Medicines Management Programme

Managed Access Protocol – PCSK9 Inhibitors

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List of Abbreviations

ASCVD	Atherosclerotic cardiovascular disease
CK	Creatine kinase
CVD	Cardiovascular disease
HeFH	Heterozygous familial hypercholesterolaemia
HSE	Health Service Executive
HTH	High Tech Hub
LDL-C	Low Density Lipoprotein-Cholesterol
MMP	Medicines Management Programme
PAD	Peripheral arterial disease
PCRS	Primary Care Reimbursement Service
PCSK9	Proprotein convertase subtilisin/kexin type 9
PFP	Pre-filled pen
SmPC	Summary of Product Characteristics

1. Proprotein convertase subtilisin/kexin type 9 inhibitors

There are two proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors available under the High Tech Arrangement:

- Alirocumab: Praluent® solution for injection in pre-filled pen (PFP) 75 mg or 150 mg (Praluent®)
- Evolocumab: Repatha® 140 mg solution for injection in SureClick PFP (Repatha®)

1.1 Licensed indications

Praluent® and Repatha® are indicated in:[i]

- adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia
- adults with established atherosclerotic cardiovascular disease (ASCVD) to reduce cardiovascular risk by lowering low-density lipoprotein-cholesterol (LDL-C) levels.

In addition, Repatha® 140 mg PFP is indicated in:[i]

- adults and paediatric patients aged 10 years and over with homozygous familial hypercholesterolaemia
- paediatric patients aged 10 years and over with heterozygous familial hypercholesterolaemia.

1.2 Reimbursement

Reimbursement of alirocumab and evolocumab is confined to the following subgroups of the licensed population:

- adults with established ASCVD[ii] (i.e. confirmed diagnosis of myocardial infarction +/- revascularisation procedures, non-haemorrhagic stroke or peripheral arterial disease (PAD) [i.e. secondary prevention] or in those who have undergone coronary artery bypass graft), with a LDL-C persistently ≥ 3.5 mmol/L
- adults with a confirmed diagnosis of heterozygous familial hypercholesterolaemia (HeFH) with a LDL-C persistently ≥ 4 mmol/L.

Table 1 outlines the LDL-C levels required for reimbursement approval of alirocumab and evolocumab under the High Tech Arrangement.

[i] Please refer to the relevant Summary of Product Characteristics for full prescribing information.

[ii] See section 2.3.1 for detailed information on the criteria for ASCVD

Table 1: LDL-C levels required for reimbursement approval of alirocumab / evolocumab under the High Tech Arrangement

	Without CVD*	With CVD*
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Reimbursement not supported	Recommended only if LDL-C is persistently ≥ 3.5 mmol/L and all other criteria are satisfied
Primary heterozygous familial hypercholesterolaemia	Recommended only if LDL-C is persistently ≥ 4 mmol/L and all other criteria are satisfied	

*Cardiovascular disease (CVD) is defined as patients who have a prior diagnosis of myocardial infarction (+/- revascularisation procedures), non-haemorrhagic stroke or peripheral arterial disease or those who have undergone coronary artery bypass graft

Prescribers are required to apply for reimbursement approval on an individual patient basis through the online application system. If a patient is recommended for reimbursement, the high tech prescription for Praluent® or Repatha® should be inputted onto the High Tech Hub (HTH). High tech prescriptions which are not hub generated for Praluent® or Repatha® will not be eligible for reimbursement by the Health Service Executive (HSE)-Primary Care Reimbursement Service (PCRS).

If a patient is recommended for reimbursement of alirocumab, reimbursement will be supported for a maximum of 26 Praluent® 75 mg or 150 mg PFP per year.

If a patient is recommended for reimbursement of evolocumab, reimbursement will be supported for a maximum of 26 Repatha® 140 mg PFP per year i.e. the patient should be prescribed a dose of 140 mg of evolocumab every two weeks. Reimbursement of the dose of 420 mg once monthly is not supported.

1.3 Reimbursement price

The reimbursement prices of one pack of Praluent® and Repatha® are outlined in table 2. A commercial-in-confidence arrangement is in place with the marketing authorisation holders to reduce the net acquisition cost of these biological medicines to the HSE.

Table 2: Reimbursement price of PCSK9 inhibitors available on the High Tech Arrangement

Medicinal Product (pack size)	Reimbursement price*
Praluent® 75 mg PFP (two pens)	€421.24
Praluent® 150 mg PFP (two pens)	€421.24
Repatha® 140 mg PFP (two pens)	€419.67

*As of 1 June 2022

2. Reimbursement criteria - Initiation

This section outlines the criteria that must be satisfied in order for a patient to be recommended for reimbursement of alirocumab and evolocumab under the High Tech Arrangement.

2.1 Prescribers

The prescribing of Praluent® and Repatha® under the High Tech Arrangement is confined to designated clinicians who have been approved by the HSE and have agreed to the terms of this managed access protocol. Applications for reimbursement approval will only be considered from these prescribers.

2.2 Patient Clinical History

In line with the exclusion criteria for the FOURIER and ODYSSEY Outcomes trial, and information contained within the relevant Summary of Product Characteristics (SmPC), reimbursement of alirocumab and evolocumab will not be considered in the following circumstances:[iii]

- patients with New York Heart Association class III or IV heart failure, or those with a last known left ventricular ejection fraction < 30%
- patients with uncontrolled hypertension defined as sitting systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg
- patients with untreated or inadequately treated hyperthyroidism or hypothyroidism as defined by thyroid stimulating hormone < lower limit of normal or > 1.5 times the upper limit of normal, respectively, and free thyroxine (T4) levels that are outside the normal range
- patients with active liver disease or hepatic dysfunction, defined as aspartate aminotransferase or alanine aminotransferase > 3 times the upper limit of normal
- patients with creatine kinase (CK) > 5 times the upper limit of normal.

2.3 Diagnosis

2.3.1 Adults with ASCVD (i.e. secondary prevention)

Patients in this group must have established ASCVD. For reimbursement approval, patients should have a prior diagnosis of myocardial infarction (with or without revascularisation procedures), non-haemorrhagic stroke (transient ischaemic attack does not qualify as non-haemorrhagic stroke for reimbursement approval) or PAD, or have undergone coronary artery bypass graft. Clinicians will be required to confirm this at the time of applying for reimbursement approval. The patient may or may not have a confirmed diagnosis of HeFH.

[iii] This list is not exhaustive; please refer to the relevant Summary of Product Characteristics for full prescribing information.

For reimbursement approval, PAD is defined as one of the following:

- previous aorto-femoral bypass surgery, limb bypass surgery, or percutaneous transluminal angioplasty revascularisation of the iliac, or infra-inguinal arteries
- previous limb or foot amputation for arterial vascular disease
- history of intermittent claudication and one or more of the following:
    - an ankle/arm blood pressure ratio < 0.90
    - significant peripheral artery stenosis (≥ 50%) documented by angiography, or by duplex ultrasound
- previous carotid revascularisation or asymptomatic carotid artery stenosis ≥ 50% as diagnosed by duplex ultrasound or angiography.

Information should be provided as part of the application for reimbursement approval to demonstrate that the patient meets the definition of established ASCVD as per the managed access protocol.

2.3.2 Adults with no ASCVD (i.e. primary prevention)

Reimbursement will only be supported for patients who do not have established ASCVD if the patient has a confirmed diagnosis of HeFH. Reimbursement is not supported for primary prevention in patients who do not have a confirmed diagnosis of HeFH.

2.3.3 Heterozygous Familial Hypercholesterolaemia (HeFH)

Evidence to support the diagnosis of HeFH must accompany the application for reimbursement approval. Diagnosis of HeFH must be made by either genetic testing, or by the Dutch Lipid Clinic Network Score or the modified UK Simon Broome criteria.

Genetic Testing

A copy of the result of genetic testing should be included with the application for reimbursement approval.

Dutch Lipid Clinic Network Score or Modified UK Simon Broome criteria

The calculation of the Dutch Lipid Clinic Network Score or the Modified UK Simon Broome criteria must be completed on the online application system. When completing either calculation, the LDL-C level that is used should be from a blood test taken prior to treatment with cholesterol-lowering medication, or the highest level recorded when on treatment.

Reimbursement of alirocumab and evolocumab under the High Tech Arrangement will only be supported for patients who are classified as having **definite FH** under these scoring systems:

- Dutch Lipid Clinic Network Score ≥ 8
- Modified UK Simon Broome points = (5 or 6) +1

2.4 Low-Density Lipoprotein Cholesterol Levels

Adults with established ASCVD must have a LDL-C level persistently ≥ 3.5 mmol/L. Patients diagnosed with HeFH who do not have established ASCVD, must have a LDL-C level persistently ≥ 4 mmol/L. Two LDL-C levels must be provided as part of the application for reimbursement approval:

1. The current LDL-C level, and the date of the corresponding blood test, must be provided. This LDL-C level must have been taken within 30 days of the date of application.
2. A previous LDL-C level, and the date of the corresponding blood test, must be provided. This LDL-C level should have been taken between three to six months prior to the current LDL-C level.

The current LDL-C level provided as part of the application for reimbursement approval (number 1 above) must be taken after confirmed adherence to treatment with ezetimibe 10 mg daily for a minimum of three months **and** one of the following:

- after confirmed adherence to high-dose statin therapy for a minimum of three months, i.e. at least 40 mg of atorvastatin daily or at least 20 mg of rosuvastatin daily, or
- after having a clinically important statin-related adverse event after a trial of treatment with at least two different statins necessitating a withdrawal of statin treatment, even after dose reduction and rechallenge (i.e. statin intolerance), or
- be a patient in whom statins are contra-indicated.

2.5 High-dose Statin Therapy

For the purposes of reimbursement approval, high-dose statin therapy is defined as at least 40 mg of atorvastatin daily or at least 20 mg of rosuvastatin daily for a period of at least three months. The clinician will be required to provide details of the drug prescribed as part of the application, and to demonstrate that the patient has taken this medicine for a period of at least three months.

For patients not on high-dose statin therapy, the clinician is required to confirm that the higher dose was trialled and not tolerated by the patient.

When reviewing applications, the HSE-Medicines Management Programme (MMP) may request evidence to demonstrate that the patient has been adherent to high-dose statin therapy for a period of at least three months.

2.6 Statin Intolerance

Intolerance to high-dose statin therapy is defined as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy. The following are required to demonstrate intolerance to high-dose statin therapy:

- the patient must have been trialled on both atorvastatin and rosuvastatin, with at least one started at the lowest starting dose, i.e. atorvastatin 10 mg daily or rosuvastatin 5 mg daily, and
- for both statins, dose reduction should have been attempted for the clinically significant adverse effect, and
- for both statins, the clinically significant adverse effect is reversible upon statin discontinuation but reproducible upon statin rechallenge where clinically appropriate, and
- one of the following:
    - other potential causes of the clinically significant adverse effect have been ruled out, or
    - the patient has developed confirmed and documented rhabdomyolysis.

A clinically significant adverse effect includes the following:

- severe myalgia (muscle symptoms without elevation of CK levels) which is proven to be temporally associated with statin treatment
- myositis (clinically important elevation of CK levels, with or without muscle symptoms) demonstrated by CK levels greater than five times the upper limit of normal on single reading, or a rising pattern on consecutive readings, and which is not explained by other causes
- unexplained, persistent elevations of serum transaminases (greater than three times the upper limit of normal) during treatment with statin therapy.

For patients deemed intolerant of high-dose statin therapy, information to include the doses, duration of treatment and the clinically significant adverse effects experienced for atorvastatin and rosuvastatin must be provided by the clinician at the time of application for reimbursement approval.

2.7 Contra-indication to Statin Therapy

For patients in whom statin therapy is contra-indicated, details of the contra-indication (including supporting evidence) must be provided at time of application for reimbursement approval. The contra-indications to statin treatment are those as defined in the SmPC of atorvastatin and rosuvastatin.

2.8 Ezetimibe Therapy

The clinician is required to confirm that the patient has confirmed adherence to treatment with ezetimibe 10 mg daily for a minimum of three months in addition to high-dose statin therapy, as outlined in section 2.4.

2.8.1 Contra-indication/Intolerance to Ezetimibe Therapy

For patients in whom ezetimibe therapy is contra-indicated or not tolerated, details of the contra-indication or intolerance (including supporting evidence) must be provided at time of application for reimbursement approval. The contra-indications to ezetimibe treatment are those as defined in the SmPC of ezetimibe.

3. Reimbursement criteria – Continuation

Ongoing reimbursement approval is conditional on a reduction of ≥ 30% in LDL-C levels from the baseline LDL-C level[iv] provided at time of application (i.e. current LDL-C level as outlined in section 2.4 above) following three months of treatment with alirocumab or evolocumab, and that this is sustained at future reviews and audits. Patients not showing this reduction in LDL-C levels after three months of treatment would be considered non-responders, or non-adherent to treatment.

Therefore, following approval of a patient for reimbursement of alirocumab or evolocumab under the High Tech Arrangement, the prescribing clinician may be required to submit a LDL-C level to the MMP at regular intervals as requested. Follow-up data may be requested by the HSE/MMP for audit purposes and provision of same is a condition of ongoing reimbursement.

4. Prescribing of Praluent® and Repatha®

Prescriptions must be generated through the HTH (details outlined separately) and approved prescriber(s) will have access to prescribe alirocumab and evolocumab.

The following confirmations are required when prescribing alirocumab or evolocumab on the HTH:

[iv] The baseline LCL-C level is defined as the LDL-C level on optimised lipid-lowering therapy prior to initiating Praluent® or Repatha®. It is equivalent to the "current LDL-C" level in section 2.4.

- confirmation that Praluent® / Repatha® is being prescribed for a MMP approved patient in accordance with the managed access protocol established in line with the terms of reimbursement approval given by the HSE
- confirmation that prescriber will assist the HSE/MMP in their conduct of audits* through provision of information as requested, to provide assurance that the product is being prescribed in line with HSE reimbursement approval and the managed access protocol
- confirmation that the patient is aware that the application for reimbursement approval is being made on their behalf and that audits may occur during which their personal data will be reviewed.

** Follow-up data may be requested by the HSE/MMP for audit purposes and provision of same is a condition of ongoing reimbursement.*