Briefing Paper for Surrey Heartlands Integrated Care System (ICS) Area Prescribing Committee (APC)

Integrated Care Partnerships (ICPs) (Surrey Downs, Guildford & Waverley, North West Surrey, East Surrey & associated partner organisations.

NICE Technology Appraisals: Local implementation

NICE TA Guidance	**Bempedoic acid with Ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia (TA694)**		
Available at	https://www.nice.org.uk/guidance/ta694		
Date of issue	28/4/21	**Implementation deadline**	28/7/21

Medicine details	
Name, brand name	Bempedoic acid (Nilemdo®) and Bempedoic acid with Ezetimibe (Nustendi®)
Manufacturer	Daiichi-Sankyo
Licensed indication	(Date of access to SPC 12/5/21) **Nilemdo®** is 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. **Nustendi®** is 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. Please note: 1. The NICE TA694 recommendation differs significantly from the licensed indication. See NICE recommendation in the summary section below. 2. Author believes that 'statin-intolerant' means that the patient is not taking a statin as opposed to a patient who cannot tolerate a high enough dose of statin to reach their LDL-C goals. 3. National guidance is currently being developed to support the definition of 'statin-intolerance'. This pathway will be brought back

	to the APC for consideration when published. Proposed date for publication, August 2021. https://www.ahsnnetwork.com/about-academic-health-science-networks/national-programmes-priorities/lipid-management-and-fh 4. The current statin intolerance pathway can be found on the Surrey Prescribing Advisory Database (PAD) https://surreyccg.res-systems.net/PAD/Guidelines/Detail/4399
Formulation	(Date of access to SPC 12/5/21) **Nilemdo®**: 180 mg Bempedoic acid film-coated tablet **Nustendi®**: 180 mg Bempedoic acid/10 mg Ezetimibe film-coated, fixed-dose combination, (FDC) tablet
Usual dosage	(Date of access to SPC 12/5/21) **Nilemdo®**: 180 mg Bempedoic acid One to be taken daily **Nustendi®**: 180 mg Bempedoic acid/10 mg Ezetimibe One to be taken daily
NICE recommended dosage/schedule	Same as SPC

Disease and potential patient group	
Brief description of disease	Coronary heart disease (CHD) is narrowed coronary arteries due to a build-up of atheroma, a fatty material, within the artery walls. It is responsible for around 180 deaths per day in the UK. [(1)] Raised blood levels of low-density lipoprotein cholesterol (LDL-C) or 'bad cholesterol' are an important risk factor for the development of CHD, which can result in angina and myocardial infarction (heart attack). [(2)] Excess LDL-C is also a risk factor for other types of vascular disease including stroke and peripheral arterial disease. Reducing serum LDL-C with lipid lowering treatments, such as statins, is a key intervention in the prevention of CHD and other types of vascular disease. Accordingly, lipid-lowering guidelines have suggested target LDL-C levels, the achievement of which can significantly reduce the risk of the patient developing vascular disease. However, many patients fail to achieve these targets and are as such at increased risk of suffering cardiovascular events. There are various reasons why patients may be unable to reach LDL-C targets. These include resistant hyperlipidaemia *i.e.,* a lipid disorder which does not respond well to treatment, intolerance to lipid lowering treatment, contraindication to lipid lowering treatment and non-adherence to treatment. Some patients who fail to reach the LDL-C target using statins meet the criteria for treatment with one of the powerful new injectable lipid lowering drugs or PCSK9 inhibitors (*viz* Evolocumab and Alirocumab) but many patients are unfortunately not eligible for treatment with these drugs. This leaves a significant treatment gap of patients with unacceptably high LDL-C levels. Any new lipid lowering treatments which can help fill this treatment gap are a welcome development.

	Bempedoic acid is a new LDL-C lowering treatment, which has been shown to lower LDL-C by around 23%. [3] It works by inhibiting an enzyme in the cholesterol synthesis pathway resulting in reduced synthesis of cholesterol in the body. It is taken as a tablet once daily. Bempedoic acid could in part help to address the treatment gap in lipid-lowering therapy. NICE (TA694) has recommended that Bempedoic acid can be combined with another LDL-C lowering drug called ezetimibe which works by reducing cholesterol uptake from the gut. Bempedoic acid will work along with the ezetimibe to lower LDL-C further.
Potential patient numbers per 100,000	NICE does not provide a costing template. It has however published a resource impact statement for TA 694 which states that no significant resource impact is anticipated. The basis for this decision is not clear. **Resource impact statement** **No significant resource impact is anticipated** NICE has recommended Bempedoic acid with ezetimibe as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia as an adjunct to diet if certain criteria are met. We do 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 the technology is a further treatment option, and the overall cost of treatment will be similar. Bempedoic acid and 2 of the other treatment options have discounts that are commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discounts. This technology is commissioned by clinical commissioning groups. Providers are NHS hospital trusts and GPs. This page was last updated: 28 April 2021[4]

Daiichi Sankyo have published a formulary application support pack outlining the financial implications associated with the use of Bempedoic acid.

Financial implications

Bempedoic acid with ezetimibe is recommended (by NICE) as a cost-effective use of NHS resources[NICE, 2021a]

NICE do 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 in England (or £9,000 per 100,000 population[NICE, 2021b].

Potential eligible population for bempedoic acid, per 100,000 population[Daiichi Sankyo UK Limited, 2019]

Population: UK (per 100,000 standardised)	Percent of patients (year 1)	Population numbers (year 1)
Per 100,000 population	73.9%	73,900
Prevalence primary hypercholesterolemia and mixed dyslipidaemia	15.4%	11,381
Proportion of patients with hypercholesterolaemia and mixed dyslipidaemia that are high risk and receiving statins	30.7%	3,494
Proportion where a statin is considered inappropriate or is contraindicated or not tolerated	15.0%	524
Proportion treated with ezetimibe or PCSK9i	53.0%	278
Proportion not appropriately controlled on ezetimibe	64.0%	178
Proportion that receive additional treatment(s)	82.0%	146
2b: Statin-intolerant patients on ezetimibe requiring further therapy and meeting threshold for PCSK9i therapy	6.7%	10
2a: Statin-intolerant patients on ezetimibe requiring further therapy and not meeting threshold for PCSK9i therapy	93.3%	136
Adult patients with primary hypercholesterolemia or mixed dyslipidaemia for whom statins are contraindicated or not tolerated, and ezetimibe alone does not control LDL-C well enough		**146**

The patient groups included in the model are:

1. % of patients who are statin-intolerant on Ezetimibe who do not meet their LDL-C goals and are eligible for PCSK9i therapy (2b) = 0.01% or **10** patients per 100,000 population at year 1

2. % of patients who are statin-intolerant on Ezetimibe who do not meet their LDL-C goals and are ineligible for PCSK9i therapy (2a) = 0.136% or **136** patients per 100,000 population at year 1

Total potential patient numbers per 100,000 population = **146** at year 1

- As the NICE recommendation is restricted to patients not taking statins but taking ezetimibe, the numbers of patients eligible for treatment will be small.

- There is no clinic database available for the RSCH clinic and so the exact number is unknown, but in the author's clinic it is estimated that there are fewer than 10 patients currently treated with ezetimibe monotherapy who would be eligible for treatment with Bempedoic acid.

(Note: A higher number of patients eligible for Bempedoic acid may be predominately residing in primary care and hence are unknown to secondary care clinics)

	• The numbers in other lipid clinics are likely to be similar. • Patients on ezetimibe monotherapy whose lipid lowering treatment is no longer being adjusted are likely to have been discharged to the care of their GP.

SUMMARY

NICE recommendation

1.1 Bempedoic acid with ezetimibe is recommended as an option for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet in adults. It is recommended 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.

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

This recommendation is not intended to affect treatment with Bempedoic acid with ezetimibe that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Please note NICE TA 694 does not recommend:

- Bempedoic Acid without concurrent Ezetimibe treatment.
- Bempedoic acid in patients at maximally tolerated doses of statin. 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.

Cost implications*

Cost of product:
Nilemdo® (180 mg Bempedoic acid): **£55.44** per 28 days (Drug tariff price April 2021)
Nustendi® (180 mg Bempedoic acid/10 mg ezetimibe): **£55.44** per 28 days (Drug tariff price April 2021)

Annual cost per patient:

Nilemdo® (180 mg Bempedoic acid): **£722.70** p/a per patient (Drug tariff price April 2021)
Nustendi® (180 mg Bempedoic acid/10 mg ezetimibe): **£722.70** p/a per patient (Drug tariff price April 2021)

Daiichi Sankyo have provided a drug acquisition cost table.
Note the cost differential per annum between prescribing **Nustendi®** and **Nilemdo®** plus generic Ezetimibe.

Drug acquisition costs

Bempedoic acid with ezetimibe can be used as separate tablets or as a fixed-dose combination[NICE, 2021a]

Drug acquisition costs (basic NHS price) are:

- £753.35 per patient per year for bempedoic acid (NILEMDO) with separate ezetimibe tablets[MIMS, 2021]
- £720.72 per patient per year for bempedoic acid with ezetimibe (NUSTENDI)[MIMS, 2021]

Basic NHS drug acquisition cost, cost per patient per year and monitoring requirements[MIMS, 2021]

Treatment	Dose[MIMS, 2021]	Basic NHS cost[MIMS, 2021]	Cost per patient per year[MIMS, 2021]	
NILEMDO	1 tablet daily	£55.44 for 28 tablets	£720.72	£753.35
Ezetimibe	1 tablet daily	£2.51 for 28x 10 mg tablets	£32.63	
NUSTENDI	1 tablet daily	£55.44 for 28 tablets	£720.72	
Alirocumab	75 mg or 150 mg every 2 weeks or 300 mg every 4 weeks	£336.00 for 2 x 75 mg OR 2 x 150 mg prefilled pens	£4,368	
Evolocumab	140 mg every 2 weeks	£340.20 for 2 x 140 mg prefilled SureClick®	£4,422.60	

Has dose escalation been considered as part of the NICE costing template?

N/A. Dose escalation is not possible under the current recommendation.

Costing information/100,000 population and per ICP within Surrey Heartlands ICS

FDC = Bempedoic acid plus Ezetimibe fixed-dose combination

	Statin-intolerant patients on Ezetimibe who do not meet their LDL-C goals *					
Integrated Care Partnership	Group 2b (eligible for PCSK9i). Approximate patient numbers at year 1.	Group 2a (ineligible for PCSK9i). Approximate patient numbers at year 1.	Group 2b (eligible for PCSK9i). Approximate drug cost Bempedoic acid 180mg plus Ezetimibe 10mg (FDC Nustendi) per annum	Group 2b (eligible for PCSK9i). Approximate drug cost Bempedoic acid 180mg (Nilemdo) plus generic Ezetimibe 10mg (separate tablets) per annum	Group 2a (ineligible for PCSK9i). Approximate drug cost Bempedoic acid 180mg plus Ezetimibe 10mg (FDC Nustendi) per annum	Group 2a (ineligible for PCSK9i). Approximate drug cost Bempedoic acid 180mg (Nilemdo) plus generic Ezetimibe 10mg (separate tablets) per annum
Guildford and Waverley	21	284	£15,135.12	15,820.35	£204,684.48	£213,951.40
North West surrey	35	473	£25,225.20	£26,367.25	£340,900.56	£356,334.55
Surrey Downs	29	397	£20,900.88	£21,847.15	£286,125.84	£299,079.95
East Surrey	18	251	£12,972.96	£13,560.30	£180,900.72	£189,090.85
Total	**103**	**1,405**	**£74,234.16**	**77,595.05**	**£1,012,611.60**	**£1,058,456.75**

***7.7% of patients in the CLEAR Serenity study (Efficacy and safety of Bempedoic acid in patients with hypercholesterolemia and statin intolerance) were taking very low dose statin defined as an average daily dose of <5mg rosuvastatin, <10mg atorvastatin, <10mg simvastatin, <20mg lovastatin, <40mg pravastatin, <40mg Fluvastatin, or <2mg pitavastatin.

Surrey Heartlands costing information per 100,000 population:

Total potential population per 100,000 = **146** (based on Daiichi Sankyo financial application support pack)

146 x £722.70 = **£105,514.20** p/a per 100,000 population prescribing Nustendi® (Bempedoic acid 180mg with Ezetimibe 10mg FDC).

Alternatively

146 x £753.35 = **£109,989.10** p/a per 100,000 population prescribing Nilemdo® (Bempedoic acid 180mg) plus separate generic Ezetimibe 10mg tablet.

Cost differential: £109,989.10 - £105,514.20 = £4,474.90 p/a per 100,000 population.

- The cost implications to our local health economy varies substantially from that stated in the NICE resource impact statement per 100,000 population.

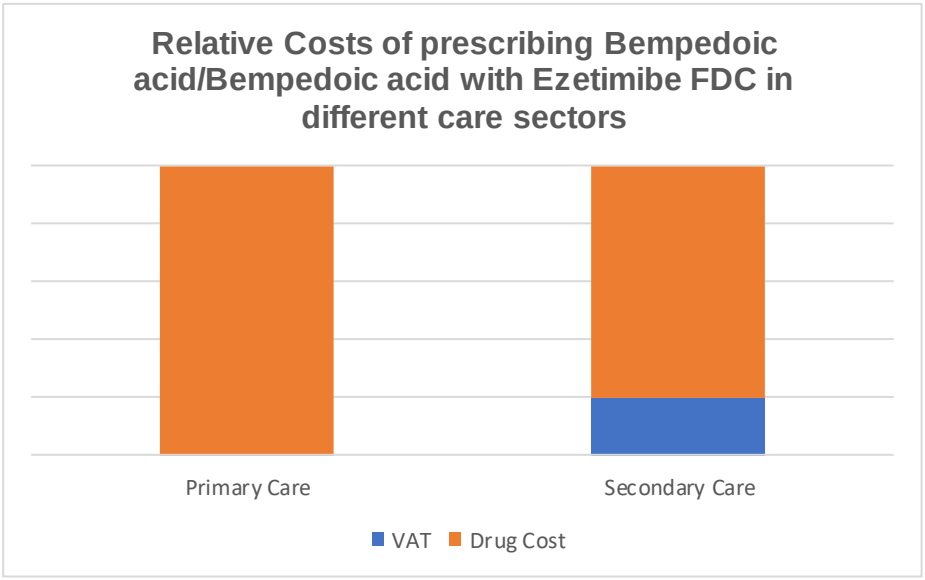
Note: Supporting evidence for FDC (Bempedoic acid plus Ezetimibe fixed-dose combination) in statin-intolerant patients is available from the CLEAR Tranquility
study which investigated Bempedoic acid and Ezetimibe given as separate tablets.
Pharmacokinetic studies have shown the two presentations to be equivalent. [5]

Availability of PAS and details (if appropriate): YES

The company Daiichi Sankyo has agreed a commercial access agreement with the Department of Health.
The level of discount is commercial in confidence.
NICE stipulates that implementation of TA694 is recommended only if the company provides Bempedoic acid and Bempedoic acid with Ezetimibe according to the commercial agreement.

Graph 1 illustrates how implementation of the commercial access agreement leads to a relatively small cost differential between prescribing in either Primary or Secondary care.

Graph 1



Availability of homecare service (if appropriate): N/A

**NICE funding requirements are based on Quality Adjusted Life Years (QALY) threshold. If there is evidence that the incremental cost rises above this threshold in the future, the APC may reconsider the commissioning status.*

Alternative treatments and cost per patient (per year / per month as appropriate)

Other NICE recommended products:

Possible alternatives to Bempedoic acid are bile acid sequestrants (Cholestyramine, Colestipol and Colesevelam) and fibrates (fenofibrate, bezafibrate, ciprofibrate). The use of these treatments would largely be confined to patients with familial hyperlipidaemias.

Appendix 1 which depicts a table of comparative costs for Lipid regulating drugs based on NHS Basic price per patient per annum.

Options not reviewed by NICE but used in standard practice:
N/A

Impact to patients

- It is anticipated that lipid clinic patients eligible for treatment with Bempedoic acid and ezetimibe will be identified at clinic attendance.
- Patients eligible for treatment with Bempedoic acid/ezetimibe may also be referred to the clinic from other hospital departments such as cardiology and endocrinology.
- Most clinic patients eligible for treatment are likely to have been established on treatment with ezetimibe already. If not, ezetimibe will be prescribed initially and Bempedoic acid added to the regimen once tolerance of ezetimibe is confirmed.
- Patients who start treatment with Bempedoic acid/ezetimibe will remain under review in clinic until LDL-C is stable. At that point patients will be discharged to the care of their GP for periodic review.

Impact to primary care prescribers

- The numbers of patients eligible for this lipid lowering combination are likely to be small.
- Practices may wish to identify patients who are eligible for treatment and consider referral to the lipid clinic.
- Prior to referral, steps should be taken to ensure that patients deemed intolerant to statins have been appropriately trialled on at least two high intensity statins i.e., Atorvastatin and Rosuvastatin as per the statin intolerance pathway.
- Once patients are established on the Bempedoic acid/Ezetimibe regimen GPs may wish to switch to the combination product (Nustendi) for simplicity of prescribing and to reduce pill burden.
- Consideration needs to be given to the long-term financial impact on the local healthcare economy, of fixed-dose combination prescribing, on patent expiry of Nustendi®.

Impact to secondary care

- Owing to the restrictive nature of the NICE recommendation the number of new clinic referrals for consideration of treatment with Bempedoic acid and Ezetimibe is likely to be small.
- No capacity issues are anticipated or any need for additional resources though this could change if NICE were to update the guidance to recommend addition of Bempedoic acid to statin treatment in patients not treated to target.
- Patients should have regular monitoring of lipids, renal function, liver function, creatine kinase and urate. We recommend clinical review and biochemical monitoring at least every three months until stable and biannually thereafter.
- It is unlikely that there will be savings on other drugs because patients offered treatment with Bempedoic acid are likely to have an LDL-C level well above target and so will have to continue taking any other non-statin lipid lowering drugs which has been prescribed.

Impact to CCGs

- NICE noted the high level of uncertainty with the evidence informing the long-term treatment effect of Bempedoic acid and its impact on Cardiovascular outcomes. The trials reported 12-week LDL-C endpoints and were underpowered for cardiovascular outcomes. Furthermore, appropriate analyses could not be undertaken based on the efficacy data directly related to the primary and secondary prevention populations.
- Therefore, the committee agreed that conservative thresholds should be adopted. An

acceptable ICER for population 2a (statins are contraindicated or not tolerated and not eligible for Alirocumab or Evolocumab) would be below £20,000 per QALY gained, and an acceptable ICER for population 2b (statins are contraindicated or not tolerated and are eligible for Alirocumab or Evolocumab) would be above £30,000 per QALY lost.
- Because of the confidential discount for Bempedoic acid and Bempedoic acid–Ezetimibe, the exact ICER for populations 2a & 2b cannot be reported.

- Clearly defined stop criteria should be developed to aid review if the treatment proves ineffective.
- Clearly defined monitoring requirements should be developed for onward prescribing in primary care.
- Education to support clinicians to appropriately assess 'statin intolerance' as per the statin-intolerance pathway.

Implementation

- Implementation should be straightforward once Bempedoic acid is available on hospital formulary. Lipid clinics already carry out the necessary monitoring which includes regular fasting lipid profiles any other necessary tests including liver and renal profiles. Prescription of Bempedoic acid will be in accordance with NICE guidance. Any patients with LDL-C above target who are intolerant of statins or are contraindicated to taking a statin but able to tolerate ezetimibe monotherapy will be considered for treatment with Bempedoic acid.

- The company's current proposed position is narrower than the marketing authorisation because:
    1. They did not anticipate Bempedoic acid would be used before ezetimibe in the treatment pathway in the NHS.
    2. 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.

Recommendation to APC

PbRe: NO

Colour classification guidelines

Recommended traffic light status (see attached guidelines):

Green

Bempedoic acid would fit into the criteria for GREEN traffic light classification as:
- Primary care prescribers are very experienced in lipid management, and specialist assessment to enable patient selection and initiation of treatment is not required
- There is no dose titration
- Monitoring of efficacy can be undertaken in primary care without specialist support
- Monitoring of toxicity can be undertaken in primary care without specialist support

The APC may consider this to be new and therefore wish to recommend specialist initiation **(BLUE)** traffic light until there is more real-world evidence.

On discussion with the manufacturer Daiichi Sankyo, they have indicated that a **GREEN** status would be a suitable recommendation.

Additional comments:
The RSCH lipid clinic plans to audit the use of Bempedoic acid/ezetimibe prospectively.

References:

1. www.nhs.uk

2. www.heartuk.org.uk

3. Ballantyne CM, Davidson MH, Macdougall DE, et al. Efficacy and safety of a novel dual modulator of adenosine triphosphate-citrate lyase and adenosine monophosphate-activated protein kinase in patients with hypercholesterolemia: results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. *J Am Coll Cardiol* 2013; 62:1154-1162.

4. NICE (National Institute for Health and Care Excellence). Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia Technology appraisal guidance [TA694] Resource Impact Statement Published: 28 April 2021. Found at: https://www.nice.org.uk/guidance/ta694/resources/resource-impact-statement-9082064701 (Accessed 13/06/21)

5. NICE (National Institute for Health and Care Excellence) Single Technology Appraisal Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515] committee papers. Found at: https://www.nice.org.uk/guidance/ta694/evidence/appraisal-consultation-committee-papers-pdf-9082103581 (Accessed 13/06/21)

6. Regional Drugs and Therapeutics centre. Cost Comparison charts Jan 2020. Found at: http://gmmmg.nhs.uk/docs/cost_comparison_charts.pdf (Accessed 10/06/21)

List of Abbreviations

Abbreviation	Full name
FDC	Bempedoic acid plus Ezetimibe fixed-dose combination
PCSK9i	Proprotein convertase subtilisin / kexin type 9 inhibitor
LDL-C	Low-density lipoprotein cholesterol
ICS	Integrated care system
ICP	Integrated care partnership
BA	Bempedoic acid
EZE	Ezetimibe
Evo/mab	Evolocumab
Ari/mab	Alirlocumab

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Appendix 1

Comparative cost table of Lipid regulating drugs per patient per annum. Costs quoted at the NHS Basic price (as of January 2020) [6]