ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

Redemplo 25 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each mL solution contains 50 mg plozasiran.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (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 in adult patients with familial chylomicronaemia syndrome (FCS) (see section 4.2 for patient selection criteria).

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the treatment of patients with FCS.

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 (TG) 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.

Posology

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

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

Elderly
No dose adjustment is required for elderly patients ≥ 65 years of age (see section 5.2).

Renal impairment
No dose adjustment is required for patients with mild (estimated glomerular filtration rate (eGFR) ≥ 60 to < 90 mL/min) or moderate (eGFR ≥ 30 to < 60 mL/min) renal impairment. Plozasiran 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).

Hepatic impairment
No dose adjustment is required for patients with elevation of aspartate aminotransferase (AST) > upper limit of normal (ULN) and total bilirubin ≤ 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 and should only be used in these patients if the anticipated clinical benefit outweighs the potential risk (see section 5.2).

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 healthcare professional.

Sites for injection include the upper arm (when administered by a caregiver), thigh, and abdomen (except for a 5 cm area around the navel). This medicinal product should not be injected into an area where the skin is tender, bruised, red, hard, or cut, or 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.

Detailed instructions for use are provided at the end of the package leaflet.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hyperglycaemia
Data suggest that plozasiran may increase blood glucose levels in some patients. Hyperglycaemia occurred in more patients on plozasiran, compared to patients on placebo in the placebo-controlled studies (see section 4.8). Some patients with diabetes or at increased risk of developing diabetes may develop a degree of hyperglycaemia requiring treatment as prescribed for diabetes. These patients should be monitored both clinically and biochemically, in accordance with national guidelines.

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

4.5 Interaction with other medicinal products and other forms of interaction

No clinical interaction studies have been conducted.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of plozasiran in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

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

Breast-feeding

It is unknown whether plozasiran/metabolites are excreted in human milk. There is no information on the excretion of plozasiran/metabolites in animal milk. A risk to newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from plozasiran therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No clinical data on the effect of this medicinal product on human fertility are available. Plozasiran had no effect on fertility in rats. The collective data from the monkeys and rats indicate that the clinical relevance of the lower reproductive organ weights noted in a subset of the male monkeys is unlikely and the risk for impact to male fertility and reproductive organ development in humans is low (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are hyperglycaemia (12.8%), headache (6.8%), nausea (4.7%), and injection site reaction (4.7%).

Adverse events leading to discontinuation of treatment were hyperglycaemia (0.7%) and urticaria (0.7%).

Tabulated list of adverse reactions

Table 1 presents the adverse reactions reported in patients treated with 25 mg plozasiran in three placebo-controlled clinical studies (two phase 2 studies in patients with severe hypertriglyceridaemia and moderate hypertriglyceridaemia and one phase 3 study in patients with FCS).

The adverse reactions are listed according to the MedDRA system organ class and by frequency. The frequency categories are defined using the following convention: 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 order of decreasing seriousness.

Table 1. Adverse reactions

System organ class	Adverse reaction	Frequency
Metabolism and nutrition disorders	Hyperglycaemia[a]	Very common
Nervous system disorders	Headache	Common
Gastrointestinal disorders	Nausea	Common
Hepatobiliary disorders	Liver disorder (ALT increased, AST increased)	Uncommon
General disorders and administration site conditions	Injection site reaction[a]	Common

ALT = alanine aminotransferase; AST = aspartate aminotransferase.
[a] See section "Description of selected adverse reactions"

Description of selected adverse reactions

Hyperglycaemia
Hyperglycaemia occurred in 12.8% and 9.8% of plozasiran and placebo patients, respectively, in the placebo-controlled studies. The proportion of patients in each group who discontinued treatment due to hyperglycaemia was 1.4% and 0% in plozasiran and placebo patients, respectively. Hyperglycaemia events in patients treated with plozasiran included blood glucose increased (1.4%), diabetes mellitus (1.4%), glycosylated haemoglobin increased (4.1%), hyperglycaemia (1.4%), and type 2 diabetes mellitus (5.4%) (see section 4.4).

Injection site reaction
Injection site reactions 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%). Incidence of injection site reaction events was highest after the first dose and decreased with subsequent doses.

Laboratory observations

Increased hepatic transaminases
In phase 2 and phase 3 clinical studies, there were more frequent elevations > ULN of serum hepatic transaminases in patients on plozasiran than placebo. Asymptomatic transient elevations of ALT and AST > 3 x ULN occurred in 1.5% and 0.7%, respectively, of participants treated with plozasiran. These elevations did not progress to exceed the threshold of > 5 × ULN and did not require dose adjustment or treatment discontinuation.

LDL-C levels
Treatment with plozasiran may increase low-density lipoprotein cholesterol (LDL-C) levels. 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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Doses as high as 100 mg plozasiran (4 times the recommended 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lipid modifying agents, other lipid modifying agents, ATC code: not yet assigned

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 TG-rich lipoprotein remnants leading to decreases in serum TG.

Pharmacodynamic effects

In the PALISADE study, 25 mg plozasiran administered every 3 months in patients with FCS decreased APOC3, TG, non-high density lipoprotein cholesterol (non-HDL-C), and very low-density lipoprotein cholesterol (VLDL-C) (see also below under “Clinical efficacy”) and increased HDL-C and LDL-C. LDL-C levels remained within the normal range for most patients. 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
Doses of 100 mg plozasiran (4 times the recommended dose) did not prolong the QT interval to any clinically relevant extent.

Clinical efficacy

PALISADE study in patients with FCS
PALISADE is a randomised, double-blind, placebo-controlled clinical 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=23), 50 mg plozasiran (N=22) or placebo (N=19) administered every 3 months. Patients with a diagnosis of FCS and fasting TGs ≥ 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 TGs > 11.3 mmol/L (> 1,000 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%]) with either 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.

The mean age was 46 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%). 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). The number of patients with genetically confirmed FCS was 41, with 34 patients without genetic confirmation of FCS. Of the patients who received plozasiran, five variants were represented: APOA5 – 2.3%, APOC2 - 2.3%, GPIHBP1 – 9.1%, LMF1 – 6.8%, LPL – 81.8%. A total of 89.3% of the patients had experienced a prior episode of pancreatitis. Percentages of patients on TG lowering therapies at baseline were as follows: 66.7% were on fibrates, 29.3% were on icosapent ethyl, omega-3 fatty acid or fish oil, and 45.3% were on statins.

The majority of patients received all 4 planned doses; 24 (92.3%) 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 TGs. At month 10, plozasiran statistically significantly reduced median fasting TG levels at the 25 mg recommended dose (see Table 2). The TG lowering effects of 50 mg plozasiran did not offer a therapeutic benefit over the recommended 25 mg dose.

In the PALISADE study, 25 mg plozasiran administered every 3 months in patients with FCS significantly reduced median fasting serum APOC3 protein by 93% ($p < 0.0001$).

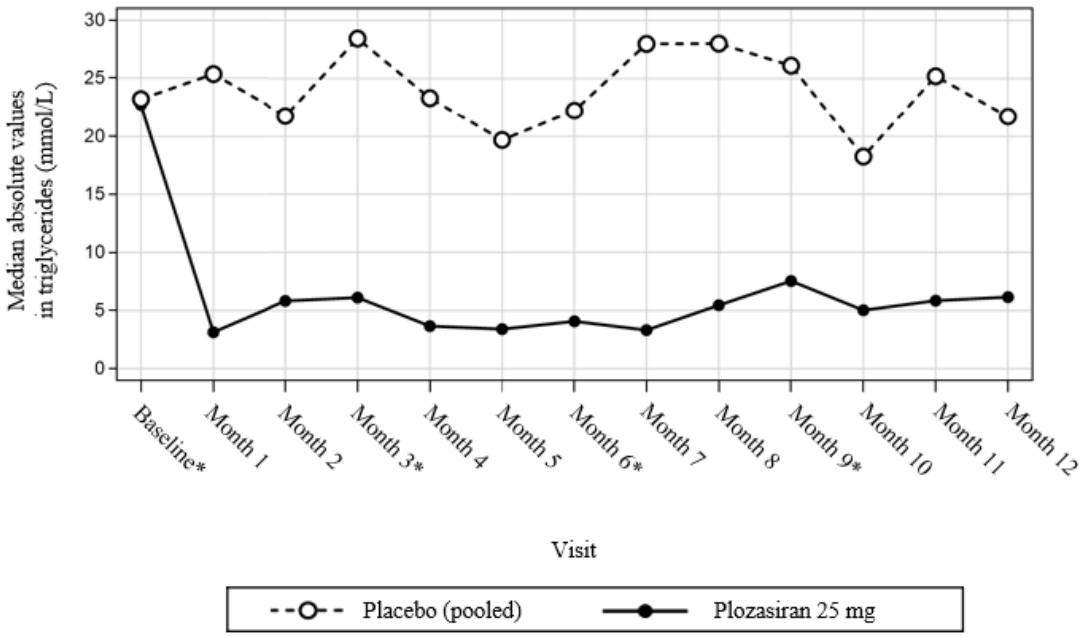
The reductions in TG levels observed in plozasiran-treated patients were apparent at month 1 (first post-baseline measurement) and remained consistent throughout the 12-month duration of the PALISADE study with relatively small peak-to-trough fluctuations (see Figure 1). Median TG levels achieved at 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 2: Median difference in percent change from baseline in fasting TG and APOC3 in patients with FCS at month 10 in PALISADE study

Treatment group	Placebo	Plozasiran 25 mg
Baseline TG (mmol/L)		
N	25	26
Median	23.2	22.7
Month 10 TG (mmol/L)		
N	19	24
Median	18.2	5.0
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		p < 0.0001
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

APOC3 = apolipoprotein C3; CI = confidence interval; FCS = familial chylomicronaemia syndrome; TG = triglyceride.

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



Number of subjects at the visit

Placebo (pooled)	25	24	23	23	23	23	22	23	22	19	19	18	19
Plozasiran 25 mg	26	25	25	25	24	24	24	24	25	25	24	22	24

* Represents the dosing schedule in PALISADE.

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

Among patients with fasting TG 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. In addition, 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; 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%) patients in the placebo group and 2 pancreatitis events occurring in 2 (4%) patients in the pooled plozasiran groups.

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. 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 [2 103 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 the PALISADE study, none of the 50 FCS patients treated with plozasiran over a period of 12 months developed treatment-induced or treatment-boosted anti-drug antibodies (ADA). There was no evidence to indicate that plozasiran pharmacodynamics or efficacy changed over time following multiple administrations of plozasiran. No adverse effects related to systemic immunoreaction were found in the plozasiran-treated patients.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with plozasiran in one or more subsets of the paediatric population in the treatment of familial chylomicronaemia syndrome (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following a single subcutaneous injection of 25 mg plozasiran, the peak plasma concentration (C_{max}) was 68.5 ng/mL. The median time to reach C_{max} (T_{max}) was 6 hours.

Plozasiran has not been administered intravenously 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

Following repeated subcutaneous injections of 25 mg plozasiran, it is distributed in plasma and extracellular body water with apparent volume of distribution (V_z/F) of 146 L in the terminal-phase of elimination. Once in systemic circulation, plozasiran is primarily distributed to the liver. In plasma, plozasiran has an unbound fraction of 22%.

In vitro studies suggest that plozasiran is not a substrate, inhibitor, or inducer of transporters. Therefore, plozasiran is not expected to cause or be affected by interactions mediated through transporters.

Biotransformation

Plozasiran is primarily metabolised by nucleases in the liver to shorter oligonucleotides of varying lengths. *In vitro* studies suggest that plozasiran is not a substrate of cytochrome P450 (CYP450) enzymes.

In vitro studies suggest that plozasiran is not a substrate, inhibitor, or inducer of CYP450 enzymes. Therefore, plozasiran is not expected to cause or be affected by interactions mediated through CYP450 enzymes.

Elimination

The terminal elimination half-life of plozasiran in plasma is approximately 3–4 hours. The mean apparent systemic clearance is 33.8 L/hour. Approximately 16–19% of plozasiran dose is excreted in the urine.

Linearity/non-linearity

Plozasiran exhibited time-invariant pharmacokinetics following repeated subcutaneous injections. Following multiple dose administrations, plasma levels of plozasiran (C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$) increased proportionally with dose within the dose range of 10–50 mg.

Pharmacokinetic/pharmacodynamic relationship(s)

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 plozasiran every 3 months.

Immunogenicity

In the PALISADE study, none of the 50 FCS patients treated with plozasiran over a period of 12 months developed treatment-induced or treatment-boosted anti-drug antibodies (ADA). There was no evidence to indicate that plozasiran pharmacokinetics changed over time following multiple administrations of plozasiran.

Special populations

Elderly
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).

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 a population pharmacokinetic analysis that included data from 23 and 4 patients with mild and moderate degrees of renal impairment, respectively. Plozasiran has not been studied in patients with severe renal impairment or end-stage renal disease (eGFR < 30 mL/min) (see section 4.2).

Hepatic impairment
No clinically significant differences in plozasiran pharmacokinetics were found in a population pharmacokinetic analysis from 4 patients with elevation of AST > ULN and total bilirubin ≤ 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).

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

Gender, race, ethnicity
No clinically significant differences in plozasiran pharmacokinetics based on gender and race or ethnicity were found in a population pharmacokinetic analysis that included data from 65 (44.5%) females and 81 (55.5%) males 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).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development.

In a pre- and post-natal development study, there was an increase in the number of stillborn pups and a subsequent reduction in live birth index at the high dose, with a body surface area (BSA) adjusted

safety margin of 3.1- and 31-fold at the preweaning and maternal/postnatal no observed adverse effect level (NOAEL).

There is no information on the excretion of plozasiran or its metabolites in animal milk.

In a 2-year rat carcinogenicity study, benign hepatocellular adenomas and a low incidence of carcinomas were noted at the high dose. Safety margins at the NOAEL are 10- and 16-fold based on BSA, and 60- and 53-fold based on AUC for males and females, respectively. Although the relevance for humans is unknown, the risk is likely low due to the high safety margins.

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

2 years

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Do not freeze.

The product may be stored at room temperature (15 °C – 25 °C) for a single period of up to 30 days.

The disposal date should be written on the outer carton (i.e. up to 30 days from the date removed from the refrigerator).

The product must be discarded if not used within the 30 days of room temperature storage or the expiry date printed on the outer carton, whichever is earlier.

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 1 pre-filled syringe.

6.6 Special precautions for disposal and other handling

This medicinal product should be inspected visually prior to administration. The solution should be clear and colourless to yellow. If the solution is cloudy or contains visible particulate matter, the content 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 °C – 25 °C) prior to injection. It should be removed from the refrigerator (2 °C – 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 only once and then placed in a sharps disposal container for disposal according to community guidelines.

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

7. MARKETING AUTHORISATION HOLDER

Arrowhead Pharmaceuticals Ireland Limited
One Spencer Dock
North Wall Quay
Dublin 1
D01 X9R7
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2041/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Mias Pharma Limited
Suite 1 – First Floor
Stafford House
Strand Road
Portmarnock
Co. Dublin
D13 WC83
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

The Marketing Authorisation Holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

- **Risk management plan (RMP)**

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

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Redemplo 25 mg solution for injection in pre-filled syringe
plozasiran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each single-dose pre-filled syringe contains plozasiran sodium equivalent to 25 mg plozasiran in 0.5 mL solution. Each mL solution contains 50 mg plozasiran.

3. LIST OF EXCIPIENTS

Sodium chloride and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use.

Single use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Disposal date (for storage at 15 °C – 25 °C): ___/___/___

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Arrowhead Pharmaceuticals Ireland Limited
One Spencer Dock
North Wall Quay
Dublin 1
D01 X9R7
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2041/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Redemplo

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

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

Redemplo 25 mg injection
plozasiran
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Redemplo 25 mg solution for injection in pre-filled syringe
plozasiran

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

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Redemplo is and what it is used for
2. What you need to know before you use Redemplo
3. How to use Redemplo
4. Possible side effects
5. How to store Redemplo
6. Contents of the pack and other information
7. Instructions for use

1. What Redemplo is and what it is used for

Redemplo contains the active substance plozasiran. It is used in adults to treat a condition called familial chylomicronaemia syndrome (FCS). FCS causes abnormally high levels of fats called ‘triglycerides’ in the blood. This can lead to inflammation of the pancreas, causing severe abdominal pain (belly pain).

Redemplo is used, together with a restricted, very low-fat diet, to lower the increased levels of triglycerides in the blood.

Plozasiran stops a protein called apolipoprotein C3 (APOC3), which slows the breakdown of fats, from being made in the liver. By doing so, it allows the body to reduce triglyceride levels in the blood.

It is important that you continue the very low-fat diet and any other lipid (fat) lowering medicines that your doctor has prescribed during treatment with Redemplo.

2. What you need to know before you use Redemplo

Do not use Redemplo if you are allergic to plozasiran (the active substance) or any of the other ingredients in this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Redemplo if you have diabetes or are at risk of developing diabetes.

Children and adolescents
Do not use Redemplo if you are under 18 years old. This medicine has not been studied in patients under 18 years old.

Other medicines and Redemplo
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

There is no information on the use of this medicine in pregnant women. Therefore, do not use Redemplo during pregnancy, unless advised to do so by your doctor.

It is not known if Redemplo passes into breast milk. It is recommended that you discuss breast-feeding with your doctor to see what is best for you and your child.

Driving and using machines
Redemplo is not expected to affect your ability to drive or use machines.

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

3. How to use Redemplo

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

You will only be given Redemplo if your doctor has confirmed you have a diagnosis of FCS.

Redemplo is available as an injection which is given under the skin (subcutaneous). The injection can be given in the upper arm (when given by a caregiver), thigh, or abdomen, but avoid the area within 5 cm around the belly button (navel).

The recommended dose is one injection of 25 mg given once every 3 months.

You or your caregiver will be instructed on how to use Redemplo according to the instructions at the end of this leaflet. When you are using the medicine for the first time, you will be closely guided and monitored by a qualified healthcare professional.

Before using this medicine, it is also important that you read, understand, and closely follow the instructions for use provided at the end of this leaflet.

If you use more Redemplo than you should
In the highly unlikely event you or someone else accidentally injects too much medicine (overdose), seek urgent medical attention.

If you forget to use Redemplo
If you miss your dose, inject your next dose of Redemplo as soon as possible and resume dosing every 3 months from the date of your last injection. Do not inject a double dose to make up for a forgotten dose.

If you stop using Redemplo
Do not stop using Redemplo unless you have agreed to do so with your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

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

Very common (may affect more than 1 in 10 people)
- elevated blood sugar levels (hyperglycaemia)

Common (may affect up to 1 in 10 people)
- headache
- nausea
- pain, itching, swelling or redness at the injection site

Uncommon (may affect up to 1 in 100 people)
- elevated liver enzymes in your blood (alanine aminotransferase and aspartate aminotransferase)

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

5. How to store Redemplo

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

Do not use this medicine after the expiry date which is stated on the carton and pre-filled syringe label after 'EXP'. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Do not freeze.

Redemplo may be stored at room temperature (15 °C – 25 °C) for up to 30 days after removal from the refrigerator. If not used within the 30 days, discard Redemplo. The disposal date should be written on the outer carton in the space provided (i.e. up to 30 days from the date of removal from the refrigerator) and not later than the expiry date stated on the carton.

Redemplo should be a clear, colourless to yellow solution. If you notice any particles in the solution, or if it is cloudy, do not use and return it to the pharmacist.

Do not mix this medicine with any other medicines.

Use each pre-filled syringe only once and then place in a sharps disposal container. Talk to your pharmacist about getting a sharps disposal container and how you will dispose of it when it is full.

Do not throw away this medicine via wastewater or household waste. Ask your pharmacist how to throw away medicine you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Redemplo contains
- The active substance is plozasiran. Each single-dose pre-filled syringe contains plozasiran sodium equivalent to 25 mg plozasiran in 0.5 mL solution.
- The other ingredients are sodium chloride and water for injections (see section 2 'Redemplo contains sodium' for further information).

What Redemplo looks like and contents of the pack
Redemplo is a solution for injection in a single-dose, glass pre-filled syringe with a needle, needle shield and plunger stopper. The solution is clear, colourless to yellow.

Pack size of 1 pre-filled syringe.

Marketing Authorisation Holder
Arrowhead Pharmaceuticals Ireland Limited
One Spencer Dock
North Wall Quay
Dublin 1
D01 X9R7
Ireland

Manufacturer
Mias Pharma Limited
Suite 1 – First Floor
Stafford House
Strand Road
Portmarnock
Co. Dublin
D13 WC83
Ireland

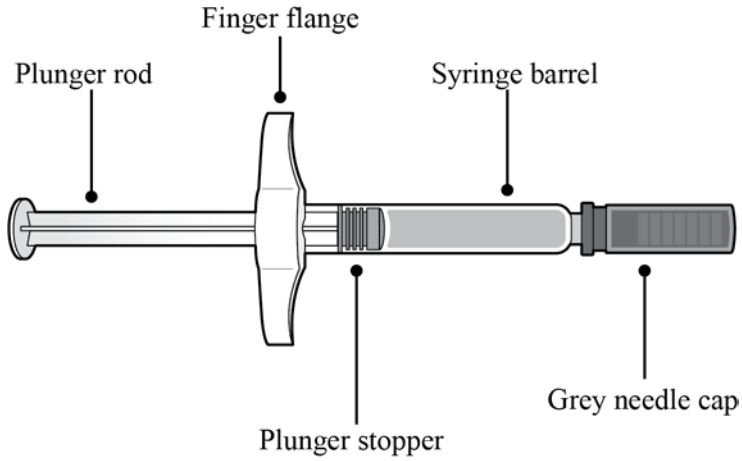
This leaflet was last revised in

Other sources of information

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

7. Instructions for use

This ‘Instructions for use’ contains information on how to inject Redemplo.

Redemplo 25 mg solution for injection in pre-filled syringe

Each carton contains one single dose Redemplo (plozasiran) solution for injection in pre-filled syringe for subcutaneous injection.

Important information you need to know before injecting Redemplo

Redemplo is for subcutaneous injection only (injection directly under the skin).

Read this ‘Instructions for use’ each time before you start using your Redemplo pre-filled syringe. There may be new information. This information does not take the place of talking to your doctor, pharmacist or nurse about your medical condition or your treatment. If you have any further questions, ask your doctor, pharmacist or nurse.

Storing Redemplo

- Keep the Redemplo pre-filled syringe in a refrigerator between 2 °C – 8 °C. Do not freeze.
- Redemplo may be stored at room temperature (15 °C – 25 °C) for up to 30 days after removal from the refrigerator. If not used within the 30 days, discard Redemplo. The disposal date should be written on the outer carton in the space provided (i.e. up to 30 days from the date of removal from the refrigerator) and not later than the expiry date stated on the carton.

If the product is not stored in any above conditions, throw away the pre-filled syringe in a sharps disposal container and use a new pre-filled syringe.

Keep Redemplo pre-filled syringe out of the sight and reach of children.

Preparing to inject Redemplo

Step 1: Gather all materials needed for the injection

On a clean, well-lit, flat work surface, place:

- 1 Redemplo pre-filled syringe in carton
- Alcohol wipes (not provided)
- Cotton ball or gauze pad (not provided)
- Adhesive bandage (not provided)
- Sharps disposal container (not provided)

Step 2: Prepare to use the Redemplo pre-filled syringe

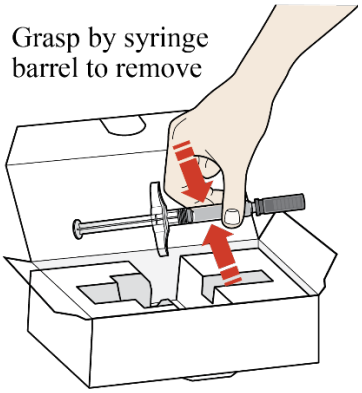


Figure A

Figure B

- Open the carton lid and remove syringe by the barrel and place on the flat surface (see **Figure A**).
  - **Do not** use the pre-filled syringe if tamper evident seal on the carton is broken.
  - **Do not** pick up or pull the pre-filled syringe by the plunger rod or needle cap.

- **Check the expiry date ('EXP')** on the Redemplo pre-filled syringe.
  - **Do not** use if the 'EXP' date or disposal date on the carton has passed.

- Wait 30 minutes for the pre-filled syringe to reach room temperature (15 °C – 25 °C) before injecting (see **Figure B**).
  - **Do not** try to warm the pre-filled syringe by using a heat source such as hot water or a microwave.
  - **Do not** remove the needle cap from the pre-filled syringe until you are ready to inject.

Step 3: Check the medicine and syringe

Figure C

Check the medicine in the pre-filled syringe (see **Figure C**).

- The medicine should be clear and colourless to yellow.
  - **Do not** use the pre-filled syringe if the medicine is cloudy or contains particles.
- It is normal to see air bubbles in the solution.

Check the pre-filled syringe (see **Figure C**).

- **Do not** use the pre-filled syringe if any part appears cracked or broken.
- **Do not** use the pre-filled syringe if the needle cap is missing or not securely attached.
- **Do not** use the pre-filled syringe if it has been dropped onto a hard surface as the syringe may be damaged.

In any of the above cases, return the pre-filled syringe to the pharmacist.

Injecting Redemplo

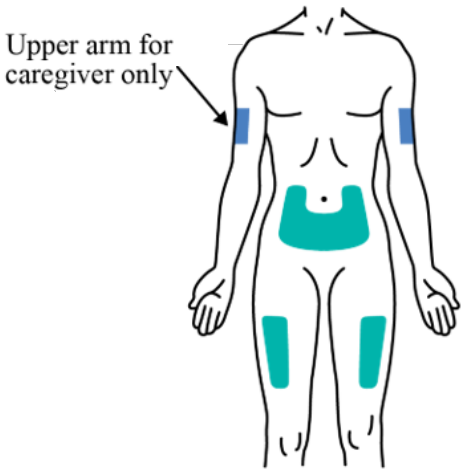
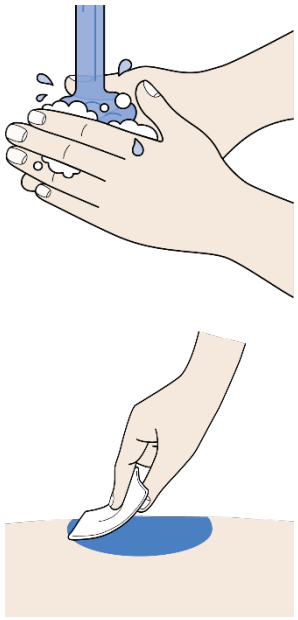
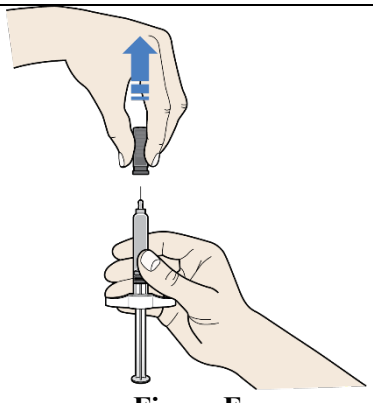
<table>
<tr><td colspan="2">Step 4: Choose your injection site</td></tr>
<tr><td> 

Figure D</td><td>You can use (see Figure D):
• Thigh
• Stomach (abdomen) except for a 5 cm area around the belly button (navel).

Caregivers can also use the outer area of the upper arm (see Figure D).

Do not choose an area where the skin is damaged (tender, bruised, red, hard, or cut), or with scars or stretch marks.

Do not inject other medicines in the same area you inject this medicine.</td></tr>
<tr><td colspan="2">Step 5: Clean the injection site</td></tr>
<tr><td> 
Figure E</td><td>• Wash your hands thoroughly with soap and water (see Figure E).
• Clean your injection site with an alcohol wipe and let your skin dry before injecting (see Figure E).
- Do not touch this area of skin again before injecting.</td></tr>
<tr><td colspan="2">Step 6: Remove the needle cap</td></tr>
<tr><td> 
Figure F</td><td>• Hold the syringe by the barrel, with the needle facing away from you.
• Pull the needle cap straight out and away from your body. (see Figure F).
- Do not twist or bend the needle cap.
• Avoid pushing the plunger before you are ready to inject.
- Do not let the needle touch any surface.
- Do not put the needle cap back onto the syringe.</td></tr>
</table>

Step 7: Pinch the skin and insert the needle

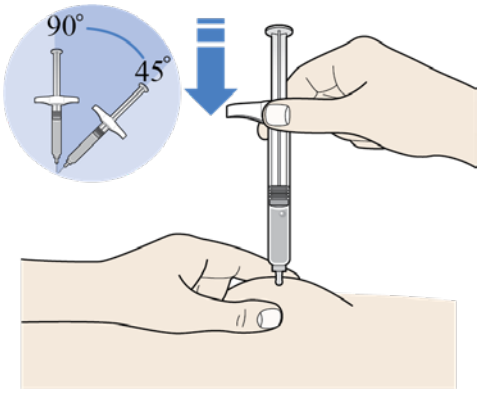


Figure G

- Hold the syringe in one hand.
- Gently pinch and hold a fold of skin at the injection site.
- Insert needle at 45° to 90° angle (see **Figure G**).
- **Keep the skin pinched while inserting the needle and during injection.**
  - **Do not** place your finger on the plunger rod before the injection.

Step 8: Hold skin pinch and push down the plunger

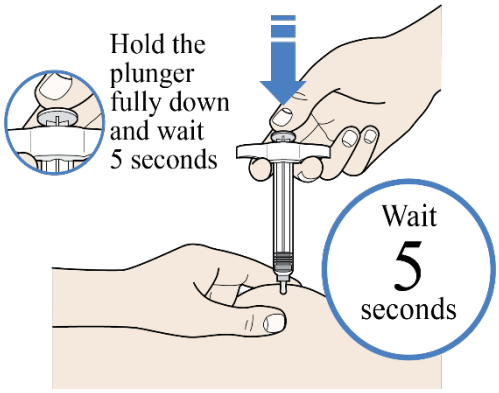


Figure H

- While pinching the skin, push the plunger rod all the way down using slow and constant pressure (see **Figure H**).
- After the plunger is pushed all the way down, **hold the plunger down and count 5 seconds with the needle fully inserted to ensure a full dose is delivered** (see **Figure H**).

Step 9: Complete the injection

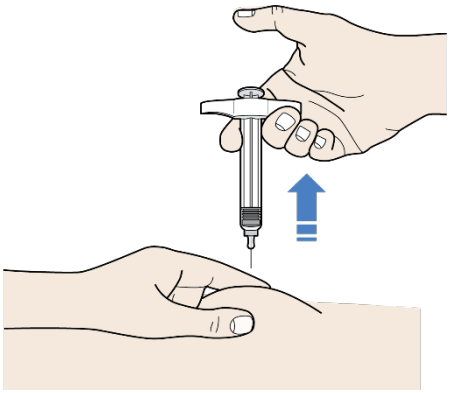


Figure I

- Gently lift the syringe off the skin (see **Figure I**).
  - **Do not** pull the plunger up by hand. Lift the whole syringe straight up.
  - **Do not** rub the injection site.
- Place the used cap and syringe in a sharps disposal container right away.
  - **Do not** put the needle cap back onto the syringe.

Disposing of Redemplo

Figure J

Do not use any medicine that is left in the used syringe.

- Put the used syringe and needle cap in a sharps disposal container right away after use.
  - **Do not put the needle cap back onto the syringe.**
- **Do not** throw away (dispose of) the syringe in your household waste (see **Figure J**). If you do not have a sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  - upright and stable during use
  - leak-resistant
  - properly labelled to warn of hazardous waste inside the container.

- When your sharps disposal container is almost full, you will need to follow your local guidelines for the right way to dispose of your sharps disposal container. There may be special local laws about how you should throw away used needles and syringes. Ask your pharmacist for more details on how you should dispose of sharps in your location.

Do not dispose of your used sharps disposal container in your household waste unless your local guidelines permit this. Do not recycle your used sharps disposal container.