swissmedic

Date: 13 September 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Givlaari

International non-proprietary name: givosiran, givosiran sodium
Pharmaceutical form: solution for injection
Dosage strength(s): Givlaari 189 mg/mL, solution for injection
Route(s) of administration: subcutaneous injection
Marketing authorisation holder: Alnylam Switzerland GmbH
Marketing authorisation no.: 67895
Decision and decision date: approved on 29.03.2021

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for givosiran, givosiran sodium in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 6 April 2022.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Treatment of acute hepatic porphyria in adults and adolescents aged 12 years and older.

2.2.2 Approved indication

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

2.2.3 Requested dosage

Summary of the requested standard dosage:
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.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	2 June 2020
Formal objection	30 June 2020
Preliminary decision	28 October 2020
Response to preliminary decision	6 December 2020
Final decision	29 March 2021
Decision	approval

Swissmedic has not assessed the primary data of this application and relies for its decision on the assessment of the foreign reference authority, the EMA. The current SwissPAR refers to the publicly available Assessment Report, Givlaari (EMA/62114/2020; EMEA/H/C/004775, first published on 09.03.2020), issued by the EMA.

3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects of this application and relies on the assessment of the foreign reference authority, the EMA. The current SwissPAR refers to the publicly available Assessment Report, Givlaari (EMA/62114/2020; EMEA/H/C/004775, first published on 09.03.2020), issued by the EMA.

4 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects of this application and relies on the assessment of the foreign reference authority, the EMA. The current SwissPAR refers to the publicly available Assessment Report, Givlaari (EMA/62114/2020; EMEA/H/C/004775, first published on 09.03.2020), issued by the EMA.

5 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects of this application and relies on the assessment of the foreign reference authority, the EMA. The current SwissPAR refers to the publicly available Assessment Report, Givlaari (EMA/62114/2020; EMEA/H/C/004775, first published on 09.03.2020) issued by the EMA.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Givlaari was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Givlaari

Composition

Active substances

Givosiran (as givosiran-sodium)

Excipients

Sodium hydroxide, phosphoric acid, water for injections. Each mL of solution contains 11 mg sodium.

Pharmaceutical form and active substance quantity per unit

Solution for injection.
Clear, colourless to yellow solution (pH of approximately 7.0; osmolality: 275 – 295 mOsm/kg).
Each mL of solution contains givosiran-sodium equivalent to 189 mg givosiran. Each vial contains 189 mg givosiran.

Indications/Uses

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

Dosage/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.

Dose adjustment following undesirable effects

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 «Warnings and precautions» and «Undesirable effects»).

Patients with impaired hepatic function

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 «Warnings and precautions»).

Patients with impaired renal function

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 m^2). Givlaari has not been studied in patients with end-stage renal disease or patients on dialysis (see «Warnings and precautions»).

Elderly patients

No dose adjustment is required in patients aged > 65 years of age (see «Pharmacokinetics»).

Children and adolescents

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

Delayed administration

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.

Mode 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.

Contraindications

Severe hypersensitivity (e.g. anaphylaxis) to the active substance or to any excipients listed in «Composition».

Warnings and precautions

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 «Properties/Effects»). 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 «Undesirable effects»). 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 «Undesirable effects»).

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 «Dosage/Administration»). 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 «Undesirable effects»).

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.

Other ingredients

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

Interactions

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.

Pregnancy, 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 «Preclinical data»). 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.

Lactation

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 «Preclinical data»). 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 «Preclinical data»).

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile

The most frequently occurring adverse reactions reported in patients treated with givosiran are injection site reactions (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 %).

The adverse reactions are arranged by organ system and according to frequency (number of patients expected to experience the reaction) using the following categories: "very common" (≥1/10),

"common" (≥1/100, <1/10), "uncommon" (≥1/1000, <1/100), "rare" (≥1/10,000, <1/1000), "very rare" (<1/10,000).

Immune system disorders
Common: Hypersensitivity.
Uncommon: Anaphylactic reaction.

Gastrointestinal disorders
Very common: Nausea (32.4 %).

Hepatobiliary disorders
Very common: Transaminase elevations (11.7 %).

Skin and subcutaneous tissue disorders
Very common : Rash (includes pruritus, eczema, erythema, rash, rash pruritic, urticaria) (15.3 %).

Renal and urinary disorders
Very common: Glomerular filtration rate decreased (includes blood creatinine increased, glomerular filtration rate decreased, chronic kidney disease (decreased eGFR), renal impairment) (12.6 %).

General disorders and administration site conditions
Very common: Injection site reactions (36 %), fatigue (22.5 %).

Description of selected undesirable effects

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 suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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.

Properties/Effects

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.

Pharmacodynamics

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 1). 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 1.

Table 1: 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.

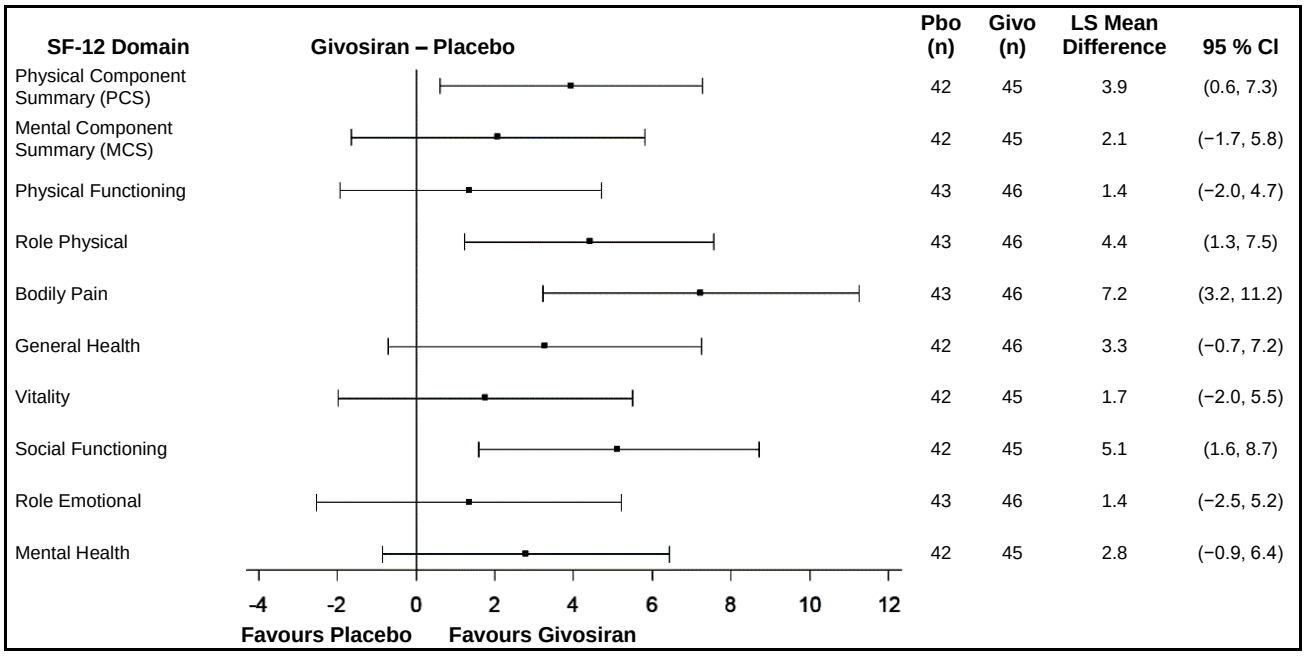
[c] Patients provided a daily self-assessment of their worst pain based on a 0 to 10 numerical rating scale (NRS). A lower score indicates fewer symptoms. Median of treatment difference and CI were estimated using the Hodges-Lehmann method; *p*-value was based on Wilcoxon rank sum test, which was conducted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

Safety and efficacy in paediatric patients

Swissmedic 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 «Dosage/Administration» and «Pharmacokinetics» for information on paediatric use).

Pharmacokinetics

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.

Metabolism

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.

Kinetics in specific patient groups

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 «Dosage/Administration» and «Warnings and precautions»).

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 «Dosage/Administration» and «Warnings and precautions»).

Elderly patients

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

Children and adolescents

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.

Gender and race

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

Preclinical 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*.
Animal studies have not been conducted to evaluate the carcinogenic potential of givosiran.

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.

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Shelf life after opening

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

Special precautions for storage

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

Instructions for 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.

Authorisation number

67895 (Swissmedic)

Packs

Each pack contains one glass vial (with a PTFE-coated chlorobutyl rubber stopper and a flip-off aluminium seal) with 1 mL solution for injection. (B)

Marketing authorisation holder

Alnylam Switzerland GmbH, Zug

Date of revision of the text

October 2020