

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

Waylivra 285 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 200 mg volanesorsen sodium, equivalent to 190 mg volanesorsen.

Each single-dose pre-filled syringe contains 285 mg of volanesorsen in 1.5 ml solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear, colourless to slightly yellow solution with a pH of approximately 8 and osmolality of 363-485 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Waylivra is indicated as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate.

4.2 Posology and method of administration

Posology

Treatment should be initiated by and remain under the supervision of a physician experienced in the treatment of patients with FCS. Prior to initiating Waylivra, secondary causes of hypertriglyceridemia (e.g. uncontrolled diabetes, hypothyroidism) should be excluded or appropriately addressed.

The recommended starting dose is 285 mg in 1.5 ml injected subcutaneously once weekly for 3 months. Following 3 months, dose frequency should be reduced to 285 mg every 2 weeks.

However, treatment should be discontinued in patients with a reduction in serum triglycerides <25% or who fail to achieve serum triglycerides below 22.6 mmol/L after 3 months on volanesorsen 285 mg weekly.

After 6 months of treatment with volanesorsen, increase of dose frequency to 285 mg weekly should be considered if response has been inadequate in terms of serum triglyceride reduction as evaluated by the supervising experienced specialist and in the condition that platelet counts are in the normal range. Patients should be re-downtitrated to 285 mg every 2 weeks if the higher 285 mg once weekly dose does not provide significant additional triglyceride reduction after 9 months.

Patients should be instructed to give the injection on the same day of the week, according to medically determined frequency of administration.

If a dose is missed and noticed within 48 hours, the patient should be directed to give the missed dose as soon as possible. If not noticed within 48 hours, then the missed dose should be skipped and the next planned injection given.

Platelet monitoring and dose adjustments

Before initiation of treatment, platelet count should be measured. If the platelet count is below $140 \times 10^9/L$ another measurement should be taken approximately a week later to reassess. If platelet count remains below $140 \times 10^9/L$ upon a second measurement, Waylivra should not be initiated (see section 4.3).

After commencing treatment, patients should have platelet levels monitored at least every two weeks, depending on the platelet levels.

Treatment and monitoring should be adjusted according to laboratory values in line with Table 1.

For any patient dose paused or discontinued due to severe thrombocytopenia, the benefits and risks of returning to treatment once platelet count $\geq 100 \times 10^9/L$ should be carefully considered. For discontinued patients, a haematologist should be consulted prior to resuming treatment.

Table 1. Waylivra monitoring and treatment recommendations

Platelet count ($\times 10^9/L$)	Dose (285 mg prefilled syringe)	Monitoring frequency
Normal (≥ 140)	Starting dose: Weekly After 3 months: Every 2 weeks	Every 2 weeks
100 to 139	Every 2 weeks	Weekly
75 to 99	Pause treatment for ≥ 4 weeks and resume treatment after platelet levels $\geq 100 \times 10^9/L$	Weekly
50 to 74^a	Pause treatment for ≥ 4 weeks and resume treatment after platelet levels $\geq 100 \times 10^9/L$	Every 2-3 days
Less than 50^{a, b}	Discontinue treatment Glucocorticoids recommended	Daily

^a See section 4.4 for recommendations regarding use of antiplatelet agents/non-steroidal anti-inflammatory drugs (NSAIDs)/anticoagulants

^b Consultation of a haematologist is needed to reconsider the benefit/risk for possible further treatment with volanesorsen.

Special populations

Elderly population

No starting dose adjustment is necessary for elderly patients. There is limited clinical data for patients aged 65 and over (see sections 5.1 and 5.2).

Renal impairment

No starting dose adjustment is necessary in patients with mild to moderate renal impairment. The safety and efficacy in patients with severe renal impairment has not been established and these patients should be closely observed.

Hepatic impairment

This medicinal product has not been studied in patients with hepatic impairment. The medicinal product is not metabolised via the cytochrome P450 enzyme system in the liver, therefore dose adjustment is unlikely to be required in patients with hepatic impairment.

Paediatric population

The safety and efficacy of this medicinal product in children and adolescents below 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.

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

The first injection administered by the patient or caregiver should be performed under the guidance of an appropriately qualified health care professional. Patients and/or caregivers should be trained in the administration of this medicinal product in accordance with the patient information leaflet.

The pre-filled syringe should be allowed to reach room temperature prior to injection. It should be removed from refrigerated storage (2 ° to 8 °C) at least 30 minutes before use. Other warming methods should not be used. It is normal to see a large air bubble. It should not be attempted to remove the air bubble.

It is important to rotate sites for injection. Sites for injection include the abdomen, upper thigh region, or outer area of the upper arm. If injected in the upper arm, the injection should be administered by another person. Injection should be avoided at the waistline and other sites where pressure or rubbing may occur from clothing. This medicinal product should not be injected into tattoos, moles, birthmarks, bruises, rashes, or areas where the skin is tender, red, hard, bruised, damaged, burned, or inflamed.

4.3 Contraindications

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

Chronic or unexplained thrombocytopenia. Treatment should not be initiated in patients with thrombocytopenia (platelet count $<140 \times 10^9/L$).

4.4 Special warnings and precautions for use

Thrombocytopenia

Waylivra is very commonly associated with reductions in platelet count in patients with FCS, which may result in thrombocytopenia (see section 4.8). Patients with lower body weight (less than 70 kg) may be more prone to thrombocytopenia during treatment with this medicinal product. Careful monitoring for thrombocytopenia is important during treatment with this medicinal product in patients with FCS (see section 4.2). Recommendations for adjustments to monitoring frequency and dosing are specified in Table 1 (see section 4.2).

Discontinuation of antiplatelet medicinal products/NSAIDs/anticoagulants should be considered for platelet levels $< 75 \times 10^9/L$. Treatment with these medicinal products must be discontinued at platelet levels $< 50 \times 10^9/L$ (see section 4.5).

Patients should be instructed to report to their physician immediately if they experience any signs of bleeding, which can include petechiae, spontaneous bruising, subconjunctival bleeding, or other unusual bleeding (including nosebleeds, bleeding from gums, stools, or unusually heavy menstrual bleeding), neck stiffness, atypical severe headache, or any prolonged bleeding.

LDL-C levels

With treatment with Waylivra, LDL-C levels may rise but will usually remain within the normal range.

Renal toxicity

Renal toxicity has been observed after administration of volanesorsen and other subcutaneously and intravenously administered antisense oligonucleotides. Monitoring for evidence of nephrotoxicity by routine urine dipstick is recommended on a quarterly basis. In the case of a positive assessment, a broader assessment of renal function, including serum creatinine and a 24-hour collection to quantify the proteinuria and assess creatinine clearance, should be performed. Treatment should be discontinued if: proteinuria of ≥ 500 mg/24 hour is recorded, or an increase in serum creatinine ≥ 0.3 mg/dL ($26.5 \mu\text{mol/L}$) that is $> \text{ULN}$ is recorded, or creatinine clearance estimated by the CKD-EPI equation is ≤ 30 mL/min/ 1.73m^2 . Treatment should also be discontinued for any clinical symptoms or signs of renal impairment pending the previous confirmatory assessments.

Hepatotoxicity

Elevations of liver enzymes have been observed after administration of other subcutaneously and intravenously administered antisense oligonucleotides. Monitoring for hepatotoxicity through serum liver enzymes and bilirubin should be assessed on a quarterly basis. Treatment should be discontinued if there is a single increase in ALT or AST $> 8 \times \text{ULN}$, or an increase $> 5 \times \text{ULN}$, which persists for ≥ 2 weeks, or lesser increases in ALT or AST that are associated with total bilirubin $> 2 \times \text{ULN}$ or INR > 1.5 . Treatment should also be discontinued for any clinical symptoms or signs of hepatic impairment or hepatitis.

Immunogenicity and inflammation

No evidence of altered safety profile or clinical response was associated with presence of anti-drug antibodies. If formation of anti-drug antibodies with a clinically significant effect is suspected, contact the marketing authorisation holder to discuss antibody testing.

Monitoring of inflammation should be assessed through quarterly assessment of erythrocyte sedimentation rate (ESR).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose of 285 mg, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No clinical drug interaction studies have been conducted.

Clinically relevant pharmacokinetic interactions are not expected between volanesorsen and substrates, inducers or inhibitors of cytochrome P450 (CYP) enzymes, and drug transporters. It is unknown whether triglyceride lowering by volanesorsen and the potentially ensuing decrease in inflammation leads to normalisation of CYP enzyme expression.

In clinical studies, this medicinal product has been used in combination with fibrates and fish oils with no impact on the medicinal product pharmacodynamics or pharmacokinetics. There were no adverse

events related to drug-drug interactions reported during the clinical program, however this is based on limited data.

The effect of concomitant administration of this medicinal product with alcohol or medicinal products known to have potential for hepatotoxicity (e.g., paracetamol) is unknown. If signs and symptoms of hepatotoxicity develop, use of the hepatotoxic medicinal product should be discontinued.

Antithrombotic agents and medicinal products that may lower platelet count

It is not known whether the risk of bleeding is increased by concomitant use of volanesorsen and antithrombotic agents or medicinal products that may lower platelet count or affect platelet function. Discontinuation of antiplatelet medicinal products/NSAIDs/anticoagulants should be considered for platelet levels $<75 \times 10^9/L$ and treatment with these medicinal products should be stopped at platelet levels $< 50 \times 10^9/L$ (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of volanesorsen 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 this medicinal product during pregnancy.

Breastfeeding

In non-clinical studies, levels of volanesorsen in milk were very low in lactating mice. Available pharmacodynamic/toxicological data in animals have shown excretion of very low amounts of volanesorsen in milk (see section 5.3). Due to the poor oral bioavailability of this medicinal product, it is considered unlikely that these low milk concentrations would result in systemic exposure from nursing.

It is unknown whether volanesorsen or metabolites are excreted in human milk.

A risk to the newborn infant cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from 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. Volanesorsen had no effect on fertility in mice.

4.7 Effects on ability to drive and use machines

Volanesorsen has no or negligible influence on the ability to drive and use machines. **4.8 Undesirable effects**

Summary of the safety profile

In clinical studies in patients with FCS, the most commonly reported adverse reactions during treatment were platelet count decreased occurring in 29%, thrombocytopenia occurring in 21% (see section 4.4), and injection site reactions occurring in 82% of patients during the pivotal studies.

Tabulated list of adverse reactions

Table 2 presents the adverse reactions from the Phase 3 studies in patients with FCS in receiving volanesorsen subcutaneously.

The frequency of adverse reactions is defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Summary of adverse reactions in clinical studies in patients with FCS (N=87)

System organ class	Very common	Common
Blood and lymphatic system disorders	Thrombocytopenia	Leukopenia Lymphopenia Eosinophilia Immune thrombocytopenic purpura Spontaneous haematoma
Immune system disorders		Immunisation reaction Hypersensitivity Serum sickness-like reaction
Metabolism and nutrition disorders		Diabetes mellitus
Psychiatric disorders		Insomnia
Nervous system disorders	Headache	Syncope Hypoaesthesia Presyncope Retinal migraine Dizziness Tremor
Eye disorders		Conjunctival haemorrhage Vision blurred
Vascular disorders		Hypertension Haemorrhage Haematoma Hot flush
Respiratory, thoracic and mediastinal disorders		Dyspnoea Pharyngeal oedema Wheezing Epistaxis Cough Nasal congestion
Gastrointestinal disorders		Nausea Diarrhoea Vomiting Abdominal distension Abdominal pain Dry mouth Gingival bleeding Mouth haemorrhage

System organ class	Very common	Common
		Parotid gland enlargement Dyspepsia Gingival swelling
Skin and subcutaneous tissue disorders		Erythema Pruritus Rash Urticaria Hyperhidrosis Petechiae Ecchymosis Night sweats Papule Skin hypertrophy Swelling face
Musculoskeletal and connective tissue disorders	Myalgia	Arthralgia Pain in extremity Arthritis Musculoskeletal pain Back pain Neck pain Pain in jaw Muscle spasms Joint stiffness Myositis Peripheral arthritis
Renal and urinary disorders		Haematuria Proteinuria
General disorders and administration site conditions	Injection site erythema Injection site pain Injection site swelling Injection site discolouration Injection site induration Injection site pruritus Injection site bruising Chills Injection site oedema	Injection site haematoma Asthenia Fatigue Injection site reaction Pyrexia Injection site hypoaesthesia Injection site haemorrhage Injection site warmth Injection site dryness Injection site pallor Injection site urticaria Injection site vesicles Malaise Feeling hot Influenza-like illness Injection site discomfort

System organ class	Very common	Common
		Injection site inflammation Injection site mass Oedema Pain Injection site paraesthesia Injection site scab Injection site papule Injection site rash Non-cardiac chest pain Vessel puncture site haemorrhage
Investigations	Platelet count decreased	Haemoglobin decreased White blood cell count decreased Blood creatinine increased Blood urea increased Creatinine renal clearance decreased Hepatic enzyme increased International normalised ratio increased Transaminases increased
Injury, poisoning and procedural complications		Contusion

Description of selected adverse reactions

Thrombocytopenia

In the pivotal Phase 3 study in patients with FCS (the APPROACH study), confirmed reductions in platelet counts to below normal ($140 \times 10^9/L$) were observed in 75% of FCS patients treated with volanesorsen and 24% of placebo patients; confirmed reductions to below $100 \times 10^9/L$ were observed in 47% of patients treated with volanesorsen compared with no placebo patients. In APPROACH 5 patients who discontinued therapy due to platelet levels included 2 patients with platelet counts $<25 \times 10^9/L$ and 3 with platelet counts between $50 \times 10^9/L$ and $75 \times 10^9/L$. It was also reported in this study that platelet count decreased was reported in 11 (33%) patients versus 1 (3%), and thrombocytopenia was reported in 4 (12%) patients vs none for subjects treated with volanesorsen compared to placebo, respectively.

In the open-label extension (CS7), confirmed reductions in platelet counts to below normal ($140 \times 10^9/L$) were observed in 52 (79%) patients overall, including 37 (74%) patients in the treatment-naïve group. Confirmed reductions to below $100 \times 10^9/L$ were observed in 33 (50%) patients overall including 24 (48%) treatment naïve patients. In the open-label extension, 11 patients discontinued due to thrombocytopenia and platelet-related events. None of these patients had any major bleeding events and all recovered to normal platelet count following drug discontinuation and administration of glucocorticoids where medically indicated. In this open-label extension study, platelet count decreased was reported in 16 (24%) and thrombocytopenia was reported in 14 (21%) patients.

For pooled data with the APPROACH study and the CS7 study, platelet count decreased was reported in 25 (29%) patients, and thrombocytopenia was reported in 18 (21%).

Immunogenicity

In the Phase 3 clinical studies (CS16 and APPROACH), 16% and 33% of volanesorsen-treated patients tested positive for anti-drug antibodies during 6-month and 12-month treatment, respectively. No evidence of altered safety profile or clinical response was associated with presence of anti-drug antibodies; however this is based on the limited long-term data (see section 4.4).

Injection site reactions

Injection site reactions defined as any local cutaneous reaction at the injection site persisting more than 2 days occurred in 79% of volanesorsen-treated patients in the APPROACH study and 81% of patients in its open-label extension (CS7). Injection site reactions occurred in 80% of volanesorsen-treated patients across both studies. These local reactions were mostly mild and typically consisted of 1 or more of the following: erythema, pain, pruritus, or local swelling. Injection site reactions did not occur with all injections and resulted in discontinuation for 1 patient in the APPROACH study and 1 patient in the open label extension (CS7).

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

There is no clinical experience with overdose of this medicinal product. In the case of overdose, patients should be carefully observed and supportive care administered, as appropriate. Symptoms of overdose are expected to be limited to constitutional symptoms and injection site reactions.

Haemodialysis is unlikely to be beneficial given that volanesorsen is rapidly distributed into cells.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: lipid modifying agents, other lipid modifying agents, ATC code: C10AX18

Mechanism of action

Volanesorsen is an antisense oligonucleotide designed to inhibit the formation of apoC-III, a protein that is recognised to regulate both triglyceride metabolism and hepatic clearance of chylomicrons and other triglyceride-rich lipoproteins. The selective binding of volanesorsen to the apoC-III messenger ribonucleic acid (mRNA) within the 3' untranslated region at base position 489-508 causes the degradation of the mRNA. This binding prevents translation of the protein apoC-III, thus removing an inhibitor of triglyceride clearance and enabling metabolism through an LPL-independent pathway.

Pharmacodynamic effects

Effects of Waylivra on lipid parameters

In APPROACH, the Phase 3 clinical study in patients with FCS, Waylivra reduced fasting triglycerides, total cholesterol, non-HDL cholesterol, apoC-III, apoB-48, and chylomicron triglyceride levels and increased LDL-C, HDL-C, and apoB (see Table 3).

Table 3: Mean baseline and percent change in lipid parameters from baseline to month 3

Lipid parameter (g/L for apoC-III, apoB, apoB-48;	Placebo (N=33)	Volanesorsen 285 mg
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mmol/L for cholesterol, triglycerides)			(N=33)	
	Baseline	% Change	Baseline	% Change
Triglycerides	24.3	+24%	25.6	-72%
Total cholesterol	7.3	+13%	7.6	-39%
LDL-C	0.72	+7%	0.73	+139%
HDL-C	0.43	+5%	0.44	+45%
Non-HDL-C	6.9	+14%	7.1	-45%
ApoC-III	0.29	+6%	0.31	-84%
ApoB	0.69	+2%	0.65	+20%
ApoB-48	0.09	+16%	0.11	-75%
Chylomicron triglycerides	20	+38%	22	-77%

Cardiac electrophysiology

At a drug concentration 4.1 times the peak drug plasma concentrations (C_{max}) of the maximum recommended dose (285 mg subcutaneous injection), volanesorsen did not prolong the heart-rate corrected QT (QTc) interval.

Clinical efficacy and safety

APPROACH study in patients with FCS

The APPROACH study is a randomised, double-blind placebo-controlled 52-week multicentre clinical study in 66 patients with FCS, evaluating volanesorsen 285 mg administered as a subcutaneous injection (33 treated with volanesorsen, 33 with placebo). Main inclusion criteria were a diagnosis of FCS (Type 1 hyperlipoproteinemia) in combination with a history of chylomicronemia evidenced by documentation of lactescent serum or documentation of fasting TG measurement ≥ 880 mg/dl. Diagnosis of FCS required documentation of at least one of the following:

- Confirmed homozygote, compound heterozygote, or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, APOC2, GPIHBP1, or LMF1)
- Post heparin plasma LPL activity of $\leq 20\%$ of normal.

Patients taking Glybera within 2 years prior to screening were excluded from the study.

Nineteen of the 33 patients in the volanesorsen group completed 12 months of study treatment.

Thirteen of these patients had dose adjustment/pause on the study. Out of the 13, 5 had a dose pause, 5 had a dose adjustment and 3 had both a dose pause and dose adjustment.

Mean age was 46 years (range 20-75 years; 5 patients ≥ 65 years old); 45% were men; 80% were White, 17% were Asian, and 3% were of other races. Mean body mass index was 25 kg/m². A history of documented acute pancreatitis was reported for 76% of patients and a history of diabetes was reported for 15% of patients; 21% of patients had a recorded history of lipaemia retinalis and 23% of patients had a recorded history of eruptive xanthomas. The median age at diagnosis was 27 years, with 23% shown to lack a known FCS genetic mutation.

At study entry, 55% of patients were on lipid lowering therapies (48% on fibrates, 29% on fish oils, 20% HMG-CoA reductase inhibitors), 27% were on pain medicinal products, 20% were on platelet aggregation inhibitors, and 14% were on nutritional supplements. Background lipid-lowering therapies remained consistent throughout the study. Patients were prohibited from receiving plasma apheresis within 4 weeks prior to screening or during the study; 11% of patients had previously received gene therapy for lipoprotein lipase deficiency (i.e., alipogene tiparvovec), on average 8 years prior to starting this study. After a 6-week diet run-in period, the mean fasting triglyceride level at baseline was 2,209 mg/dL (25.0 mmol/L). Compliance with diet and alcohol restriction was reinforced through periodic counselling sessions during the study.

Waylivra led to a statistically significant reduction in triglyceride levels as compared to placebo at the primary efficacy endpoint, defined as percent change from baseline to Month 3 in fasting triglycerides,

in addition to a lower incidence of pancreatitis over the 52-week treatment period in a post-hoc analysis (Table 4).

At the primary efficacy endpoint, the treatment difference between volanesorsen and placebo in mean fasting triglyceride percent change was -94% (95% CI: -122% -67%; $p < 0.0001$, with a decrease of -77% from baseline (95% CI: -97, -56) in patients receiving volanesorsen and an increase of 18% from baseline (95% CI: -4, 39) in patients receiving placebo (Table 4).

Table 4: Mean change from baseline in fasting triglycerides in the phase 3 placebo-controlled study in patients with FCS at month 3 (APPROACH)

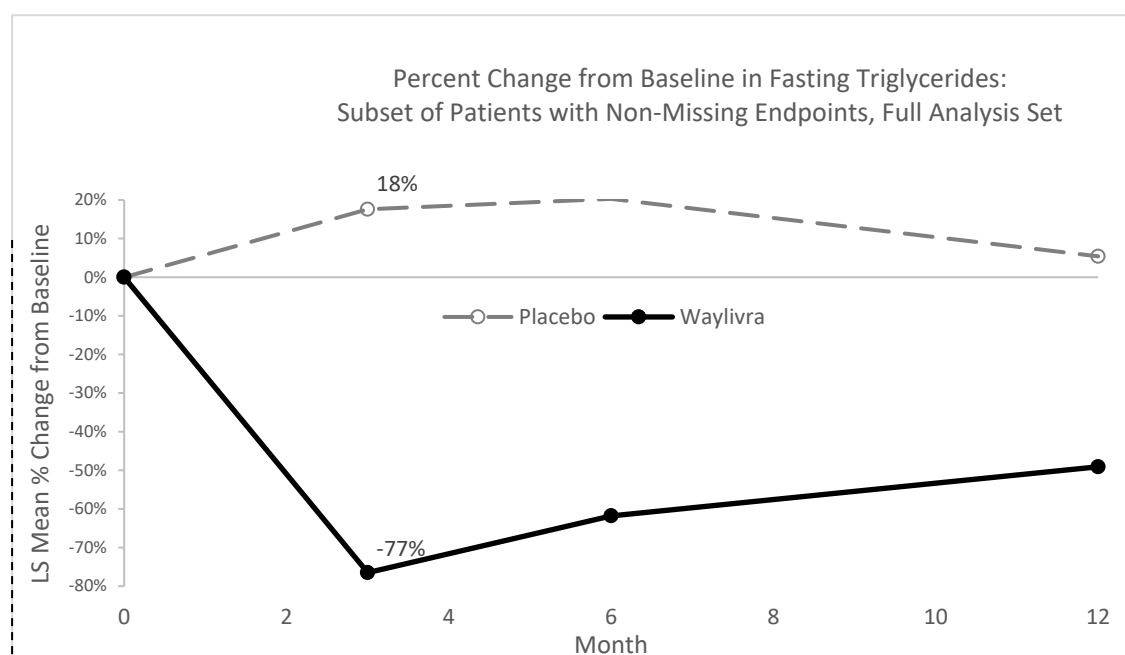
	Placebo (N=33)	Volanesorsen 285 mg (N = 33)	Relative difference in change vs placebo
LS mean percent change (95% CI)	+18% (-4, 39)	-77% (-97, -56)	-94%* (-122, -67)
LS mean absolute change (95% CI) mg/dL or mmol/L	+92 (-301, +486) mg/dL +1 (-3, +5) mmol/L	-1,712 (-2,094, -1,330) mg/dL -19 (-24, -15) mmol/L	-1,804 (-2,306, -1,302) mg/dL -20 (-26, -15) mmol/L

* p -value < 0.0001 (primary efficacy endpoint)

Difference= LS Mean of [volanesorsen % Change – Placebo % Change] (ANCOVA model)

Onset of the reduction was rapid with separation from placebo seen as early as 4 weeks and maximum response seen at 12 weeks, with clinically and statistically significant triglyceride reduction maintained over 52 weeks (Figure 1). The mean fasting triglyceride percent change was significantly different between volanesorsen and placebo arms at 3, 6, and 12 months; the volanesorsen arm included patients who did not complete dosing but who returned for assessments over the 52-week study. There were no significant differences in treatment effect across the stratification factors of presence or absence of concurrent omega-3 fatty acids or fibrates.

Figure 1: LS mean percent change in fasting triglycerides in phase 3 study in patients with FCS (APPROACH)



LS mean percent change from baseline in fasting triglycerides based on the observed data are displayed.

Difference= LS mean of [volanesorsen % change – placebo % change] (ANCOVA model)

p-value from ANCOVA model < 0.0001 at month 3 (primary efficacy endpoint), month 6 and month 12

Additional efficacy results for changes in triglyceride are presented in Table 5. Most patients receiving volanesorsen experienced a clinically significant reduction in triglycerides.

Table 5: Additional results for changes in triglycerides in the APPROACH study (primary endpoint at month 3)

Parameter at month 3^a	Placebo (N=31)	Volanesorsen 285 mg (N=30)
Percent of patients ^b with fasting plasma triglyceride < 750 mg/dL (8.5 mmol/L)*	10%	77%
Percent of patients ^c with ≥ 40% reduction in fasting triglycerides**	9%	88%

^a The month 3 endpoint was defined as the average of week 12 (Day 78) and week 13 (Day 85) fasting assessments. If 1 visit was missing, then the other visit was used as the endpoint.

^b The denominator for percentage calculation was the total number of patients in FAS with baseline fasting triglyceride ≥ 750 mg/dL (or 8.5 mmol/L) in each treatment group.

^c The denominator for percentage calculation was the total number of patients in each treatment group.

* p-value = 0.0001

**p-value < 0.0001

P-values from logistic regression model with treatment, presence of pancreatitis and presence of concurrent omega-3 fatty acids and/or fibrates as factors, and logarithm-transformed baseline fasting triglycerides as a covariate.

In the APPROACH study, the numerical incidence of pancreatitis in patients treated with volanesorsen was lower compared with placebo (3 patients 4 events in 33 placebo patients vs 1 patient 1 event in 33 volanesorsen patients).

An analysis of patients with a history of recurrent pancreatitis events (≥ 2 events in the 5 years prior to Study Day 1) showed a significant reduction in pancreatitis attacks in volanesorsen-treated patients compared to placebo treated patients (p=0.0242). In the volanesorsen group, of the 7 patients who had 24 adjudicated pancreatitis attacks in the prior 5 years, none of the patients experienced a pancreatitis attack during the 52 week treatment period. In the placebo group, of the 4 patients who had 17 adjudicated pancreatitis attacks in the prior 5 years, 3 patients experienced 4 pancreatitis attacks during the 52-week treatment period.

Open-label extension study in patients with FCS

CS7 is a multicentre, open-label extension Phase 3 study designed to evaluate the safety and efficacy of dosing and extended dosing with volanesorsen in patients with FCS. All patients enrolled either had participated in the APPROACH Study, in the CS16 Study, or were new FCS patients and had completed qualification assessments prior to receiving volanesorsen 285 mg once per week or a reduced frequency for safety or tolerability reasons determined in their index study. A total of 68 patients have been treated in this study including 51 treatment-naïve patients, 14 patients who had received volanesorsen in Study CS6, and 3 patients who had received volanesorsen in Study CS16. Fifty patients had a dose pause, 45 had a dose adjustment and 41 had both a dose pause and a dose adjustment.

Data from Study CS7 is provided in Table 6. The percent change in fasting TG from Index Study Baseline to Open-label Month 3 for the APPROACH- and CS16-volanesorsen patients was -49.2%

and -64.9%, respectively. The percent change in fasting TG from index study baseline to open-label month 6, month 12 and month 24 for the APPROACH-volanesorsen patients was -54.8%, -35.1% and -50.2%, respectively.

Table 6: Summary of fasting triglycerides (mean (SD, SEM), mg/dL) over time in study CS7 (N=68)

Time point	Treatment-naïve group (open-label study baseline ^a , N=51)			APPROACH-volanesorsen (index study baseline ^a , N=14)			CS16-volanesorsen (index study baseline ^a , N=3)		
	n	Observed value	% change from baseline	n	Observed value	% change from baseline	n	Observed value	% change from baseline
Baseline ^a	51	2341 (1193, 167)	-	14	2641 (1228, 328)	-	3	2288 (1524, 880)	-
Month 3	47	804 (564, 82)	-59.8 (37.0, 5.4)	14	1266 (812, 217)	-49.2 (34.8, 9.3)	3	855 (651, 376)	-64.9 (9.1, 5.3)
Month 6	49	1032 (695, 99)	-45.5 (42.9, 6.1)	13	1248 (927, 257)	-54.8 (23.8, 6.6)	3	1215 (610, 352)	-43.0 (19.7, 11.4)
Month 12	45	1332 (962, 143)	-36.3 (44.2, 6.6)	12	1670 (1198, 346)	-35.1 (45.6, 13.2)	3	1351 (929, 536)	-41.6 (36.3, 21.0)
Month 15	34	1328 (976, 167)	-35.6 (48.1, 8.2)	10	1886 (1219, 386)	-26.5 (57.4, 18.1)	2	1422 (190, 135)	3.4 (23.3, 16.5)
Month 18	27	1367 (938, 181)	-37.5 (45.6, 8.8)	7	1713 (1122, 424)	-38.4 (32.2, 12.2)	2	1170 (843, 596)	-24.0 (31.9, 22.6)
Month 24	21	1331 (873, 190)	-40.5 (47.4, 10.3)	5	1826 (1743, 780)	-50.2 (32.2, 14.4)	2	1198 (1177, 832)	-26.3 (56.0, 39.6)

^a Baseline values for treatment-naïve group were taken from the open-label study CS7 and baseline for APPROACH-volanesorsen and CS16-volanesorsen groups were taken from the respective index study.

Elderly population

Clinical studies included 4 patients with FCS aged 65 treated with volanesorsen in randomised control studies (phase II study CS2, 1 patient; APPROACH 3 patients), and 6 patients aged 65 and over in the open-label extension study (CS7). No overall differences in safety or effectiveness were observed between these patients and younger patients, however data are limited in this subpopulation.

Paediatric population

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

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption

Following subcutaneous injection, peak plasma concentrations of volanesorsen are typically reached in 2 to 4 hours. The absolute bioavailability of volanesorsen following a single subcutaneous administration is approximately 80% (most likely higher because an AUC of 0 to 24 hours was used and volanesorsen has a half-life of >2 weeks).

Following a dose of 285 mg once weekly in patients with FCS, the estimated geometric mean (coefficient of variation % of geometric mean) steady-state C_{\max} is 8.92 $\mu\text{g/ml}$ (35%), $\text{AUC}_{0-168\text{h}}$ is 136 $\mu\text{g}\cdot\text{h/ml}$ (38%), and C_{trough} is 127 ng/ml (58%) in patients who remain negative for anti-drug antibody. An alternative dosing regimen of 285 mg volanesorsen every two weeks results in a $C_{\text{trough,ss}}$ of approximately 58.0 ng/ml with C_{\max} and AUC similar compared to the once weekly dosing regimen.

Distribution

Volanesorsen was rapidly and widely distributed to tissues following subcutaneous or intravenous administration in all species evaluated. The estimated steady-state volume of distribution (V_{ss}) in patients with FCS is 330 L. Volanesorsen is highly bound to human plasma proteins (>98%) and the binding is concentration independent.

In vitro studies show that volanesorsen is not a substrate or inhibitor of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptides (OATP1B1, OATP1B3), bile salt export pump (BSEP), organic cation transporters (OCT1, OCT2), or organic anion transporters (OAT1, OAT3).

Biotransformation

Volanesorsen is not a substrate for CYP metabolism, and is metabolised in tissues by endonucleases to form shorter oligonucleotides that are then substrates for additional metabolism by exonucleases. Unchanged volanesorsen is the predominant circulating component.

In vitro studies indicate that volanesorsen is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 or inducer of CYP1A2, CYP2B6, or CYP3A4.

Elimination

Elimination involves both metabolism in tissues and excretion in urine. Urinary recovery of the parent drug was limited in humans with < 3% of administered subcutaneous dose recovered within 24 hours post dose. The parent drug and 5- to 7-mer chain-shortened metabolites accounted for approximately 26% and 55% of oligonucleotides recovered in urine, respectively. Following subcutaneous administration, terminal elimination half-life is approximately 2 to 5 weeks.

In animals, elimination of volanesorsen was slow and occurred mainly via urinary excretion, reflecting rapid plasma clearance principally to tissues. Both volanesorsen and shorter oligonucleotide metabolites (predominantly 7-mer metabolites (generated either from 3'-deletions or 5'-deletions)) were identified in human urine.

Linearity/non-linearity

Single- and multiple-dose pharmacokinetics of volanesorsen in healthy volunteers and patients with hypertriglyceridemia have shown that the C_{\max} of volanesorsen is dose-proportional over a dose range of 100 to 400 mg and the AUC is slightly more than dose-proportional over the same dose range. Steady-state was reached approximately 3 months after starting volanesorsen. Accumulation in C_{trough}

was observed (7- to 14-fold) and little or no increase in C_{max} or AUC was observed following weekly SC administration over a dose of 200 to 400 mg. Some accumulation in AUC and C_{max} was observed for the 50 to 100 mg dose. Since the administered dose will be 285 mg every two weeks, or 142.5 mg weekly, little increase in C_{max} or AUC is expected upon multiple dosing in the clinical setting.

Special populations

Renal impairment

A population pharmacokinetic analysis suggests that mild and moderate renal impairment has no clinically relevant effect on the systemic exposure of volanesorsen. No data are available in patients with severe renal impairment.

Hepatic impairment

The pharmacokinetics of volanesorsen in patients with hepatic impairment is unknown.

Age, sex, weight, and race

Based on the population pharmacokinetic analysis, age, body weight, sex, or race has no clinically relevant effect on volanesorsen exposure. There are limited data available in subjects >75 years of age.

Anti-volanesorsen antibody formation affecting pharmacokinetics

The formation of binding antibodies to volanesorsen appeared to increase total C_{trough} by 2- to 19-fold.

5.3 Preclinical safety data

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

Dose and time-dependent reductions in platelet counts were observed in Cynomolgus monkey repeated dose studies. The decrease was gradual, self-sustaining and did not decrease to adverse levels. In individual monkeys, severe thrombocytopenia was noted in the 9 month study of drug treated groups at clinically relevant exposures and has also been observed in clinical studies. The decrease in platelet counts was not acute and decreased to below 50,000 cells/ μ l. Platelet counts recovered after cessation of treatment, but decreased again below 50,000 cells/ μ l after treatment was resumed in some monkeys. Decreased platelet counts were also observed in rodent repeated dose studies. A mode of action for the observed thrombocytopenia is currently not known.

In nonclinical studies, levels of volanesorsen in milk were very low in lactating mice. The concentrations in breast milk of mice were >800 fold lower than effective tissue concentrations in maternal liver. Due to the poor oral bioavailability of volanesorsen, it is considered unlikely that these low milk concentrations would result in systemic exposure from nursing (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for 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

5 years

This medicinal product can be removed from refrigeration and stored, in the original carton, at room temperature (below 30 °C) for up to 6 weeks. In this 6-week period, it can be kept as needed between refrigerated and room temperature (up to 30 °C). This medicinal product must be discarded immediately if not used within the 6 weeks after the first time it is removed from refrigerated storage.

6.4 Special precautions for storage

Store in a refrigerator (2 ° - 8 °C).

Do not freeze.

Store in the original carton in order to protect from light.

6.5 Nature and contents of container

Single-dose, type I glass pre-filled syringe with a siliconised chlorobutyl rubber stopper and staked needle with shield, filled to deliver 1.5 ml of solution.

Pack sizes of one pre-filled syringe or multipacks containing 4 (4 packs of 1) pre-filled syringes.

Not all pack sizes may be marketed.

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 slightly yellow. If the solution is cloudy or contains visible particulate matter, the contents must not be injected and the medicinal product should be returned to the pharmacy. Use each pre-filled syringe only once and then place 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

Akcea Therapeutics Ireland Ltd.
St. James House
72 Adelaide Road, Dublin 2
D02 Y017
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1360/001
EU/1/19/1360/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 May 2019
Date of latest renewal: 04 April 2025

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

- A. MANUFACTURER(S) 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**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Almac Pharma Services (Ireland) Ltd
Finnabair Industrial Estate
Dundalk
Co. Louth
A91 P9KD
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 web-portal.

The marketing authorisation holder shall submit the first periodic safety update report 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.

- **Additional risk minimisation measures**

Prior to launch of Waylivra in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media,

distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The objective of the programme is to provide information on the risks of thrombocytopaenia and bleeding; advise on platelet monitoring and provide details about the dose frequency adjustment algorithm.

The MAH shall ensure that in each Member State where Waylivra is marketed, all healthcare professionals, patients and carers who are expected to prescribe, dispense and use Waylivra have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack
- **The physician educational material** should contain:
 - The Summary of Product Characteristics
 - Guide for healthcare professionals
- **The Guide for healthcare professionals** shall contain the following key elements:
 - Relevant information on thrombocytopaenia and severe bleeding
 - Details of the population at higher risk for thrombocytopaenia and bleeding (e.g. those with weight less than 70 kg), and patients for which Waylivra is contraindicated (i.e. patients with chronic or unexplained thrombocytopaenia)
 - Platelet monitoring recommendations including dosage adjustment recommendations, both before and during treatment.
 - That patients should be made aware of the possibility of thrombocytopaenia and to seek medical attention immediately in case of signs of bleeding. Patients must be reminded to read the patient leaflet and the patient/carers guide.
 - Duration of treatment covered by each prescription should be commensurate with, and encourage adherence to, the dosing and monitoring frequency of volanesorsen treatment.
 - Information about the FCS disease registry and the post authorisation safety study (PASS) study and the importance of contributing to those studies.
- **The patient information pack** should contain:
 - Patient information leaflet
 - A patient/carers guide
- **The Patient/carers guide** shall contain the following key messages:
 - Relevant information on thrombocytopaenia and severe bleeding
 - Importance of monitoring platelet levels
 - Possible need for dose adjustments or treatment pauses based on platelet test results
 - Need to be aware of and alert to the signs of thrombocytopaenia and the importance of seeking immediate assistance from a health professional
 - Information about the FCS disease registry and the PASS study and encouragement to participate in those studies.
 - Reporting of any adverse drug reaction to a health professional

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
<p>Non-interventional PASS: the applicant should conduct and submit the results of a study based on a Registry in order to evaluate the safety of Waylivra on thrombocytopenia and bleeding(including incidence rate, severity and outcomes) in FCS patients according to the dose recommendation and dose algorithm and investigate adherence with platelet monitoring and dose adjustment requirements.</p> <p>The applicant will ensure the long term follow-up of patients in the Registry.</p>	Q4 2028

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON – SINGLE PACK****1. NAME OF THE MEDICINAL PRODUCT**

Waylivra 285 mg solution for injection in pre-filled syringe
volanesorsen

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 200 mg volanesorsen sodium, equivalent to 190 mg volanesorsen.
Each single-dose pre-filled syringe contains 285 mg of volanesorsen in 1.5 ml solution.

3. LIST OF EXCIPIENTS

Water for injections, hydrochloric acid and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.
Read the package leaflet before use.
Subcutaneous 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. May be kept at room temperature for up to 6 weeks.
Date of first removal from fridge:

Keep the syringe in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Akcea Therapeutics Ireland Ltd.
St. James House
72 Adelaide Road, Dublin 2
D02 Y017
Ireland

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/19/1360/001
EU/1/19/1360/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Waylivra

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON – MULTIPACK WITH BLUE BOX****1. NAME OF THE MEDICINAL PRODUCT**

Waylivra 285 mg solution for injection in pre-filled syringe
volanesorsen

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 200 mg volanesorsen sodium, equivalent to 190 mg volanesorsen.
Each single-dose pre-filled syringe contains 285 mg of volanesorsen in 1.5 ml solution.

3. LIST OF EXCIPIENTS

Water for injections, hydrochloric acid and sodium hydroxide

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
Multipack: 4 (4 packs of 1) pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use
Read the package leaflet before use.
Subcutaneous 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. May be kept at room temperature for up to 6 weeks.
Keep the syringe in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Akcea Therapeutics Ireland Ltd.
St. James House
72 Adelaide Road, Dublin 2
D02 Y017
,
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/19/1360/001
EU/1/19/1360/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Waylivra

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**INNER CARTON – MULTIPACK WITHOUT BLUE BOX****1. NAME OF THE MEDICINAL PRODUCT**

Waylivra 285 mg solution for injection in pre-filled syringe
volanesorsen

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 200 mg volanesorsen sodium, equivalent to 190 mg volanesorsen.
Each single-dose pre-filled syringe contains 285 mg of volanesorsen in 1.5 ml solution.

3. LIST OF EXCIPIENTS

Water for injections, hydrochloric acid and sodium hydroxide

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
1 pre-filled syringe. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use
Read the package leaflet before use.
Subcutaneous 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. May be kept at room temperature for up to 6 weeks.
Date of first removal from fridge:

Keep the syringe in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Akcea Therapeutics Ireland Ltd.
St. James House
72 Adelaide Road, Dublin 2
D02 Y017
Ireland

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/19/1360/001
EU/1/19/1360/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Waylivra

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
--

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

Waylivra 285 mg injection
volanesorsen
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

1.5 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Waylivra 285 mg solution for injection in pre-filled syringe volanesorsen

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

1. What Waylivra is and what it is used for

Waylivra contains the active substance volanesorsen, which helps to treat a condition called familial chylomicronemia syndrome (FCS). FCS is a genetic disease which gives rise to abnormally high levels of fats called triglycerides in the blood. This can lead to inflammation of your pancreas, causing severe pain. Together with a controlled low-fat diet, Waylivra helps to lower the levels of triglycerides in your blood.

Waylivra may be given after you have already received other medicines used to lower the levels of triglycerides in blood without them having much effect.

You will only be given Waylivra if genetic testing has confirmed you have FCS and your risk for pancreatitis is considered very high..

You should continue the very low-fat diet that your doctor has prescribed during treatment with Waylivra.

This medicine is intended for patients aged 18 years and above.

2. What you need to know before you use Waylivra

Do not use Waylivra:

- if you are allergic to volanesorsen or any of the other ingredients in this medicine (listed in section 6).
- if you have a condition called thrombocytopenia, which means that you have a very low number of platelets in your blood (less than $140 \times 10^9/L$). You may notice this if you have an injury which causes bleeding and it takes a long time to stop (more than 5-6 minutes for a skin scratch). Your doctor will test for this before treatment with this medicine is started. You may not know that you have this condition until this point, or what might have caused it.

If any of the above apply to you, or you are not sure, talk to your doctor, nurse or pharmacist before using Waylivra.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Waylivra if you have or have had any of the following medical problems:

- Very high triglyceride levels which are not due to FCS.

- A low number of platelets, a type of cell in your blood that clump together to help it clot (thrombocytopenia); your doctor will do a blood test before you start using this medicine to check the number of platelets in your blood.

- Any liver or kidney problems.

Blood tests

Your doctor will do a blood test before you start using this medicine to check the number of platelets, and then at regular intervals once you have started using Waylivra to check on platelet levels.

You should see your doctor immediately if you have any signs of low platelet levels, such as unusual or prolonged bleeding, patches of red appearing on the skin (called petechiae), unexplained bruising, bleeding which will not stop, or nosebleeds, or if you get neck stiffness or a severe headache.

Your doctor may also do a blood test every 3 months to check for signs of damage to your liver. You should see your doctor immediately if you have any signs of liver damage, such as yellowing of your skin and eyeballs, pain or swelling in your abdomen, feeling or being sick, confusion or a general feeling of being unwell.

If necessary, your doctor may change how often you use this medicine, or may stop it for a period. It may be necessary to consult a doctor specialising in blood disorders to determine whether you should continue treatment with Waylivra or not.

Urine tests

Your doctor may do a urine and/or blood test every 3 months to check for signs of damage to your kidneys. You should see your doctor immediately if you have any signs of kidney damage, such as swelling in your ankles, legs and feet, passing smaller amounts of urine than usual, shortness of breath, feeling sick, confusion or feeling very tired or drowsy.

Diet

Before starting this medicine, you should be on a diet designed to help lower triglyceride levels in your blood.

It is important that you maintain this triglyceride-lowering diet whilst using Waylivra.

Children and adolescents

Do not use Waylivra if you are under 18 years old. Waylivra has not been studied in patients under 18 years old.

Other medicines and Waylivra

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. It is important to tell your doctor if you are already being treated with any of the following:

- Medicines to prevent blood clots, e.g., acetylsalicylic acid, dipyridamol or warfarin.

- Other medicines that may change how your blood clots, including non-steroidal anti-inflammatory medicines like ibuprofen, medicines used to prevent heart attacks and strokes such as clopidogrel, ticagrelor and prasugrel, antibiotics such as penicillin, medicines such as ranitidine (used to reduce stomach acid), and quinine (used to treat malaria).

- Medicines that may cause problems with your liver, such as paracetamol.

Waylivra with alcohol

The effect of using Waylivra with alcohol is not known. You should avoid alcohol during treatment with this medicine due to risk of liver issues.

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. It is preferable to avoid the use of Waylivra during pregnancy.

It is not known if Waylivra 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

Waylivra is not likely to affect your ability to drive or use machines.

Sodium

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

3. How to use Waylivra

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

Before you are given this medicine other causes of high levels of triglycerides, such as diabetes or problems with your thyroid, will be ruled out by your doctor.

Your doctor will tell you how often you should take this medicine. They may change how often you use it, or may stop it for a period or permanently, depending on the results of your blood and urine tests or occurrence of side effects.

You or your caregiver will be trained on how to use Waylivra according to the instructions in this leaflet. Waylivra should be injected under your skin (subcutaneous or 'SC' administration) in the way the doctor, nurse or pharmacist has shown you, and you should make sure you inject all of the liquid in the syringe. Each single-use, pre-filled syringe of this medicine gives you a dose of 285 mg in 1.5 ml.

Before using this medicine, it is important that you read, understand, and closely follow the instructions for use.

Instructions for use are provided at the end of this leaflet.

If you use more Waylivra than you should

If you inject too much Waylivra, contact your doctor or pharmacist, or attend a hospital emergency department immediately, even if there are no symptoms.

If you forget to use Waylivra

If you miss a dose, contact your doctor to ask when to take your next dose. If a dose is missed and noticed within 48 hours, you should give the missed dose as soon as possible. If not noticed within 48 hours, then the missed dose should be skipped and the next planned injection given. Do not inject more than one dose within 2 days.

If you stop using Waylivra

Do not stop using Waylivra unless you have discussed stopping your medicine 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.

Serious side effects

If you get any of the following side effects, contact your doctor immediately:

- Symptoms that could indicate low counts of platelets in your blood (platelets are cells important for blood clotting). You should see your doctor immediately if you have any signs of low platelet levels, such as unusual or prolonged bleeding, patches of red appearing on the skin (called petechiae), unexplained bruising, bleeding which will not stop, or nosebleeds, or if you get neck stiffness or a severe headache.

Other side effects

Very common (may affect more than 1 in 10 people)

- Injection site reactions (rash, pain, redness, heat or warmth, dryness, swelling, itching, tingling, hardening, hives, blistering, pimples, bruising, bleeding, numbness, paleness, change in colour or a burning feeling at the injection site). You can reduce the likelihood of having injection site reaction if you wait for Waylivra to reach room temperature before injecting, and by applying ice to the injection site after injecting.
- Headache
- Muscle pain
- Chills

Common (may affect up to 1 in 10 people)

- Blood tests showing unusually high levels of white blood cells in your blood
- Blood tests showing unusually low levels of white blood cells in your blood (known as lymphopenia)
- Easy or excessive bruising, or bruising without an obvious cause
- Bleeding under the skin that appears as a rash, bleeding from the gums or mouth, blood in the urine or stools, nosebleed, or unusually heavy menstrual period
- An allergic reaction, the symptoms of which include skin rash, joint stiffness or fever
- Blood or protein in the urine
- Changes to the results of some blood tests, including:
 - o an increase in the level of some constituents in your blood: creatinine, urea, transaminases, liver enzymes
 - o an increase in blood clotting time
 - o a fall in levels of haemoglobin in your blood
 - o a fall in the rate of blood passing through the kidneys
- Diabetes, the symptoms of which include increased thirst, frequent need to pass urine (particularly at night), extreme hunger, severe tiredness, and unexplained weight loss
- Difficulty sleeping
- Numbness, tingling or pins and needles, feeling faint or fainting, dizziness or shaking
- Visual disturbances, such as flashing lights or brief, temporary blindness in one eye, bleeding under the surface of the eye, or blurred vision
- High blood pressure
- Hot flush, increased sweating, night sweats, feeling hot, pain, flu-like illness or a general feeling of being unwell
- Cough, difficulty breathing, a blocked nose, swelling of the throat, wheezing
- Feeling or being sick, dry mouth, diarrhoea, swelling of the neck, face or gums, stomach pain or swelling, indigestion
- Skin redness, rash, pimples, thickening or scarring, or itchiness of the skin known as 'hives' (urticaria)
- Pain in the hands or feet, pain in the large joint of the arms and legs including the elbows, wrists, knees and ankles, other joint pain or stiffness, back pain, neck pain, jaw pain, muscle spasms, or other body pains
- Severe tiredness (fatigue), weakness or lack of energy, fluid retention, chest pain unrelated to the heart

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 Waylivra

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 syringe label after 'EXP'. Please note that the expiry date refers to the last day of that month.

Store in a refrigerator (2 ° - 8 °C).

Store in the original carton to protect from light.

Waylivra can be kept at room temperature (up to 30 °C) in the original carton for up to 6 weeks after removing from the refrigerator. During this time this medicine may be kept at either room temperature or put back into the refrigerator, as needed. Record the date you first remove the pack from the refrigerator on the outer carton in the space indicated. If you do not use it within 6 weeks after first removing from the refrigerator, discard the medicine. If the expiry date on the syringe label has passed during the 6 week period at room temperature, do not use the syringe and discard it.

Do not use this medicine if the solution is cloudy or contains particles; it should be clear and colourless to slightly yellow.

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

6. Contents of the pack and other information

What Waylivra contains

The active substance is volanesorsen. Each ml contains 200 mg volanesorsen sodium, equivalent to 190 mg volanesorsen. Each single-dose pre-filled syringe contains 285 mg of volanesorsen in 1.5 ml solution.

The other ingredients are water for injections, sodium hydroxide and hydrochloric acid (to adjust acidity level, see section 2 under 'Sodium').

What Waylivra looks like and contents of the pack

Waylivra is provided in a carton as a single-dose syringe with needle and needle cap, pre-filled with a clear, colourless to pale yellow solution. It is filled to deliver 1.5 ml of solution upon full depression of the syringe's plunger.

It is available as either a carton containing 1 pre-filled syringe, or as a multipack of 4 (4 packs of 1-pack cartons) pre-filled syringes.

Marketing Authorisation Holder

Akcea Therapeutics Ireland Ltd.
St. James House
72 Adelaide Road, Dublin 2
D02 Y017
Ireland

Manufacturer

Almac Pharma Services Ireland Ltd.
Finnabair Industrial Estate

Dundalk
Co. Louth
Ireland

This leaflet was last revised in

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:

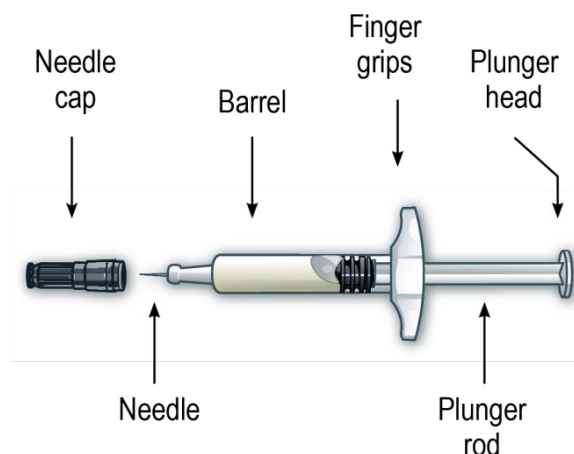
<http://www.ema.europa.eu>.

Instructions for use

Waylivra is an injection given under the skin with a single-use, disposable, pre-filled syringe.

Do not use Waylivra until you completely understand the procedure described below. If you have any questions about how to use Waylivra, please contact your doctor or pharmacist.

Pre-filled syringe components



Get ready to inject

1. Wash hands and gather supplies

Wash your hands thoroughly with soap (for at least 3 minutes) and dry them well. Place the following items on a clean, flat surface in a well-lit area (Figure A).

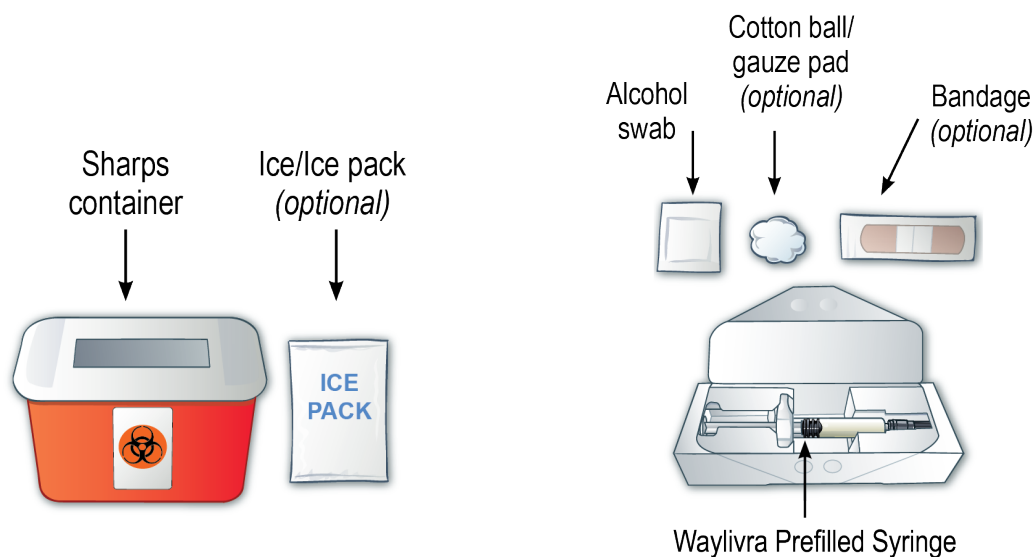


Figure A

2. Allow the injection to reach to room temperature

If the syringe was in the refrigerator, allow the pre-filled syringe to reach room temperature by

removing it from the refrigerator at least 30 minutes before the injection.

Injection with cold liquid may cause injection site reactions such as pain, redness, or swelling.

Do not warm syringe in any other way, such as by microwave or warm water.



Figure B

3. Check the expiry date

Check the expiry date on the carton.

The expiry date on the package refers to the life of the medicine when refrigerated.

The date you first remove the pack from the refrigerator should be recorded on the outer carton in the space indicated.

Do not use Waylivra if the expiry date has passed or if it was stored for longer than 6 weeks at room temperature. Call your doctor or pharmacist to get a new supply.

4. Remove the syringe and inspect the medicine

Open the carton and remove the syringe by grasping the syringe barrel and pulling it straight out (Figure C).

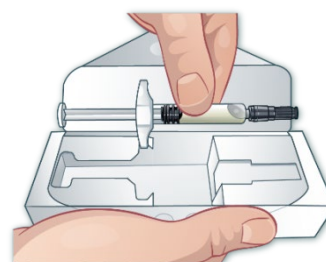


Figure C

Look at the liquid in the syringe. The medicine should be clear to slightly yellow in colour. It is normal to see a large air bubble (Figure D).

Do not try to remove the air bubble before injecting. Injecting the solution with the air bubble is harmless.

Do not use the pre-filled syringe if the liquid is cloudy or has floating particles.

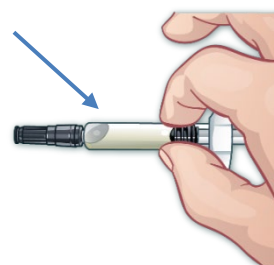


Figure D

5. Choose an injection site

If self-injecting:

Stomach – Stomach area as shown, except for 2 inches around the belly button.

Thighs – Front, middle area as shown (Figure E).

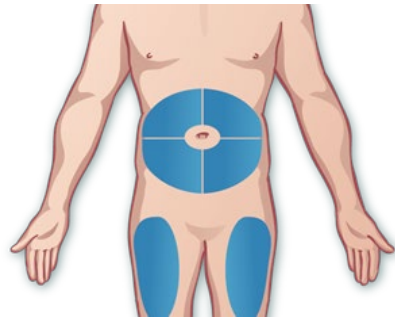


Figure E

If administering an injection to someone else as a caregiver, in addition to the above sites:

Arms – Back of upper area as shown (Figure F).

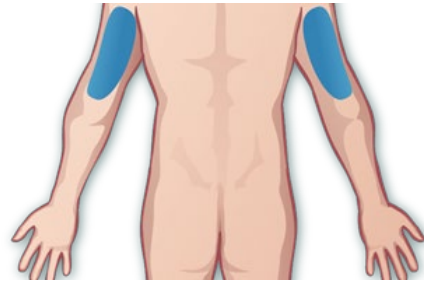


Figure F

For all injections:

Alternate the injection area for each injection.

Avoid injecting at the waistline where your clothing may rub or press the injection area.

Do not inject into tattoos, moles, scars, birthmarks, bruises, rashes, or areas where the skin is tender, red, hard, damaged, burned, or inflamed.

Talk to your healthcare provider if you are unsure of where to inject.

Injecting

6. Prepare injection site

Clean your chosen injection site with an alcohol pad (Figure G).

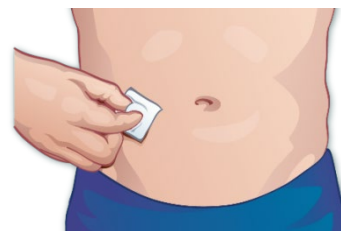


Figure G

7. Remove needle cap

Remove the needle cap by holding the barrel of the syringe with the needle pointing away from you and pulling the needle cap straight off (Figure H).

You may see a drop of liquid at the tip of the needle. This is normal.

Do not hold the plunger rod or the plunger head while removing the needle cap.

Do not use the pre-filled syringe if the needle appears damaged.

Do not use the pre-filled syringe if it is dropped with the needle cap removed.

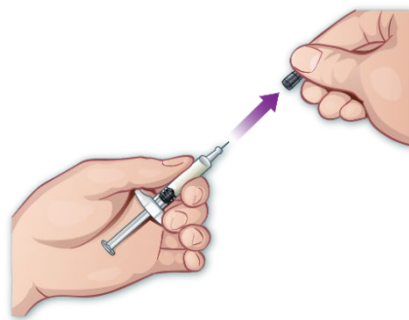


Figure H

8. Pinch the skin

Using your free hand, pinch the skin around the injection site (Figure I).



Figure I

9. Insert needle

Insert the needle into the injection site with a quick, firm motion without touching the plunger head. The needle should be inserted at a 45 degree angle to the skin surface (Figure J).

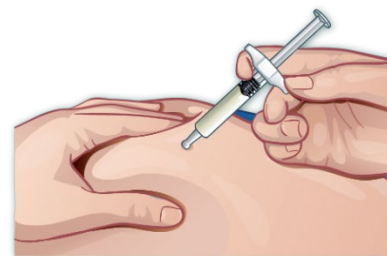


Figure J

10. Inject Waylivra

Inject the liquid by holding the syringe with your thumb on the plunger, and **slowly push** the plunger down as far as it will go, until the syringe is completely empty (Figure K and L).

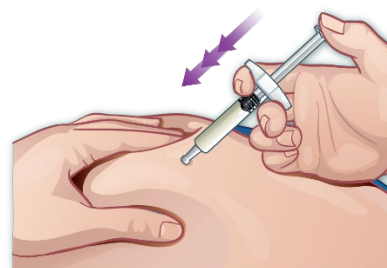


Figure K



Figure L

11. Remove Needle

Remove the needle from the injection site by pulling out at the same angle it was inserted (Figure M).

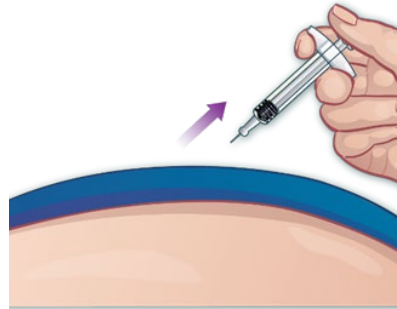


Figure M

After the Injection

12. Dispose of the Used Syringe into a Sharps Container

Immediately after the injection, dispose of the used syringe as instructed by your healthcare professional, usually into a sharps disposal container (Figure N) by following these steps.

Throw away the needle cap after injecting.

Do not recap the syringe.

If you do not have a sharps disposal container, you may use a household container that is:

- Made of heavy-duty plastic,
- Capable of being closed with a tight-fitting, Puncture-resistant lid, without sharps being able to come out,
- Upright and stable during use,
- Leak-resistant,
- Properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for proper disposal of the sharps container. There may be special local laws regarding how you should throw away used needles and syringes. Ask your pharmacist or see your local public health government website (where available) for more details on how you should dispose of sharps in your location.



Figure N

Do not dispose of your used sharps disposal container in your household waste.

Do not recycle your used sharps disposal container.

Always keep your sharps container away from children and pets.

13. Treat the Injection Site

If you see blood where you've injected, press the site lightly with the sterile cotton ball or gauze and bandage if needed (Figure O).

Do not rub the site after you've injected.



Figure O

You may also apply ice to the injection site to reduce pain, redness, or discomfort (Figure P).



Figure P

Storage

Storage information

When you first receive Waylivra the pre-filled syringes should be stored in their packaging in the refrigerator (2 °C-8 °C).

Waylivra can be stored at room temperature (8 °C-30 °C), in the outer carton to protect from light, for up to 6 weeks. During this 6 week period, this medicine can be stored at either room temperature or put back in the refrigerator.

Do not freeze the Waylivra pre-filled syringe.

Do not take out of the packaging or remove the needle cap until you are ready to inject.

Discard this medicine immediately if not used within the 6 weeks after the first time it is removed from the refrigerator. You should refer to the date you have written on the carton to be sure.