▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – GIVLAARI® (GIVOSIRAN) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Givosiran

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each vial contains 189 mg givosiran.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to yellow solution, essentially free of particles (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 DOSE AND METHOD OF ADMINISTRATION

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

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.

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 Section 4.4 Special Warning and Precautions for Use and Section 4.8 Adverse Effects (Undesirable Effects)].

Special populations

Elderly

No dose adjustment is required in patients aged > 65 years of age (see Section 5.2 Pharmacokinetic properties).

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.

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 m^2). Givlaari has not been studied in patients with end-stage renal disease or patients on dialysis (see Section 4.4 Special Warning and Precautions for Use).

Paediatric population

No dose adjustment is required for patients aged ≥ 12 to < 18 years of age (see Section 5.2 Pharmacokinetic properties). 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. List of Excipients.

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 Pharmacodynamic Properties). 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 Adverse Effects (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.

Effects on laboratory tests

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 Adverse Effects (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 Section 4.2 Dose and Method of 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 Section 4.8 Adverse Effects (Undesirable Effects)].

Blood homocysteine increased

Blood homocysteine levels may be increased in patients with AHP, vitamin deficiencies, or chronic kidney disease. During treatment with Givlaari, increases in blood homocysteine levels have been observed compared to levels before treatment [see Section 4.8 Adverse Effects (Undesirable Effects)]. The clinical relevance of the elevations in blood homocysteine during treatment with Givlaari is unknown.

Measurement of blood homocysteine levels prior to initiating treatment and monitoring for changes during treatment with Givlaari is recommended. In patients with elevated homocysteine levels, consider supplementation with vitamin B6.

Use in renal impairment

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.

Use in the elderly

There are no special precautions for the use of Givlaari in the elderly.

Paediatric use

The safety and efficacy of Givlaari in children aged < 12 years of age has not been established. No data are available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

In vitro studies indicated that givosiran does not directly inhibit or induce CYP isozymes; however, due to its pharmacological effects on the hepatic heme biosynthesis pathway, givosiran has the potential to reduce the activity of CYP450 enzymes in the liver. 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

Effects on fertility

There are no data available on the effects of givosiran on human fertility. No adverse effects on male or female fertility were observed with givosiran in rats at subcutaneous doses up to 30 mg/kg/week (9 times the recommended clinical dose adjusted for body surface area and dosing frequency).

Use in pregnancy

Category B3

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. 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 fetus.

Embryofetal development studies have been performed with givosiran in rats and rabbits, and involved subcutaneous administration during organogenesis up to maternotoxic dose levels.

No adverse effects on embryofetal development were observed in rats at doses up to 5 mg/kg/day (10 times the recommended clinical dose adjusted for body surface area and dosing frequency). Increased post-implantation loss as a result of increased early resorptions was observed in rabbits at ≥1.5 mg/kg/day (6 times the normalised clinical dose), and abortions occurred at higher doses (5 mg/kg/day or after a single 20 mg/kg dose). An increased incidence of skeletal variations of the sternebrae was seen at 20 mg/kg. Malformations were not observed. The adverse effects on embryofetal development in the rabbit are considered to be secondary to marked maternal toxicity, and not to reflect a direct effect of givosiran on the developing embryo or fetus.

In a pre-/postnatal development study in rats, maternal administration at ≤30 mg/kg every 6 days during gestation and lactation had no effect on growth and development of the offspring.

Use in lactation

It is unknown whether givosiran is excreted in human milk. A risk to the newborns/infants cannot be excluded. Excretion of givosiran in milk has been demonstrated in rats. 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.

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 ADVERSE EFFECTS (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
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 suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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. ALAS1 is the first and rate-limiting enzyme of heme synthesis in the liver. Its expression is induced in AHP due to a loss-of-function gene mutation in a downstream heme synthesis enzyme. Givosiran acts to reduce elevated levels of liver *ALAS1* mRNA. This leads to reduced circulating levels of neurotoxic heme 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 trials

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.

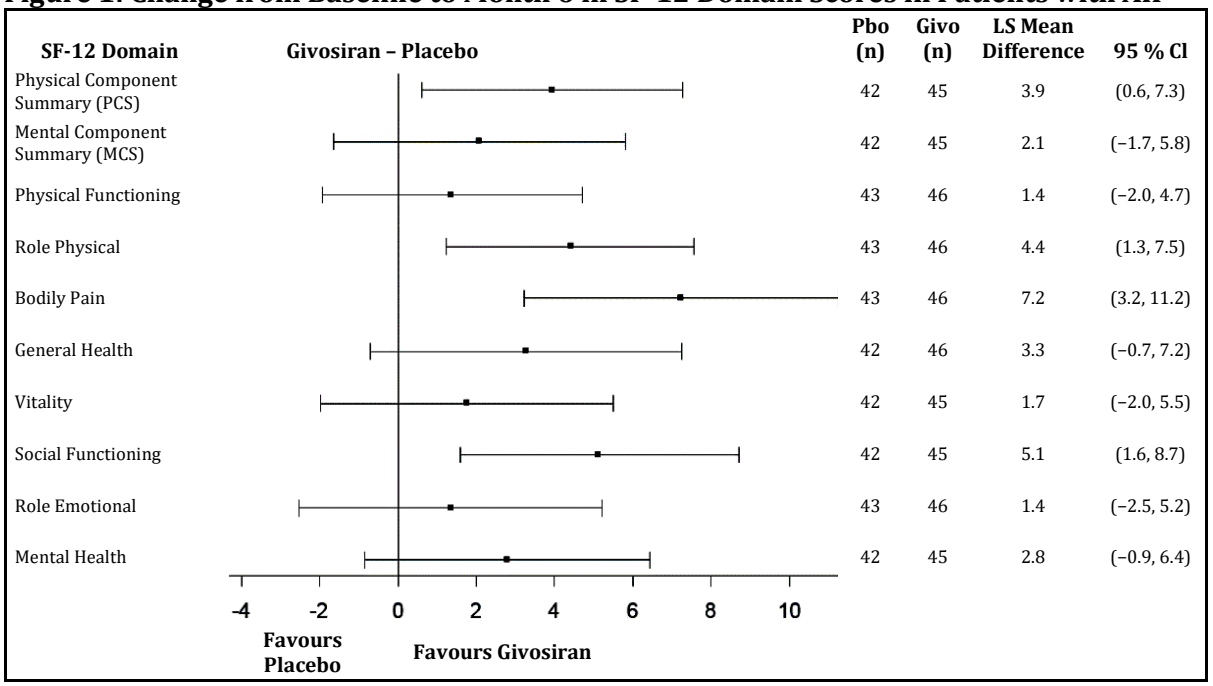
[b] Based on negative binomial regression model. A rate ratio < 1 represents a favourable outcome for givosiran.

[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.

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_{0-24}) 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 (Vd/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.

Excretion

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 Section 4.2 Dose and Method of Administration and Section 4.4 Special Warnings and Precautions for Use).

Renal impairment
Adult patients with mild renal impairment (eGFR ≥ 60 to < 90 mL/min/1.73 m^2), moderate renal impairment (eGFR ≥ 30 to < 60 mL/min/1.73 m^2) or severe renal impairment (eGFR ≥ 15 to < 30 mL/min/1.73 m^2) 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 m^2). No studies have been conducted in patients with end-stage renal disease or patients with dialysis (see Section 4.2 Dose and Method of Administration and Section 4.4 Special Warnings and Precautions for Use).

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

Genotoxicity

Givosiran was negative in assays for mutagenicity in bacteria (Ames test), and for clastogenicity *in vitro* (chromosomal aberration assays in human lymphocytes) and *in vivo* (rat bone marrow micronucleus test).

Carcinogenicity

The carcinogenic potential of givosiran was investigated in a 26-week study in transgenic (Tg-rasH2) mice and in an 85- to 89-week study in Sprague Dawley rats. Both studies involved once monthly subcutaneous administration. Givosiran was not carcinogenic in transgenic mice up to the highest dose tested, 1500 mg/kg/month (yielding >300 -times the exposure in patients at the recommended dose of 2.5 mg/kg/month, based on plasma AUC). Male rats showed an increase in hepatocellular adenomas with treatment at 100 mg/kg/month (40 times the exposure in patients). No treatment-related increase in tumour incidence was observed in male rats at ≤50 mg/kg/month (relative exposure, 17) or in female rats up to the highest dose tested (≤100 mg/kg/month; relative exposure, 33).

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

In Australia, information on the shelf-life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 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.

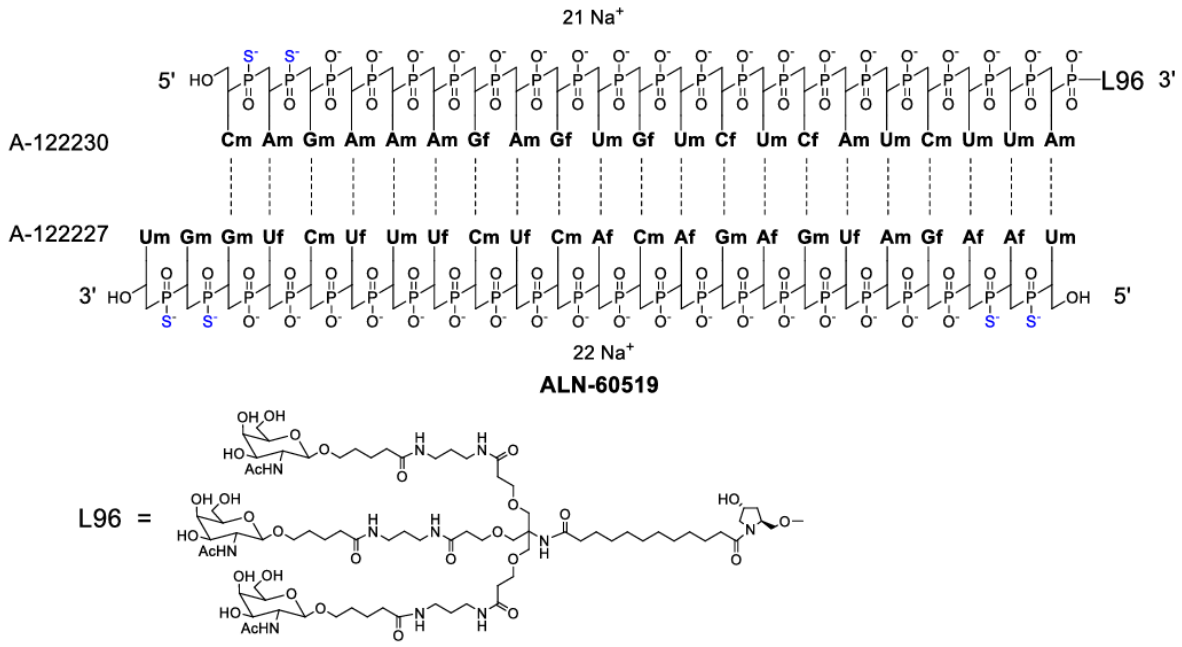
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Each vial is for a single use in a single patient only. Discard any unused portion left in a vial, as the product contains no preservatives.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

1639325-44-2 (givosiran sodium)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Medison Pharma Australia Pty Ltd
1 Bligh Street
Sydney NSW 2000
Australia

Phone: 1800 566 020

Email: MedInfo.Australia@Medisonpharma.com
www.medisonpharma.com.au

9 DATE OF FIRST APPROVAL

28 November 2023

10 DATE OF REVISION

25 July 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	New sponsor details