

Missing Information: Carcinogenicity	
Risk minimization measures	Routine risk communication: • Information is provided in the Preclinical safety data (Section 5.3) of the SmPC, that givosiran did not exhibit a genotoxic potential *in vitro* and *in vivo*, and that animal studies have not been conducted to evaluate the carcinogenic potential of givosiran. Routine risk minimization activities recommending specific clinical measures to address the risk: • NA.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: A 104-week carcinogenicity study in rats is ongoing, therefore this study has been included as missing information until the study results are available.

II.C Post-authorization Development Plan

II.C.1 Studies that are conditions of the marketing authorization

There are no studies that are conditions of the marketing authorization in Switzerland or specific obligations of Givlaari.

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

- **Study ALN-AS1-002:**

Study ALN-AS1-002 is an ongoing, multicenter, open-label extension study designed to evaluate the long term safety and clinical activity of givosiran in AIP patients who have completed a previous early study of givosiran. Sixteen patients transitioned to this study with different initial doses of givosiran and eventually switched to 2.5 mg/kg monthly. In this study patients will receive givosiran up to 48 months.

- **Study ALN-AS1-003:**

Study ALN-AS1-003 is an ongoing, open-label study to evaluate the safety and efficacy of longer-term givosiran dosing in adult patients with AHP who previously completed the double-blind portion of the study and will provide an opportunity to further evaluate the safety profile of givosiran. In this study, patients will receive up to 3 years of exposure to givosiran administered doses of 2.5 mg/kg or 1.25 mg/kg monthly.

- **Company Sponsored AHP Registry:**

The Sponsor plans to conduct a prospective observational longitudinal Company-sponsored AHP registry, to characterize the longer-term safety and effectiveness of givosiran in a real-world cohort of AHP patients. The registry will also collect and evaluate information on pregnancy complications, birth outcomes, breast feeding and infant outcomes in women exposed to givosiran during pregnancy.