Medicines Management Programme

Managed Access Protocol –

Bempedoic Acid 180 mg film-coated tablets (Nilemdo®)

&

Bempedoic Acid 180 mg + Ezetimibe 10 mg film-coated tablets (Nustendi®)

Medicine	Date of addition to Managed Access Protocol
Bempedoic acid (Nilemdo®)	01/09/2024
Bempedoic acid + ezetimibe (Nustendi®)	01/09/2024

Approved by	Professor Michael Barry, Clinical Lead, MMP	
Date approved:	Version 1.0	27/08/2024

Table of Contents

List of tables

List of abbreviations

ACL	Adenosine triphosphate citrate lyase
ASCVD	Atherosclerotic cardiovascular disease
CDS	Community Drug Schemes
CK	Creatine kinase
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
EAS	European Atherosclerosis Society
FH	Familial hypercholesterolaemia
HSE	Health Service Executive
LDL-C	Low-density lipoprotein cholesterol
MAP	Managed Access Protocol
mg	Milligrams
mmol/L	Millimoles/litre
MMP	Medicines Management Programme
NPC1L1	Niemann-Pick C1-Like 1
PCSK9	Proprotein convertase subtilisin/kexin type 9
SmPC	Summary of Product Characteristics

1. Bempedoic acid

There are two licensed medicinal products available on the Community Drug Schemes (CDS) containing bempedoic acid:

- Nilemdo® 180 milligrams (mg) film-coated tablets; each film-coated tablet contains 180 mg of bempedoic acid
- Nustendi® 180 mg/10 mg film-coated tablets; each film-coated tablet contains 180 mg of bempedoic acid and 10 mg of ezetimibe.

Bempedoic acid is an adenosine triphosphate citrate lyase (ACL) inhibitor that lowers low-density lipoprotein cholesterol (LDL-C) by inhibition of cholesterol synthesis in the liver.

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. The molecular target of ezetimibe has been shown to be the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols.

1.1 Licensed indications

Nilemdo® 180 mg film-coated tablets are indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Nilemdo® 180 mg film-coated tablets are also indicated in adults with established or at high risk for atherosclerotic cardiovascular disease (ASCVD) to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- in patients on a maximum tolerated dose of a statin with or without ezetimibe, or
- alone or in combination with ezetimibe in patients who are statin-intolerant, or for whom a statin is contraindicated.

Nustendi® 180 mg/10 mg film-coated tablets are indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin in patients unable to reach LDL-C goals with the maximum

tolerated dose of a statin in addition to ezetimibe,

- alone in patients who are either statin-intolerant or for whom a statin is contraindicated, and are unable to reach LDL-C goals with ezetimibe alone,
- in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin.

Nustendi® 180 mg/10 mg film-coated tablets are also indicated in adults with established or at high risk for ASCVD to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- in patients on a maximum tolerated dose of a statin and not adequately controlled with additional ezetimibe treatment, or
- in patients who are either statin-intolerant, or for whom a statin is contraindicated, and not adequately controlled with ezetimibe treatment, or
- in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets.

1.2 Reimbursement

Reimbursement of bempedoic acid 180 mg film-coated tablets (Nilemdo®) and bempedoic acid 180 mg plus ezetimibe 10 mg film-coated tablets (Nustendi®) under the CDS is supported only for adults, who meet the criteria outlined in this managed access protocol (MAP). All criteria must be satisfied in order for reimbursement to be supported.

Reimbursement is confined to adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, who have a high or very-high cardiovascular risk and who do not reach their LDL-C target levels of 1.8 millimoles/litre (mmol/L) and 1.4 mmol/L, respectively, when:

- the maximally tolerated statin dose in combination with ezetimibe does not appropriately control LDL-C levels, or
- statins are contraindicated or not tolerated and ezetimibe monotherapy does not appropriately control LDL-C levels.

An application for reimbursement approval is required to be submitted on an individual patient basis through the online application system.

Table 1 outlines the licensed therapeutic dosages of bempedoic acid 180 mg film-coated tablets (Nilemdo®) and bempedoic acid 180 mg plus ezetimibe 10 mg film-coated tablets (Nustendi®). Please refer to the relevant Summary of Product Characteristics (SmPC) for further prescribing information.

Table 1: Licensed therapeutic dosages of bempedoic acid 180 mg film-coated tablets (Nilemdo®) and bempedoic acid 180 mg plus ezetimibe 10 mg film-coated tablets (Nustendi®)

Medicinal product (medicine(s))	Route of administration	Dosage
Nilemdo® 180 mg film-coated tablets (bempedoic acid 180 mg)	oral	one tablet daily
Nustendi® 180 mg/10 mg film-coated tablets (bempedoic acid 180 mg/ezetimibe 10 mg)	oral	one tablet daily

mg: milligrams

If a patient is recommended for reimbursement of bempedoic acid 180 mg film-coated tablets (Nilemdo®) and bempedoic acid 180 mg plus ezetimibe 10 mg film-coated tablets (Nustendi®), reimbursement is supported in line with the licensed therapeutic dosages specified in Table 1. Reimbursement of dosages in excess of the licensed therapeutic dosages (as outlined in Table 1) is not supported.

1.3 Reimbursement price

The reimbursement prices of the presentations of bempedoic acid 180 mg film-coated tablets and bempedoic acid 180 mg plus ezetimibe 10 mg film-coated tablets on the CDS are outlined in Table 2. A commercial-in-confidence arrangement is in place with the marketing authorisation holder to reduce the net acquisition cost of bempedoic acid and bempedoic acid plus ezetimibe to the Health Service Executive (HSE).

Table 2: Reimbursement codes and prices for the presentations of bempedoic acid and bempedoic acid plus ezetimibe available under the Community Drug Schemes

Medicinal product (medicine(s))	Pack size (tablets)	Reimbursement	
		Code	Price
Nilemdo® 180 mg film-coated tablets (bempedoic acid 180 mg)	28	67228	€51.41
Nustendi® 180 mg/10 mg film-coated tablets (bempedoic acid 180 mg/ezetimibe 10 mg)	28	67229	€51.41

mg: milligrams
Correct as at 01/09/2024

2. Reimbursement criteria

This section outlines the criteria that must be satisfied in order for an adult to be recommended for reimbursement of bempedoic acid 180 mg film-coated tablets and bempedoic acid 180 mg plus ezetimibe 10 mg film-coated tablets under the CDS.

2.1 Submission of applications

Due to the information that is required to be submitted, the clinician responsible for the initiation of treatment should complete the online application. Approval for reimbursement support should be in place prior to issuing a prescription for reimbursement under the CDS.

Clinicians are responsible for ensuring that the patient or their representative/guardian is aware that the application for reimbursement approval is being made on their behalf.

2.2 Patient age

Applications for reimbursement approval of bempedoic acid 180 mg film-coated tablets (Nilemdo®) and bempedoic acid 180 mg plus ezetimibe 10 mg film-coated tablets (Nustendi®) will only be considered for adults aged 18 years and older at the time of application, in line with the licensing of these medicinal products.

2.3 Dyslipidaemia

For reimbursement approval, clinicians will be required to confirm that the individual has primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia at the time of application.

2.4 Cardiovascular risk

For reimbursement approval, clinicians will be required to confirm that the individual has a high or very-high total cardiovascular risk at the time of application. The definitions of high or very-high total cardiovascular risk categories (table 3) are as per the *2019 European Society of Cardiology (ESC) /European Atherosclerosis Society (EAS) Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk*.

Table 3: Definition of very-high or high total cardiovascular risk categories

Cardiovascular risk category	People with any of the following:
Very-high-risk	• Documented ASCVD, either clinical or unequivocal on imaging • DM with target organ damage*, or at least three major risk factors, or early onset of Type 1 DM of long duration (> 20 years) • Severe CKD (eGFR < 30 ml/minute/1.73 m^2) • A calculated SCORE ≥ 10% for 10-year risk of fatal CVD • FH with ASCVD or with another major risk factor
High-risk	• Markedly elevated single risk factors, in particular total cholesterol > 8 mmol/L, LDL-C > 4.9 mmol/L, or blood pressure > 180/110 mmHg • FH without other major risk factors • DM without target organ damage*, with DM duration ≥ 10 years or another additional risk factor • Moderate CKD (eGFR 30 – 59 ml/minute/1.73 m^2) • A calculated SCORE ≥ 5% and < 10% for 10-year risk of fatal CVD

ASCVD: Atherosclerotic cardiovascular disease; CKD: Chronic kidney disease; CVD: Cardiovascular disease; DM: Diabetes mellitus; eGFR: Estimated glomerular filtration rate; FH: Familial hypercholesterolaemia; LDL-C: Low-density lipoprotein cholesterol; SCORE: Systematic coronary risk estimation

*Target organ damage is defined as microalbuminuria, retinopathy, or neuropathy.

2.5 Low-density lipoprotein cholesterol levels

Reimbursement of bempedoic acid 180 mg film-coated tablets (Nilemdo®) and bempedoic acid 180 mg plus ezetimibe 10 mg film-coated tablets (Nustendi®) under the CDS is supported for individuals who do not reach the LDL-C target levels for their total cardiovascular risk category, despite confirmed adherence to the maximum tolerated dosages of statins and ezetimibe:

- Adults with a very-high total cardiovascular risk must have a LDL-C persistently ≥ 1.4 mmol/L
- Adults with a high total cardiovascular risk must have a LDL-C persistently ≥ 1.8 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. 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. This LDL-C level should have been taken at least three months prior to the current LDL-C level.

A copy of the blood test results showing the current LDL-C level and the date of the corresponding blood test must be provided as part of the application for reimbursement approval.

2.6 Lipid-lowering therapy

The current LDL-C level provided as part of the application for reimbursement approval 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 confirmed adherence to maximum-tolerated statin therapy for a minimum of three months, where the individual was unable to tolerate high-dose statin therapy, or
- after having a clinically important statin-related adverse event(s) after a trial of treatment with at least two different statins necessitating a withdrawal of statin treatment, even after dose reduction and/or rechallenge (i.e. statin intolerance), or
- be an individual in whom statins are contraindicated.

When reviewing applications, the HSE-Medicines Management Programme (MMP) may request evidence to validate the patient's current or prior treatment with statins and ezetimibe, as outlined in the submitted application, e.g. printout of dispensed medicinal products.

2.6.1 High-dose/maximum-tolerated 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. For individuals on maximum-tolerated statin therapy (i.e. not on high-dose statin therapy), the clinician is required to confirm that the high-dose statin therapy was trialled and not tolerated by the individual.

The clinician is required to provide details of the medicine prescribed as part of the application, and to demonstrate that the individual has taken this medicine for a period of at least three months.

2.6.2 Statin intolerance

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

- the individual must have been trialled on at least two statins, with at least one started at the lowest starting dose[i], 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 individual has developed confirmed and documented rhabdomyolysis.

A clinically significant adverse effect includes any of the following:

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

For individuals deemed intolerant of statin therapy, information to include the doses, duration of treatment and the clinically significant adverse effects experienced for two statins must be provided by the clinician at the time of application for reimbursement approval.

2.6.3 Contraindication to statin therapy

For individuals in whom statin therapy is contraindicated, details of the contraindication

[i] Atorvastatin = 10 mg daily; pravastatin = 10 mg daily; rosuvastatin = 5 mg daily; simvastatin = 5 mg daily.

(including supporting evidence) must be provided at the time of application for reimbursement approval. The contraindications to statin treatment are those as defined in the relevant SmPCs.

2.6.4 Ezetimibe therapy

The clinician is required to confirm that the individual has confirmed adherence to treatment with ezetimibe 10 mg daily for a minimum of three months at the time of the current LDL-C level provided as part of the application for reimbursement approval.

For individuals in whom ezetimibe therapy is contraindicated or not tolerated, details of the contraindication or intolerance (including supporting evidence) must be provided at the time of application for reimbursement approval. The contraindications to ezetimibe treatment are those as defined in the SmPC for ezetimibe.

2.6.5 Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors therapy

Reimbursement of bempedoic acid 180 mg film-coated tablets (Nilemdo®) and bempedoic acid 180 mg plus ezetimibe 10 mg film-coated tablets (Nustendi®) is not supported for patients established on treatment with PCSK9 inhibitors.

2.7 Patient clinical history/status

In line with the SmPCs for Nilemdo® and Nustendi®, applications for reimbursement approval will not be considered in individuals who meet any of the contraindications for treatment as outlined in the relevant SmPCs.

3. Reimbursement criteria – Requirement for outcome data

Follow-up data may be requested by the MMP for audit purposes and provision of same is a condition of ongoing reimbursement. It is the responsibility of the clinician to ensure that the patient or their representative/guardian is aware that the provision of follow-up data is a condition of reimbursement, and that audits may occur during which their personal data will be reviewed.

4. Prescribing for approved patients

Please refer to the SmPCs for Nilemdo® and Nustendi® for full prescribing information including monitoring and patient counselling requirements.

Prior to issuing a prescription for reimbursement on the CDS, the clinician should ensure that the individual has been approved for reimbursement support, following review of an application submitted to the MMP.

Where an individual is approved for reimbursement of bempedoic acid, reimbursement support is in place for both bempedoic acid 180 mg film-coated tablets (Nilemdo®) or bempedoic acid 180 mg plus ezetimibe 10 mg film-coated tablets (Nustendi®).

In line with the reimbursement criteria, patients are expected to be in receipt of ezetimibe (+/-statin therapy) for reimbursement of bempedoic acid to be supported. Nilemdo® and Nustendi® are flat-priced; where a patient is prescribed bempedoic acid and ezetimibe in combination, consideration should be given to prescribing bempedoic acid and ezetimibe fixed-dose combination (Nustendi®) in preference to bempedoic acid (Nilemdo®) and ezetimibe as separate medicinal products. This reduces the tablet burden for the individual and the net acquisition cost of treatment to the HSE.