Pending CCG approval

NHS
Pan Mersey
Area Prescribing Committee

BEMPEDOIC ACID tablets (Nilemdo® ▼) and BEMPEDOIC ACID-EZETIMIBE tablets (Nustendi® ▼) for primary hypercholesterolaemia or mixed dyslipidaemia: a multiple prescribing statement

The Pan Mersey Area Prescribing Committee recommends the prescribing of BEMPEDOIC ACID tablets (Nilemdo® ▼) and BEMPEDOIC ACID-EZETIMIBE tablets (Nustendi® ▼) for primary hypercholesterolaemia or mixed dyslipidaemia in accordance with NICE TA694.

GREEN

NICE technology appraisal (TA) 694 recommends bempedoic acid with ezetimibe as an option for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet in adults, only if:

- statins are contraindicated or not tolerated,
- ezetimibe alone does not control low-density lipoprotein cholesterol well enough, **and**
- the company provides bempedoic acid and bempedoic acid with ezetimibe according to the commercial arrangement.[1]

Bempedoic acid with ezetimibe can be used as separate tablets or a fixed-dose combination.[1]

NICE TA 694 does not recommend monotherapy with bempedoic acid.[1]

The nature of the commercial arrangement means that bempedoic acid (Nilemdo®) and bempedoic acid-ezetimibe (Nustendi®) can be prescribed across primary and secondary care settings. There is an NHS England central primary care rebate for bempedoic acid and bempedoic acid-ezetimibe.

NICE does not expect this guidance to have a significant impact on resources; that is, the resource impact of implementing the recommendations in England will be less than £5 million per year (or £9,000 per 100,000 population). This is because bempedoic acid and bempedoic acid-ezetimibe are further treatment options and the overall cost of treatment will be similar.

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

BEMPEDOIC ACID tablets (Nilemdo® ▼)
for primary hypercholesterolaemia or mixed dyslipidaemia

Effectiveness

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.[2] Clinical trial evidence suggests that bempedoic acid with ezetimibe may help lower LDL-C levels when other lipid-lowering therapies have not reduced them enough. In studies 1002-048 (CLEAR Tranquility)[3] and 1002-046 (CLEAR Serenity)[4] bempedoic acid significantly reduced LDL-C from baseline to week 12 compared with placebo as an add-on to ezetimibe in statin intolerant patients (CLEAR Tranquilty: $p < 0.001$; -23.5% bempedoic acid vs +5.0% placebo, CLEAR Serenity: $p < 0.001$; -22.6% bempedoic acid vs -1.2% placebo).[2] Bempedoic acid also significantly reduced non-high density lipoprotein cholesterol (non-HDL-C), apolipoprotein B, and total cholesterol.[2]

There is no data directly comparing bempedoic acid with ezetimibe with either alirocumab or evolocumab. An indirect comparison of trials suggests that bempedoic acid with ezetimibe may not be as effective at reducing LDL-C levels as alirocumab or evolocumab.[1]

The position recommended by NICE is narrower than the marketing authorisation (which allows bempedoic acid alone or in combination with a statin without ezetimibe), because the company did not anticipate bempedoic acid would be used before ezetimibe in the treatment pathway in the NHS. During the appraisal, the company decided that it was no longer seeking a recommendation in the maximally tolerated statin population because the incremental cost-effectiveness ratio (ICER) estimates were too high to be recommended for routine use in the NHS.[1] The NICE committee was concerned about the clinical effectiveness of bempedoic acid because of the lack of long-term data on cardiovascular (CV) outcomes in the pivotal trials, and that appropriate subgroup analyses relating to CV risk and heterozygous familial hypercholesterolaemia could not be provided. However, it noted that further data were unlikely to become available.[1]

Safety

Contraindications: hypersensitivity to the active substance or to any of the excipients, pregnancy, breast-feeding and concomitant use with simvastatin > 40 mg daily.[2]

The most commonly reported adverse reactions with bempedoic acid during pivotal trials were hyperuricaemia, pain in extremity, and anaemia.[2] Gout was reported in 1.4% of patients treated with bempedoic acid and 0.4% of patients treated with placebo. In both groups, patients were more likely to have a medical history of gout and/or baseline levels of uric acid above the upper limit of normal (ULN).[2] Anaemia was reported in 2.5% of patients treated with bempedoic acid and 1.6% of patients treated with placebo.[2]

Increases in serum transaminases (AST and/or ALT) have also been reported but were not associated with other evidence of liver dysfunction.[2] Refer to SPC for full details.

Cost[5]

Annual cost of treatment with bempedoic acid 180mg daily is £723 at the NHS List price (which does not take the commercial arrangement into consideration).

Drug regime	Annual cost
Bempedoic acid 180mg plus ezetimibe 10mg (separate agents)	£756
Bempedoic acid-ezetimibe 180mg/10mg (fixed dose combination)	£723

Patient factors[2]

Women of childbearing potential must use effective contraception during treatment. Patients should be advised to stop taking bempedoic acid before stopping contraceptive measures if they plan to become pregnant.

No dose adjustment necessary in elderly patients, in patients with mild or moderate renal impairment, or in patients with mild or moderate hepatic impairment (Child-Pugh A or B).

There is limited information in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2). Clinical studies did not include patients with end stage renal disease (ESRD) on dialysis or in patients with severe hepatic impairment (Child-Pugh C).

Prescribing information

- The recommended dose of bempedoic acid is one 180mg tablet once daily, taken orally with or without food and swallowed whole.[2]
- NICE TA 694 does not recommend the use of bempedoic acid in combination with a statin or as monotherapy[1]

Implementation notes[2]

- Treatment should be discontinued if hyperuricaemia accompanied with symptoms of gout appear.
- Liver function tests (LFTs) should be performed at initiation of therapy. Although not specified by the SPC, it is advisable to recheck LFTs within 3 months of starting treatment and at 12 months, but not again unless clinically indicated.
- Bempedoic acid should be discontinued if an increase in transaminases of > 3× the upper limit of normal (ULN) persists. Ezetimibe should be prescribed separately and continued (unless contraindicated).
- After discontinuation, LFTs should be rechecked after 1 month and if LFTs have returned to baseline it is advisable to defer restarting bempedoic acid and seek advice from a lipidologist (through the e-referral advisory service for GPs).
- If transaminases remain consistently high (> 3× ULN) after stopping bempedoic acid then referral to hepatology or for liver ultrasound should be considered. Bempedoic acid should not be restarted, and advice should be sought from a lipidologist (through the e-referral advisory service for GPs).
- Additional monitoring for adverse reactions may be warranted in patients with severe renal impairment and patients with ESRD on dialysis.
- Periodic liver function tests should be considered for patients with severe hepatic impairment.

References

1. National Institute for Health and Care Excellence. Technology Appraisal 694; Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia, 28 April 2021. Accessed online 28 April 2021.
2. Daiichi Sankyo UK Limited. Summary of Product Characteristics; Nilemdo 180mg film-coated tablets, 01 April 2020. Accessed online 12 May 2021.
3. U.S. National Library of Medicine. ClinicalTrials.gov; Evaluation of the Efficacy and Safety of Bempedoic Acid (ETC-1002) as Add-on to Ezetimibe Therapy in Patients With Elevated LDL-C (CLEAR Tranquility). Accessed online 12 May 2021.
4. U.S. National Library of Medicine. ClinicalTrials.gov; Evaluation of the Efficacy and Safety of Bempedoic Acid (ETC-1002) in Patients With Hyperlipidemia and Statin Intolerant (CLEAR Serenity). Accessed online 12 May 2021.
5. NHS Business Services Authority. Dictionary of medicines and devices (dm+d) browser. Accessed online 12 May 2021.

BEMPEDOIC ACID-EZETIMIBE tablets (Nustendi® ▼) for primary hypercholesterolaemia or mixed dyslipidaemia

Effectiveness

Bempedoic acid is an ACL inhibitor that lowers LDL-C by inhibition of cholesterol synthesis in the liver. Clinical trial evidence suggests that bempedoic acid with ezetimibe may help lower LDL-C levels when other lipid-lowering therapies have not reduced them enough. In study 1002-048 (CLEAR Tranquility)[3] bempedoic acid with ezetimibe significantly reduced LDL-C from baseline to week 12 compared with placebo and ezetimibe (p <0.001; -23.5% bempedoic acid vs +5.0% placebo).[2] Bempedoic acid with background ezetimibe also significantly reduced non-HDL-C, apo B, and TC.[2] Study 1002-053 (a 4-arm, multi-centre, randomised, double-blind, parallel-group, 12-week trial) was a sensitivity anaylsis of 301 patients receiving bempedoic acid-ezetimibe (n=86), bempedoic acid (n=88), ezetimibe (n=86), or placebo once daily (n=41) as add-on to a maximum tolerated statin therapy. Bempedoic acid-ezetimibe significantly reduced LDL-C from baseline to week 12 compared with placebo (-38.0%; 95% CI: -46.5%, -29.6%; p < 0.001) and also significantly reduced non-HDL-C, apo B, and TC.[2] Ezetimibe has been shown to reduce the frequency of CV events but the effect of bempedoic acid on CV morbidity and mortality has not been determined.[2] There is no data directly comparing bempedoic acid with ezetimibe with either alirocumab or evolocumab. An indirect comparison of trials suggests that bempedoic acid with ezetimibe may not be as effective at reducing LDL-C levels as alirocumab or evolocumab.[1]

The position recommended by NICE is narrower than the marketing authorisation (which allows bempedoic acid alone or in combination with a statin without ezetimibe), because the company did not anticipate bempedoic acid would be used before ezetimibe in the treatment pathway in the NHS. During the appraisal, the company decided that it was no longer seeking a recommendation in the maximally tolerated statin population because the ICER estimates were too high to be recommended for routine use in the NHS.[1] The NICE committee was concerned about the clinical effectiveness of bempedoic acid because of the lack of long-term data on CV outcomes in the pivotal trials, and that appropriate subgroup analyses relating to CV risk and heterozygous familial hypercholesterolaemia could not be provided. However, it noted that further data were unlikely to become available.[1]

Safety

Contraindications: hypersensitivity to the active substance or to any of the excipients, pregnancy, breast-feeding and concomitant use with simvastatin > 40 mg daily.[2] The most commonly reported adverse reactions are hyperuricaemia and constipation.[2] Pain in extremity has also been reported.[2]

In the pooled placebo-controlled trials of bempedoic acid, gout was reported in 1.4% of patients taking bempedoic acid and 0.4% of patients taking placebo. In both groups, patients were more likely to have a medical history of gout and/or baseline levels of uric acid above the ULN.[2] Anaemia was reported in 2.5% of patients treated with bempedoic acid and 1.6% of patients treated with placebo.[2] Increases in serum transaminases (AST and/or ALT) have also been reported but were not associated with other evidence of liver dysfunction.[2]

Refer to SPC for full details.

Cost[4]

Annual cost of treatment with bempedoic acid 180mg /ezetimibe 10mg daily is £723 at the NHS List price (which does not take the commercial arrangement into consideration).

Drug regime	Annual cost
Bempedoic acid 180mg plus ezetimibe 10mg (separate agents)	£756
Bempedoic acid-ezetimibe 180mg/10mg (fixed dose combination)	£723

Patient factors[2]

Women of childbearing potential must use effective contraception during treatment. Patients should be advised to stop taking bempedoic acid before stopping contraceptive measures if they plan to become pregnant.

No dose adjustment necessary in elderly patients, in patients with mild or moderate renal impairment, or in patients with mild hepatic impairment (Child-Pugh A).

Not recommended in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.

There is limited information in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2). Clinical studies did not include patients with ESRD on dialysis.

Prescribing information

- The recommended dose of bempedoic acid-ezetimibe is one 180 mg/10 mg tablet once daily, taken orally with or without food and swallowed whole.
- Dosing should occur either at least 2 hours before or at least 4 hours after administration of a bile acid sequestrant.[2]
- NICE TA 694 does not recommend the use of bempedoic acid-ezetimibe in combination with a statin.[1]

Implementation notes[2]

- Treatment should be discontinued if hyperuricaemia accompanied with symptoms of gout appear.
- Liver function tests (LFTs) should be performed at initiation of therapy. Although not specified by the SPC, it is advisable to recheck LFTs within 3 months of starting treatment and at 12 months, but not again unless clinically indicated.
- Bempedoic acid-ezetimibe should be discontinued if an increase in transaminases of > 3× the upper limit of normal (ULN) persists. Ezetimibe should be prescribed separately and continued (unless contraindicated).
- After discontinuation, LFTs should be rechecked after 1 month and if LFTs have returned to baseline it is advisable to defer restarting bempedoic acid and seek advice from a lipidologist (through the e-referral advisory service for GPs).
- If transaminases remain consistently high (> 3× ULN) after stopping bempedoic acid then referral to hepatology or for liver ultrasound should be considered. Bempedoic acid should not be restarted, and advice should be sought from a lipidologist (through the e-referral advisory service for GPs).
- Additional monitoring for adverse reactions may be warranted in patients with severe renal impairment and patients with ESRD on dialysis.
- If treatment is started for a patient taking warfarin, other coumarin anticoagulants, or fluindione, the INR should be appropriately monitored.

References

1. National Institute for Health and Care Excellence. Technology Appraisal 694; Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia, 28 April 2021. Accessed online 28 April 2021.
2. Daiichi Sankyo UK Limited. Summary of Product Characteristics; Nustendi 180mg/10mg film-coated tablets, 27 March 2020. Accessed online 12 May 2021.
3. U.S. National Library of Medicine. ClinicalTrials.gov; Evaluation of the Efficacy and Safety of Bempedoic Acid (ETC-1002) as Add-on to Ezetimibe Therapy in Patients With Elevated LDL-C (CLEAR Tranquility). Accessed online 12 May 2021.
4. NHS Business Services Authority. Dictionary of medicines and devices (dm+d) browser. Accessed online 14 May 2021.