waylivra®
(volanesorsen) injection 285 mg/1.5 mL

PRESCRIBING GUIDE

Waylivra is indicated as an adjunct to diet in adult patients with genetically confirmed familial chylomicronaemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate.[1]

Prescribing information can be found on the back page of this guide.

AKCEA® THERAPEUTICS

CONTENTS

Reference:
1. Waylivra. Summary of Product Characteristics, May 2019.

▼ 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.

INTRODUCTION

This prescribing guide is intended to provide the critical information you need to prescribe Waylivra to your patients and to help you manage their ongoing care. Please refer to the Waylivra Summary of Product Characteristics for full prescribing information.

Familial chylomicronaemia syndrome (FCS)

When an adult patient has genetically confirmed FCS and is at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate, the next step is to initiate treatment.

What is Waylivra (volanesorsen)?[1]

Waylivra is an antisense oligonucleotide designed to inhibit the formation of apoC-III. ApoC-III is a protein that is recognised to regulate both triglyceride metabolism and hepatic clearance of chylomicrons and other triglyceride-rich lipoproteins. By inhibiting apoC-III, Waylivra reduces the level of triglycerides in the blood and, as a result, fat accumulation in the body.

INITIATING WAYLIVRA

What lipid lowering methods has the patient tried so far?

What is the patient's dietary situation?
Have they been keeping to their fat restrictions and following a suitable diet?
Has the patient failed on other lipid lowering therapies?

How are their platelet levels?

Is their baseline platelet count below 140 x 10^9/L?
Have they previously discontinued Waylivra?

Are they able to travel?

Are they willing or able to travel to regular hospital appointments?
Would they benefit from receiving visits at home from a dedicated nurse?

What are their goals for treatment?

How much does the convenience of their treatment influence them?

What are their concerns around treatment?

Are they concerned about side effects?
Do they have concerns about injecting themselves?

Do they have any affected family members?

Are they comfortable discussing or receiving their treatment in front of family members or loved ones?

Are they comfortable with injecting themselves?

Will they adhere to their treatment plan?
Do they have the dexterity to self-inject Waylivra?

Do they understand the risks and monitoring requirements of Waylivra?

Do they know that the Akcea Connect service is available to them?

WAYLIVRA DOSING

Before Injecting Waylivra

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

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

For any patient dose-paused or discontinued due to severe thrombocytopenia, the benefits and risks of returning to treatment once the platelet count has returned to levels ≥100 x 10^9/L should be carefully considered. For discontinued patients, a haematologist should be consulted prior to resuming treatment.

Waylivra dosing

Recommended starting dose	285 mg in 1.5 ml injected subcutaneously once weekly for 3 months
After 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	Consider an increase in dose frequency to 285 mg weekly 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
	However: 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

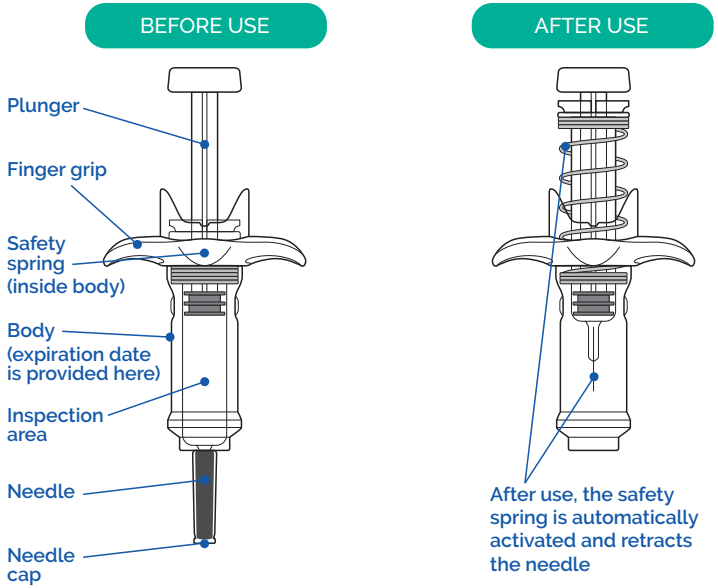
Further recommendations for adjustments to dosing and monitoring frequency are specified in Table 1 on page 14 of this booklet, and in section 4.2 of the Waylivra Summary of Product Characteristics.

WAYLIVRA SYRINGE

The Waylivra Pre-Filled Syringe

Waylivra comes as a solution for injection in a pre-filled syringe, containing one 285mg dose of volanesorsen.

The solution should be clear and colourless to slightly yellow, with no cloudiness or visible particulate matter.



Delivery

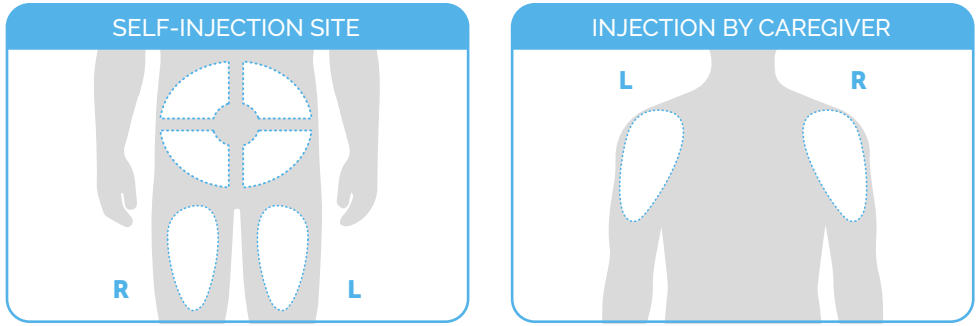
Waylivra will be delivered to the patient's home (or chosen location) by HealthNet Homecare, part of the Akcea Connect service. This is a free-of-charge post-prescription service funded by Akcea Therapeutics UK Ltd. The Akcea Connect service has been set up to support patients prescribed Waylivra to help ensure that they receive the monitoring, nurse support, home-support, advice and training they need.

See Page 15 of this brochure for further information on the Akcea Connect service.

ADMINISTERING WAYLIVRA

Waylivra is for subcutaneous use only. The dose should be administered once a week, on the same day, or according to the medically determined frequency of administration.

Sites for injection include the abdomen, upper thigh region, or outer area of the upper arm. It is important to rotate sites for injection. Patients should use the My Waylivra Treatment Tracker to note down their injection site.



Please note: Injection into the upper arm should only be performed by another person, such as a caregiver or the patient's dedicated Akcea Connect nurse.

Patients should be instructed to **AVOID** injection at the following sites:

- At the waistline and other sites where pressure or rubbing may occur from clothing
- Into tattoos, moles, birthmarks, bruises, rashes, or areas where the skin is tender, red, hard, bruised, damaged, burned, or inflamed
- The 3 cm area around the belly button

Patient and caregiver training

Patients and caregivers should be trained in the subcutaneous administration of Waylivra – the first injection administered by them should be performed under the guidance of an appropriately qualified healthcare professional. Every patient will receive materials to support management of their condition and injections, in addition to the support available from their dedicated Akcea Connect nurse.

SAFETY INFORMATION

Monitoring Requirements

Waylivra is very commonly associated with reductions in platelet count in patients with FCS, which may result in thrombocytopenia. Patients with lower body weight (less than 70kg) may be more prone to thrombocytopenia during treatment with this medicinal product.

Careful monitoring for thrombocytopenia and treatment adjustment if needed is important during treatment.

- After commencing treatment, patients should have platelet levels monitored at least every two weeks, depending on the platelet levels. More information about platelet monitoring can be found on page 14.

Blood and urine analysis

Blood and urine samples of patients undergoing Waylivra treatment should at various points be analysed for:

- Renal function and evidence of nephrotoxicity (serum creatinine, proteinuria and creatinine clearance) – quarterly monitoring (by routine dipstick) recommended
- Hepatotoxicity (serum liver enzymes, bilirubin) – quarterly monitoring recommended
- Erythrocyte sedimentation rate – quarterly monitoring recommended
- Anti-drug antibodies – if suspected, contact the marketing authorisation holder to discuss antibody testing

Monitoring through Akcea Connect, a voluntary patient service

Akcea has commissioned the services of Spire Pathology to analyse the necessary blood and urine samples. Spire Pathology is one of the UK's largest networks of accredited laboratories. They have 22 specialist laboratories and 200 staff carrying out millions of tests per year.

Pathology samples will be collected or coordinated by the Akcea Connect nurse and delivered to one of Spire Pathology's laboratories or collection points. Sample analysis will occur within 4 hours of Spire Pathology receiving the sample. The Akcea Connect nurse will communicate the sample results to the referring clinical team, the patient and HealthNet Homecare.

Side effects of Waylivra

The most common side effects of Waylivra are injection site reactions, including injection site erythema, pain, pallor, swelling, pruritus, discolouration, induration, bruising and oedema. These events are usually either self-limiting or can be managed using symptomatic treatment. Platelet count decrease and thrombocytopenia are also very common side effects. See page 14 of this guide for more information.

ADVERSE REACTIONS

SYSTEM ORGAN CLASS	VERY COMMON (may affect more than 1 in 10 people)	COMMON (may affect up to 1 in 10 people)
Blood and lymphatic system disorders	Thrombocytopenia	Leukopenia, 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, Hypoaesthesia, Presyncope, Retinal migraine, Syncope, Dizziness, Tremor
Eye disorders		Conjunctival haemorrhage, Vision blurred
Vascular disorders		Haematoma, Hypertension, Haemorrhage, Hot flush
Respiratory, thoracic and mediastinal disorders		Epistaxis, Cough, Dyspnoea, Nasal congestion, Pharyngeal oedema, Wheezing
Gastrointestinal disorders		Nausea, Diarrhoea, Dry mouth, Gingival bleeding, Mouth haemorrhage, Parotid gland enlargement, Vomiting, Abdominal pain, Abdominal distension, Dyspepsia, Gingival swelling
Skin and subcutaneous tissue disorders		Erythema, Pruritus, Urticaria, Hyperhidrosis, Rash, Petechiae, Ecchymosis, Night sweats, Papule, Skin hypertrophy, Swelling face
Musculoskeletal and connective tissue disorders		Myalgia, Arthralgia, Pain in extremity, Arthritis, Back pain, Musculoskeletal pain, Neck pain, Muscle spasms, Joint stiffness, Myositis, Pain in jaw, Polymyalgia rheumatica
Renal and urinary disorders		Haematuria, Proteinuria
General disorders and administration site conditions	Injection site: Erythema, Pain, Pallor, Swelling, Pruritus, Discolouration, Induration, Bruising, Oedema	Asthenia, Fatigue, Injection site haematoma, Injection site reaction, Injection site urticaria, Injection site warmth, Chills, Pyrexia, Injection site dryness, Injection site haemorrhage, Injection site hypoaesthesia, Injection site vesicles, Malaise, Feeling hot, Influenza-like illness, Injection site discomfort, Injection site inflammation, Injection site mass, Pain, Injection site paraesthesia, Injection site scab, Injection site papule, Oedema, Non-cardiac chest pain, Vessel puncture site haemorrhage
Investigations	Platelet count decreased	Blood creatinine increased, Blood urea increased, Creatinine renal clearance decreased, Transaminases increased, White blood cell count decreased, Haemoglobin decreased, Hepatic enzyme increased, International normalised ratio increased
Injury, poisoning and procedural complications		Contusion

SPECIAL CONSIDERATIONS

Thrombocytopenia

- Waylivra is associated with a reduction in platelet counts, which may result in thrombocytopenia
- Waylivra should not be initiated in patients with a baseline platelet count below 140 x 10^9/L
- Patients with platelet counts <140 x 10^9/L after initiation of Waylivra should have their platelet counts monitored more frequently (see Table 1)
- If platelet count is <25 x 10^9/L after initiation of Waylivra, the treatment should be discontinued and steroid therapy should be considered
- For discontinued patients, a haematologist should be consulted prior to resuming treatment

Table 1.
Waylivra thrombocytopenia monitoring and treatment recommendations

Platelet Count (x10^9/L)	Dose (285 mg pre-filled 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 ≥ 100 x 10^9/L	Weekly
50 to 74[a]	Pause treatment for ≥4 weeks and resume treatment after platelet levels ≥ 100 x 10^9/L	Every 2-3 days
Less than 50[a,b]	Discontinue treatment Glucocorticoids recommended	Daily

a Discontinuation of antiplatelet medicinal products/NSAIDs/anticoagulants should be considered for platelet levels <75 x 10^9/L. Treatment with these medicinal products must be discontinued at platelet levels <50 x 10^9/L.
b Consultation of a haematologist is needed to reconsider the benefit/risk for possible further treatment with Waylivra.

Discontinuation

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

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.

ABOUT AKCEA CONNECT

AKCEA CONNECT®

The Akcea Connect service is a voluntary, post-prescription service fully funded by Akcea Therapeutics UK Ltd.

It provides:

- Delivery of Waylivra to the patient's home or chosen location
- A dedicated Akcea Connect nurse, who will visit the patient's home on a fortnightly basis, or as often as is clinically necessary, to perform required monitoring and provide support
- Face-to-face nursing support and materials to help support life with FCS
- Blood and urine analysis through the services of Spire Pathology

The Akcea Connect service offers free, private and personalised support to patients and caregivers and is available across the United Kingdom.

We have developed a number of materials, provided free of charge to patients enrolled in the Akcea Connect service, in addition to information for HCPs. These materials will be available in each patient's home care pack, and you can order extra materials by contacting your Akcea Therapeutics UK Ltd. account manager or via the Akcea Connect Service.

- Introduction to Waylivra
- Waylivra injection guide
- Akcea Connect patient booklet
- My Waylivra treatment tracker

If you have any further questions or concerns about the Akcea Connect service and the support available, or would like further information on how to set up the Akcea Connect service in your hospital, please don't hesitate to contact your Akcea Connect dedicated nurse, or contact us at:

Tel: **+44 (0)800 2062574**

Email: **akcea@healthnethomecare.co.uk**

Prescribing Information: Waylivra ▼ (volanesorsen 285 mg solution for injection in pre-filled syringe) Consult Summary of Product Characteristics (SmPC) before prescribing

Indications: As an adjunct to diet in adults with genetically confirmed familial chylomicronaemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride-lowering therapy has been inadequate. **Dosage and administration:** Treatment should be initiated and supervised by a physician experienced in FCS. Recommended starting dose is 285 mg in 1.5 mL administered subcutaneously once weekly for 3 months, after which dose frequency should be reduced to 285 mg once every 2 weeks. Treatment should be discontinued in patients with a reduction in serum triglycerides of <25% or who fail to achieve serum triglycerides below 22.6 mmol/L after 3 months. After 6 months, an increase in dose frequency to 285 mg weekly should be considered if serum triglyceride reduction is inadequate and platelet counts are in the normal range. Patients should be down titrated to 285 mg every 2 weeks if there is no significant additional triglyceride reduction after 9 months. Injections should be administered on the same day of the week according to the medically determined frequency of administration. *Missed doses:* Missed doses noticed within 48 hours should be given as soon as possible. If not noticed within 48 hours, a 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 x 10^9/L, another measurement should be taken approximately a week later to reassess. If the platelet count remains below 140 x 10^9/L upon a second measurement, Waylivra should not be initiated. Patients on Waylivra should have their platelet counts monitored every 2 weeks. If a platelet count of 100 to 139 x10^9/L is recorded, the frequency of platelet monitoring should be increased to every week. Treatment should be paused for at least 4 weeks if a platelet count lower than 100 x 10^9/L is recorded and treatment should not be restarted until the platelet level has reached ≥100x10^9/L. Platelet monitoring should be undertaken every week for patients with platelet counts in the range of 75 to 99 x 10^9/L or every 2–3 days for patients with platelet counts in the range 50 to 74 x 10^9/L. Treatment should be discontinued in patients with a platelet count <50 x 10^9/L. For any patient dose paused or discontinued due to severe thrombocytopenia, the benefits and risks of returning to treatment once a platelet count ≥100 x 10^9/L should be carefully considered. For discontinued patients, a haematologist should be consulted prior to resuming treatment. *Elderly:* Limited data exist for patients aged 65 years and over. *Renal impairment:* Limited data exist for patients with severe renal impairment; patients with severe renal impairment should be closely observed on treatment. *Hepatic impairment:* Waylivra is not metabolised via the cytochrome P450 enzyme system; no dose adjustment is expected to be required. Paediatric use: No data are available in children and adolescents below 18 years of age. Method of administration: Subcutaneous use only. Patients and/or caregivers should be trained in subcutaneous administration of Waylivra. The first injection administered by a patient/caregiver should be under the guidance of an appropriately qualified healthcare professional. Injection sites include the abdomen, upper thigh, outer area of upper arm. Rotate injection sites. Avoid tattoos, scars, birthmarks, rash or injured skin. Remove from refrigeration at least 30 minutes before use and allow syringe to reach room temperature prior to injection. Do not use other warming methods. It is normal to see a large air bubble; there should be no attempt to remove this. **Contraindications:** Hypersensitivity to active substance or excipients, chronic or unexplained thrombocytopenia. Treatment should not be initiated if platelet count <140 x 10^9/L. **Warnings and precautions:** Consult SmPC for full details. **Thrombocytopenia:** Waylivra is very commonly associated with reductions in platelet count, which may result in thrombocytopenia. Lower body weight (≤70kg) may increase risk. Follow the SmPC recommendations for adjustments to frequency of platelet monitoring and dosing as necessary. Consider discontinuation of antiplatelet medicinal products/NSAIDs/anticoagulants for platelet levels <75 x 10^9/L; discontinue treatment with these products at platelet levels <50 x 10^9/L. Advise patients to report any signs of bleeding to their physician immediately, including 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 Waylivra treatment, LDL-C levels may rise but will usually remain within the normal range. **Renal toxicity:** Monitor patients for evidence of nephrotoxicity by routine urine dipstick quarterly. In the case of a positive result, broader assessment of renal function is required. Discontinue treatment if proteinuria is ≥500 mg/24 hours, a ≥0.3 mg/dL (26.5 µmol/L) increase in serum creatinine that is over the upper limit of normal (ULN) is recorded, or if creatinine clearance is ≤30 mL/min/1.73 m^2. Discontinue treatment if there are any clinical symptoms or signs of renal impairment pending confirmatory assessments. **Hepatotoxicity:** Assess hepatotoxicity through serum liver enzymes and bilirubin quarterly. Discontinue treatment if there is a single increase in alanine transaminase (ALT) or aspartate aminotransferase (AST) >8 x ULN, an increase >5 x ULN that persists for ≥2 weeks, or lesser increases in ALT or AST that are associated with total bilirubin >2 x ULN or international normalised ratio >1.5. Discontinue treatment if there are 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). **Interactions:** No clinical drug interaction studies have been conducted. Clinically relevant interactions are not expected between volanesorsen and substrates, inducers or inhibitors of cytochrome P450 enzymes, and drug transporters. No adverse events related to drug–drug interactions were reported during the clinical programme. Discontinue hepatotoxic medicinal products if signs and symptoms of hepatotoxicity develop. Risk of increased bleeding with concomitant use of Waylivra and antithrombotics or products that lower platelet count is not known. Discontinuation of such products should be considered if platelet levels reduce to <75 x 109/L and stopped if platelets reach <50 x 10^9/L. Pregnancy and lactation: Avoid the use of Waylivra in pregnancy. Decision to be made whether to discontinue breastfeeding or discontinue Waylivra during lactation, taking into account the relative benefits for the woman and child. Undesirable effects: Consult SmPC for full details. Very common (≥1/10): thrombocytopenia, injection-site reactions, platelet-count reductions. Common (≥1/100 to <1/10): leukopenia, eosinophilia, immune thrombocytopenic purpura, spontaneous haematoma, immunisation reaction, hypersensitivity, serum sickness-like reaction, diabetes mellitus, insomnia, headache, hypoaesthesia, presyncope, retinal migraine, syncope, dizziness, tremor, conjunctival haemorrhage, vision blurred, haematoma, hypertension, haemorrhage, hot flush, epistaxis, cough, dyspnoea, nasal congestion, pharyngeal oedema, wheezing, gastrointestinal disorders including nausea, diarrhoea, vomiting and abdominal pain, skin and subcutaneous disorders including erythema, pruritis, rash and urticaria, musculoskeletal and connective tissue disorders including myalgia, arthralgia and pain in extremities, renal and urinary disorders including haematuria and proteinuria, general disorders including asthenia and fatigue, and changes in lab parameters including renal, hepatic and haematological, and contusion.

Legal Category: POM

Package Quantities and Basic NHS Price: £11,394.00 Marketing Authorisation Holder: Akcea Therapeutics Ireland Ltd, Regus House, Harcourt Centre, Harcourt Road, Dublin 2, Ireland

Marketing Authorisation Number: EU/1/18/1296/001, EU/1/18/1296/002

Further information is available from Akcea Therapeutics UK Ltd, Regus Building, Wellington Way, Weybridge, Surrey, KT13 0TT, UK

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Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ Adverse events should also be reported to Akcea Therapeutics UK Ltd Email: MedInfoUK@akceatx.com Telephone: +44 (0) 330 159 0174

If you would like any further information on Akcea Therapeutics UK Ltd. please contact:
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Email: MedInfoUK@akceatx.com

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