

## **SUMMARY OF THE RISK MANAGEMENT PLAN FOR GIVLAARI (GIVOSIRAN)**

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 (ie, missing information).

Givlaari's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how givosiran should be used.

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 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 Givlaari's RMP.

### **I. The medicine and what it is used for**

Givlaari is indicated for the treatment of acute hepatic porphyria (AHP) in adults and adolescents aged 12 years and older. 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 website under the medicine's webpage <https://www.ema.europa.eu/en/medicines/human/EPAR/givlaari>.

### **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 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 (eg, 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 givosiran is not yet available, it is listed under “missing information” below.

## 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 (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	<ul style="list-style-type: none"> <li>• Hepatic Effects (including Hepatic Neoplasia)</li> <li>• Renal Effects</li> <li>• Pancreatitis</li> <li>• Clinical Consequences of Increased Blood Homocysteine Levels, in Particular Thromboembolic Events</li> </ul>
Missing information	<ul style="list-style-type: none"> <li>• Longer-term safety (&gt;3 years)</li> <li>• Use in patients with moderate or severe hepatic impairment</li> <li>• Use in patients with end-stage renal disease or on dialysis</li> <li>• Use in pregnant or lactating women and effects on pregnancy outcomes</li> </ul>

## II.B Summary of Important Risks

Important Potential Risk: Hepatic Effects (including Hepatic Neoplasia)	
Evidence for linking the risk to the medicine	<p>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&gt;8xULN discontinued treatment, and one patient with ALT&gt;5xULN interrupted treatment and restarted givosiran at a lower dose of 1.25 mg/kg once monthly.</p> <p>There have been no reports of transaminase (ALT and AST) &gt;3xULN concurrent with total bilirubin&gt;2xULN on givosiran, and no cases of hepatitis or Hy’s law.</p> <p>In a carcinogenicity study, an increased incidence of benign hepatocellular adenomas in male rats and preneoplastic lesions in female rats were observed at exposures of 42x and 15x the clinical</p>

<b>Important Potential Risk: Hepatic Effects (including Hepatic Neoplasia)</b>	
	<p>dose in humans, respectively. No evidence of carcinogenicity at dose levels up to 1500 mg/kg/month was observed in a 26-week carcinogenicity study of givosiran in Tg-rasH2 mice.</p> <p>No hepatic malignancies were reported in the givosiran clinical studies.</p>
Risk factors and risk groups	<p>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 [Schmitt 2018; Stewart 2012; Willandt 2015].</p>
Risk minimization measures	<p><u>Routine risk communication:</u></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Preneoplastic lesions in rats observed in a carcinogenicity study are described in Section 5.3 Preclinical safety data of the SmPC.</li> </ul> <p><u>Routine risk minimization activities recommending specific clinical measures to address the risk:</u></p> <ul style="list-style-type: none"> <li>• 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</li> <li>• 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</li> <li>• 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.</li> <li>• 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.</li> </ul> <p><u>Other routine risk minimization measures beyond the Product Information:</u></p> <ul style="list-style-type: none"> <li>• Legal status: Prescription-only medication</li> </ul>
Additional pharmacovigilance activities	<p><u>Additional pharmacovigilance activities:</u></p> <p>Hepatic effects (including hepatic neoplasia) will be monitored and further characterized in the post-authorization observational study.</p>

<b>Important Potential Risk: Renal (Kidney) Effects</b>	
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 [Pallet 2015].
Risk minimization measures	<p><u>Routine risk communication:</u></p> <ul style="list-style-type: none"> <li>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.</li> </ul> <p><u>Routine risk minimization activities recommending specific clinical measures to address the risk:</u></p> <ul style="list-style-type: none"> <li>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</li> </ul> <p><u>Other routine risk minimization measures beyond the Product Information:</u></p> <ul style="list-style-type: none"> <li>Legal status: Prescription-only medication</li> </ul>
Additional pharmacovigilance activities	<p><u>Additional pharmacovigilance activities:</u></p> <p>Reports related to renal function will be monitored and further characterized in the post-authorization observational study.</p>

<b>Important Potential Risk: Pancreatitis</b>	
Evidence for linking the risk to the medicine	<p>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.</p> <p>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 [Bonkovsky 2014; Corden 2018; Stinton 2010]</p>

<b>Important Potential Risk: Pancreatitis</b>	
	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 [Bonkovsky 2014; Corden 2018; Stinton 2010]
Risk minimization measures	<u>Routine risk communication:</u> <ul style="list-style-type: none"> <li>Not Applicable</li> </ul> <u>Routine risk minimization activities recommending specific clinical measures to address the risk:</u> <ul style="list-style-type: none"> <li>Not Applicable</li> </ul> <u>Other routine risk minimization measures beyond the Product Information:</u> <ul style="list-style-type: none"> <li>Legal status: Prescription-only medication</li> </ul>
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Reports indicative of pancreatitis will be monitored and further characterized in the post-authorization observational study.

<b>Important Potential Risk: Clinical Consequences of Increased Blood Homocysteine Levels, in Particular Thromboembolic Events</b>	
Evidence for linking the risk to the medicine	<p>Across the givosiran clinical studies, as of the final analysis of Study 002 and Study 003, 16 of 111 patients (14.4%) had AEs coded to the terms representing the medical concept of blood homocysteine increased. The majority of events were assessed as mild or moderate in severity. Two events were considered severe and serious due to medical significance.</p> <p>An analysis of homocysteine levels in Study 003 using exploratory blood samples showed that homocysteine levels during givosiran treatment were increased compared to available baseline levels.</p> <p>In Study 003, 100% of patients with significant homocysteine levels, defined as <math>\geq 100 \mu\text{M}</math> for 12 months, had at least one adverse event, compared to 97.0% of patients with non-significant homocysteine elevations. Thromboembolic events were reported in 31.8% of patients with significant homocysteine elevations compared to 15.2% of patients with non-significant homocysteine elevation.</p> <p>With the current data it is unclear if there is a correlation of elevations of homocysteine and adverse events.</p>
Risk factors and risk groups	Patients with AHP may have elevated homocysteine levels at baseline. Homocysteine levels may be higher in patients with more active disease [To-Figueras 2010; Ventura 2020]
Risk minimization measures	<u>Routine risk communication:</u>

<b>Important Potential Risk: Clinical Consequences of Increased Blood Homocysteine Levels, in Particular Thromboembolic Events</b>	
	<ul style="list-style-type: none"> <li>The effect of givosiran on blood homocysteine levels are described in the Special warnings and precautions for use (Section 4.4) and Undesirable effects (Section 4.8) of the SmPC.</li> </ul> <p><u>Routine risk minimization activities recommending specific clinical measures to address the risk:</u></p> <ul style="list-style-type: none"> <li>Recommendation that blood homocysteine levels be measured prior to initiating treatment and monitored for changes during treatment is included in the Special warnings and precautions for use, Section 4.4 of the SmPC.</li> <li>Recommendation for physicians to consider homocysteine-lowering therapy in patients with elevated homocysteine levels is also included in Section 4.4 of the SmPC.</li> </ul> <p><u>Other routine risk minimization measures beyond the Product Information:</u></p> <ul style="list-style-type: none"> <li>Legal status: Prescription-only medication</li> </ul>
Additional pharmacovigilance activities	<p><u>Additional pharmacovigilance activities:</u></p> <p>Reports indicative of homocysteine elevations will be monitored and further characterized in the post-authorization observational study.</p>

<b>Missing Information: Longer-Term Safety (&gt;3 Years)</b>	
Risk minimization measures	<p><u>Routine risk communication:</u></p> <ul style="list-style-type: none"> <li>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.</li> </ul>
Additional pharmacovigilance activities	<p><u>Additional pharmacovigilance activities:</u></p> <p>Long-term safety will be evaluated as part of the post-authorization observational study.</p>

<b>Missing Information: Use in Patients with Moderate or Severe Hepatic Impairment</b>	
Risk minimization measures	<p><u>Routine risk communication:</u></p> <ul style="list-style-type: none"> <li>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.</li> </ul>
Additional pharmacovigilance activities	<p><u>Additional pharmacovigilance activities:</u></p> <p>Use in patients with moderate or severe hepatic impairment will be evaluated as part of the post-authorization observational study.</p>

<b>Missing Information: Use in Patients with ESRD or on Dialysis</b>	
Risk minimization measures	<u>Routine risk communication:</u> <ul style="list-style-type: none"> <li>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.</li> </ul>
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Use in patients with ESRD or on dialysis will be evaluated as part of the post-authorization observational study.

<b>Missing Information: Use in Pregnant or Lactating Women and Effects on Pregnancy Outcomes</b>	
Risk minimization measures	<u>Routine risk communication:</u> <ul style="list-style-type: none"> <li>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.</li> </ul> <u>Routine risk minimization activities recommending specific clinical measures to address the risk:</u> <ul style="list-style-type: none"> <li>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.</li> </ul>
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Use in pregnancy or lactation and effects on pregnancy outcome will be evaluated as part of the post-authorization observational study.

## **II.C Post-authorization development plan**

### **II.C.1 Studies which are conditions of the marketing authorization**

There are no studies that are conditions of the marketing authorization or specific obligation of Givlaari.

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

- Study 002:

Study 002 is a completed, 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 received givosiran up to 48 months.

- Study 003:

Study 003 is a completed, 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 received up to 3 years of exposure to givosiran administered doses of 2.5 mg/kg or 1.25 mg/kg monthly.

- Post-Authorization Observational Study:

The Sponsor is conducting a post-authorization observational study to characterize the longer-term safety and effectiveness of givosiran in a real-world cohort of AHP patients. The study will also collect and evaluate information on pregnancy complications, birth outcomes, breast feeding and infant outcomes in women exposed to givosiran during pregnancy.