ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Givlaari 189 mg/mL solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains givosiran sodium equivalent to 189 mg givosiran.

Each vial contains 189 mg givosiran.

Excipients with known effect

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to yellow solution (pH of approximately 7.0; osmolality: 275 – 295 mOsm/kg).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Givlaari is indicated for the treatment of acute hepatic porphyria (AHP) in adults and adolescents aged 12 years and older.

4.2 Posology and method of administration

Therapy should be initiated under the supervision of a healthcare professional experienced in the management of porphyria.

Posology

The recommended dose of Givlaari is 2.5 mg/kg once monthly, administered via subcutaneous injection. Dosing is based on actual body weight.

The patient dose (in mg) and volume (in mL) should be calculated as follows:

Patient body weight (kg) × dose (2.5 mg/kg) = total amount (mg) of medicinal product to be administered.

Total amount (mg) divided by vial concentration (189 mg/mL) = total volume of medicinal product (mL) to be injected.

Missed dose
If a dose is missed, treatment should be administered as soon as possible. Dosing should be resumed at monthly intervals following administration of the missed dose.

Dose modification for adverse reactions
In patients with clinically relevant transaminase elevations, who have dose interruption and subsequent improvement in transaminase levels, a dose resumption at 1.25 mg/kg once monthly could be considered (see sections 4.4 and 4.8).

Special populations

Elderly
No dose adjustment is required in patients aged > 65 years of age (see section 5.2).

Hepatic impairment
No dose adjustment is necessary in patients with mild hepatic impairment (bilirubin ≤ 1× the upper limit of normal (ULN) and aspartate aminotransferase (AST) > 1×ULN, or bilirubin > 1×ULN to 1.5×ULN). Givlaari has not been studied in patients with moderate or severe hepatic impairment (see section 4.4).

Renal impairment
No dose adjustment is necessary in patients with mild, moderate, or severe renal impairment (estimated glomerular filtration rate [eGFR] ≥ 15 to < 90 mL/min/1.73 m²). Givlaari has not been studied in patients with end-stage renal disease or patients on dialysis (see section 4.4).

Paediatric population
No dose adjustment is required for patients aged ≥ 12 to < 18 years of age (see section 5.2). The safety and efficacy of Givlaari in children aged < 12 years of age has not been established. No data are available.

Method of administration

For subcutaneous use only.

This medicinal product is provided as a ready-to-use solution in a single use vial.

- The required volume of Givlaari should be calculated based on the recommended weight-based dose.
- The maximum acceptable single injection volume is 1.5 mL. If the dose is more than 1 mL, more than one vial will be needed.
- Doses requiring more than 1.5 mL should be administered as multiple injections (the total monthly dose divided equally between syringes with each injection containing approximately the same volume) to minimise potential injection site discomfort due to injection volume.
- This medicinal product should be injected subcutaneously into the abdomen; alternative injection sites include the thigh or upper arm.
- For subsequent injections or doses, rotating the injection site is recommended.
- This medicinal product should not be administered into scar tissue or areas that are reddened, inflamed, or swollen.

4.3 Contraindications

Severe hypersensitivity (e.g. anaphylaxis) to the active substance or to any excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients with AHP subtypes other than acute intermittent porphyria (AIP)

The efficacy and safety data in patients with AHP subtypes other than AIP (hereditary coproporphyria (HCP), variegate porphyria (VP) and ALA dehydratase-deficient porphyria (ADP)) are limited (see

section 5.1). This should be taken into consideration when assessing the individual benefit-risk in these rare AHP subtypes.

Anaphylactic reaction

In clinical studies, anaphylaxis occurred in one patient who had a history of allergic asthma and atopy (see section 4.8). Signs and symptoms of anaphylaxis should be monitored. If anaphylaxis occurs, administration of this medicinal product should be immediately discontinued, and appropriate medical treatment should be instituted.

Transaminase elevations

Transaminase elevations have been observed in patients treated with givosiran. Transaminase elevations primarily occurred between 3 to 5 months following initiation of treatment (see section 4.8).

Liver function tests should be performed prior to initiating treatment. These tests should be repeated monthly during the first 6 months of treatment, and as clinically indicated thereafter. Interrupting or discontinuing treatment should be considered for clinically relevant transaminase elevations. In case of subsequent improvement in transaminase levels, resumption of treatment at a 1.25 mg/kg dose after interruption could be considered (see section 4.2). 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).

Blood homocysteine increased

Blood homocysteine levels may be increased in patients with AHP, vitamin deficiencies, or chronic kidney disease. During treatment with givosiran, increases in blood homocysteine levels have been observed compared to levels before treatment (see section 4.8). The clinical relevance of the elevations in blood homocysteine during treatment with givosiran is unknown. However, homocysteine elevations have been previously associated with an increased risk of thromboembolic events.

Measurement of blood homocysteine levels prior to initiating treatment and monitoring for changes during treatment with givosiran is recommended. In patients with elevated homocysteine levels, homocysteine-lowering therapy can be considered.

Effects on renal function

Increases in serum creatinine levels and decreases in eGFR have been reported during treatment with givosiran. In the placebo-controlled study, the median increase in creatinine at month 3 was 6.5 µmol/L (0.07 mg/dL) and resolved or stabilised by month 6 with continued monthly treatment with 2.5 mg/kg givosiran.

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.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per mL, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

In a clinical drug-drug interaction study, givosiran resulted in a weak to moderate reduction in activity of certain CYP450 enzymes in the liver thereby increasing plasma exposures:

- CYP1A2: 1.3-fold increase in C_{max} and 3.1-fold increase in $AUC_{0-\infty}$ of caffeine
- CYP2D6: 2.0-fold increase in C_{max} and 2.4-fold increase in $AUC_{0-\infty}$ of dextromethorphan

- CYP2C19: 1.1-fold increase in C_{max} and 1.6-fold increase in $AUC_{0-\infty}$ of omeprazole
- CYP3A4: 1.2-fold increase in C_{max} and 1.5-fold increase in $AUC_{0-\infty}$ of midazolam
- CYP2C9: no effect on the exposure of losartan

Caution is recommended during the use of medicinal products that are substrates of CYP1A2 or CYP2D6 while on treatment with Givlaari as this medicinal product may increase or prolong their therapeutic effect or alter their adverse event profiles. Consider decreasing the CYP1A2 or CYP2D6 substrate dosage in accordance with the approved product labelling.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of givosiran in pregnant women. Studies in animals have shown reproductive toxicity in the presence of maternal toxicity (see section 5.3). The use of this medicinal product could be considered during pregnancy taking into account the expected health benefit for the woman and potential risks to the foetus.

Breast-feeding

It is unknown whether givosiran is excreted in human milk. A risk to the newborns/infants cannot be excluded. Available pharmacodynamic/toxicological data in animals have shown excretion of givosiran in milk (see section 5.3). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Givlaari therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effects of givosiran on human fertility. No impact on male or female fertility was detected in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Givlaari has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently occurring adverse reactions reported in patients treated with givosiran are injection site reactions (ISRs) (36 %), nausea (32.4 %) and fatigue (22.5 %). The adverse reactions resulting in discontinuation of treatment were elevated transaminases (0.9 %) and anaphylactic reaction (0.9 %).

Tabulated list of adverse reactions

The adverse reactions are presented as MedDRA preferred terms under the MedDRA system organ class (SOC) by frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency of the adverse reactions is expressed according to the following categories:
- Very common (≥ 1/10)
- Common (≥ 1/100 to < 1/10)
- Uncommon (≥ 1/1 000 to < 1/100)

Table 1: Adverse reactions

System organ class	Adverse reaction	Frequency
Immune system disorders	Anaphylactic reaction	Uncommon
	Hypersensitivity	Common
Gastrointestinal disorders	Nausea	Very common
	Pancreatitis	Common
Hepatobiliary disorders	Transaminase elevations	Very common
Skin and subcutaneous tissue disorders	Rash[a]	Very common
Renal and urinary disorders	Glomerular filtration rate decreased[b]	Very common
General disorders and administration site conditions	Injection site reactions	Very common
	Fatigue	Very common
Investigations	Blood homocysteine increased[c]	Common

[a] Includes pruritus, eczema, erythema, rash, rash pruritic, urticaria.
[b] Includes blood creatinine increased, glomerular filtration rate decreased, chronic kidney disease (decreased eGFR), renal impairment.
[c] Includes blood homocysteine abnormal, hyperhomocysteinemia, blood homocysteine increased.

Description of selected adverse reactions

Liver function tests
In the placebo-controlled study, 7 (14.6 %) patients treated with givosiran and one (2.2 %) patient treated with placebo had an increased alanine aminotransferase (ALT) more than 3 times the ULN. In 5 patients treated with givosiran the transaminase elevations resolved with ongoing dosing at 2.5 mg/kg. Per protocol, one patient (with variegate porphyria) with ALT more than 8 times the ULN discontinued treatment and one patient with ALT more than 5 times the ULN interrupted treatment and resumed dosing at 1.25 mg/kg. ALT elevations in both patients resolved.

Injection site reactions
In placebo-controlled and open-label clinical studies, injection site reactions have been reported in 36 % of patients and generally have been mild or moderate in severity, mostly transient and resolved without treatment. The most commonly reported symptoms included erythema, pain, and pruritus. Injection-site reactions occurred in 7.8 % of injections and did not result in discontinuation of treatment. Three patients (2.7 %) experienced single, transient, recall reactions of erythema at a prior injection site with a subsequent dose administration.

Immunogenicity
In placebo-controlled and open-label clinical studies, 1 of 111 patients with AHP (0.9 %), developed treatment emergent anti-drug antibodies (ADA) during treatment with givosiran. ADA titres were low and transient with no evidence of an effect on clinical efficacy, safety, pharmacokinetic or pharmacodynamic profiles of the medicinal product.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Various alimentary tract and metabolism products, ATC code: A16AX16

Mechanism of action

Givosiran is a double-stranded small interfering ribonucleic acid (siRNA) that causes degradation of aminolevulinic acid synthase 1 (*ALAS1*) messenger ribonucleic acid (mRNA) in hepatocytes through RNA interference, resulting in a reduction of induced liver *ALAS1* mRNA towards normal. This leads to reduced circulating levels of neurotoxic intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG), the key causal factors of attacks and other disease manifestations of AHP.

Pharmacodynamic effects

In the placebo-controlled study in patients with AHP receiving givosiran 2.5 mg/kg once monthly (ENVISION), median reductions from baseline in urinary ALA and PBG of 83.7 % and 75.1 %, respectively, were observed 14 days after the first dose. Maximal reductions in ALA and PBG levels were achieved around month 3 with median reductions from baseline of 93.8 % for ALA and 94.5 % for PBG and were sustained with repeated once monthly dosing.

Observed data and modelling demonstrated that once monthly dosing with 2.5 mg/kg givosiran resulted in a greater reduction and less fluctuation in ALA levels compared with doses less than 2.5 mg/kg or dosing once every 3 months.

Clinical efficacy

The efficacy of givosiran was evaluated in a randomised, double-blind, placebo-controlled, multinational study (ENVISION).

ENVISION
A total number of 94 patients with AHP (89 patients with acute intermittent porphyria (AIP), 2 patients with variegate porphyria (VP), 1 patient with hereditary coproporphyria (HCP), and 2 patients with no identified mutation in a porphyria-related gene) were randomised 1:1 to receive once monthly subcutaneous injections of givosiran 2.5 mg/kg or placebo during the 6-month double-blind period. Patients randomised to givosiran included 46 patients with AIP, 1 patient with VP, and 1 patient with HCP. In this study, inclusion criteria specified a minimum of 2 porphyria attacks requiring hospitalisation, urgent healthcare visit, or intravenous (IV) hemin administration at home in the 6 months prior to study entry. Hemin use during the study was permitted for the treatment of acute porphyria attacks. The median age of patients in the ENVISION study was 37.5 years (range 19 to 65 years); 89.4 % of patients were female, and 77.7 % were white. The treatment arms were balanced with respect to historical annualised porphyria attack rate (overall median baseline rate of 8 per year), prior hemin prophylaxis, use of opioid medicinal products, and patient-reported measures of chronic symptoms between attacks.

The major efficacy measure was the annualised attack rate (AAR) of composite porphyria attacks during the 6-month double-blind period and consisted of three components: attacks requiring hospitalisation, urgent healthcare visit, or IV hemin administration at home. This composite efficacy measure was evaluated as the primary endpoint in patients with AIP, and as a secondary endpoint in

the overall population of patients with AHP. Treatment with this medicinal product resulted in a significant reduction of the AAR of composite porphyria attacks, compared with placebo, of 74 % in patients with AIP (Table 2). Comparable results were seen in patients with AHP, with a reduction of 73 %. Consistent results were observed for each of the 3 components of the composite porphyria attack endpoint.

The results observed over 6 months were maintained through Month 12, with a median AAR (Q1, Q3) of 0.0 (0.0, 3.5) observed for patients with continued dosing with the medicinal product during the open-label extension period.

Givosiran reduced porphyria attacks compared to placebo in patients with AHP across all pre-specified subgroups, including age, sex, race, region, baseline body mass index (BMI), prior hemin prophylaxis use, historical attack rate, prior chronic opioid use when not having attacks, and the presence of prior chronic symptoms when not having attacks.

Additional clinical efficacy endpoints were studied in AIP patients and are summarised in Table 2.

Table 2: Clinical Efficacy Results in Patients with AIP during the 6-Month Double-Blind Period of the ENVISION Study

Endpoint	**Placebo (N=43)**	**Givosiran (N=46)**
Annualised attack rate of composite porphyria attacks[a]		
Mean AAR (95 % CI)[b]	12.5 (9.4, 16.8)	3.2 (2.3, 4.6)
Rate ratio (95 % CI)[b] (givosiran/placebo)	0.26 (0.16, 0.41)	
P-value[b]	< 0.001	
Median AAR, (Q1, Q3)	10.7 (2.2, 26.1)	1.0 (0.0, 6.2)
Number of patients with 0 attacks (%)	7 (16.3)	23 (50.0)
Annualised days of hemin use		
Mean (95 % CI)[b]	29.7 (18.4, 47.9)	6.8 (4.2, 10.9)
Ratio (95 % CI)[b] (givosiran/placebo)	0.23 (0.11, 0.45)	
P-value[b]	< 0.001	
Daily worst pain score[c]		
Baseline, median (Q1, Q3)	3.3 (1.9, 5.6)	2.2 (1.2, 4.5)
Median of treatment difference (95 %) (givosiran-placebo)	−10.1 (−22.8, 0.9)	
P-value	< 0.05	
PCS of SF-12[d]		
Baseline, mean (SD)	38.4 (9.4)	39.4 (9.6)
Change from baseline at Month 6, LS mean (95 % CI)	1.4 (−1.0, 3.9)	5.4 (3.0, 7.7)
LS mean difference (95 % CI) (givosiran-placebo)	3.9 (0.6, 7.3)	
Nominal P-value	< 0.05	

AAR, Annualised Attack Rate; AIP, Acute Intermittent Porphyria; CI, Confidence Interval; Q1, Quartile 1; Q3, Quartile 3; LS, Least Square; PCS, Physical Component Summary; SF-12, the 12-item Short-Form Health Survey

[a] Composite porphyria attacks includes three components: attacks requiring hospitalisation, urgent healthcare visits, or IV hemin administration at home.

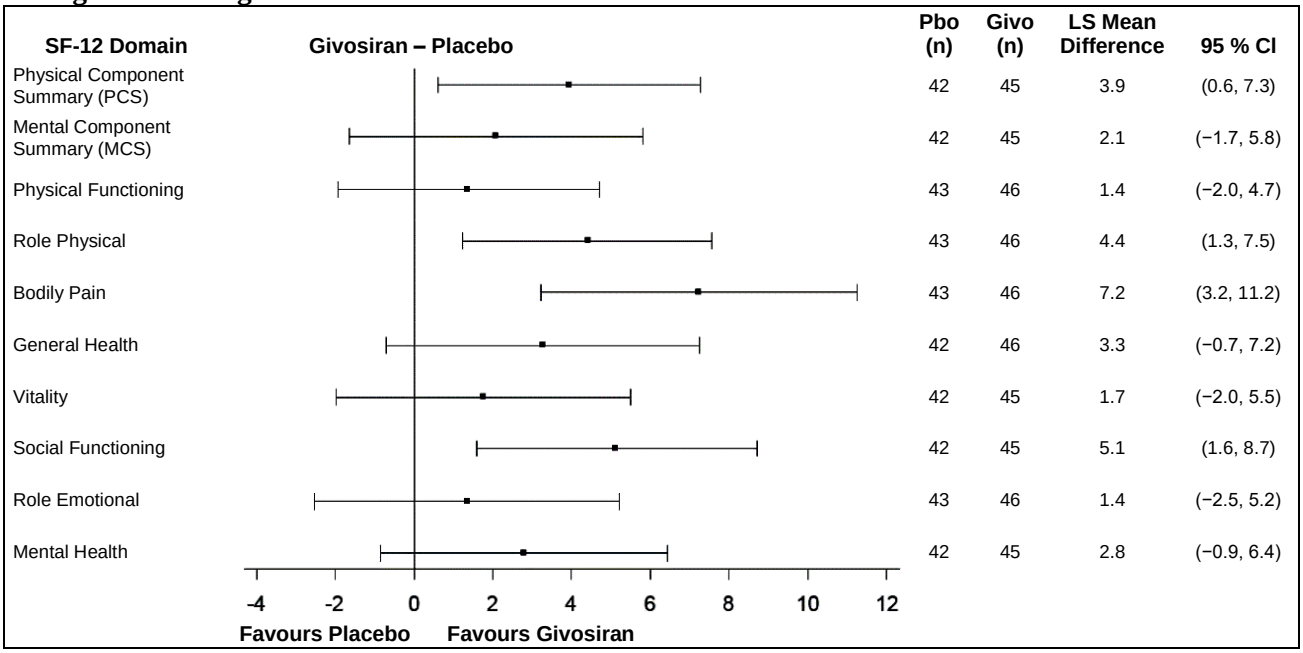
[b] Based on negative binomial regression model. A rate ratio < 1 represents a favourable outcome for givosiran.

[c] Patients provided a daily self-assessment of their worst pain based on a 0 to 10 numerical rating scale (NRS). A lower score indicates fewer symptoms. Median of treatment difference and CI were estimated using the Hodges-Lehmann method; *p*-value was based on Wilcoxon rank sum test, which was conducted post-hoc after data showed a significant deviation from normal distribution.

[d] A higher score indicates improved health-related quality of life; analysed using the mixed-effect model repeated measures (MMRM) method. The endpoint was not formally tested for statistical significance; a nominal p-value was reported.

In addition to greater improvement from baseline in the SF-12 PCS score compared to patients treated with placebo at Month 6, there was consistent evidence of effect favouring this medicinal product in bodily pain, role-physical, and social functioning domains, but not in the general health, physical functioning, role-emotional, vitality, and mental health domains (Figure 1).

Figure 1: Change from Baseline to Month 6 in SF-12 Domain Scores in Patients with AIP



AIP, Acute Intermittent Porphyria; CI, Confidence Interval; Givo, givosiran; Pbo, placebo; LS, Least Square; MCS, Mental Component Summary; PCS, Physical Component Summary; SF-12, the 12-item Short-Form health survey version 2.

In a patient global assessment (Patient Global Impression of Change – PGIC) a larger proportion of patients with AIP treated with givosiran (61.1 %) than with placebo (20 %) rated their overall status as "very much improved" or "much improved" since the start of the study.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with this medicinal product in all subsets of the paediatric population in the treatment of AHP (see section 4.2 and section 5.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following subcutaneous administration, givosiran is rapidly absorbed with a time to maximum plasma concentration (t_{max}) of 0.5 to 2 hours. At the 2.5 mg/kg once monthly dose, the steady-state peak plasma concentrations of givosiran (C_{max}) and area under the curve from time of dosing up to 24 hours after dosing (AUC_{24}) were 321 ± 163 ng/mL and 4130 ± 1780 ng·h/mL, respectively, and corresponding values for the active metabolite were 123 ± 79.0 ng/mL and 1930 ± 1210 ng·h/mL, respectively.

Distribution

Givosiran is greater than 90 % bound to plasma proteins over the concentration range observed in humans at the 2.5 mg/kg once monthly dose. The population estimate for the steady state apparent volume of distribution (V_d/F) for givosiran and for the active metabolite was 10.4 L. Givosiran and its active metabolite distribute primarily to the liver after subcutaneous dosing.

Biotransformation

Givosiran is metabolised by nucleases to oligonucleotides of shorter lengths. Active metabolite AS(N-1)3' givosiran (with equal potency as that of givosiran) was a major metabolite in plasma with 45 % exposure ($AUC_{0–24}$) relative to givosiran at the 2.5 mg/kg once monthly dose. *In vitro* studies indicate that givosiran does not undergo metabolism by CYP450 enzymes.

Elimination

Givosiran and its active metabolite are eliminated from plasma primarily by metabolism with an estimated terminal half-life of approximately 5 hours. The population estimate for apparent plasma clearance was 36.6 L/h for givosiran and 23.4 L/h for AS(N-1)3' givosiran. After subcutaneous dosing, up to 14 % and 13 % of the administered givosiran dose was recovered in urine as givosiran and its active metabolite, respectively, over 24 hours. The renal clearance ranged from 1.22 to 9.19 L/h for givosiran and 1.40 to 12.34 L/h for the active metabolite.

Linearity/non-linearity

Givosiran and its active metabolite exhibited linear pharmacokinetics in plasma over the 0.35 to 2.5 mg/kg dose range. At doses greater than 2.5 mg/kg, plasma exposure increased slightly greater than dose-proportionally. Givosiran exhibited time-independent pharmacokinetics with chronic dosing at the recommended dose regimen of 2.5 mg/kg once monthly. There was no accumulation of givosiran or the active metabolite in plasma after repeated once monthly dosing.

Pharmacokinetic/pharmacodynamic relationship

Plasma concentrations of givosiran are not reflective of the extent or duration of pharmacodynamic activity. Since givosiran is a liver targeted therapy, concentrations in plasma decline rapidly due to uptake by the liver. In the liver, givosiran exhibits a long half-life leading to extended duration of pharmacodynamic effect maintained over the monthly dosing interval.

Special populations

Elderly
No studies have been conducted in patients aged > 65 years. Age was not a significant covariate in the pharmacokinetics of givosiran.

Gender and race
In clinical studies there was no difference in the pharmacokinetics or pharmacodynamics of givosiran based on gender or race.

Hepatic impairment
Adult patients with mild hepatic impairment (bilirubin ≤ 1×ULN and AST > 1×ULN, or bilirubin > 1×ULN to 1.5×ULN) had comparable plasma exposure of givosiran and its active metabolite and similar pharmacodynamics (percent reduction in urinary ALA and PBG) as patients with normal hepatic function. No studies have been conducted in patients with moderate or severe hepatic impairment (see sections 4.2 and 4.4).

Renal impairment
Adult patients with mild renal impairment (eGFR ≥ 60 to < 90 mL/min/1.73 m²), moderate renal impairment (eGFR ≥ 30 to < 60 mL/min/1.73 m²) or severe renal impairment (eGFR ≥ 15 to < 30 mL/min/1.73 m²) had comparable plasma exposure of givosiran and its active metabolite and similar pharmacodynamics (percent reduction in urinary ALA and PBG) as patients with normal renal function (eGFR ≥ to 90 mL/min/1.73 m²). No studies have been conducted in patients with end-stage renal disease or patients with dialysis (see sections 4.2 and 4.4).

Paediatric population
Available data suggest that body weight but not age was a significant covariate in the pharmacokinetics of givosiran. At the 2.5 mg/kg dose, a similar exposure is expected in adolescents aged 12 years or older, as in adults with the same body weight.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction and development. In the repeat-dose toxicity studies conducted in rats and monkeys, the rat was identified as the most sensitive species to givosiran-related effects, with the liver being identified as the primary target organ of toxicity in both the rat and monkey. No adverse findings were associated with chronic, weekly administration of givosiran to rats and monkeys at doses that achieved exposure multiples of 3.5- and 26.3-fold, respectively when compared to exposures achieved in patients receiving the maximum recommended human dose.

Genotoxicity/carcinogenicity

Givosiran did not exhibit a genotoxic potential *in vitro* and *in vivo*.

Carcinogenicity studies were conducted in Tg-rasH2 mice and Sprague Dawley rats. Evaluation of givosiran in a 26-week carcinogenicity study in Tg-rasH2 mice showed no evidence of carcinogenicity at dose levels up to 1500 mg/kg/month. The 2-year rat carcinogenicity study resulted in neoplastic effects limited to an increased incidence of hepatocellular adenomas in males at the dose of 100 mg/kg/month (42 times the plasma exposure levels achieved at the maximum recommended human dose (MRHD), based on AUC). In addition, proliferative preneoplastic lesions in the liver were observed in females at doses of 50 mg/kg/month (15 times the plasma exposure levels achieved on MRHD, based on AUC). The relevance of this finding for the intended target population is unknown.

Reproductive toxicity

Embryo-foetal development studies have been performed in rats and rabbits during organogenesis. Givosiran showed marked maternal toxicity in rabbits (including mean maternal body weight loss) and resulted in increased post-implantation loss as a result of increased early resorptions and a low incidence of skeletal variations. These findings are considered an indirect effect, secondary to maternal toxicity. No adverse developmental effects were observed in rats administered the maternally toxic dose of approximately 9 times the normalised maximum recommended human dose.

In a postnatal development study in rats, there was no effect on growth and development of the offspring.

No adverse effects were observed in the fertility of male and female rats when administered with givosiran.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (pH adjustment)
Phosphoric acid (pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

Once the vial is opened, the medicinal product should be used immediately.

6.4 Special precautions for storage

Do not store above 25 °C.
Keep vial in the outer carton to protect from light.

6.5 Nature and contents of container

Glass vial with a fluoropolymer-coated rubber stopper and a flip-off aluminium seal. Each vial contains 1 mL solution for injection.

Pack size of one vial.

6.6 Special precautions for disposal and other handling

This medicinal product is for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Alnylam Netherlands B.V.
Antonio Vivaldistraat 150
1083 HP Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/20/1428/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 March 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Alnylam Netherlands B.V.
Antonio Vivaldistraat 150
1083 HP Amsterdam
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Givlaari 189 mg/mL solution for injection
givosiran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains givosiran sodium equivalent to 189 mg givosiran in 1 mL of solution.

3. LIST OF EXCIPIENTS

Excipients:
Sodium hydroxide
Phosphoric acid
Water for injections
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
189 mg/1 mL
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Keep vial in the outer carton to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Alnylam Netherlands B.V.
Antonio Vivaldistraat 150
1083 HP Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1428/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Givlaari

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Givlaari 189 mg/mL solution for injection
givosiran
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

189 mg/1 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Givlaari 189 mg/mL solution for injection
givosiran

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Givlaari is and what it is used for

What Givlaari is

Givlaari contains the active substance ‘givosiran’.

What Givlaari is used for

Givlaari is used to treat acute hepatic porphyria in adults and adolescents aged 12 years and older.

What acute hepatic porphyria is

Acute hepatic porphyria is a rare illness that runs in families. It is caused by a defect in one of the proteins that make a molecule called haem in the liver. Because there is a problem in one of the proteins required to make haem, there is a build-up of some of the substances that are used to produce haem, namely aminolevulinic acid (ALA) and porphobilinogen (PBG). Having too much ALA and PBG can injure nerves and cause serious attacks of pain, nausea, muscle weakness and changes in mental functioning. Some people with acute hepatic porphyria may also have symptoms, such as pain and nausea, in between attacks. Longer-term complications that can be seen in people with acute hepatic porphyria include high blood pressure, chronic kidney disease and liver disease.

How Givlaari works

This medicine works by lowering the amount of an enzyme, called ALAS1, that controls how much ALA and PBG are made by the liver. By lowering ALAS1, the liver makes less ALA and PBG. This can help to reduce the effects of this illness.

2. What you need to know before you are given Givlaari

You must not be given Givlaari

- if you have ever had a severe allergic reaction to givosiran or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or nurse before you are given this medicine.

Severe allergic reaction

- Tell your doctor or nurse straight away if you get any signs of a severe allergic reaction. The signs are listed in "Serious side effects" in section 4.
- If you have a severe allergic reaction, your doctor or nurse will stop using the medicine straight away and you may need to take other medicines to control the symptoms.

Liver problems

Using this medicine can affect your liver. You will have blood tests to check your liver function before you start treatment with Givlaari and periodically during treatment. If these tests show abnormal results, your doctor or nurse will decide whether to interrupt treatment or stop treatment permanently. Abnormal results have been seen in some patients treated with this medicine, mainly between 3 to 5 months after starting treatment.

Kidney problems

Using this medicine can affect your kidneys, especially if you have already been diagnosed with kidney problems. Your doctor will check how your kidneys are working while you are using this medicine, especially if you already have kidney problems.

Tests for homocysteine levels

While receiving this medicine, blood tests may show an increase in homocysteine, a type of amino acid, compared to your homocysteine levels before starting treatment. Your doctor will check the levels of homocysteine in your blood before and during treatment. If your homocysteine levels are elevated, your doctor may give you homocysteine-lowering therapy.

Children

This medicine should not be used in children below 12 years of age because there is no experience of using the medicine in this age group.

Other medicines and Givlaari

Tell your doctor or pharmacist if you are using, have recently used or might be using any other medicines.

When using certain medicines, this medicine may prolong or increase their effect or change their side effects.

Pregnancy

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or nurse for advice before using this medicine.

Breast-feeding

Studies in animals suggest this medicine may pass into breast milk. If you are breast-feeding ask your doctor for advice before taking this medicine. Your doctor will then help you decide whether to stop breast-feeding or to stop treatment with Givlaari taking into account the benefit of breast-feeding for your child and benefit of therapy for you.

Driving and using machines

This medicine is unlikely to have any effect on your ability to drive or use machines.

Givlaari contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per mL, that is to say essentially 'sodium-free'.

3. How Givlaari is given

How much Givlaari is given

Your doctor will work out how much medicine to give you. The amount will depend on your body weight.

- The recommended dose is 2.5 milligrams for every kilogram you weigh
- You will be given the medicine once a month (every 4 weeks)
- If blood tests show problems with your liver, your doctor may interrupt Givlaari treatment or stop treatment permanently. Your doctor may consider starting again at a lower dose.

How Givlaari is given

This medicine will be given to you once every month by a doctor or nurse. It is given as an injection under the skin (subcutaneously) into your stomach area (abdomen), or in some cases, your upper arm or thigh. The site of the injection will be rotated. If the dose is more than 1 mL, more than one vial will need to be used and more than one subcutaneous injection may need to be given.

If you are given too much Givlaari

In the unlikely event that your doctor or nurse gives you too much (an overdose) they will check you for side effects.

If you miss your dose of Givlaari

If you have missed an appointment for your injection, talk to your doctor or nurse as soon as possible. If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Severe allergic reactions (uncommon: may affect up to 1 in 100 people)

Tell your doctor or nurse straight away if you get any of the following signs of a severe allergic reaction (anaphylactic reaction) – the injection will need to be stopped and you may need to take other medicines to manage the reaction:
- swelling – mainly of the lips, tongue or throat which makes it difficult to swallow or breathe
- breathing problems or wheezing
- feeling dizzy or fainting
- rash, hives
- itching

Other side effects

Tell your doctor or nurse if you notice any of the following side effects:

Very common: may affect more than 1 in 10 people
- Nausea
- Redness, pain, itching or swelling at the site of the injection (injection site reaction)
- Skin rashes including red, itchy, or dry skin, eczema, or hives
- Feeling tired
- Blood tests showing an increase in transaminases, which are liver enzymes (a sign of possible liver inflammation)
- Blood tests showing an increase in creatinine, a substance removed from your body by your kidneys, or decrease in glomerular filtration rate (signs of possible kidney problems)

Common: may affect up to 1 in 10 people
- A type of allergic reaction (hypersensitivity) – with symptoms such as hives, rash, swelling of eyes, mouth or face, difficulty breathing, itching.
- Inflammation of the pancreas (pancreatitis).
- Blood test showing an increase in homocysteine (a type of amino acid)

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Givlaari

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after EXP. The expiry date refers to the last day of that month.

This medicine is for single use only. Once the product is opened, use immediately.

Do not store above 25 °C.

Keep vial in the outer carton to protect from light.

Do not throw away any medicines via wastewater or household waste. Your doctor or nurse will throw away any medicines that are no longer being used. These measures will help protect the environment.

6. Contents of the pack and other information

What Givlaari contains

- The active substance is givosiran.
- Each mL contains givosiran sodium equivalent to 189 mg givosiran.
- The other ingredients are sodium hydroxide, phosphoric acid and water for injections.

What Givlaari looks like and contents of the pack

This medicine is a clear, colourless to yellow solution for injection.

Each pack contains one vial of 1 mL solution for injection.

Marketing Authorisation Holder and Manufacturer

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Antonio Vivaldistraat 150
1083 HP Amsterdam
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

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The following information is intended for healthcare professionals only:

Instructions for use

For subcutaneous use only.

- Collect materials not included in the pack that are needed for administration which will include a sterile syringe (1 mL or 3 mL), 21-gauge (G) or a larger needle, 25 G or 27 G needle and a sharps container.
- Calculate the required volume of Givlaari based on the recommended weight-based dose. If the dose is more than 1 mL, more than one vial will need to be used and more than one subcutaneous injection may need to be given. The maximum acceptable single injection volume to be administered is 1.5 mL.
- To withdraw Givlaari, hold the vial upright or tilt at a slight angle and ensure the flat edge of the needle is pointed downwards.
- Draw up the indicated injection volume with the 21 G or larger needle.

- Divide doses requiring volumes greater than 1.5 mL equally into multiple syringes, with each injection containing approximately the same volume.
- Point the needle and syringe straight up and tap the syringe to move any bubbles to the top. Once the bubbles are at the top, gently push the plunger to force the bubbles out of the syringe. Check to make sure you still have the correct amount of medicine in the syringe.
- Once the dose is prepared and in the administration syringe, replace the 21 G or larger needle with either a 25 G or 27 G needle.
- Note: Do not push this medicine into the 25 G or 27 G needle.
- Injection can be into the abdomen, or if required, the back or side of the upper arms, or the thighs. Consider rotating injection sites. Do not administer into scar tissue or areas that are reddened, inflamed, or swollen.
- Note: When administering subcutaneous injections into the abdomen, a 5.0 cm diameter circle around the navel should be avoided.
- Clean the area you intend to inject with an alcohol swab and wait for the area to dry completely.
- Ensure proper injection technique. Do not inject into a vein or muscle.
- Pinch and elevate the skin at the selected injection site. Insert the needle at a right angle (90 degrees) to deliver the injection just below the skin. In patients with little subcutaneous tissue or if the needle size is longer than 2.5 cm, the needle should be inserted at a 45-degree angle.
- Do not press down on the plunger while piercing the skin. Once the needle is inserted through the skin, release the pinched skin and administer the dose in a slow and steady manner. Once this medicine has been administered count for at least 5 seconds before withdrawing the needle from the skin. Lightly press gauze or cotton ball on the injection site as needed. Do not put the needle cap back on.
- Note: Don’t aspirate after inserting the needle to prevent tissue damage, haematoma, and bruising.
- If more than one injection is needed for a single dose of Givlaari, the injection sites should be at least 2 cm apart from previous injection locations.
- Only use the vial once. After you inject the dose, dispose of any unused medicine in the vial according to local regulations.
- Use the syringes, transfer needles and injection needles only once. Dispose of any used syringes and needles in accordance with local requirements.