▼ 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 – REDEMPLO® (PLOZASIRAN) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Plozasiran

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose pre-filled syringe contains plozasiran sodium equivalent to 25 mg plozasiran in 0.5 mL solution.

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

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to yellow solution with a pH of approximately 4.7 – 5.6 and osmolality of 320 – 380 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

REDEMPLO is indicated as an adjunct to diet to reduce triglyceride levels for adult patients with familial chylomicronaemia syndrome (FCS) for whom standard triglyceride lowering therapies have been inadequate (see Section 4.2 for patient selection criteria).

4.2 DOSE AND METHOD OF ADMINISTRATION

Patients and/or caregivers should be trained to administer plozasiran under the supervision of a physician experienced in the treatment of patients with FCS in accordance with Consumer Medicine Information and Instructions for Use documents.

Patient selection

When considering the use of REDEMPLO, it is important that FCS diagnosis of a patient is established by either genetic testing, or by the presence of the following clinical criteria: fasting triglyceride levels ≥ 10 mmol/L (≥ 880 mg/dL) that are refractory to standard lipid-lowering therapy and at least one of the following: prior history of acute pancreatitis not caused by alcohol or cholelithiasis, history of recurrent hospitalisations for severe abdominal pain without other explainable cause, history of childhood pancreatitis, or family history of hypertriglyceridaemia-induced pancreatitis.

Dosage

The recommended dosage of plozasiran is 25 mg administered as a single subcutaneous injection every 3 months.

If a dose is missed, administer REDEMPLO as soon as possible. Thereafter, dosing should be resumed every 3 months from the most recently administered dose.

Special populations

Elderly population

No dose adjustment is necessary for elderly patients ≥ 65 years of age (see Section 5.2 Pharmacokinetic properties).

Renal impairment

No dose adjustment is necessary for patients with mild (estimated glomerular filtration rate (eGFR) ≥ 60 to < 90 mL/min) or moderate (eGFR ≥ 30 to < 60 mL/min) renal impairment. REDEMPLO has not been studied in patients with severe renal impairment or end stage renal disease (eGFR < 30 mL/min) and should only be used in these patients if the anticipated clinical benefit outweighs the potential risk (see Section 5.2 Pharmacokinetic properties).

Hepatic impairment

No dose adjustment is necessary in patients with elevation of aspartate aminotransferase (AST) > upper limit of normal (ULN) and total bilirubin ≤ ULN, or in total bilirubin (total bilirubin > 1.0 to 1.5×ULN). REDEMPLO has not been studied in patients with moderate or severe hepatic impairment and should only be used in these patients if the anticipated clinical benefit outweighs the potential risk (see Section 5.2 Pharmacokinetic properties).

Paediatric population

The safety and efficacy of this medicinal product in children and adolescents <18 years of age have not yet been established. No data are available.

Method of administration

This medicinal product is intended for subcutaneous use only. It should not be administered intramuscularly or intravenously.

Each pre-filled syringe is for single use only.

The first injection administered by the patient or caregiver should be performed under the guidance of an appropriately qualified health care professional.

Sites for injection include upper arm (when administered by caregiver), thigh, and abdomen (except within two inches of the navel). This medicinal product should not be injected into an area where the skin is tender, bruised, red, hard, cut, with scars or stretch marks. This medicinal product should not be injected in the same area where other medicines are injected.

For instructions on handling of the medicinal product before administration, see Section 6.6 Special precautions for disposal.

Refer to the Instructions for Use for detailed instructions for the administration of the medicinal product.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use in the elderly

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

Paediatric use

No data available.

Endocrine and Metabolism

Modest increases in HbA1c were observed in the Phase 3 study, particularly in patients with prediabetes or diabetes at baseline (see Section 4.8 Adverse effects). Treatment-emergent adverse events related to hyperglycaemia occurred more frequently in plozasiran-treated patients than placebo (see Section 4.8 Adverse effects).

Monitor patients with or at risk of impaired glucose tolerance for changes in glycaemic parameters accordingly.

Monitoring and Laboratory Tests

Lipid parameters should be monitored periodically during treatment with REDEMPLO, particularly in patients who demonstrate elevated low-density lipoprotein-cholesterol (LDL-C) while on therapy or in patients at high risk for cardiovascular disease.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No clinical drug interaction studies have been conducted.

Plozasiran uptake by the liver is assisted by asialoglycoprotein receptor. *In vitro*, plozasiran is not a substrate of cytochrome P450 (CYP450) enzymes or the following transporters, BCRP, P-glycoprotein, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3 and OCT2. *In vitro*, plozasiran was not an inhibitor of CYP450 enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4), inducer of CYP1A2, 2B6 or 3A4 or inhibitor of BCRP, BSEP, P-glycoprotein, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 at clinically relevant concentrations. Clinically relevant pharmacokinetic interactions are not expected between plozasiran and concomitant medications involving inhibition or modification of CYP450 enzymes or commonly encountered drug transporters.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No clinical data on the effect of this medicinal product on human fertility are available. In a fertility and early embryonic development study in rats, males and females were administered subcutaneously (SC) with vehicle or plozasiran at doses up to 50 mg/kg or rat specific surrogate at 25 mg/kg. Males were treated once weekly before and throughout cohabitation, while females received treatment once every 3 days before and throughout mating until the time of implantation.

There were no adverse effects on mating and fertility in males or females up to 50 mg/kg (achieving up to 92-fold in females and 130-fold in males the plasma AUC at a clinical dose level of 25 mg).

Use in pregnancy – Pregnancy Category B1

There are no data on the effect of plozasiran in pregnant women.

In an embryofetal development study in rats, plozasiran was administered up to 60 mg/kg SC once daily during the period of organogenesis. Another group received 60 mg/kg/day SC rat-specific surrogate during the same period. There was no evidence of drug-related embryofetal toxicity or fetal malformations up to 60 mg/kg/day plozasiran (achieving 83-fold the plasma AUC at a clinical dose level of 25 mg). At maternally toxic doses there were embryofetal toxicities including increases in post-implantation loss at 60 mg/kg, lower fetal body weights, and fetal skeletal developmental variations at ≥15 mg/kg (20-fold the plasma AUC at a clinical dose of 25 mg). No adverse embryofetal developmental effects were observed in the group that received the rat specific surrogate, where less maternotoxicity was observed, or in a rabbit embryofetal development study with daily SC doses of plozasiran up to 180 mg/kg (achieving 628-fold the plasma AUC at a clinical dose of 25 mg) during the period of organogenesis.

In a pre/postnatal development study in rats, plozasiran was administered up to 80 mg/kg SC once a week during gestation (from implantation) through lactation. There were no adverse effects on pups that could be attributed to maternal exposure of up to 24 mg/kg SC weekly (achieving 30-fold the plasma AUC at a clinical dose of 25 mg). Lower offspring body weight was seen at maternal weekly SC doses ≥24 mg/kg. No adverse effects were noted on offspring development up to 80 mg/kg SC weekly (achieving 193-fold the plasma AUC at a clinical dose of 25 mg).

As a precautionary measure, it is preferable to avoid the use of REDEMPLO during pregnancy.

Use in lactation

It is unknown whether plozasiran or metabolites are excreted in human milk or the effects on milk production or milk quality.

There is no information on the excretion of plozasiran/metabolites in animal milk. In a pre/postnatal study in rats, lower weight gain was seen in breast-fed pups following maternal exposure, likely due to the pharmacology of plozasiran affecting milk quality.

A risk to the newborn infant cannot be excluded.

Consider whether to discontinue breast-feeding or to discontinue/abstain from REDEMPLO 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

REDEMPLO 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 common adverse reaction is hyperglycaemia (12.8%).

Tabulated list of treatment-emergent adverse events and adverse reactions

Table 1 and Table 2 summarize treatment-emergent adverse events and adverse reactions observed from three clinical trials with 25 mg plozasiran (one phase 3 study in patients with FCS and two phase 2 studies in patients with severe hypertriglyceridemia and moderate hypertriglyceridemia).

Table 1: Treatment-Emergent Adverse Events (TEAEs) Occurring in >2% of Patients in Phase 2 and Phase 3 Clinical Studies with Plozasiran 25 mg[a]

TEAE, n (%)	Placebo N=173	Plozasiran 25 mg N=148
Hyperglycaemia[b]	17 (9.8)	19 (12.8)
Injection Site Reaction[c]	2 (1.2)	7 (4.7)
COVID-19	21 (12.1)	23 (15.5)
Headache	8 (4.6)	10 (6.8)
Nausea	2 (1.2)	7 (4.7)
Lipase increased	3 (1.7)	6 (4.1)
Sinusitis	2 (1.2)	6 (4.1)
Palpitations	0 (0.0)	4 (2.7)
Blood pressure increased	0 (0.0)	4 (2.7)

Abbreviation: TEAE=treatment-emergent adverse event.
[a] Frequency greater in plozasiran treated patients versus placebo treated patients irrespective of causality.
[b] Hyperglycaemia included observed preferred terms: diabetes mellitus, diabetes mellitus inadequate control, glucose tolerance impaired, glucose urine present, glycosylated haemoglobin increased, haematocrit decreased, hyperglycaemia, type 2 diabetes mellitus, and blood glucose increased.
[c] Injection Site Reaction included observed preferred terms: injection site erythema, injection site pain, injection site pruritus, and injection site reaction.

The following adverse reactions (Table 2) are listed according to the MedDRA system organ class and by frequency. The frequency categories are defined using the following conventions: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse drug reactions

System Organ Class	Adverse reaction	Frequency
Metabolism and nutrition disorders	Hyperglycaemia[a]	very common
Nervous system disorders	Headache	common
General disorders and administration site conditions	Injection site reaction[b]	common

[a] Hyperglycaemia included observed preferred terms: diabetes mellitus, diabetes mellitus inadequate control, glucose tolerance impaired, glucose urine present, glycosylated haemoglobin increased, haematocrit decreased, hyperglycaemia, type 2 diabetes mellitus, and blood glucose increased.
[b] Injection Site Reaction included observed preferred terms: injection site erythema, injection site pain, injection site pruritus, and injection site reaction.

Description of selected adverse reactions

Hyperglycaemia

Plozasiran was associated with small, non-progressive increases in HbA1c. At Month 10 (after three doses), median HbA1c increases were +0.20% (baseline <5.7%, n=31), +0.45% (baseline 5.7–<6.5%, n=6) and +0.75% (baseline ≥6.5%, n=4). HbA1c values generally plateaued thereafter and remained stable between Months 12 and 24 in the open-label extension.

Hyperglycaemia (e.g., diabetes mellitus, glycosylated haemoglobin increased, hyperglycaemia, type 2 diabetes mellitus, and blood glucose increased) occurred at a rate of 12.8% in patients treated with plozasiran compared with 9.8% in patients treated with placebo, but discontinuation due to hyperglycaemia was uncommon (0.68%).

Patients with pre-existing diabetes or impaired glycaemic control should undergo monitoring of HbA1c or blood glucose according to standard clinical practice.

Injection Site Reactions

Injection site reaction occurred in 4.7% and 1.2% of plozasiran and placebo patients, respectively, in the placebo-controlled studies. All of these adverse reactions were mild in severity. No patients discontinued treatment or required alterations or delays in dosing due to injection site reactions. Injection site reaction events in patients treated with plozasiran included injection site erythema (0.7%), injection site pain (2.7%), and injection site reaction (1.4%).

Laboratory Observations

Increased Hepatic Transaminases

In Phase 2 and Phase 3 clinical studies, there were more frequent elevations > the upper limit of normal (ULN) of serum hepatic transaminases in patients on plozasiran than placebo. These elevations did not progress to exceed the clinically relevant threshold of >5 × ULN and did not require dosage adjustment or treatment discontinuation.

LDL-C Levels

Treatment with REDEMPLO is associated with increases in LDL-C. In clinical studies, median LDL-C increased from approximately 0.55 mmol/L at baseline to 1.0–1.1 mmol/L by Month 10, with levels generally plateauing thereafter.

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

Doses as high as 100 mg (4 times the recommended clinical dose) were administered in Phase 1 studies and did not result in any safety concerns. There is no specific treatment for plozasiran overdose. In the event of an overdose, the patient should be treated symptomatically and supportive measures instituted as required.

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: lipid modifying agents, other lipid modifying agents, proposed ATC code: C10AX20 plozasiran.

Mechanism of action

Plozasiran is a small interfering RNA (siRNA, double-stranded oligonucleotide) conjugated with N-acetylgalactosamine to facilitate delivery to and uptake by hepatocytes. In hepatocytes, plozasiran selectively degrades the mRNA for apolipoprotein C3 (APOC3) through the RNA interference mechanism resulting in reduced levels of hepatic and serum APOC3 protein. This, in turn, enhances the activity of lipoprotein lipase and hepatocyte uptake of triglyceride-rich lipoprotein remnants leading to decreases in serum triglycerides.

Pharmacodynamic effects

In the PALISADE study, 25 mg plozasiran administered every 3 months in patients with FCS decreases APOC3, triglyceride (TG), non-high density lipoprotein cholesterol (non-HDL-C), and very low-density lipoprotein cholesterol (VLDL-C), and increases HDL-C and LDL-C. The median reductions in fasting serum APOC3 protein and TG at Month 1 were 95% and 85%, respectively, suggesting pharmacodynamic steady-state is achieved following the first dose.

Cardiac electrophysiology

A dose of 100 mg plozasiran (4 times the recommended dose) did not prolong the QT interval to any clinically relevant extent.

Clinical trials

PALISADE phase 3 study in patients with FCS

PALISADE is a randomised, double-blind, placebo-controlled study in 75 adult patients with FCS maintained on a low-fat diet. Patients ≥ 18 years of age received 4 single subcutaneous injections of either 25 mg plozasiran (N=26), 50 mg plozasiran (N=24) or placebo (N=25) administered every three months. Plozasiran 50 mg is not an approved dosage regimen for FCS. Patients with a diagnosis of FCS and fasting triglycerides ≥ 10 mmol/L (≥ 880 mg/dL) that were refractory to standard lipid-lowering therapy were included.

A diagnosis of FCS was defined as patients with a history of fasting triglycerides > 11.3 mmol/L (>1000 mg/dL) and either:

- A supportive genetic test (N=41 [54.7%]), or evidence of low lipoprotein lipase (LPL) activity, or
- Clinically diagnosed FCS (N=34 [45.3%]) further defined as:
  - with either recurrent episodes of acute pancreatitis not caused by alcohol or cholelithiasis, or
  - history of childhood pancreatitis, or
  - family history of hypertriglyceridaemia-induced pancreatitis, or

- history of recurrent hospitalisations for severe abdominal pain without other explainable cause.

Mean age was 46.0 years with more patients in the 50 mg plozasiran group being < 50 years of age (83.3%) than in the 25 mg plozasiran or placebo groups (57.7% and 56.0%, respectively). The number of patients ≥ 65 years of age was 9 (12%), and those ≥ 75 years of age was 2 (3%). The five prototypical variants (all study participants) were represented: APOA5 – 2.3%, APOC2 - 2.3%, GPIHBP1 – 9.1%, LMF1 – 6.8%, LPL – 81.8%.

Approximately half of the patients in each treatment group were male. Most patients were white (73.3%) or Asian (21.3%). Mean body mass index (BMI) was 25.5 kg/m^2; 53.3% of subjects were overweight (BMI ≥ 25 kg/m^2).

A total of 89.3% of the patients had experienced a prior episode of pancreatitis. Percentages of patients on triglyceride lowering therapies at baseline were: 66.7% on fibrates, 29.3% on icosapent ethyl, omega-3 fatty acid or fish oil, and 45.3% were on statins. At study entry, 26.7% of patients were not using background TG lowering therapies.

The majority of patients received all four planned doses: 23 (88.5%) patients in the 25 mg plozasiran group, 22 (91.7%) patients in the 50 mg plozasiran group and 19 (76.0%) patients in the placebo group.

The primary efficacy endpoint was median percent change from baseline at month 10 in fasting triglycerides. At month 10, Plozasiran statistically significantly reduced median fasting triglyceride levels at the 25 mg recommended dose (see Table 3). The triglyceride lowering effects of 50 mg plozasiran did not offer a therapeutic benefit over the recommended 25 mg dose.

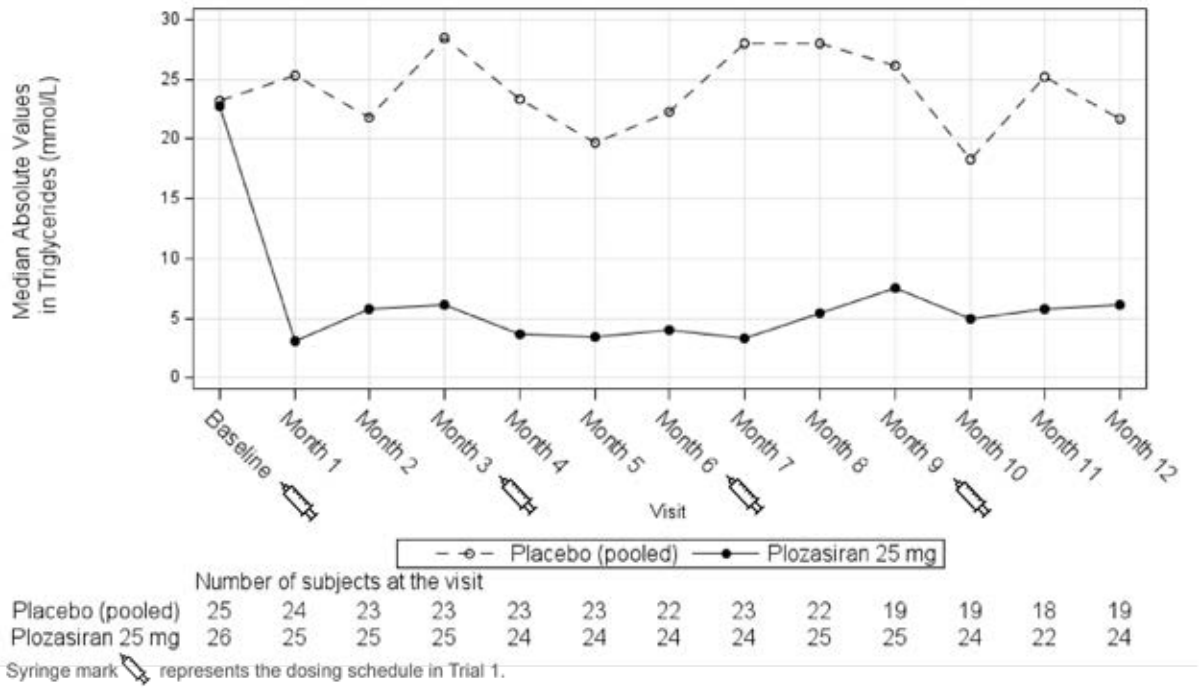
The reductions in triglyceride levels observed in plozasiran-treated patients were apparent at month 1 (first post-baseline measurement) and remained consistent throughout the 12-month duration of PALISADE study with relatively small peak-to-trough fluctuations (see Figure 1). Median triglyceride levels achieved at several timepoints throughout the treatment period were below the recognised threshold of 5.7 mmol/L (500 mg/dL) for increased risk of acute pancreatitis (see Figure 1).

Table 3: Median difference in percent change from baseline in fasting triglycerides and APOC3 in patients with FCS at month 10 in PALISADE

Treatment group	placebo (N=25)	plozasiran 25 mg (N=26)
Baseline TG (mmol/L)		
N	25	26
Median	23.2	22.7
Min, Max	8.4, 50.0	9.3, 63.3
Month 10 TG (mmol/L)		
N	19	24
Median (mmol/L)	18.2	5.0
Min, Max	2.6, 58.9	0.9, 32.2
Median percent change at month 10 from baseline in fasting TG	-17	-80
Difference from placebo		-58.7
95% CI		[-89.6, -27.9]
P-value		< 0.0001

Treatment group	placebo (N=25)	plozasiran 25 mg (N=26)
Median percent change at month 10 from baseline in fasting APOC3	-1.3	-93.0
Difference from placebo		-90.5
95% CI		[-108.3, -72.7]
P-value		p < 0.0001

Figure 1: Median absolute fasting triglyceride levels in patients with FCS during PALISADE



When compared to placebo, the combined doses of 25 mg and 50 mg plozasiran significantly reduced the incidence of acute pancreatitis (odds ratio, 0.169; 95% CI: 0.030, 0.942; P=0.0292). The odds of acute pancreatitis were 83% lower in the pooled plozasiran groups compared with the placebo group, with 7 pancreatitis events occurring in 5 (20%) subjects in the placebo group and 2 pancreatitis events occurring in 2 (4%) subjects in the pooled plozasiran groups.

Among patients with fasting triglyceride measurements at month 10, all patients in the 25 mg plozasiran group experienced decreases from baseline and approximately 80% of patients experienced at least a > 50% decrease from baseline.

A prespecified subgroup analysis of genetically confirmed versus clinically diagnosed FCS patients showed that the patients had a similar triglyceride response to plozasiran independent of their confirmed genetic characteristics.

PALISADE Open Label Extension (OLE) study in patients with FCS

Of the 64 patients who completed 12 months of randomised study treatment, 62 (97%) entered the OLE period, where all patients received plozasiran. Of these patients, 18 (29%) received placebo

(placebo/plozasiran group) and 44 (71%) received plozasiran (plozasiran/plozasiran group) during the randomised period.

As expected, median absolute values of fasting TGs at OLE baseline (month 12) were higher in patients who received placebo in the randomised period (placebo/plozasiran group; 23.76 mmol/L [2103 mg/dL]) compared to the plozasiran/plozasiran group (6.31 mmol/L [558 mg/dL]). Notably, for those in the placebo/plozasiran group, median TGs had already fallen to a level similar to the plozasiran/plozasiran group after the first month of plozasiran treatment (month 13; 3.67 mmol/L [325 mg/dL; -87.96%] and 6.0 mmol/L [531 mg/dL; -75.23%] in the placebo/plozasiran and plozasiran/plozasiran groups, respectively); allowing for the expected variability in fasting TGs and measurements taken at trough, these reductions were sustained through month 18 of the OLE period.

Immunogenicity

In PALISADE study, over the double-blind period of 12 months, none of the 50 FCS-patients treated with plozasiran developed treatment-induced or treatment-boosted anti-drug antibodies (ADA). In the ongoing open label extension period, there was only 1 subject who developed new-onset ADA against plozasiran with low titers after switching to active plozasiran from placebo. There was no evidence to indicate that plozasiran pharmacokinetics, pharmacodynamics or efficacy changed over time following multiple administrations of REDEMPLO. No adverse effects related to systemic immunoreaction were found in the plozasiran-treated patients.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following a single subcutaneous injection of 25 mg plozasiran, the mean peak plasma concentration (C_{max}) is 110 ng/mL. The median time to reach C_{max} (T_{max}) is 4.1 hours.

Plozasiran has not been dosed by intravenous administration in any clinical studies, therefore, absolute bioavailability data in humans are not available. Following subcutaneous administration in cynomolgus monkeys, the absolute bioavailability of plozasiran was estimated to be 40%.

Distribution

Plozasiran is distributed in plasma and extracellular body water. In plasma, plozasiran has an unbound fraction of approximately 20%. Plozasiran is distributed in plasma and extracellular body water with apparent mean volume of distribution (V_z/F) of 137 L in the terminal-phase of elimination. Based on animal studies, once in systemic circulation, plozasiran is expected to be primarily distributed to the liver.

Metabolism

Plozasiran is primarily metabolised by nucleases in the liver to shorter nucleotides of varying lengths. *In vitro* studies suggest that plozasiran is not a substrate of cytochrome P450 enzymes.

Excretion

The terminal elimination half-life of plozasiran in plasma is approximately 3-4 hours. The mean apparent systemic clearance is 25.1 L/hour. Approximately 16-19% of plozasiran dose is excreted in urine.

Linearity/non-linearity

Plozasiran exhibited linear and time-invariant pharmacokinetics following single or repeated subcutaneous injections within the dose range of 10 mg to 50 mg. The plasma exposure of plozasiran (C_{max}, AUC_{0-t} and AUC_{0-inf}) values increased proportionally to the dose.

Pharmacokinetic/Pharmacodynamic Relationships

Plozasiran is active inside hepatocytes with prolonged pharmacodynamic activity that is disconnected from its pharmacokinetic profile in the plasma compartment. The long duration of action is beyond the plasma elimination half-life of 3-4 hours. Pharmacodynamic response is likely saturated at the recommended dose of 25 mg every 3 months.

Special Populations

Elderly (≥ 65 years of age)

No clinically significant differences in plozasiran pharmacokinetics based on age were found in a population pharmacokinetic analysis conducted with data from adult healthy subjects and patients (N=146, age 65-74 years [N=16]; age 75-85 years [N=4]) (see Section 4.2 Dose and method of administration).

Renal impairment

No clinically significant differences in plozasiran pharmacokinetics based on mild (eGFR ≥ 60 to < 90 mL/min) or moderate (eGFR ≥ 30 to < 60 mL/min) renal impairment were found in the population pharmacokinetic analysis that included data from 23 and 4 subjects with mild and moderate degrees of renal impairment, respectively. Plozasiran has not been tested in patients with severe renal impairment or end stage renal disease (eGFR < 30 mL/min) (see Section 4.2 Dose and method of administration).

Hepatic impairment

No clinically significant differences in plozasiran pharmacokinetics were found in the population pharmacokinetic analysis that included data from 4 subjects with mild and transient elevation of total bilirubin ≤ 1× ULN and AST > 1× ULN, or total bilirubin > 1.0 to 1.5× ULN and any AST. Plozasiran has not been studied in patients with moderate or severe hepatic impairment (see Section 4.2 Dose and method of administration).

Gender and Race

No clinically significant differences in plozasiran pharmacokinetics based on gender or race were found in the population pharmacokinetic analysis that included data from 65 (44.5%) female and 81 (55.5%) male subjects with diverse race or ethnicity (67.1% White, 11.0% Black, 9.6% Asian, 2.1% Native Hawaiian or Pacific Islander, and 10.3% multiracial or unknown).

Other special populations

Plozasiran plasma exposures (C_{max} and AUC) are typically lower in patients with higher body weights or body mass index (BMI) without reduced treatment efficacy and therefore no dose adjustment is recommended for heavier patients.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Plozasiran was negative for mutagenicity in the bacterial mutation (Ames) assay, negative for induction of micronuclei in cultured TK6 lymphoblastoid cells and negative in a mouse micronucleus test.

Carcinogenicity

In a 26-week study in CByB6F1-Tg[HRAS]2Jic mice, plozasiran was administered subcutaneously every 8 weeks at dose levels up to 120 mg/kg (achieving up to 95-fold the plasma AUC at a clinical dose level of 25 mg). Plozasiran was not carcinogenic up to the highest dose evaluated.

In a 2-year rat carcinogenicity study with subcutaneous administration of plozasiran every 8 weeks, hepatocellular adenomas and a low incidence of carcinomas were noted in males at 50 mg/kg and females at 100 mg/kg. No evidence of carcinogenicity was noted at 25 mg/kg in males and 40 mg/kg in females (82- and 72-fold the plasma AUC at a clinical dose of 25 mg in males and females, respectively). In addition, while the relevance of these tumours to humans is unknown, the available evidence suggests these findings may be specific to rodents and coupled with the high safety margins and the absence of identified genotoxicity, the risk to humans is low.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride
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 Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C. (Refrigerate. Do Not Freeze).

REDEMPLO is a sterile, clear, colourless to yellow solution. REDEMPLO should be inspected visually for particulate matter and discoloration prior to administration.

REDEMPLO can be kept at room temperature (less than 25°C) in the original carton for up to 30 days after removing from the refrigerator.

6.5 NATURE AND CONTENTS OF CONTAINER

Single-dose, type I glass pre-filled syringe with a bromobutyl stopper and needle with shield. Each pre-filled syringe contains 0.5 mL solution for injection.

Pack size of one pre-filled syringe.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

This medicinal product should be inspected visually prior to administration. The solution should be clear and colourless to yellow. If the solution is cloudy, discoloured, or contains visible particulate matter, the contents must not be injected, and the medicinal product should be returned to the pharmacy.

The pre-filled syringe should be allowed to reach room temperature (15-25°C) prior to injection. It should be removed from the refrigerator (2-8°C) at least 30 minutes before use. Other methods of warming (e.g., hot water or microwave) should not be used.

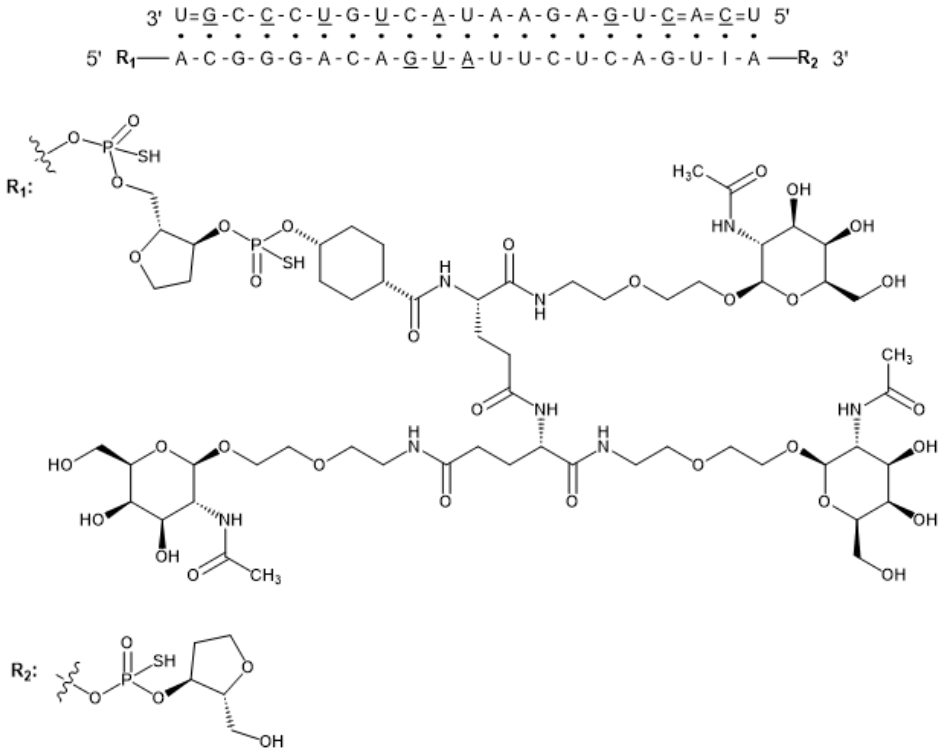
Each pre-filled syringe should be used once and then placed in a sharps disposal container for disposal according to community guidelines.

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

6.7 PHYSICOCHEMICAL PROPERTIES

Plozasiran sodium is a small interfering ribonucleic acid (siRNA) duplex, comprising two complementary, fully synthetic RNA strands. It is a white to off-white powder, free of foreign particulate matter, and is freely soluble in water and the formulation buffer (0.5 mM sodium phosphate monobasic, 0.5 mM sodium phosphate dibasic) and 0.9% sodium chloride (normal saline). The pH of a 1% aqueous solution is 6.2 - 6.4.

Chemical structure



Abbreviations: A = 2'-O-methyl adenosine; A = 2'-fluoro (2'-deoxy-2'-fluoro) adenosine; C = 2'-O-methyl cytidine; C = 2'-fluoro cytidine; G = 2'-O-methyl guanosine; G = 2'-fluoro guanosine; I = 2'-O-methyl inosine; U = 2'-O-methyl uridine; U = 2'-O-fluoro uridine; - (single line) = phosphodiester linkage; = (double line) = phosphorothioate linkage; · (middle dot) depicts base pairing between the two strands

CAS number

2379776-40-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

Arrowhead Australia Pty Ltd

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9 DATE OF FIRST APPROVAL

24 April 2026

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	New/initial PI document